DECODING DEMENTIA

Traumatic Brain Injuries and Dementia: Exploring the Connection

Authors: Andre Buser, Victor Adafinoaiei (Dec 2023)

Context

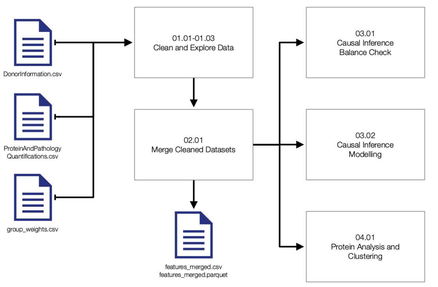
Background: Traumatic Brain Injuries (TBI) are a significant public health issue, with far-reaching implications for individuals and society. These injuries are known to increase the risk of neurodegenerative diseases, particularly dementia. However, the intricate relationship between TBI and dementia remains an enigma, posing challenges in developing effective prevention and treatment strategies.

Research Aim: This study, "Decoding Dementia," spearheaded by Andre Buser and Victor Adafinoaiei, embarks on a journey to unravel the complexities of this relationship. Our primary objective is to deepen our understanding of the outcomes, determinants, and consequences of TBIs, and how they potentially escalate the risk of developing dementia.

Methodology: Our approach leverages causal inference to explore how demographic and clinical factors influence dementia risk post-TBI. This method provides a refined analysis, allowing us to draw more precise and impactful conclusions.

Expected Impact: The insights garnered from this study aim to fill critical gaps in our understanding of TBI and dementia. By illuminating these connections, our research holds the potential to inform and transform prevention strategies, therapeutic interventions, and policy-making, ultimately improving healthcare outcomes for those affected by TBIs and dementia.

Decoding Dementia Workflow



Building on the Foundations

Related Work: The quest to decode the complex relationship between Traumatic Brain Injury (TBI) and dementia does not exist in isolation. It is built upon the foundational work of previous research, which has significantly shaped and guided our study. In this chapter, we delve into several key studies that have informed our approach, offering novel insights and methodologies in understanding dementia, especially in the context of TBI.

"What Do Machines Tell Us About Dementia? Machine Learning Applied to Aging, Dementia, and Traumatic Brain Injury Study" by Moura and Oliveira (2021):

- **Highlight:** This study underscored the utility of machine learning in identifying genetic markers linked to dementia, providing a roadmap for our molecular data analysis.
- **Impact:** Their approach influenced our methods in handling and interpreting large sets of data, especially in relation to TBI and aging.

"Harnessing the potential of machine learning and artificial intelligence for dementia research" by Ranson et al. (2023):

- **Highlight:** Ranson et al. emphasized the role of unsupervised learning in dementia research.
- **Contribution:** Their insights were instrumental in shaping our analysis of the Allen Institute's dataset, particularly in employing unsupervised learning techniques.

"Identification of causal effects of neuroanatomy on cognitive decline requires modeling unobserved confounders" by Pölsterl et al. (2022):

- **Highlight:** This paper introduced innovative methods for estimating causal effects in neuroimaging, relevant to our investigation of TBI and its links to dementia.
- **Significance:** Their methodological framework provided a blueprint for our approach in modeling the causal relationships between TBI and dementia outcomes.

The Data

Foundation of Our Analysis: At the heart of our study lies a the dataset, sourced from the Aging, Dementia, and Traumatic Brain Injury Study by the Allen Institute for Brain Science (2017). This comprehensive dataset forms the backbone of our investigation, providing a detailed look into the factors that contribute to dementia, particularly following Traumatic Brain Injuries (TBI).

ALLEN INSTITUTE

AGING, DEMENTIA and TBI STUDY

https://aging.brain-map.org/

Description and Importance	Records	Attributes
DonorInformation.csv contains detailed information about individual donors, including various age-related characteristics.	107	19
ProteinAndPathologyQuantifications.csv offers quantified measurements related to proteins and pathologies associated with brain aging or neurodegenerative disorders.	377	33
group_weights.csv contains subject and sampling weights as calculated and described in the Allen Institute's 'Technical White Paper: Weighted Analyses' (2016).	107	2

Analyzing the Impact of Traumatic Brain Injury on Dementia Risk: Causal Inference

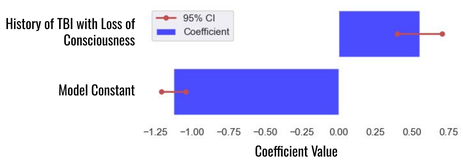
Unadjusted Model - Exploring TBI and Dementia Link

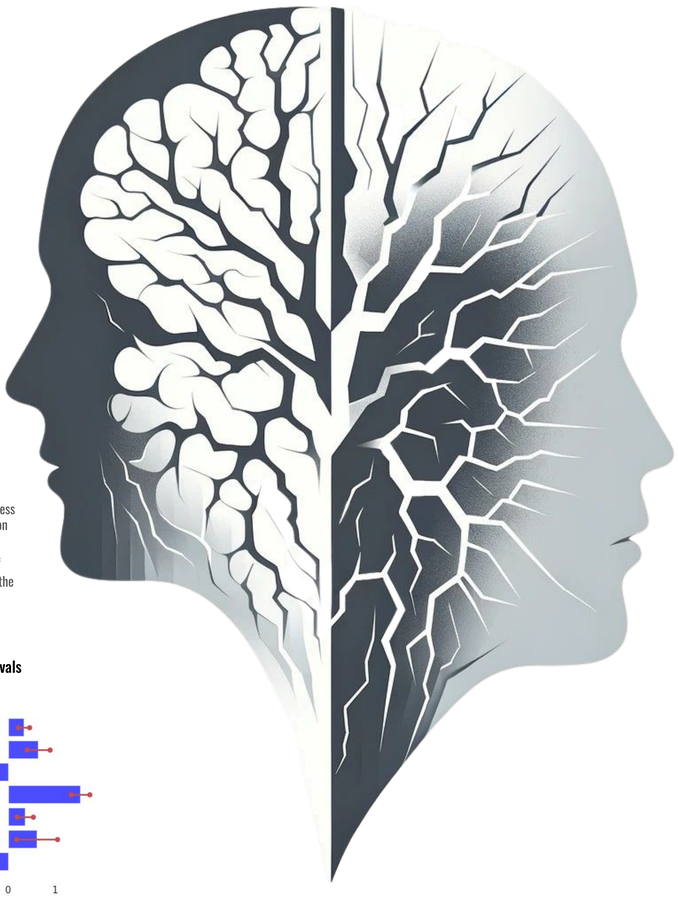
In our study, we employed a Generalized Linear Model (GLM) with a binomial family and a Logit link function, specifically chosen for its suitability in analyzing binary outcomes such as the presence or absence of dementia.

Analyzing a dataset of 107 observations, our model demonstrated strong effectiveness with a Pseudo R-squared value of 0.3663. The significant coefficients in our model, -1.1238 for the constant and 0.5521 for the 'ever_tbi_w_loc_clean' variable, were particularly revealing. These values, each with a p-value less than 0.000, confirmed their statistical significance. Most notably, **our results indicated that a history of Traumatic Brain Injury (TBI) with loss of consciousness significantly elevates the risk of dementia diagnosis.**

In practical terms, for **every one-unit increase in the 'ever_tbi_w_loc_clean' score, the odds of being diagnosed with dementia increased by approximately 73.70%, with all other variables held constant.**

Logistic Regression Coefficients with 95% Confidence Intervals (Unadjusted Model with Group Weights)





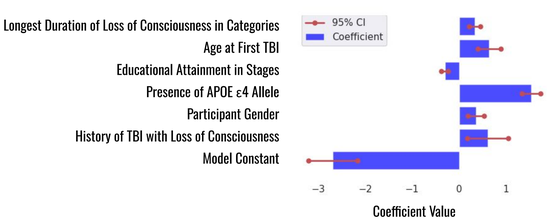
Adjusted Model - A Refined Approach

In our analysis of dementia, we initially used a Generalized Linear Model (GLM) focusing on pre-mortality variables while excluding 'num_tbi_w_loc' due to its skewed distribution. This led to a dataset of 100 donors.

However, the high Pseudo R-squared value (0.9828) from the GLM suggested potential overfitting. **To address this and ensure robustness, we expanded the dataset to 3969 records by duplicating records based on 'group_weight'.** We then employed logistic regression using sm.Logit for a comparative analysis.

Lastly, our study established a substantial link between traumatic brain injuries (TBI) and an elevated risk of dementia. **Key findings indicate that TBIs, especially those involving loss of consciousness, alongside the presence of the APOE ε4 allele and male gender, significantly increase dementia risk, while higher education levels seem to offer some protective effects.**

Logistic Regression Coefficients with 95% Confidence Intervals (Unadjusted Model with Group Weights)



ANOVA Analysis of Biomarker Clusters

Top 5 Biomarker Findings: We identified the top five most significant biomarkers and visually represented their diverse patterns across different clusters using box plots. This approach effectively highlights the varying expressions of biomarkers, providing clear insights into their distribution.

In-depth Examination of Disparities: Our analysis revealed pronounced disparities in critical factors such as protein levels among the clusters. These variations are not random but indicate distinct biological or pathological characteristics inherent to each cluster, which are crucial for understanding the complex dynamics of these biomarkers.

Statistical Validation: We employed robust statistical methods, including ANOVA, to validate our findings. Notably, all five biomarkers showed significant differences across clusters, as indicated by high F-values. Furthermore, the p-values are extremely low strongly negate the probability of these differences occurring by mere chance.

Implications and Insights: These results offer valuable insights into the distinct properties of each cluster, shedding light on potential pathways and mechanisms at play. Our findings pave the way for more targeted research and interventions, tailored to the unique characteristics of each biomarker cluster.

Biomarker	Description
ab42_over_ab40_ratio_FWM	Aβ42/Aβ40 ratio in Frontal White Matter, indicating Alzheimer's disease risk.
ab42_over_ab40_ratio_PCx	Aβ42/Aβ40 ratio in Posterior Cortex, a marker for amyloid plaque formation.
ptau_ng_per_mg_PCx	Elevated phosphorylated tau in Posterior Cortex, associated with Alzheimer's.
ptau_ng_per_mg_FWM	Phosphorylated tau levels in Frontal White Matter, indicating neurodegeneration.
tau_ng_per_mg_PCx	Total tau protein in Posterior Cortex, a marker for neuronal damage.

Box Plots for the top five proteins exhibit varying patterns across the identified clusters