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Brain age in chronic traumatic brain injury

Gershon Spitz [a,*], Amelia J. Hicks [a], Caroline Roberts [a], Christopher C. Rowe [b,c], Jennie Ponsford [a]

[a] Monash-Epworth Rehabilitation Research Centre, Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Clayton 3168, Australia
[b] Department of Molecular Imaging and Therapy, Austin Health, Heidelberg 3084, Australia
[c] Florey Department of Neuroscience and Mental Health, University of Melbourne, Parkville 3052, Australia

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ABSTRACT

Traumatic brain injury (TBI) is associated with greater 'brain age' that may be caused by atrophy in grey and white matter. Here, we investigated 'brain age' in a chronic TBI (≥10 years) sample. We examined whether 'brain age' increases with years post injury, and whether it is associated with injury severity, cognition and functional outcome. We recruited 102 participants with moderate to severe TBI aged between 40 and 85 years. TBI participants were assessed on average 22 years post-injury. Seventy-seven healthy controls were also recruited. Participants' 'brain age' was determined using T1-weighted MRI images. TBI participants were estimated to have greater 'brain age' compared to healthy controls. 'Brain age' gap was unrelated to time since injury or long-term functional outcome on the Glasgow Outcome Scale-Extended. Greater brain age was associated with greater injury severity measured by post traumatic amnesia duration and Glasgow Coma Scale. 'Brain age' was significantly and inversely associated with verbal memory, but unrelated to visual memory/ability and cognitive flexibility and processing speed. A longitudinal study is required to determine whether TBI leads to a 'one-off' change in 'brain age' or progressive ageing of the brain over time.

1. Introduction

Aging is a time-dependent functional decline that is driven by progressive accumulation of cellular damage throughout life (López-Otín et al., 2013). Recent evidence suggests that traumatic brain injury (TBI)—one of the leading causes of death and disability worldwide—leads to greater 'brain age' (Cole et al., 2015; Gan et al., 2021). Atrophy of grey and white matter, alongside other pathological processes, may drive elevated 'brain age' in TBI (Savjani et al., 2017; Feltrin et al., 2018; Graham and Sharp, 2019; Harris et al., 2019). Establishing whether TBI leads to a 'one-off' loss in cellular volume, progressive, or accelerated 'brain age' is of considerable importance to the field and has significant ramifications for patient management.

Normal brain aging follows coordinated and sequenced patterns of grey matter and white matter loss as well as cerebrospinal fluid expansion (Good et al., 2001; Raz et al., 2003; Resnick et al., 2003; Terribilli et al., 2011; Storsve et al., 2014), allowing for the development of reference curves of healthy brain aging using machine learning (Franke and Gaser, 2019). The *brain age gap* is the discrepancy between an individual's estimated 'brain age' using machine learning and their chronological age. An elevated brain age gap has been observed in mild cognitive decline, Alzheimer's disease, and psychiatric disorders (Franke and Gaser, 2019).

Traumatic brain injury results in loss of grey and white brain matter (Raz et al., 1997; Fjell et al., 2009; Douaud et al., 2014). However, given that some studies have found progressive loss of brain volume, it has been postulated that TBI may also lead to ongoing, accelerated, 'brain age' (Sidaros et al., 2009; Cole et al., 2018; Feltrin et al., 2018; Harris et al., 2019). Progressive changes in brain structure following TBI may be further exacerbated over time through interaction with the neurobiological processes of ageing. Thus, it is possible that TBI leads to a 'one-off' loss in cellular volume, progressive, or accelerated 'brain age'. A single study has quantified 'brain age' in moderate to severe TBI at an average of 2.4 years (*Range* = 0.1 – 47 years) post-injury, reporting that: a) individuals with moderate to severe TBI showed greater brain age compared to healthy controls; b) the brain age gap increased with time post injury, suggesting TBI leads to accelerated ageing; c) greater brain age gap was associated with worse cognition (Cole et al., 2015).

* Corresponding author at: Monash-Epworth Rehabilitation Research Centre, Ground Floor, 185-187 Hoddle St, Richmond 3121, Australia.
E-mail address: Gershon.Spitz@monash.edu (G. Spitz).

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However, this cohort were only a relatively short time post-injury and had an average age of 38 years. Such an 'ageing' effect, if present would be expected to be greater in individuals who were older at injury and at longer time post-injury.

Here, we examined whether older individuals (*Mean age* = 57 years) with moderate to severe TBI assessed 10 years or more post-injury continue to show greater 'brain age' compared to demographically similar healthy controls. We investigated whether 'brain age' was associated with time post-injury, injury severity measures, aspects of cognition, and functional outcome, measured concurrently. We hypothesised that individuals with moderate-severe TBI assessed 10 years or more post-injury would show an elevated 'brain age' gap, compared to healthy controls; 2) that 'brain age' gap would increase with time post-injury; and 2) that greater 'brain age' gap would be associated with greater injury severity, as well as 3) poorer cognition and 4) lower functional outcome, after controlling for sex, premorbid IQ, and injury severity.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

All participants (or their legal guardian) provided written informed consent prior to any study procedures in accordance with the Declaration of Helsinki. The study was approved by the Austin Health Human Research Ethics Committee (HREC/17/Austin/202).

2.2. Participants

This study included 102 participants with TBI aged between 40 and 85 (71% male; mean age = 56.5 years, *SD* = 11.3; Table 1), who were an average of 22 years post injury at study enrolment (*SD* = 6.2, *Range* = 10 – 33 years). 47% of the TBI sample had visible focal lesions on T1-weighted images. Participants were recruited from an ongoing longitudinal head injury outcome study populated by consecutive admissions to a TBI inpatient rehabilitation unit. Eligible TBI participants had sustained a single moderate to severe TBI (defined using the Mayo classification (Malec et al., 2007) at age 16 or more, at least 10 years previously, were aged 40 years or over at the time of study enrolment, and did not report high levels of alcohol or drug use so that participants with possible brain injury from substance abuse were excluded.

We evaluated the possibility of recruitment bias in our study sample by comparing key sample demographic and injury-related variables between the current study sample and the rest of the longitudinal head injury outcome study participants (n = 1983) meeting similar inclusion criteria and admission date. The current sample did not differ with this larger longitudinal cohort on gender ($p = 0.941$), age at injury ($p = 0.350$), duration of PTA ($p = 0.804$), GCS ($p = 0.466$), or mechanism of injury ($p = 0.064$). However, the current study was more highly educated ($p < 0.001$). Refer to Supplementary Table 1 for detailed sample comparisons.

Seventy-seven healthy controls (53% male; mean age = 59.8 years, *SD* = 11.5, *Range* = 40 – 87 years) were recruited from the general community via newspaper advertisements and social media. Eligible healthy controls were those aged 40 years or over at study enrolment and had no history of TBI or any loss of consciousness.

Both TBI and healthy control participants were required to have a) sufficient English language skills, cognitive capacity and general medical health to complete study measures, b) absence of chronic substance abuse or severe psychiatric disturbances, c) absence of other neurological conditions, and d) absence of contraindications for MRI.

2.3. Clinical evaluations

Participants completed a research interview to provide demographic information and medical history. Injury-related information (Glasgow Coma Scale (GCS) scores, duration of post-traumatic amnesia (PTA), CT results) were obtained from medical records. PTA was measured prospectively using the Westmead Post Traumatic Amnesia Scale (Shores et al., 1986). Time since injury was defined as the time between injury and the clinical evaluation. Participants completed cognitive tests of memory, processing speed, and cognitive control (SI Table 2). Cognitive tests were chosen on the basis that they had shown sensitivity to TBI-related cognitive impairment in previous studies. Functional outcome was assessed with the Glasgow Outcome Scale Extended (GOSE; (Jennett et al., 1981). Premorbid IQ was assessed using the Wechsler Test of

Table 1
Participant characteristics and clinical features.

	TBI (n = 102)	Control (n = 77)	Group comparison, p-value
Male sex, n (%)	72 (70.6)	41 (53.2)	0.017
Mean age at study enrolment (SD), y	56.5 (11.3)	59.8 (11.5)	0.063
Mean WTAR FSIQ (SD)	100.2 (9.2)	105.8 (7.6)	<0.001
Mean Education (SD), y	12.6 (2.6)	13.7 (2.4)	0.004
Mean time since injury, y (SD)	22.0 (6.2)		
Mechanism of injury, n (%)			
Motor vehicle accident	65 (63.7)		
Fall	4 (3.9)		
Assault	2 (2.0)		
Bicycle	6 (5.9)		
Pedestrian	18 (17.6)		
Other	7 (6.9)		
Mean PTA, days (SD)	31.0 (29.8)		
Worst GCS, mean (SD)	7.5 (4.24)		
Worst GCS category, n (%)			
3–8	56 (64.4)		
9–12	12 (13.8)		
13–15	19 (21.8)		
PTA category, n (%)			
< 1 day	2 (2.0)		
1–7 days	23 (23.0)		
7–28 days	34 (34.0)		
> 28 days	41 (41.0)		
Abnormal CT results, n (%)	91 (89.2)		
Focal brain lesion, n (%)	48 (47.1)		
GOSE category[a]			
Severe disability	4 (4.0)		
Moderate disability	38 (38.0)		
Good recovery	58 (58.0)		
Orthopaedic trauma[b]			
Spine	18 (17.8)		
Chest	32 (31.7)		
Abdomen	15 (14.9)		
Limb	35 (44.6)		
Face	29 (28.7)		
Psychiatric disorder, lifetime[c]			
Major depressive disorder	11 (14.3)	19 (19.4)	30 (33.7)
Alcohol use disorder	10 (13)	17 (17.4)	27 (30.4)
Substance use disorder	2 (2.6)	3 (3)	5 (5.6)
Generalised anxiety disorder	3 (3.9)	2 (2)	5 (5.9)
Panic disorder	1 (1.3)	2 (2.1)	3 (3.4)
Posttraumatic stress disorder	0 (0)	4 (4.1)	4 (4.1)
Agoraphobia	0 (0)	1 (1)	1 (1)

Abbreviations: WTAR FSIQ = Wechsler Test of Adult Reading Full-Scale Intelligence Quotient; PTA = Post Traumatic Amnesia; GCS = Glasgow Coma Score; CT = Computed Tomography; GOSE = Glasgow Outcome Scale-Extended.
[a] GOSE categories were collapsed for brevity. Lower and upper severe disability were categorised into Severe disability. Lower and upper moderate disability were collapsed into Moderate disability. Lower and upper good recovery were collapsed into Good recovery.
[b] Presence of moderate or major trauma.
[c] Captured using the Mini International Neuropsychiatric Interview (MINI).

Adult Reading (WTAR). The Mini International Neuropsychiatric Interview was used to capture lifetime rates of psychiatric diagnoses.

2.4. Brain MRI acquisition parameters

T1-weighted images were acquired using a Siemens Magnetom Skyra 3T scanner (Erlangen, Germany) with the following parameters: TR = 1900 ms, TE = 2.43 ms, flip angle = 7°, 176 slices with 1.0 × 1.0 × 1.0mm voxels.

2.5. MRI Pre-processing and analysis

T1-weighted brain age estimates were obtained for each participant using the pre-processing and analysis pipeline developed by Cole et al. (2015). We implemented this pipeline using the brainageR (https://github.com/james-cole/brainageR) package in R, which generates a brain-predicted age value from raw T1-weighted MRI scans. brainageR segmented and normalised raw T1-weighted MRI scans. Images of segmented T1-weighted images were visually inspected for quality control. Normalised T1-weighted images were vectorized and grey matter, white matter, and CSF vectors masked. Grey matter, white matter, and CSF volumes are used to predict a single brain age value with the previously trained brain age model (Cole et al., 2015) using kernlab (Karatzoglou et al., 2004). The brain age model implemented in brainageR was previously trained on 3377 healthy individuals from seven publicly-available datasets, who had a mean age of 40.1 years (*SD* = 21.8, *Range* = 18 – 90 years). Refer to Cole et al. (2015) for full methodological details.

2.6. Statistical analysis

Statistical analyses were conducted in R, version 4.0.3(R Core Team, 2020). Unless otherwise stated, all statistical analyses were two-tailed and used a significance level of $p < 0.05$. Predicted brain age was initially corrected due to a known bias whereby brain predicted age is *overestimated* for younger individuals and *underestimated* for older individuals. This bias was corrected by taking into account the influence of chronological age on predicted brain age. To adjust for this age bias, we applied the correction that was implemented by de Lange et al. (2020). We first fit $Y = \alpha \times \Omega + \beta$, where Y is the modelled predicted age as a function of chronological age (Ω), α represents the slope, and β is the intercept. The derived values of the slope (α) and intercept (β) were used to correct predicted brain age using the following calculation: $\textit{Corrected predicted brain age} = \textit{Predicted brain age} + [\Omega - (\alpha \times \Omega + \beta)]$. The result of this correction is shown in SI Fig. 1.

Our key measure of brain aging was the *brain age gap*, which was calculated by subtracting each participant's chronological age from their corrected predicted 'brain age' ($\textit{Brain age gap} = \textit{Corrected predicted brain age} - \textit{Chronological age}$). Positive 'brain age' gap values indicate a biologically older brain and negative brain age gap values suggest a biologically younger brain. Linear regressions were used to examine the association between 'brain age' gap, group membership (TBI versus control), time since injury, measures of injury severity (post traumatic amnesia, Glasgow Come Scale), and outcome measures (cognition, Glasgow Outcome Scale-Extended).

All analyses included the following covariates: sex, age at assessment, and premorbid IQ, to control for their potential relationship with grey matter, white matter, and CSF volumes. Analyses that included only TBI participants also controlled for duration of PTA, to examine the significance of 'brain age' gap over and above the severity of injury and its influence on brain atrophy (Wilde et al., 2006). GCS was not controlled for in these analyses due to a higher proportion of missing data, compared to PTA. We calculated effect size for all regression analyses using the *effectsize* package in R (Ben-Shachar et al., 2020). The effect size was approximate *partial-d*, which is the standardised difference between two groups or conditions, with variance from other predictors partialled out. Where appropriate, we compared linear regressions models to one another using the *performance* package in R (Lüdecke et al., 2021).

We performed a sensitivity analysis when investigating whether brain age gap was associated with time since injury by using an independent participant sample (n = 87) recruited from the same TBI inpatient rehabilitation unit at an earlier time post-injury. Participants in the current study sample were recruited at an average of 22 years since injury whereas the sensitivity sample was recruited at an average of 1.6 years since injury (*Range* = 0.2 – 5.5 years, see SI Table 3 for sample demographics). This analysis was conducted to control for the possibility that the relationship between brain age gap and time since injury depends on the chronicity of the sample.

A sensitivity analysis was performed to examine the potential bias of focal lesions within the TBI group on 'brain age' estimation and related findings. We re-analysed three key findings, excluding those TBI participants with focal lesions: 1) brain age gap comparison between healthy control and TBI participants; 2) the relationship between brain age gap and time since injury; and 3) the relationship between injury severity and brain age gap. Moreover, we examined whether there was a difference between those TBI participants with and without focal lesions. These analyses can be found in Supplementary Figures 8 and 9.

To explore the association between brain age gap and cognition, we first conducted exploratory factor analysis to reduce the large number of cognitive tests into a parsimonious set of robust factors. The main factor analysis was conducted using only the TBI sample, although the same analysis for healthy controls can be found in Supplementary materials (SI Fig. 4,5,6). The TBI sample size was deemed to be sufficient for a factor analysis, given the requirement for at least five cases for each variable entered in the factor analysis (Hatcher, 1994). Exploratory factor analysis was conducted using the *fa* function from the *Psych* package in R (Revelle, 2020). We used oblique rotation to allow correlation between factors. We determined the number of factors to extract using parallel analysis with the *fa.parallel* function within the *Psych* package. Parallel analysis contrasts the observed data eigenvalues to those of a random data matrix of the same size. Factors are retained if the difference between observed and random data is positive. Variables were deemed to have a good factor loading if they had a loading of ± 0.32 or above (Tabachnick et al., 2007). Bartlett factor scores were extracted for each factor and modelled as a function of brain age gap using linear regression. Factor scores indicate the standing of each individual on the extracted factors.

2.7. Data availability

The data and scans from this study will be made available in de-identified format to researchers via the Federal Interagency Traumatic Brain Injury Research (FITBIR) database (https://fitbir.nih.gov/). Analysis code related to this paper is available on the Open Science Framework (https://osf.io/ser5u/).

3. Results

3.1. Biological brain ageing following TBI compared to healthy controls

As expected, TBI participants had biologically 'older' brains than healthy controls ($\beta = 4.51, SE = 1.11, p = < 0.001, [95\%CI: 2.32, 6.70], partial - d = 0.62$; Fig. 1). TBI participants had mean *brain age gap* between chronological and predicted brain age of 1.6 years ($SE = 0.73$, $[95\%CI: 0.17, 3.07]$). In contrast, healthy control participants had mean *brain age gap* between chronological and predicted brain age of −2.89 years ($SE = 0.80$, $[95\%CI: -4.48, -1.31]$).

3.2. Biological brain age and time since injury

Evidence for *accelerated* brain aging was examined using a cross-

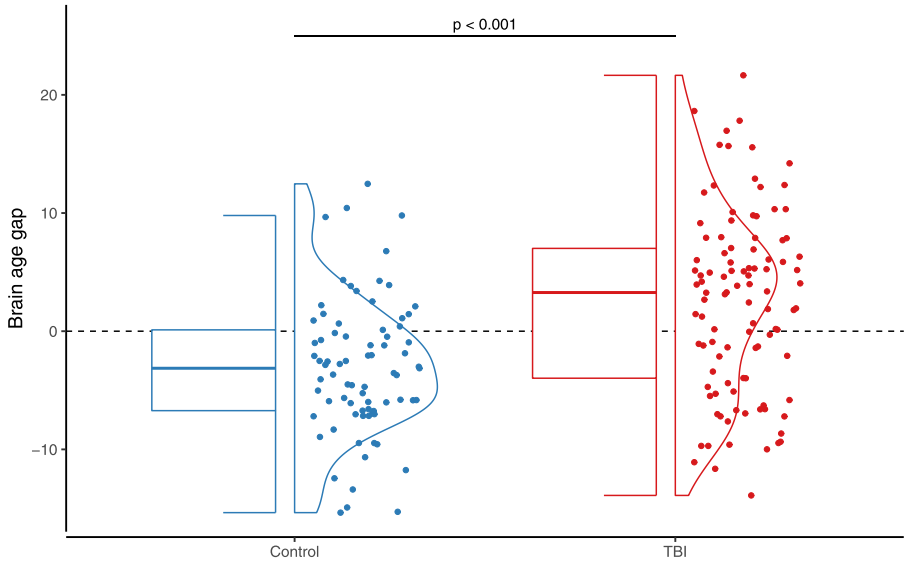

Fig. 1. Brain age gap is greater in chronic TBI.

sectional analysis, regressing brain age gap as a function of years since injury, controlling for duration of PTA, sex, age at assessment, and premorbid IQ. This analysis aligns with a previous study examining this same relationship in TBI (Cole et al., 2015), which found that brain age gap increased with time since injury. In the current study, brain age gap was not associated with time since injury ($\beta = 0.02, SE = 0.12, p = 0.837, [95\%CI: -0.21, 0.25]$,$partial - d = 0.04$, Fig. 2).

Participants in the current study sample, however, were recruited at an average of 22 years since injury, compared to an average of 2.4 years since injury in the previous study (Cole et al., 2015). To determine whether our non-significant results were due to the chronicity of our study sample, we conducted a sensitivity analysis in an independent cohort ($n = 87$) recruited at an earlier time since injury (*Mean time since injury* = 1.6 years, *Range* = 0.2 – 5.5 years, see SI Table 3 for sample demographics). Due to the absence of a premorbid IQ measure in this sample, years of education was added as a covariate in this analysis. Our finding was upheld. Brain age gap was not associated with time post injury in this independent 'acute' sample ($\beta = 0.45, SE = 0.61, p = .0466, [95\%CI: -0.77, 0.1.66]$ $partial - d = 0.16$, SI Fig. 2).

3.3. Injury severity and biological brain age

We assessed the relationship between GCS scores, PTA duration, and brain age gap using separate linear regressions, controlling for gender, age at assessment, and premorbid IQ. Individuals scoring 3–8 (severe) on the Glasgow Coma Scale had greater brain age gap than those scoring 13–15 (mild; $\beta = -4.95, SE = 2.09, p = 0.021, [95\%CI: -9.12, -0.78]$, $partial - d = -0.53$, Fig. 3A). Brain age gap did not differ between any of the other Glasgow Coma Scale severity categories ($p > 0.05$).

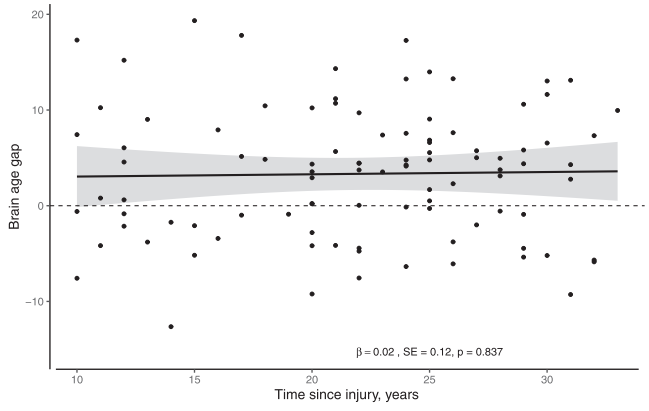

Fig. 2. Brain age gap does not increase with time since injury.

Individuals with longer duration of PTA had greater brain age gap, which was best modelled using a quadratic effect ($\beta = -15.55, SE = 7.15, p = 0.026, [95\%CI: -29.19, -1.91], partial - d = -0.47$, Fig. 3B; see SI Table 4 for model comparison). That is, the relationship between PTA and brain age gap plateaued at high PTA duration.

3.4. The influence of focal lesions and psychiatric comorbidity on brain age gap estimates

We examined whether focal lesions and history of psychiatric disorders were associated with brain age gap, potentially introducing bias in our key findings (SI Figures 8, 9, and 10). Excluding participants with focal lesions did not change our key findings. The significant difference between groups remained ($\beta = 5.67, SE = 1.15 p < 0.001, [95\%CI: 3.38, 7.95], partial - d = 0.87$), greater brain age gap was associated with PTA ($\beta = -14.00, SE = 6.70, p = 0.042, [95\%CI: -27.46, -0.55]$, $partial - d = -0.59$) and GCS (3–8 vs 13–15: $\beta = -5.69, SE = 2.65, p = 0.037, [95\%CI: -11.04, -0.35], partial - d = -0.67$), and there was no relationship between time since injury and brain age gap ($\beta = 0.19, SE = 0.16, p = 0.232, [95\%CI: -0.13, 0.51], partial - d = 0.34$). Within the TBI group, brain age gap did not differ between those with and without a focal lesion gap ($\beta = -0.98, SE = 1.52, p = 0.521, [95\%CI: -4.00, 2.04], partial - d = -0.13$). Last, lifetime prevalence of psychiatric disorders had no associated with brain age gap ($\beta = 0.18, SE = 1.15, p = 0.878, [95\%CI: -2.09, 2.44], partial - d = 0.02$; SI Figure 10).

3.5. Brain age gap and cognitive and functional outcomes

3.5.1. Cognition

We examined the relationship between brain age gap and cognition in the TBI sample. A replication of these analyses in the healthy control sample can be found in Supplementary Figures 6 and 7. Exploratory factor analysis was conducted using the TBI sample only. Parallel analysis suggested the extraction of four factors (SI Fig. 3). Variables were deemed to have a good factor loading if they had a loading of ± 0.32 or above. Exploratory factor analysis extracted factors representing *verbal memory I and II*, *visuospatial ability and memory*, and *cognitive*

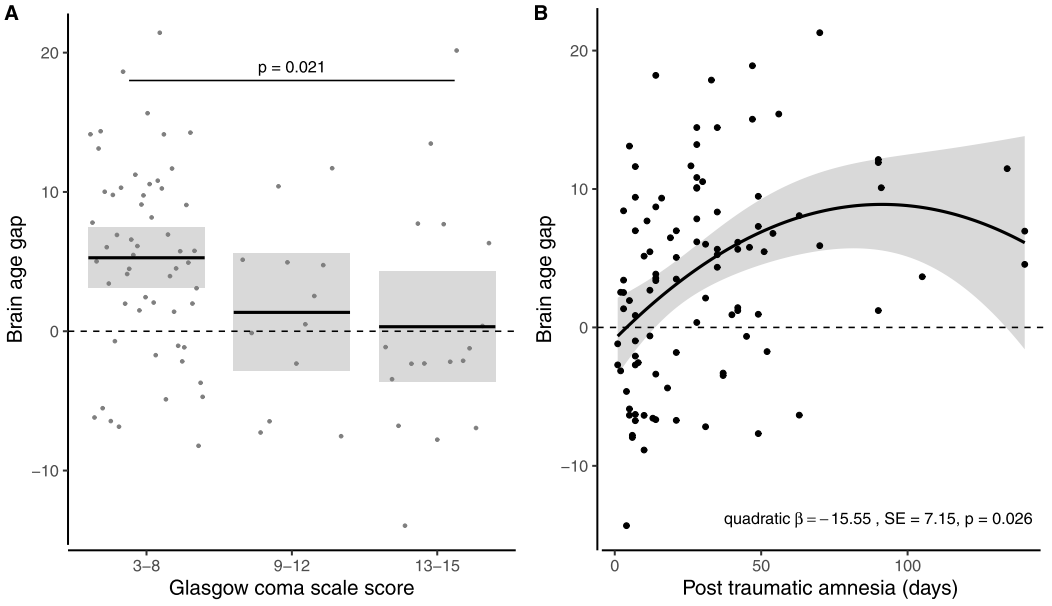

Fig. 3. Worse injury severity is associated with greater brain age gap.

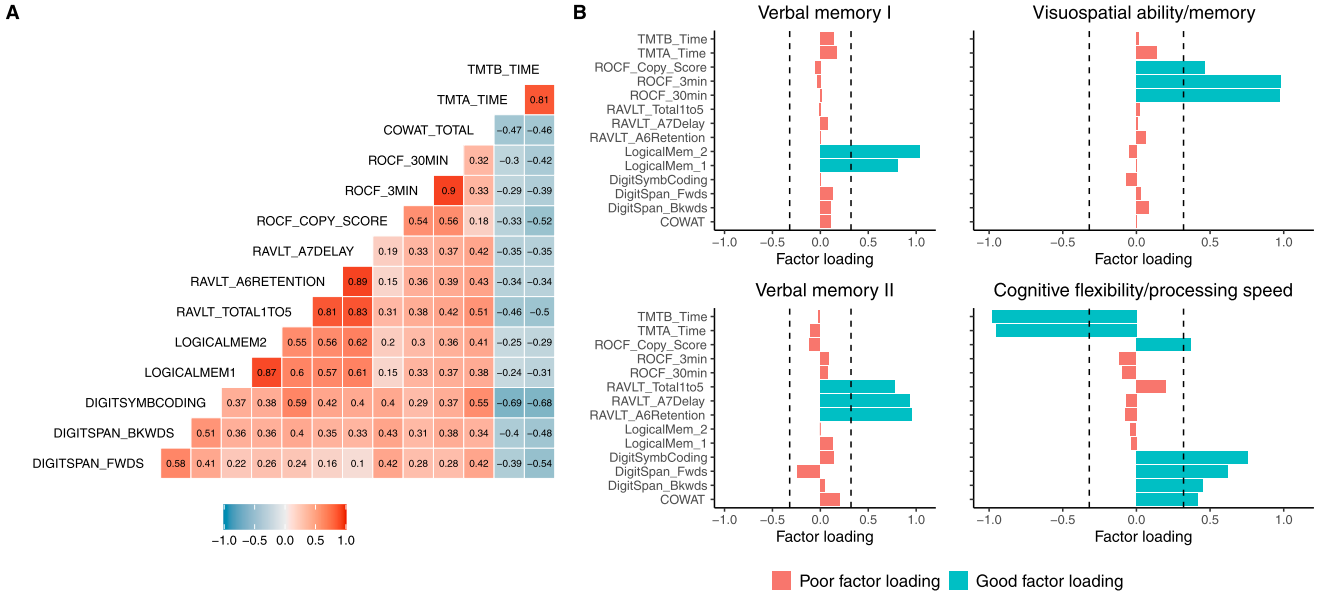

Fig. 4. Neuropsychological test dimensionality reduction using factor analysis.

flexibility/processing speed (Fig. 4).

Factor scores were extracted for each individual, providing information about each participant's standing on the four factors. We regressed these factor scores against brain age gap to determine whether brain 'age' was associated with specific cognitive abilities (Fig. 5). Regressions controlled for duration of PTA, sex, age at assessment, and premorbid IQ. (Sensitivity analyses were also conducted that excluded duration of PTA as a confounding variable, which can be found in Supplementary Figure 7). Greater brain age gap was associated with poorer verbal memory II ($\beta = -0.03, SE = 0.01, p = 0.011, [95\%CI: -0.06, -0.01], partial - d = -0.54$). There was no significant association between brain age gap and verbal memory I ($\beta = -0.01, SE = 0.01, p = 0.440, [95\%CI: -0.04, 0.02], partial - d = -0.16$) visuospatial memory/ability ($\beta = -0.01, SE = 0.01, p = 0.435, [95\%CI: -0.04, 0.02], partial - d = -0.16$), or cognitive flexibility/processing speed ($\beta = 0.01, SE = 0.01, p = 0.291, [95\%CI: -0.04, 0.01], partial - d = 0.22$).

3.5.2. *Glasgow outcome scale-Extended*

We assessed the relationship between the Glasgow Outcome Scale-Extended disability categories and brain age gap using linear regression, controlling for PTA, gender, age at assessment, and premorbid IQ. No significant difference was detected between the groups ($p > .05$, Fig. 6).

4. Discussion

Recent evidence suggests that traumatic brain injury (TBI) leads to greater 'brain age' (Cole et al., 2015; Gan et al., 2021). However, only a single study has examined 'brain age' in moderate to severe TBI at an

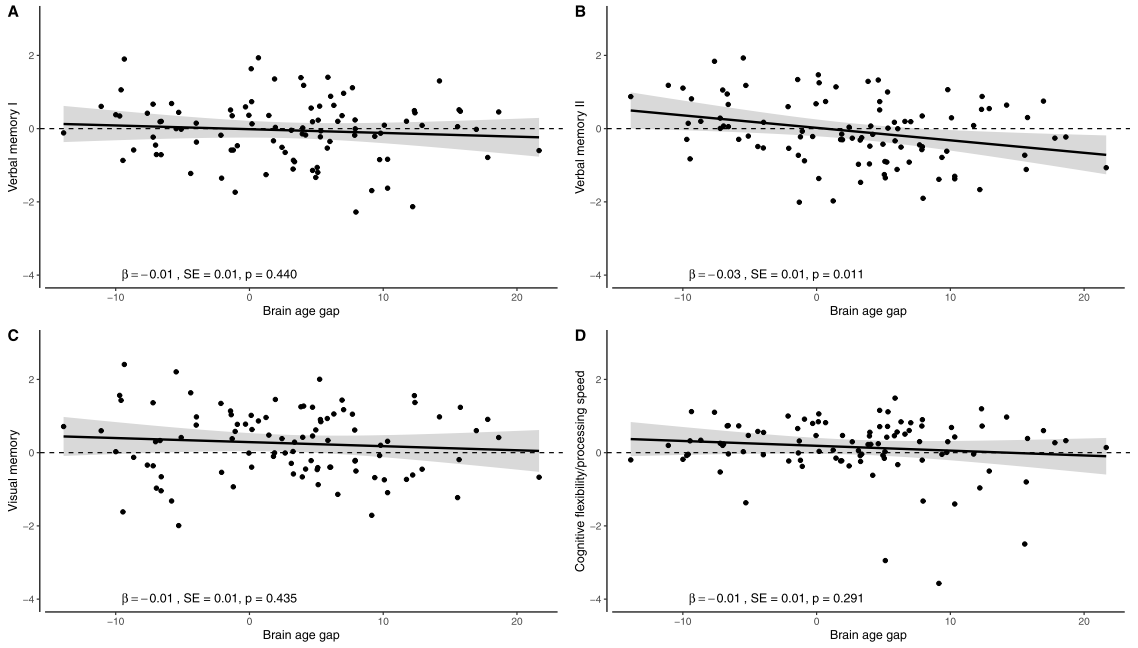

Fig. 5. Brain age gap and cognition in TBI.

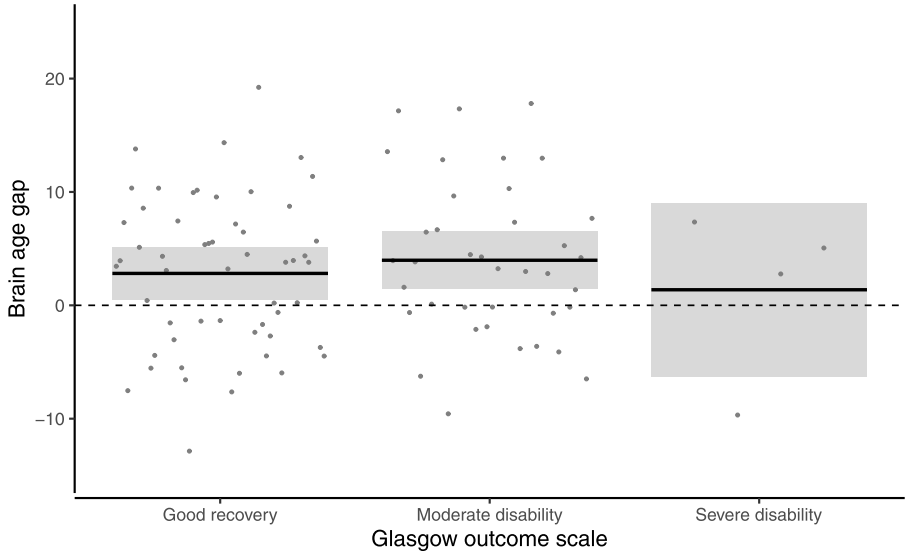

Fig. 6. Brain age gap and chronic disability.

average of 2.4 years post-injury in a relatively young sample (*Mean age* = 38 years), finding the 'brain age' *accelerated* over time (Cole et al., 2015). The current study examined whether these findings persisted in a sample comprising older moderate to severely injured TBI patients (*Mean age* = 57 years) who were in the chronic period following injury (≥10 years). This sample was ideal to investigate the potential impact of TBI on 'brain age', given i) the older age of participants age of assessment, and ii) the long follow-up period at assessment, thus providing an opportunity for *ageing*-related processes to either accumulate or interact with injury-related neuropathological processes.

We found that in this chronic period, individuals with TBI continued to present with elevated 'brain age', on average 1.6 years older than expected relative to their chronological age. In comparison, the previous study by Cole et al. (2015) reported a 'brain age' gap of 4.6 years for grey matter and 6 years for white matter. This discrepancy in brain age gap magnitude is unexpected, given the chronic nature of our sample and the hypothesis that TBI leads to accelerated 'brain age'. If true, our sample, on average, should have presented with greater brain age gap. The reasons for this discrepancy are not immediately clear, given the similar clinical characteristics of the two samples. In fact, it may be that younger individuals experience relatively larger changes to their 'brain age' following TBI. In contrast, age-related atrophy of grey and white matter may attenuate further loss due to TBI in the elderly. Moreover, the sample in the current study are more severe, on average, based on GCS. Therefore, given the positive association between GCS and the brain age gap, we should have detected relatively *elevated* brain age gap in our sample.

One interesting avenue of future investigation is the large variation of brain age in our sample. Although the average brain age gap following TBI was rather marginal (1.6), brain age gap ranged from

−14—indicating a *younger* brain—to 22—indicating an *older* brain. Thus, some individuals are 'super agers' who may be protected from pathological changes in 'brain age' following TBI, perhaps driven by genetic and environmental factors. On the other hand, there are some individuals who show significantly elevated 'brain age' that may suggest some vulnerability to a brain insult. Therefore, both extremes of the brain age gap distribution may offer valuable insight about ageing.

Another explanation for the discrepancy in findings is the possibility that TBI may not lead to an accelerated, time-dependent, process of ageing. Indeed, establishing whether TBI leads to a 'one-off' loss in cellular volume, progressive (changing at the same rate), or accelerated (increases in rate over time) 'brain age' is of considerable importance to the field and has significant ramifications for patient management and treatment. The study by Cole et al (2015) suggested 'brain age' accelerated following TBI, inferred through a cross-sectional analysis that showed that brain age gap increased exponentially as a function of years since injury, but only up to an average of 2.4 years. In our study we found no evidence of a relationship between brain age gap and years post injury. A possible explanation for our finding was the chronicity of our sample, which spanned between 10- and 33-years post-injury. It is possible that *accelerated* 'brain age' is confined to the early period following TBI that we were unable to measure in our chronic sample. To address this limitation, we conducted a sensitivity analysis in an independent sample that spanned two months to five years post-injury. However, once again we found no evidence of *accelerated* 'brain age'. Here, we argue that inferring developmental processes from cross-sectional data imposes certain limitations and can lead to misleading conclusions (Kraemer et al., 2000). To answer questions pertaining to a *time-dependent* developmental process, longitudinal data are required.

In the current study, we show that greater brain age gap is specifically related to greater injury severity. It is also associated with poorer verbal memory, rather than visuospatial ability/memory or cognitive flexibility and processing speed. Moreover, we found no significant association between brain age gap and functional outcomes. In their study, Cole et al. found an association between brain ageing and cognitive flexibility and processing speed. A key difference between their study and ours is that in the present study we controlled for the severity of injury to ensure we examined the utility of our brain age measure over and above the general influence of the initial injury severity. Therefore, the association between brain age gap and cognitive flexibility and processing speed may have been conflated with the general severity of injury, rather than specific makers of biological 'brain age' following TBI. Indeed, in our sensitivity analysis that excluded PTA as a confound brain age gap was associated with performance on all cognitive domains.

One limitation of the current study is the specific brain age measure. That is, the brain age measure in our study is spatially unspecific; it does not provide a detailed account of whether specific regions in the brain are driving our findings. Indeed, it may be that TBI results in greater 'brain age' in certain regions of the brain while other areas are more resilient to the injury. Moreover, two individuals may have the same 'brain age' gap that is driven by pathological changes in different brain regions and possibly different neuropathologies. Indeed, the brain mechanisms driving similar brain age estimates may differ across disorders and populations. Similarly, changes in the same grey and white matter structures may be driven by different underlying 'upstream' neuropathological causes. This has significant implications for potential pharmacological and other invasive and non-invasive treatments.

Another limitation of the 'brain age' measure used in this study is that is focuses on a relatively narrow set of brain features in order to capture 'ageing': variations in brain volume. Although changes in brain volume is a robust finding in ageing, a host of other changes occur throughout the brain that would have provided a richer characterization of 'brain age', such as changes in white matter microstructure and changes in functional connectivity, or changes in brain network architecture. Future brain age models in TBI should provide a means of exploring the brain features that underpin each individual's brain age estimate, beyond grey matter, white matter, and CSF expansion.

Like many of the other studies investigating 'brain age', the cross-sectional nature of our sample precludes us from interpreting whether our findings indeed reflect a 'one off' change in brain structure, accelerated changes in 'brain age' over time, or whether both temporal profiles exist following TBI. Studies reporting accelerated volume changes following TBI suggest that perhaps 'brain age' would display a similar profile (Sidaros et al., 2009; Cole et al., 2018; Feltrin et al., 2018; Harris et al., 2019). However, given there is not a direct correspondence between brain volume and 'brain age' estimates this needs to be investigated directly.

Lastly, it is worth noting that the TBI and healthy controls differed on key variables. Our TBI sample comprised a greater number of males, had lower IQ, and a lower level of education. This was addressed in this study by including these factors as covariates in all of our analyses. However, it is possible that this did not account for complex nonlinear interactions between these variables and other measures. The discrepancy between groups does not affect our key findings regarding time since injury and cognition.

The strength of this study foremost lies in the unique sample collected in the chronic phase (>10 years) following TBI. Increasingly, TBI is being viewed as a lifelong process that can in certain cases lead to diseases of ageing. This study sample can provide insight into whether patterns of disease or neuropathology encountered early following TBI persist in the chronic period. In the case of 'brain age', we confirm persistent elevated brain age gap decades following the injury.

Greater 'brain age' at both acute and chronic periods implies that individuals with TBI may be exposed earlier in their lives to diseases traditionally associated with old age. However, the variability within our TBI sample suggests that certain individuals may be resilient to these effects. Clinically, our findings suggest that we should examine in detail the characteristics, both demographic and biological, of those individuals demonstrating resilience. On the other hand, and perhaps more importantly, we should identify those at risk of elevated 'brain age' and intervene early to promote healthy ageing.

In conclusion, our findings demonstrate that a single moderate to severe TBI results in white and grey matter loss that persists for many years following injury. The lack of evidence from our study that this loss is increasing over time leads us to question whether the term brain age is applicable in the context of TBI. This is an ageing and chronic cohort of individuals that should be the focus of future studies in order to determine whether certain environmental, genetic, and other biological factors protect against pathological processes of ageing following TBI.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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