“Predicting Dementia from Traumatic Brain Injury”

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1. Project Description:
   1. In this analysis, we propose to predict whether or not the incidence of dementia is related to the presence of traumatic brain injury (TBI) at any point in life. We will use logistic regression to assess the likelihood of having dementia, given the presence of absence of ever having TBI, covarying for various clinical, protein, and RNA markers. The analysis will be both predictive, in that we are trying to predict dementia status given TBI status and covariate measurements, and also inferential in that we are interested in quantifying the relationship of TBI and covariates with dementia. In addition to predicting the likelihood of dementia, we want to measure the true effect that certain covariates have on that likelihood.
2. Data Description
   1. Collection Process
      1. The samples in this study were collected from patients who were enrolled in the ACT study. Participants in ACT were randomly selected for a longitudinal study organized by Kaiser Permanente. For our project using the Allen Institute data, we have data collected from 107 participants in the ACT study who passed away.

Controls with no known TBI with loss of consciousness were best-matched to non-controls based on a decision tree algorithm considering exact age, closest year of death, post-mortem interval, and closest date of death. If exact-age matches could not be found, they considered controls with incrementally increasing differences in age.

For each of these 107 deceased participants, the Allen Institute collected neuropathology protein measurements and performed RNA-sequencing on the collected tissue.

Of these 107 participants, we have 77 complete samples. Of roughly 50K genes, these 77 subjects had measurements from all 4 considered regions in the brain.

* 1. Units of Measurement
     1. Clinical covariates like age are measured in years. TBI incidence is measured as a binary variable. Dementia is measured as a binary variable.
     2. Neuropathology measures were measured as concentrations of proteins in a given sample, typically in picograms (pg) per milligram (mg).
     3. RNA-sequencing data was measured in terms what is called “Fragments Per Kilobase of Transcript per Million Mapped Reads” (FPKM). FPKM infers the expression level of a gene (concentration of an RNA transcript) based on observations of fragments of that transcript. Basically, if we have a sequence of a gene which we can analogize to a “string” of DNA bases, we measure how a given gene was expressed based on how many times we see parts of the DNA string.
  2. Data Structure
     1. We have a set of deceased participants who voluntarily agreed to allow their brains to be studied post-mortem. For each participant’s brain, RNA-sequencing and neuropathology measurements were taken from 4 locations in the brain: cortical gray matter in the temporal and parietal cortices, subcortical gray matter in the hippocampus, and parietal white matter.

1. Outcome Variable
   1. Binary variable indicating whether or not the patient had dementia
2. Unusual Methodologies
   1. There do not seem to be very many unusual methodological aspects apparent at the early stages of data exploration. There are a few outliers when looking at Tau Protein vs. Traumatic Brain Injury in the Frontal White Matter and in the Parietal Cortex. There are clear outliers in the Frontal White Matter when plotting Tau Protein Pathology vs. Amyloid Beta-42 Pathology and there seems to be one outlier in Tau Protein vs. Dementia Status (our response variable) in the Frontal White Matter. There may also be multicollinearity between the presence of the Tau Protein and Traumatic Brain Injury status in the Parietal Cortex, though this relationship is relatively weak.
3. References
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   2. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia Risk After Traumatic Brain Injury vs Nonbrain TraumaThe Role of Age and Severity. *JAMA Neurol.* 2014;71(12):1490–1497. doi:10.1001/jamaneurol.2014.2668
   3. Shively S, Scher AI, Perl DP, Diaz-Arrastia R. Dementia Resulting From Traumatic Brain InjuryWhat Is the Pathology?. *Arch Neurol.* 2012;69(10):1245–1251. doi:10.1001/archneurol.2011.3747