DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Are there differences in brain structure between people with a lifetime history of TBI compared to controls with no TBI history in mid adulthood?

Proposing Author: Alice Theadom

Author's Email: Alice.theadom@aut.ac.nz

P.I. Sponsor: Originally Richie Poulton
(if the proposing author is a student or colleague of an original PI)

Today's Date: 15/09/23

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Background:

There are a projected 36,000 new traumatic brain injuries (TBI) in New Zealand every year[1], with one in three people experiencing at least one TBI before age 25.[2] Up to 95% of injuries are classified as being of mild severity.[1] However, even 'mild' TBIs can lead to chronic functional deficits in up to half of cases.[3,4] There is evidence that the effects of TBI can be cumulative, particularly if multiple TBIs are sustained before the brain has had a chance to recover and repair.[5] In the longer term an increased risk of developing neurodegenerative disorders such as Alzheimer's Disease has been identified following a history of TBI.[6] However, our understanding of why some people experience chronic deficits and develop longer-term neurological disorders while others do not is limited. The answer may well lie in microscopic changes in the brain.

Whilst routine CT scans do not always show changes in the brain following TBI, advances in MRI technology can now detect microstructural changes associated with TBI. A more novel approach to MRI termed fixed-based analysis (FBA) enables the investigation of specific fibre populations within voxels ('fixels') even in the presence of crossing fibre populations. The specificity of this technique identifies it as a prime candidate to be used in TBI research.[7]

Objective of the study:

This analysis aims to explore whether there are differences in grey and white matter volume and white matter integrity between people who have with a history of TBI and those who do not.

By looking at lifetime TBI history data and MRI scans extracted from the Dunedin study, we will be able to disentangle if there are any effects of TBI sustained over the lifetime within the general population on the structure of the brain in mid-adulthood.

Research questions:

1. Are there differences in white and grey matter volume and white matter integrity in people who experienced at least one TBI over their lifetime compared to those without a TBI history?
2. Does the severity of TBI, age of TBI, date of last TBI, the time between injuries, experience of loss of consciousness or number of TBIs experienced influence the links between TBI and white and grey matter volume and white matter integrity?
3. Do any relationships identified between TBI and brain structure remain after controlling for sex, dependence on alcohol or drug use, and neurological disorder.

Data analysis methods:

The study population will include members of the Dunedin study who have lived to 45 years or older and for whom MRI scan data was collected at phase 45.
Descriptive statistics will be used to describe the sample (e.g., sex, childhood socioeconomic status, ethnicity) and the proportion of people affected by TBI over their lifetime, severity of TBI experienced, distribution of age of first and last TBI, total number of TBIs, time between injuries, mechanisms of injury(ies) and loss of consciousness. Tests of difference will be conducted to determine if there are any differences in sociodemographic variables of people who experienced a TBI and those who did not (e.g. sex, ethnicity, socioeconomic status).
A series of regression models will be used to determine if there is a link between TBI and brain structure as determined by MRI scans at phase 45 and determining the influence of nuances in TBI history such as number, severity, age of injury, loss of consciousness or time between injuries. Regression models will then determine whether any links between TBI and brain structure identified remain after controlling for variables known to be linked to brain structure in mid adulthood such alcohol and substance dependence and sex.

Variables needed at which ages:

Study number
TBI history by participant (Number of lifetime TBI)
Age at time of first TBI
Age of last TBI
Severity of each TBI
Loss of consciousness following TBI
Mechanism of injury(ies)
Time between injuries
Sex
Highest childhood SES
Self-identified ethnicity
Substance use dependence between 16 and 38
Alcohol use dependence between 16 and 38
Neurological disorder (as identified in general health survey)
Full fMRI scans (task and rest) at age 45

Significance of the Study (for theory, research methods or clinical practice):

There is currently significant public concern about TBI's potential longer-term impacts. This study will help determine any effects of TBI history on the brain's structure in mid-adulthood. Current studies are limited by sample size, retrospective data collection or a focus only on athletes. This analysis will enable us to identify any impacts on brain structure in a large, general population sample. If there are

no differences in brain structure identified between those with and without a history of TBI, this will provide much needed reassurance to the general public. However, if differences identified, this may assist in enhancing our understanding of the longer-term impacts of TBI on the brain and identification of those at risk of brain health impacts later in life.

References:

1. Feigin VL, Theadom A, Barker-Collo S, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *The Lancet Neurology* 2013; **12**(1): 53-64.
2. McKinlay A, Grace RC, Horwood LJ, Fergusson DM, Ridder EM, MacFarlane MR. Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. *Brain Injury* 2008; **22**(2): 175-81.
3. Madhok DY, Rodriguez RM, Barber J, et al. Outcomes in Patients With Mild Traumatic Brain Injury Without Acute Intracranial Traumatic Injury. *JAMA Network Open* 2022; **5**(8): e2223245.
4. Theadom A, Parag V, Dowell T, et al. Persistent problems 1 year after mild traumatic brain injury: a longitudinal population study in New Zealand. *British Journal of General Practice* 2016; **66**(642): e16-23.
5. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA : the journal of the American Medical Association* 2003; **290**(19): 2549-55.
6. LoBue C, Munro C, Schaffert J, et al. Traumatic Brain Injury and Risk of Long-Term Brain Changes, Accumulation of Pathological Markers, and Developing Dementia: A Review. *Journal of Alzheimers Disease* 2019; **Epub ahead of print**.
7. Mito R, Parker DM, Abbott DF, Makdissi M, Pedersen M, Jackson GD. White matter abnormalities characterise the acute stage of sports-related mild traumatic brain injury. *Brain*

Data Security Agreement

Provisional Paper Title	Is a lifetime history of TBI linked to changes in brain structure in mid-adulthood?
Proposing Author	Alice Theadom
Today's Date	04/08/2023

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement: (customize as necessary)

AT	I am current on Human Subjects Training [CITI www.citigrogram.org] or equivalent.
AT	My project is covered by the Dunedin Study's ethics approval
AT	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • has an antivirus client installed as well as being patched regularly.
AT	I will not "sync" the data to a mobile device.
AT	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact my PI Sponsor or Study Director, Richie Poulton (richie.poulton@otago.ac.nz).
AT	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
AT	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.*
AT	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: _____ _____