Lifetime TBI and cognitive domain deficits in late life: The PROTECT-TBI cohort study

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Summary

TBI causes cognitive impairment but it remains contested which cognitive domains are most affected. Further, moderate-severe TBI is known to be deleterious, but studies of mild TBI (mTBI) show a greater mix of negative and positive findings . This study examines the longer-term cognitive effects of TBI severity and number of mild TBI in later life. We examined a subset (n=15,764) of the PROTECT study, a cohort assessing risk factors for cognitive decline (ages between 50 and 90). Participants completed cognitive assessments annually for four years. Cognitive tests were grouped using a Principal Components Analysis (PCA) into working memory, episodic memory, attention, processing speed and executive function. Lifetime TBI severity and number were retrospectively recalled by participants using the Brain Injury Screening Questionnaire (BISQ). Linear Mixed Models examined the effect of severity of head injury (non-TBI head strike, mild TBI (mTBI) and moderate-severe TBI) and number of mTBI at baseline and over time. mTBI was considered as a continuous and categorical variable (groups: 0 mTBI, 1 mTBI, 2 mTBIs, 3 mTBIs and 4+ mTBIs). Of the participants 5,725 (36.3%) reported at least one mild TBI and 510 (3.2%) at least one moderate-severe TBI, while 3,711 (23.5%) had suffered at worst a non-TBI head strike and 5,818 (32.9%) reported no head injuries. The participants had suffered their last reported head injury an average (SD) of 29.6 (20.0) years prior to the study. Regarding outcomes, there was no worsening in longitudinal cognitive trajectories over the study duration but at baseline there were significant cognitive deficits associated with TBI. At baseline, compared to those without head injury, individuals reporting at least one moderate-severe TBI had significantly poorer attention (B=-0.163, $p<0.001$), executive scores (B=-0.151, $p=0.004$) and processing speed (B=-0.075, p=0.033). Those who had suffered at least a single mTBI also demonstrated significantly poorer attention scores at baseline compared to the no head injury group (B=-0.052, p=0.001). Compared to those with no mTBI, those in the 3 mTBI group manifested poorer baseline executive function (B=-0.149, p=0.025) and attention scores (B=-0.085, p=0.015). At baseline, those who had suffered 4 or more mild TBIs demonstrated poorer attention (B=-0.135, $p<0.001$), processing speed (B=-0.072, p=0.009) and working memory (B=-0.052, p=0.036), compared to those reporting no mTBI. TBI is associated with fixed, dose, and severity-dependent cognitive deficits. The most sensitive cognitive domains are attention and executive function, with approximately double the effect compared to processing speed and working memory. Post-TBI cognitive rehabilitation should be targeted appropriately to domain-specific effects. Significant long-term cognitive deficits were associated with ≥ 3 lifetime mTBI, a critical consideration when counselling individuals post-TBI about continuing high-risk activities.

Introduction

In the United Kingdom 2% of the population (~1.4 million people) attend emergency each year with a head injury[1]. It is the leading cause of death in people under 40. Traumatic Brain Injury (TBI) increases risk of dementia by 1.5 – 3 times and estimates suggest that TBI contributes between 3.4% and 15% of dementia burden[2,3]. While it is clear that TBI cause cognitive deficits, the time course of these deficits, the cognitive domains most affected and the impact of repeat TBI remain subjects of debate.

The Centres for Disease Control states that TBI is "caused by a bump, blow, or jolt to the head, or penetrating head injury". Importantly, not all head injuries cause TBI. A TBI, by definition, must disrupt the normal function of the brain[4]. TBIs vary in severity from "mild" (a transient alteration in mental status or loss of consciousness of less than 30 minutes) to "severe" (extended period of amnesia or unconsciousness greater than 30 minutes), as defined by the Mayo TBI Severity Classification System[5]. Definitions of TBI continue to develop and some include intracranial lesions on imaging, focal neurological deficits or cognitive/emotional symptoms [6].

TBI and cognitive deficit time course: fixed steps or accelerating decline?

TBI results in acute, direct neuronal damage and some studies suggest that subsequent to the acute period there is a chronic accumulation of pathological tau, amyloid beta and TDP-43 with concomitant microglial activation, that persists for years post-injury[7]. Pre-clinical research suggests that the initial acute injury should result in a precipitous cognitive impairment while the chronic phase of accumulating proteinopathies should result in a progressive dementia-like process and thus more rapid cognitive decline over subsequent decades [8] (see Figure 1). However, these pre-clinical findings remain contested given the small study samples, uncontrolled confounders and predominant male populations in the studies [9,10] . Indeed, the more rapid cognitive decline has not yet been borne out in the literature. While TBI has been shown to cause a sudden cognitive deficit that improves then stabilises in the months after the injury[11,12], studies have not consistently demonstrated a subsequent and more rapid cognitive decline[13–16].

Cognitive domains affected by Moderate-Severe TBI

Moderate-severe TBI has been associated with deficits in a number of cognitive domains, including episodic memory, processing speed, attention, working memory and executive function[17–19]. Episodic memory deficits (67.5%) and attention deficits (56.7%) are the most frequent subjective complaints reported 4 years following moderate-severe TBI[20]. Interestingly, a 2007 meta-analysis[21] found that in the years following moderate-severe TBI, deficits in processing speed (cohen's d = 1.10) were greater than attention span (cohen's d = 1.01). By contrast, working memory deficits, while important, are substantially smaller according to a recent meta-analysis that included studies of participants between 4 and 39 years post injury (verbal working memory Cohen's d = 0.37 and visuospatial working memory Cohen's d = 0.69)[12]. While there has not been a large quantitative synthesis of the effect of moderate-severe TBI on executive function there is a large body of evidence supporting its clinical importance in TBI sufferers[22]. The developing literature on specific cognitive domain

effects of TBI continue to inform evidence-based guidelines[23] for cognitive rehabilitation post TBI.

Mild TBI: How many is too many?

It has been understood for some time that moderate-severe TBI causes neurological damage and global cognitive impairment, but recent human studies have demonstrated that a single mTBI can cause similar pathophysiological changes, including diffuse axonal injury, altered neurotransmitter activity and modified levels of brain excitability[24,25]. Epidemiological studies have had mixed results however, with a preponderance of studies indicating a single mTBI has no discernible cognitive effects[26]. Studies have also examined whether multiple mTBIs can cause cognitive deficits comparable to a single moderate-severe TBI and how many can be incurred before these deficits become apparent. A number of studies of young athletes have found that individuals who had suffered either 2+ or 3+ mTBIs had significantly worsened cognitive outcomes[27–29] several years following the injury, although several others have found no association[30,31]. Most of these studies examining the cognitive effect of multiple mTBI examined only athletes, focussed on those in their 20s, were cross-sectional in design and did not follow participants for more than 7 years.

There is a paucity of studies examining the effect of TBI on cognitive domains in a long term, longitudinal cohort. This study uses the Brain Injury Screening Questionnaire (BISQ)[32], a validated retrospective screening tool for head injuries to assess the impact of lifetime TBI. It is the largest study to date to explore the cognitive effects of TBI and examines both baseline cognitive scores and cognitive change over time. Specifically, it considers changes in old age whereas most studies have considered populations in younger adulthood. It focuses on two key questions: (I) Which cognitive domains are most susceptible to mTBI and moderate-severe TBI in the long term? and (II) Do increasing numbers of mTBI worsen cognitive baseline scores and/or cognitive trajectories?

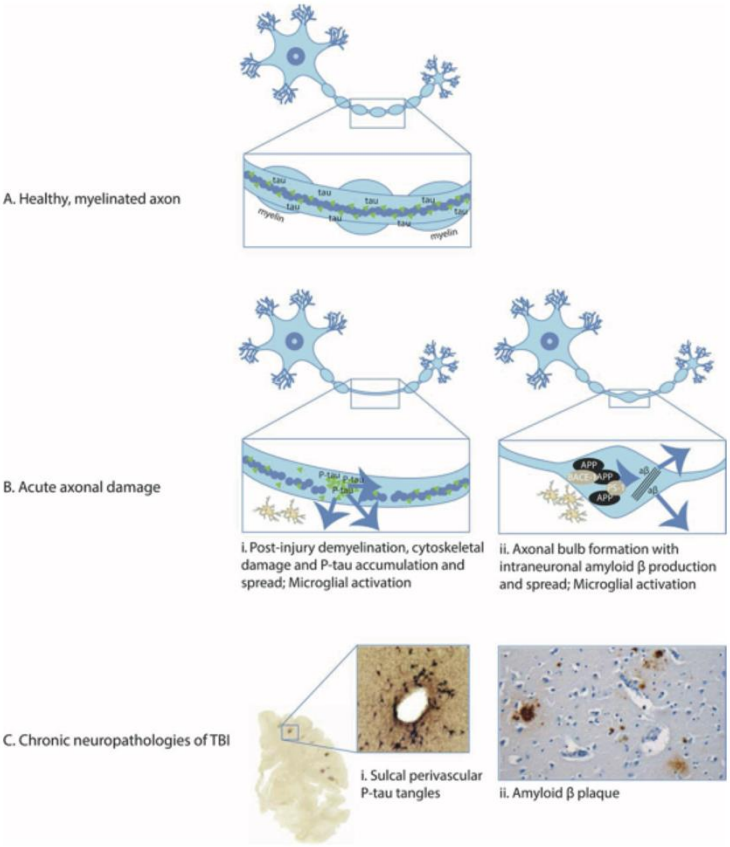

Figure 1: Post TBI Acute neuropathologies and chronic neurodegeneration (A) Healthy, myelinated axon prior to traumatic brain injury (TBI). (B) Acute axonal damage with demyelination of the axon (panels i and ii). (C) Chronic neuropathologies. (i) Tau pathology (ii) Amyloid B plaques. Taken from Graham NS, Sharp DJ. Understanding neurodegeneration after traumatic brain injury: from mechanisms to clinical trials in dementia. *Journal of Neurology, Neurosurgery & Psychiatry* 2019;**90:**1221-1233[3]. This figure has been copied in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/)

Methods

Participant Population

The PROTECT study, launched in November 2015, (www.protectstudy.org.uk) is an ongoing online investigation of a large cohort of 50 to 90 year old individuals examining genetic and epidemiological risk factors for cognitive decline[33]. Individuals were required to have access to a computer and were excluded from the study if they had a diagnosis of dementia at baseline. Ethics approval was gained from the UK London Bridge National Research Ethics Committee (Ref. 13/LO/1578). Participants had a baseline assessment (Wave 1) and up to four years of annual assessments (Waves 2 - 5). The entire PROTECT cohort comprises ~ 28,000 participants but this study included only the subset for whom TBI data was available (n = 15,764). Comprehensive descriptions of the study have been published previously[33].

Classification of TBI

Information on TBI was gathered using the Brain Injury Screening Questionnaire (BISQ)[32], which was an optional but encouraged self-administered survey within the PROTECT study. The BISQ screens for lifetime history of head injuries and captures the aetiology of the injury (sports related, motor vehicle crashes etc.), the age of first/last TBI, the number of injuries and the severity or each episode (length of time unconscious/dazed or confused).

Each reported head injury was classified, based on available data, into three categories according the Mayo TBI Severity Classification System:

1. Non-TBI Head Strike - a head injury without any subsequent loss of consciousness or dazed or confused episode.
2. mTBI – a head injury followed by loss of consciousness (LOC) of less than 30 minutes or a dazed or confused episode.
3. Moderate-severe TBI – a head injury followed by a LOC of 30 minutes or longer.

In the first analysis individuals were grouped based on the worst injury they had suffered (i.e. No head injury (comparison group), Non-TBI Head Strike, mTBI or moderate-severe TBI). This was then followed by an analysis of the effect of the number of mTBI. Ideally, we would have explored the effects of increasing numbers of both mild and moderate-severe TBI but there were not a sufficient sample of those with multiple moderate-severe TBI to explore this. Using the BISQ data each instance of mTBI reported was summed into a total and those who had not had a TBI were used as the comparison group. To assess whether any association between numbers of mTBI and cognitive outcomes existed mTBI number was first examined as a continuous variable. Then, to establish a threshold at which the number of mTBI may cause a significant deterioration, mTBI was examined as a categorical variable examining the following groups: 0 mTBI (comparison group), 1 mTBI, 2 mTBIs, 3 mTBIs and 4+ mTBIs. In order to reduce confounding in this part of the analysis all those who had suffered a moderate-severe TBI were excluded from this second part of the analysis.

Calculation of cognitive domain scores

The PROTECT Study included three batteries of cognitive tests. The PROTECT Cognitive Test Battery (PCTB) comprised the Digit Span test, Paired Associates Learning Test, Baddeley

Grammatical Reasoning Test (Verbal Reasoning) and the Spatial Working Memory (Self ordered search) test. There has been 4 years of follow up for this battery. The second cognitive battery, COGTRACK, involved a number of tests assessing reaction time, processing speed, attention and episodic memory (see appendix A for battery descriptions). This testing battery was ceased after 3 years of follow up. The third cognitive battery was added after 3 years of the study running and included the Stroop switching task and the Trail Making Test B. The uptake of the third testing battery has been considerably smaller (n = 5,184 vs 15,764) and there has only been a small portion of those individuals (n = 714) with 1 year follow up for these tests. As such, only baseline analysis, not longitudinal analysis, was performed for executive function scores.

The participants were asked to perform 3 repeats of each cognitive test at least 12 hours apart within the space of a week. The mean of the repeats was taken to be the test score for that wave. Naturally, not all participants completed three repeats. In those who did there were significant learning effects (i.e. scores improved with test repetition), thus the number of test repeats within each wave was included as a covariate in all of our analyses.

In order to develop cognitive domain scores an orthogonal rotated principal components analysis was performed on the baseline values of 11 outcome measures. Four were taken from the PCTB (Digit Span, Paired Associates Learning, Verbal Reasoning, Self-Ordered Search) and seven measures were taken from the COGTRACK assessment (Picture recognition Original stimuli accuracy, Picture recognition new stimuli accuracy, Attentional Intensity Index, Sustained Attention Index, Attentional Fluctuation Index, Cognitive Reaction Time, Memory Retrieval Speed) (see appendix A for details).

For the main PCA the KMO test result was 0.717 and the Bartlett's Test of Sphericity p-value was <0.001 indicating an acceptable fit[34]. The tests grouped into four dimensions (see appendix B).

In ordered to ensure that the constructs remained valid throughout the waves the PCA analysis was repeated for each wave and it was confirmed that the tests reliably aggregated into the same four groupings. Additional PCAs for each wave were performed on the subset that contained TMTB and Stroop Tests. The KMO test result was 0.69, the TMTB and Stroop tests reliably aggregated into their own component and the results were otherwise unchanged.

Each test score for all waves was standardised based on baseline mean and standard deviations. Tests in which higher scores indicated poorer performance (e.g. reaction time tests) were inverted, such that higher Z scores always indicated better performance. All Z scores were winsorized to between 5 and -5 SD from the mean.

Domain scores were calculated from the mean of the Z scores of the tests grouped by the PCA. The following domain scores were computed:

1. Working Memory - Digit Span, Paired Associates Learning and Self-Ordered Search. The Verbal reasoning task was excluded from this domain score as it did not fit conceptually within working memory, despite being linked by the PCA.

2. Episodic Memory - Picture recognition Original stimuli accuracy and Picture recognition New stimuli accuracy
3. Processing Speed/Reaction Time - Attentional Intensity Index, Cognitive Reaction Time and Memory Retrieval Speed
4. Attention - Sustained Attention Index and Attentional Fluctuation Index
5. Executive - Trail Making Test B and Stroop Switching Test

The domain scores were assessed for normal distribution by examining visually and testing for skewness. If the skewness was greater than 1 or less than -1 the score was transformed into a normal distribution. The attention domain score was negatively skewed and thus was inverted, log transformed and re-standardised to achieve a normal distribution.

Classification of covariates

Sex was coded in binary; 0 = men, 1 = women. Education was coded as a 6-level ordinal variable; 1 = Secondary Education, 2 = Post-secondary education, 3 = Vocational Qualification, 4 = Undergraduate degree, 5 = Post graduate degree, 6 = Doctorate. 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 [35], as vascular risk factors are known contributors to cognitive decline and may confound the effect of TBI. Vascular risk was calculated as a score out of five, the sum of the following 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.

Statistical Analysis

For all analyses partially and fully adjusted models were run. Model construction was decided using fitting parameters Akaike Information Criteria and Bayesian Information Criteria. It is known that rates of cognitive decline change with age and thus rather than using a simple time in study variable as the "time" variable, this study used a grand mean-centered "age at each wave" as the "time" variable. Furthermore, to account for non-linear decline of cognitive scores an age^2 was also included. Partially adjusted models controlled for age, age^2, sex, education status and number of repeats in the wave and included an interaction for either TBI severity or mTBI number and age at each wave. Models also including a TBI severity*age^2 were considered but ultimately excluded as they worsened model fit. Fully adjusted models additionally controlled for smoking, the composite vascular risk score and any history of psychiatric diagnoses. Fully adjusted models are reported and discussed in this paper, partially adjusted model results are included in the supplementary data (see appendix C) and are discussed if there are discrepancies between fully and partially adjusted models.

Intergroup differences for continuous variables were assessed using ANOVA and for categorical variables using Chi-Squared analysis (see table 1). Linear mixed models (LMMs) were used to examine the effect of TBI cognitive domain scores at study baseline (irrespective of age) and on score trajectories (dependent on age). The first analysis used those who had not had a head injury as the comparator group, and assessed cognitive outcomes of those with with Non-TBI head strikes, mTBI and moderate-severe TBI. As a supplement to this an

analysis was also run also using the mTBI group as the comparator (Supplementary Tables 5 and 6). The second analysis compared those with 1, 2, 3 or 4+ mTBI with those who had suffered no mTBI and the third examined mTBI number as a continuous variable. The models specified a random intercept and slope (time varying age variable) while the other terms were treated as fixed effects. Statistical analyses were performed using R (Version 4.0.3).

Results

Participant Characteristics

The cohort consisted of 15,764 participants of whom 6,227 (39.5%) reported at least one TBI and 510 (3.2%) at least one moderate-severe TBI (Table 1). Compared to those with no TBI history, those who had suffered mild or moderate-severe TBI had higher rates of previous and current smoking, hypertension, stroke, coronary disease, diabetes, high cholesterol, and psychiatric disease as well as marginally higher rates of attrition throughout the study. The participants had suffered their last reported head injury an average (SD) of 29.6 (20.0) years prior to the study and their first head injury an average of 38.7 (18.5) years prior.

Effect of TBI severity on cognitive outcome

At baseline, in the fully adjusted model, compared to those without head injury, individuals reporting at least one moderate-severe TBI had significantly poorer attention (B=-0.163, 95%CI [-0.237, -0.088], p<0.001), executive scores (B=-0.151, 95%CI [-0.254, -0.049], p=0.004) and processing speed (B=-0.075, 95%CI [(-0.144, -0.006], p=0.033) (Figure 2A and Table 2). Those who had suffered at least a single mild TBI also demonstrated significantly poorer attention scores at baseline (B=-0.052, 95%CI [-0.082, -0.022], p=0.001). Interestingly, compared to those who reported no head injuries, those who report non-TBI head strikes (B=0.099, 95%CI [0.063, 0.134], p<0.001) and mild TBI (B=0.074, 95%CI [0.042, 0.107], p<0.001) had significantly better episodic memory scores at baseline. Compared to those with mTBI, the moderate-severe TBI group had significantly worse attention scores (B = -0.103, 95% CI [-0.176, -0.03], p = 0.006**)** and episodic memory (B = -0.14, 95% CI [-0.218, -0.061], p **<** 0.001) (Supplementary Table 6). There were no significant differences between head injury severity groups in the trajectories of cognition with increasing age.

mTBI number and cognitive outcomes

At baseline, in the fully adjusted model, increasing numbers of mTBI (measured as a continuous variable) was significantly associated with deficits in attention (B=-0.025, 95%CI -0.033, -0.016], p < 0.001), executive function (B=-0.021, 95%CI [-0.038, -0.004], p = 0.015), processing speed (B=-0.011, 95%CI [-0.019, -0.003], p=0.005) and working memory (B=-0.009, 95%CI [-0.016, -0.002], p=0.011) (Figure 2C and Table 3). Conversely, there was a trend in those who had suffered mTBI to have a better trajectory of episodic memory decline over time (B=0.007, 95%CI [0.002, 0.013], p=0.014) although there was no effect for episodic memory at baseline. Considering mTBI number as a categorical variable, in the fully adjusted model, those in the 3 mTBI group, manifested poorer executive function (B=-0.149, 95%CI [-0.279, -0.019], p=0.025) and attention scores (B=-0.085, 95%CI [-0.152, -0.017], p=0.015) (Figure 2B and Table 4). Those who had suffered 4 or more mTBIs demonstrated poorer attention (B=-0.135, 95%CI [-0.194, -0.076], p<0.001), processing speed (B = -0.072, 95%CI [-0.126, -0.018], p=0.009) and working memory (B=-0.052, 95%CI [-0.1, -0.003], p=0.036) at baseline compared to those with no mTBI. Interestingly, at baseline those who had one mild TBI had significantly better working memory (B=0.049, 95%CI [0.021, 0.078], p=0.001) and episodic memory (B=0.051, 95%CI [0.015, 0.087], p=0.006) compared to those who reported

no mTBI. There were no significant differences between the mTBI groups (0 mTBI vs 1, 2, 3 or 4+ mTBI) in cognitive trajectories with increasing age.

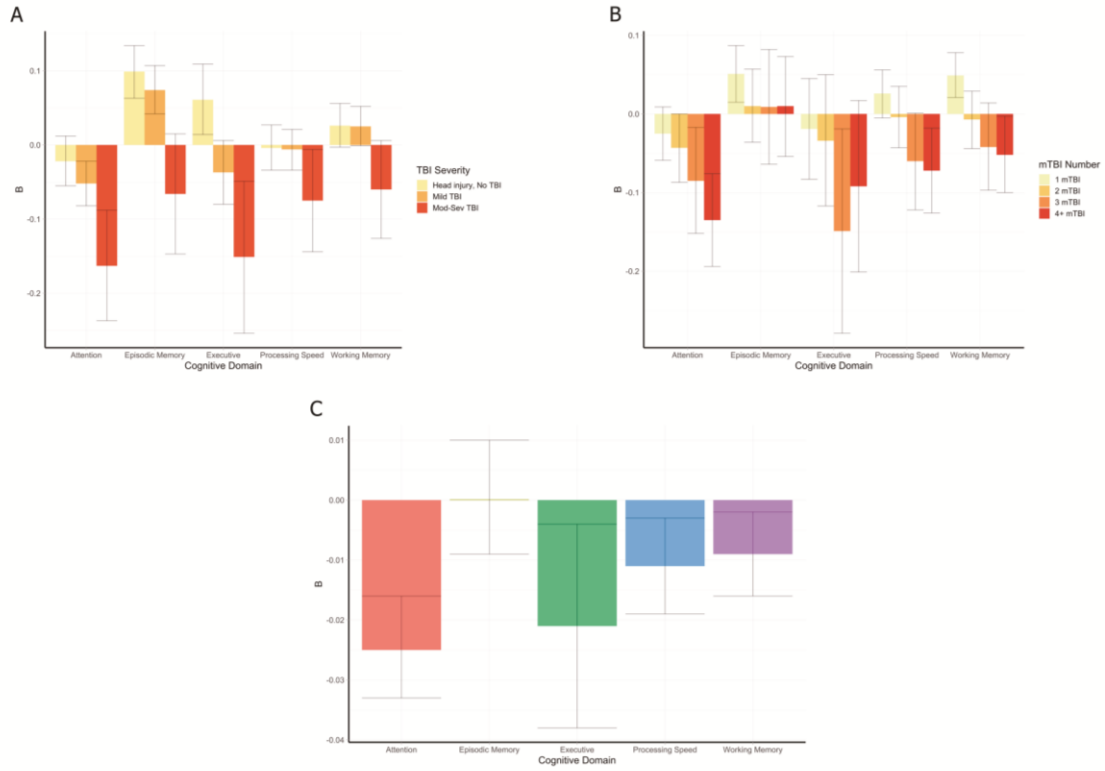

Figure 2: Box plots with 95% confidence intervals to showing the effect sizes of various TBI effects at baseline. Part A shows the effect of worst reported TBI severity on cognitive domains at baseline. The comparison group were those who had reported no previous head injuries. Part B shows the effect of the number of mild TBIs reported (categorical) on cognitive domains at baseline. The comparison group were those who had reported no previous mild TBIs. Those with a moderate-severe TBI were excluded from this analysis. Part C shows the effect of the number of mild TBI (continuous) on cognitive domains at baseline (e.g. For each additional reported mTBI there was a worsening of 0.021 standard deviations in attention score).

	Total (n = 15,764)	Uninjured (n = 5,818, 32.9%)	Non-TBI Head Strike (n = 3,711, 23.5%)	Mild TBI (n = 5,725, 36.3%)	Moderate to Severe TBI (n = 510, 3.2%)	Significance of intergroup differences (p)
Age (mean +/- SD) (n = 15,764)	62.7 +/- 7.3	62.9 +/- 7.1	62.7 +/- 7.2	62.4 +/- 7.3	62.9 +/- 7.7	**0.001****
Sex (M%/F%) (n = 15,764)	24.4% vs 75.6%	17.2% vs 82.8%	22.4% vs 77.6%	32.0 % vs 68.0%	37.3% vs 62.7%	**<0.001****
Highest Educational Attainment (%) (n = 15,762)[a]	1 - 13.0% 2 - 11.1% 3 - 20.0% 4 - 33.8% 5 - 18.1% 6 - 4.0%	1 - 14.4%, 2 - 11.3%, 3 - 19.9%, 4 - 33.1%, 5 - 17.8%, 6 - 3.5%	1 - 12.4%, 2 - 10.8%, 3 - 19.2%, 4 - 35.5%, 5 - 17.7%, 6 - 4.5%	1 - 12.1%, 2 - 11.3%, 3 - 20.6%, 4 - 33.2%, 5 - 18.7%, 6 - 4.2%	1 - 12.2%, 2 - 8.8%, 3 - 19.0%, 4 - 37.6%, 5 - 18.4%, 6 - 3.6%	**<0.001****
Ethnicity (n = 15,764) (% White European)	97.3%	97.4%	97.4%	97.4%	96.0%	0.047*
Smoking Status (n = 15,608) (%)[b]	1 – 55.3% 2 – 41.4% 3 – 2.8%	1 – 59.3% 2 – 38.2% 3 – 2.5%	1 – 56.8% 2 – 40.6% 3 – 2.6%	1 – 50.6% 2 – 46.2% 3 – 3.3%	1 – 51.9% 2 – 42.7% 3 – 5.4%	**<0.001****
Hypertension (Y%) (n = 15,612)	23.8%	23.4%	23.0%	24.7%	26.1%	0.137
Stroke (Y%) (n = 15,612)	1.4%	1.0%	1.3%	1.7%	3.4%	**<0.001****
Coronary Disease (Y%) (n = 15,612)	4.3%	3.5%	4.2%	5.1%	7.0%	**<0.001****
Diabetes (Y%) (n = 15,612)	3.4%	2.9%	3.2%	4.1%	4.0%	**0.006****
High Cholesterol (n = 15,612)	8.0%	7.4%	7.9%	8.4%	10.4%	0.047*
Any history of psychiatric illness (n = 15,271)	33.6%	31.0%	33.6%	38.6%	42.5%	**<0.001****
Total Number of Head Injuries (mean +/- SD) (n = 15,764)	2.2 +/- 3.1	0	2.7 +/- 2.4	3.8 +/- 3.5	4.7 +/- 4.7	**<0.001****
Age at first head injury (mean +/- SD) (n = 6236)	25.4 +/- 19.8	NA	27.0 +/- 21.1	24.8 +/- 19.2	23.9 +/- 17.4	**<0.001****
Years since first injury at wave 1 (mean +/- SD) (n = 5983)	38.7 +/- 18.5	NA	34.1 +/- 19.6	39.1 +/- 18.1	39.9 +/- 7.1	**<0.001****
Age at last head injury (mean +/- SD) (n = 5034)	35.71 +/- 21.3	NA	34.1 +/- 22.7	35.9 +/- 20.8	36.5 +/- 20.7	**<0.001****
Years since last injury at wave 1 (mean +/- SD) (n = 4574)	29.6 +/- 20.0	NA	31.0 +/- 20.8	29.2 +/- 19.6	29.5 +/- 19.2	**<0.001****
Follow up (% of baseline)						
Wave 1 (Baseline)	100% (15764)	100% (5818)	100% (3711)	100% (5725)	100% (510)	-
Wave 2 (~ 1 year)	81.6% (12858)	82.7% (4813)	82.1% (3049)	80.2% (4592)	79.2% (404)	**0.002****
Wave 3 (~ 2 years)	70.0% (11036)	71.4 % (4156)	70.5% (2618)	68.5% (3920)	67.1% (342)	**0.002****
Wave 4 (~ 3 years)	58.7% (9257)	60.3% (3508)	59.2% (2200)	57.0% (3263)	56.1% (286)	**0.003****
Wave 5 (~ 4 years)	45.3% (7148)	46.9% (2278)	45.6% (1692)	43.7% (2503)	44.1% (225)	**0.007****

Table 1: Summary of study population characteristics in comparing those with no TBI, non-TBI head strikes, mild TBI and severe TBI.
[a]Educational Status coded as follows; 1 = Secondary Education (GSCE/O levels), 2 = Post-secondary education (College, A levels, NVQ3 or below), 3 = Vocational Qualification (Diploma, certificate, BTEC, NVQ4 and above or similar), 4 = Undergraduate degree (BA, BSc etc.), 5 = Post graduate degree (MA, MSc, etc), 6 = Doctorate (PhD)
[b]Smoking status coded as follows: 1 - Never smoked, 2 - Prev smoker, 3 - Current smoker)
*p<0.05
**p<0.01.

	Executive		Working Memory		Episodic Memory		Processing Speed		Attention	
Variable	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P
Effect at study baseline										
Non-TBI Head Strike	0.061 (0.014, 0.109)	**0.012***	0.026 (-0.003, 0.056)	0.079	0.099 (0.063, 0.134)	**<0.001****	-0.004 (-0.034, 0.027)	0.823	-0.022 (-0.055, 0.012)	0.204
Mild TBI	-0.037 (-0.08, 0.006)	0.089	0.025 (-0.001, 0.052)	0.061	0.074 (0.042, 0.107)	**<0.001****	-0.006 (-0.034, 0.021)	0.65	-0.052 (-0.082, -0.022)	**0.001****
Moderate-Severe TBI	-0.151 (-0.254, -0.049)	**0.004****	-0.06 (-0.126, 0.006)	0.076	-0.066 (-0.147, 0.015)	0.109	-0.075 (-0.144, -0.006)	**0.033***	-0.163 (-0.237, -0.088)	**<0.001****
Trajectories over increasing age (5-year increments)										
Age[a]	-	-	-0.007 (-0.018, 0.003)	0.183	-0.027 (-0.042, -0.012)	**<0.001****	-0.139 (-0.152, -0.126)	**<0.001****	0.026 (0.006, 0.045)	**0.01****
Age^2	-	-	-0.023 (-0.026, -0.02)	**<0.001****	-0.017 (-0.021, -0.012)	**<0.001****	-0.008 (-0.012, -0.003)	**<0.001****	-0.026 (-0.032, -0.019)	**<0.001****
Non-TBI Head Strike*Age	-	-	-0.006 (-0.022, 0.011)	0.5	-0.023 (-0.046, 0)	0.051	0.008 (-0.013, 0.028)	0.478	-0.018 (-0.048, 0.012)	0.236
Mild TBI*Age	-	-	-0.007 (-0.021, 0.008)	0.372	0.007 (-0.013, 0.027)	0.49	0.014 (-0.004, 0.033)	0.125	-0.007 (-0.034, 0.019)	0.587
Moderate-Severe TBI*Age	-	-	-0.012 (-0.047, 0.023)	0.497	0.032 (-0.017, 0.08)	0.198	0.025 (-0.019, 0.069)	0.272	0.04 (-0.024, 0.104)	0.217

Table 2: Summary of Linear Mixed Model results examining effect of head injury category (most severe injury sustained) on cognition domain scores in model adjusted for Sex, Age, Education, Smoking status, combined vascular risk score and history of psychiatric diagnoses. This model compares all head injury groups to individuals in the cohort who have had no head injuries i.e. a B of -0.211 at baseline means that the group had a mean score -0.211 standard deviations lower than those with no head injuries.

The executive function model was examined only at baseline because at the time of this study there was only a small cohort of individuals with longitudinal data and the follow up was for a maximum of 1 year.

*p<0.05

**p<0.01

[a]The unit of age is 5 year increments i.e. the B indicates the number of standard deviations change in cognitive score with each additional 5 years of age

	Executive		Working Memory		Episodic Memory		Processing Speed		Attention	
Variable	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P
Effect at study baseline										
mTBI number	-0.021 (-0.038, -0.004)	**0.015***	-0.009 (-0.016, -0.002)	**0.011***	0 (-0.009, 0.01)	0.936	-0.011 (-0.019, -0.003)	**0.005****	-0.025 (-0.033, -0.016)	**<0.001****
Trajectories over increasing age (5-year increments)										
Age	-	-	-0.028 (-0.035, -0.021)	**<0.001****	-0.036 (-0.045, -0.027)	**<0.001****	-0.134 (-0.142, -0.126)	**<0.001****	0.012 (0, 0.024)	**0.048***
Age^2	-	-	-0.022 (-0.025, -0.019)	**<0.001****	-0.016 (-0.021, -0.012)	**<0.001****	-0.008 (-0.012, -0.004)	**<0.001****	-0.026 (-0.033, -0.02)	**<0.001****
mTBI number*Age	-	-	-0.001 (-0.005, 0.004)	0.764	0.007 (0.002, 0.013)	**0.014***	-0.001 (-0.006, 0.005)	0.812	-0.003 (-0.01, 0.005)	0.504

Table 3: Summary of Linear Mixed Model Results examining effect of numbers of lifetime mTBI as a continuous variable on cognitive domain scores. This model compares all mTBI groups to individuals in the cohort who have had no TBI. It is adjusted for age, sex, education, cognitive test repeats in wave, vascular risk scores, smoking status and a history of psychiatric diagnoses. This analysis excluded those who had a previous moderate-severe TBI. Age is grand-mean centred and measured in units of 5 years i.e. an effect size of age of -0.196, means that with each increase of 5 years of age the domain score will on average decrease by 0.196 standard deviations.

The executive function model was examined only at baseline because at the time of this study there was only a small cohort of individuals with longitudinal data and the follow up was for a maximum of 1 year.

*p<0.05

**p<0.01

	Executive		Working Memory		Episodic Memory		Processing Speed		Attention	
Variable	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P	B (95 CI)	P
Effect at study baseline										
1 mTBI	-0.019 (-0.083, 0.045)	0.566	0.049 (0.021, 0.078)	**0.001****	0.051 (0.015, 0.087)	**0.006***	0.026 (-0.005, 0.056)	0.104	-0.025 (-0.059, 0.009)	0.145
2 mTBI	-0.034 (-0.117, 0.05)	0.432	-0.007 (-0.044, 0.029)	0.688	0.01 (-0.036, 0.057)	0.661	-0.004 (-0.043, 0.035)	0.85	-0.043 (-0.087, 0)	**0.05***
3 mTBI	-0.149 (-0.279, -0.019)	**0.025***	-0.042 (-0.097, 0.014)	0.143	0.009 (-0.064, 0.082)	0.815	-0.06 (-0.122, 0.001)	0.055	-0.085 (-0.152, -0.017)	**0.015***
4+ mTBI	-0.092 (-0.201, 0.017)	0.099	-0.052 (-0.1, -0.003)	**0.036***	0.01 (-0.054, 0.073)	0.759	-0.072 (-0.126, -0.018)	**0.009****	-0.135 (-0.194, -0.076)	**<0.001****
Trajectories over increasing age (5-year increments)										
Age	-	-	-0.024 (-0.032, -0.016)	**<0.001****	-0.042 (-0.053, -0.031)	**<0.001****	-0.137 (-0.147, -0.127)	**<0.001****	0.013 (-0.002, 0.028)	0.081
Age^2	-	-	-0.023 (-0.026, -0.02)	**<0.001****	-0.017 (-0.022, -0.012)	**<0.001****	-0.009 (-0.013, -0.004)	**<0.001****	-0.026 (-0.033, -0.02)	**<0.001****
1 mTBI*Age	-	-	-0.011 (-0.027, 0.005)	0.192	0.02 (-0.002, 0.043)	0.075	0.021 (0, 0.041)	**0.045***	0.003 (-0.027, 0.032)	0.861
2 mTBI*Age	-	-	-0.017 (-0.038, 0.003)	0.101	-0.004 (-0.032, 0.025)	0.811	0 (-0.026, 0.026)	0.997	-0.004 (-0.043, 0.034)	0.824
3 mTBI*Age	-	-	0.008 (-0.024, 0.04)	0.633	0.031 (-0.013, 0.076)	0.169	-0.004 (-0.044, 0.037)	0.859	-0.024 (-0.084, 0.036)	0.427
4+ mTBI*Age	-	-	-0.004 (-0.032, 0.024)	0.797	0.019 (-0.021, 0.058)	0.352	-0.004 (-0.04, 0.031)	0.806	-0.001 (-0.054, 0.052)	0.964

Table 4: Summary of Linear Mixed Model Results examining effect of numbers of lifetime mTBI (1, 2, 3 or 4+.) on cognitive domain scores. This model compares all mTBI groups to individuals in the cohort who have had no TBI. The model is adjusted for age, sex, education, cognitive test repeats in wave, vascular risk scores, smoking status and a history of psychiatric diagnoses. This analysis excluded those who had a previous moderate-severe TBI. Age is grand-mean centred and measured in units of 5 years i.e. an effect size of age of -0.196, means that with each increase of 5 years of age the domain score will on average decrease by 0.196 standard deviations.

The executive function model was examined only at baseline because at the time of this study there was only a small cohort of individuals with longitudinal data and the follow up was for a maximum of 1 year.

*p<0.05

**p<0.01

Discussion

TBI is associated with chronic, fixed deficits rather than accelerating cognitive decline

Grouping participants either by TBI severity or by mild TBI numbers showed consistently that there were no worsened trajectories of cognitive decline over time for those who had suffered a TBI. Rather, there were significant deficits at baseline that remained fixed for the duration of the study. Specific effects on domains are discussed in subsequent sections. On average participants had their last TBI 29.6 years prior to the study and only 1.3% of TBI sufferers had their last TBI in the preceding 3 months. Thus, the effects largely reflect the chronic phase of TBI. The findings are consistent with the Ruttan et al (2008) meta-analysis that demonstrated that cognitive deficits post moderate-severe TBI remained stable over time from the 1 year to the 4.5+ years epochs[13,36].

By contrast, pre-clinical models of TBI suggest that chronic changes should cause long term neurodegeneration and thus an accelerative cognitive decline rather than just an additive, fixed injury. For example, microglia remain active at the site of injury for years after the injury and are thought to contribute to the chronic effects of diffuse axonal injury and the accumulation of pathological proteins[6–8]. Furthermore, the tau proteinopathy caused by the injury and inflammation performs progressive self-seeding, in which it spreads in a prion like fashion. In mouse models of TBI P-tau is initially only present at the injury site, after 6 months it is detected in the contralateral hemisphere[8,37,38]. The apparent conflict between the pre-clinical and clinical results may on one hand merely indicate a lack of mouse model fit for human cognitive studies but on the other hand it may suggest that the chronic inflammatory changes in the brain provide some level of protection from or prevention of chronic neurodegeneration, as some studies indicate[39]. In either case, the results from this study and other epidemiological studies suggest that in the chronic phase of a TBI an individual will experience fixed cognitive deficits rather than a persistent, accelerative neurodegenerative process.

Cognitive domain deficits associated with TBI

This study found that a history of moderate-severe TBI was associated with significantly poorer attention, executive and global cognitive scores at baseline but did not affect the trajectories of these cognitive scores as they aged. Of the cognitive domain scores attention was the most sensitive to moderate-severe TBI, followed by executive function and processing speed. The secondary analysis examining the effect of numbers of mTBI corroborated this hierarchy finding again that attention was most sensitive the effects of mTBI, followed by executive function, processing speed and working memory, with no significant effect reported for episodic memory. These findings are supported by evidence that cortical frontal regions are the most common direct foci of primary TBI injury (e.g. from forces of a punch or motor vehicle) and secondary injury, from the coup/contra-coup bruising effect of rapid cranial acceleration and deceleration[40]. Furthermore, previous imaging studies have identified the poles of the frontal lobe as one of the most common sites of grey matter atrophy and axonal rarefaction post-TBI[41,42]. But these findings are at odds with the findings of the CENTER-TBI study (n = 1554)[43] which found that 6 months after TBI one of the most affected domains was learning and memory whereas tests of attention and executive function

tended to be less impacted. These differences are not as striking, when considering that CENTER-TBI used verbal memory tests to assess memory whereas this study used visual memory and that some of the tests they classified as processing speed measures (e.g. TMTB) this study classified as executive function (e.g. TMTB). Even with this considered, the findings of no association with episodic memory is perplexing as much of the self-reported data on TBI that that have found that episodic and working memory are the most frequently reported complaints several years post-TBI[20]. Explaining this, Vakil (2005) argued that the profile of memory deficits is consistent with predominant patterns of frontal injury rather than medio-temporal injury or pure amnesia. Deficits are more pronounced in recall rather than recognition tasks, indicating that memory problems occur secondary to executive dysfunction[44]. Understanding the most vulnerable cognitive domains is critical as it allows for evidence-based prioritisation in post-TBI cognitive rehabilitation[23].

Three or more mTBI associated with significant cognitive deficits

This study found that those who reported three mTBI had significantly worse executive function and attention scores, and those who reported 4+ mTBI had worsened attention, processing speed and working memory. Whereas most studies for repeated mTBI have focussed on young athletes in the acute or sub-acute phase (<3 months post) this study examined the mid to late life general population largely in the chronic phase of TBI (>3 months post). This is a critically important result. It gives a clear threshold at which mid to late life cognitive deficits can be realistically expected. Legal regulations and medical guidelines around when to stop higher risk activities, such as contact sports, are hotly debated[45]. Most experts agree that recommendations to cease the higher risk activity should be case by case depending upon the severity of the injury, the extent of the ongoing deficits and the force of subsequent TBI-inducing force (vis-a-vis "Fighters Chin" syndrome[46]). However, such assessments can be insensitive to small effects, often lack a pre-TBI baseline and assess current rather than future function. When making recommendations for those who have suffered recurrent TBI clinicians should be cognizant that some long-term cognitive deficits can be expected after 3 or more mTBI. Although the effect sizes for the cognitive deficits at 3 or 4+ mTBI were small (i.e. all $B < 0.2$), the effects were dose-dependent. That is, the deficit increased step-wise with increased numbers of reported mTBI (see tables 3 and 4) and thus recommendations should indicate that each additional mTBI increases risk of substantial cognitive decline. As previously mentioned there was no greater decline in cognitive scores with time in study for those with higher numbers of mTBI suggesting that in the chronic phase, mTBI causes a dose dependent, fixed cognitive deficit.

Ability to recall historical TBI associated with better memory

Interestingly, those in the Non-TBI head strike or mild TBI group (table 2), had significantly better episodic memory compared to those who had no head injuries. Similarly, those in the 1 mTBI group had significantly better episodic and working memory compared to those with no mTBI. This likely reflects that accurately recalling events from many years ago requires good episodic memory. It is likely that some individuals reporting no historical TBIs or head injuries may have in fact had prior injuries but lack the memory capacity to recall them. This may have led to an underestimation of the effect of TBI on cognition as it is likely that some

of the “healthy” comparison group had in fact suffered TBI. This highlights an inherent weakness in the retrospective design of this study, which is discussed further below.

Strengths and Limitations

The key strengths of this study are the large sample size, the longitudinal design and comprehensiveness of the BISQ screening tool. The sample size of 15,764 makes this study nearly twice as large as any other study examining cognitive test outcomes post-TBI. This allowed for detection of small effect sizes and for reliable and powerful subgroup analysis. The longitudinal design of the study allowed for inspection of trajectories of cognitive scores rather than just cross-sectional associations. The BISQ characterises each discrete head injury and the context in which it happened, allowing for a quantitative breakdown of injuries by number and timing.

The main limitations of this study include missing data, unmeasured confounders, retrospective recall of injuries, challenges with follow-up and difficulties with domain interpretation. There are a number of unmeasured covariates such as lower socioeconomic status, physical health and history of alcohol/drug use, that are known to affect cognitive scores and be associated with higher rates of TBI, potentially confounding the results. The retrospective design of the study, with elderly participants often recalling details of events more than three decades in the past, may have caused an underreporting of head injuries and thus an underestimate of the size of their effect. While the comprehensive, structured nature of the BISQ improves the accuracy of the data collection, results should be interpreted with the understanding of mixed reliability of long-term recall in older individuals. The longitudinal follow up at four years was 45.3%, although a significant loss to follow up it is comparable to other longitudinal studies of ageing. This issue of missing follow up data was mitigated using the linear mixed model design. While the PCA is a useful tool for reducing dimensionality, the domains produced are imperfect constructs. For the domain of executive function both the Trail Making Test B and Stroop Switching Task are timed and partly reflect processing speed. Thus, results may partially reflect deficits in speed rather than executive function. Further, the episodic memory relied purely on a measure of pictorial recall rather than tests of verbal, numeric or narrative memory and thus its generalisability to the commonly understood idea of episodic memory is limited.

Conclusion

TBI in the chronic phase is associated with fixed, dose and severity dependent cognitive deficits rather than more rapid rates of cognitive decline. The most sensitive cognitive domains are attention and executive function, with approximately double the effect compared to processing speed and working memory. Post-TBI cognitive rehabilitation should thus be targeted based on the domain specific effects. Finally, significant long-term cognitive deficits begin to be seen after only three lifetime mTBI. This should be carefully considered when counselling individuals post-TBI about continuing high risk activities.

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