Overview

1. The Concussion, Traumatic Brain Injury (TBI) and Alzheimer’s Disease (AD) connection
2. Alzheimer’s Disease Neuroimaging Initiative (ADNI) overview – available data
3. Using ADNI Data to understand the relationships between AD and TBI
4. Current Progress
5. Next Steps
Concussion, Traumatic Brain Injury (TBI) and the Alzheimer’s Disease (AD) connection

- TBI nearly doubles the risk of AD, especially in males
  - Fleminger et al., 2003; Barnes et al., 2011; Moretti et al., 2012; Crane et al., 2016; Li et al., 2017
- Overlapping blood/CSF biomarkers: tau, amyloid beta, and alpha synuclein (Uryu et al., 2007)
- Acceleration of white matter degradation and cortical thinning

What Happens to Traumatized Brain?

Direct impact
Torsion/twisting
Shearing forces
Vascular damage
Hemorrhages
Tissue loss (gray matter [GM] and white matter [WM])
Disconnection of WM
Diminished “reserve”
TBI Pathophysiology

- Primary Injury
- Secondary Injury
- Late effects


Progressive brain atrophy after TBI

TBI Accelerates Brain Atrophy


Experimental TBI

- 3xTg-AD transgenic mice
- Controlled unilateral TBI
- Time course of APP deposition and clearance is shown

CSF t-tau UP in Former Pro Football Players

Table 1 CSF biomarkers in 3 groups

<table>
<thead>
<tr>
<th></th>
<th>Former athletes group</th>
<th>HC group</th>
<th>AD group</th>
<th>ANOVA p Value</th>
<th>Post hoc p values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>22</td>
<td>5</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>55.9 ± 12.2</td>
<td>57.4 ± 5.2</td>
<td>60.0 ± 6.6</td>
<td>0.530</td>
<td>0.665</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.95 ± 2.2</td>
<td>14.8 ± 1.6</td>
<td>14.42 ± 2.7</td>
<td>0.810</td>
<td>0.997</td>
</tr>
<tr>
<td>A(\beta)_{1-42}, pg/mL</td>
<td>750.0 ± 182.1</td>
<td>835.0 ± 168.2</td>
<td>363.3 ± 70.9</td>
<td>&lt;0.001\textsuperscript{b}</td>
<td>0.694</td>
</tr>
<tr>
<td>p-tau, pg/mL</td>
<td>44.8 ± 13.6</td>
<td>41.1 ± 9.6</td>
<td>111.9 ± 44.4</td>
<td>&lt;0.001\textsuperscript{b}</td>
<td>0.858</td>
</tr>
<tr>
<td>t-tau, pg/mL</td>
<td>349.3 ± 182.6</td>
<td>188.8 ± 39.9</td>
<td>857.0 ± 449.3</td>
<td>&lt;0.001\textsuperscript{b}</td>
<td>0.003\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Abbreviations: A\(\beta\)\(_{1-42}\) = \(\beta\)-amyloid; AD = Alzheimer disease; ANOVA = analysis of variance; HC = healthy controls; p-tau = phosphorylated tau181; t-tau = total tau.

* Dunnett T3 post hoc analysis.


tau-PET Imaging in TBI, PTSD and Controls

TBI and AD Both Relate to Amyloid


Perspectives of NDDs and TBI

- Pathologic similarity or trigger for NDD
- Our work relies on Classical View
- If CTE is distinct, trigger biomarkers are unlikely to exist

Alzheimer’s Disease Neuroimaging Initiative (ADNI) overview

- Clinical data (history, exam, cognitive, neuropsychiatric, functional measures)
- Blood (lipids, proteins, etc.)
- Genetics
- CSF
- MRI Scanning Sequences
- PET Imaging
ADNI Imaging by Phase, Since 2004

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<tbody>
<tr>
<td>Structural T1 MRI Scans</td>
<td>1.5T and 3T MRI Scans</td>
<td>Only 3T MRI Scans</td>
</tr>
<tr>
<td>T2 Dual Echo MRI Scans</td>
<td>2D FLAIR MRI Scans</td>
<td>2D FLAIR MRI Scans</td>
</tr>
<tr>
<td>¼ subjects same 3T MRI</td>
<td>T2*-weighted MRI Scans</td>
<td>T2*-weighted MRI Scans</td>
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<tr>
<td></td>
<td>Diffusion MRI on GE Scanners</td>
<td>Two-tiered approach</td>
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<tr>
<td></td>
<td>Resting State MRI on Phillips Scanners</td>
<td>Basic</td>
</tr>
<tr>
<td></td>
<td>ASL MRI on Siemens Scanners</td>
<td>Advanced</td>
</tr>
</tbody>
</table>

ADNI and Cortical Thickness

- Left hemisphere mean thickness ranges from $< -0.3$ (yellow) to $> +0.3$ (cyan) mm thickness
- Color scale in mm:
  - $-0.05$ to $-0.15$ dark red
  - $-0.20$ bright red
  - $-0.25$ orange, and
  - $< -0.30$ yellow
  - $+0.05$ to $+0.15$ blue
  - Less than $\pm 0.05$ mm are gray

AD-Vulnerable Areas Based on Cortical Thickness

ADNI Imaging Biomarkers Predict Cognitive Decline in Mild Cognitive Impairment (MCI)

- Distinguish those that progress and those that do not and also correlate ($|r| \geq 0.2$) with ADAS-Cog change
  - FDG-PET summary measure (UC Berkeley)
  - AV45 cortical summary measure (UC Berkeley) [Best]
  - Entorhinal cortex thickness (UCSF, FreeSurfer)
- These markers, singly or in combination, could be used to improve clinical trial design by:
  - Inclusion of people more likely to progress
  - Exclusion of people more likely to stay stable, or
  - Stratifying by risk group
Using ADNI Data to understand the relationships between AD and TBI

• Limited subjects, as TBI was an EXCLUSION
• Nevertheless, some subjects with mTBI are included, allowing study of TBI/AD connection
• How has this been done?
• How shall we study this?

ADNI Data Show Early AAO with TBI+ History

• Li et al. (2016) Examined TBI and age at onset (AAO) of cognitive impairment
• All participants had mild cognitive impairment or Alzheimer’s Disease
  ○ 62 participants with TBI (green) and 1197 without TBI (brown)
• TBI subjects had an earlier AAO
Subgroups of TBI and Age at Onset

- Mild TBI (mTBI) and more severe TBI (sTBI) are associated with significantly earlier AAO than no TBI (top)
- MCI subjects with TBI had significantly earlier AAO than MCI subjects with no history of TBI
- AD subjects with TBI had trend to earlier AAO than AD subjects with no history of TBI


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TBI in Childhood or Adulthood in ADNI

- Li examined age at injury (AAI) and long-term cognitive outcomes
- 31 subjects with childhood and 32 subjects with adult TBI (cTBI, aTBI)
- cTBI had better cognitive performance on the Boston Naming Test (BNT) and Rey Auditory Verbal Learning Test (RAVLT), but self-reported more cognitive impairments
Self-reported mTBI and Cortical Thickness in ADNI

- Self-reported mTBI and cortical thickness
- Cortical thickness and AD-related biomarkers
- 45 self-reported mTBI and 45 matched controls
- Preclinical AD + mTBI had reduced mean cortical thickness in AD-vulnerable regions
  - inferior parietal cortex
  - superior parietal cortex
  - Precuneus


Current Progress

- Pilot Study of TBI vs Controls (not part of ADNI) generated interest in ADNI
- Obtained ADNI access and acquired data
- Planned Analyses of ADNI to study TBI-AD link
- Identified concussion/TBI subjects in ADNI
- Pulled specific subgroups of TBI subjects
- Identified matched control subjects
- Moved data to Palmetto Cluster
Pilot Study of TBI vs Controls

In 36 TBI subjects vs matched controls (n=72), cortical thickness was decreased (thinning), after regressing out the effects of age and sex, in several areas:

- anterior and posterior cingulate cortex
- superior and orbital frontal cortex
- medial and parahippocampal gyrus

p < 0.01

Identified TBI+ Subjects in ADNI

<table>
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<tr>
<th>“Patient”</th>
<th>TBI+ Subjects</th>
<th>TBI+ %</th>
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<tbody>
<tr>
<td>CN = 755</td>
<td>CN = 20</td>
<td>CN = 20/755 = 2.7</td>
</tr>
<tr>
<td>SMC = 115</td>
<td>SMC = 7</td>
<td>SMC = 7/115 = 6.1</td>
</tr>
<tr>
<td>MCI = 565</td>
<td>MCI = NR</td>
<td>MCI = NR</td>
</tr>
<tr>
<td>EMCI = 340</td>
<td>EMCI = 20</td>
<td>EMCI = 20 = 20/340 = 5.9</td>
</tr>
<tr>
<td>LMCI = 184</td>
<td>LMCI = 27</td>
<td>LMCI = 27 = 27/184 = 14.7</td>
</tr>
<tr>
<td>AD = 412</td>
<td>AD = 11</td>
<td>AD = 11 = 11/412 = 2.7</td>
</tr>
<tr>
<td>Total = 2394</td>
<td>Total = 85</td>
<td>Total = 85/2394 = 3.6%</td>
</tr>
</tbody>
</table>
Hypotheses about AD and TBI

- Clinical phenomena relate to brain changes
- TBI and AD progress and influence each other
- TBI may lead to biomarkers that relate to brain damage
- Biomarkers overlap and reveal disease mechanisms
- TBI damages the brain and its connections
- Brain changes relate to both clinical findings and biomarkers
- Genetics, sex, education, and other factors need to be considered

Main Hypotheses and Rationale

- Biomarkers unique to TBI+ subjects relate to the mechanisms through which TBI increases AD risk
- Correlations between many known risks can be used to strengthen analytic approaches to identify unknown or subtle risk factors for TBI-associated AD risk
- Focusing on DTI imaging for this analysis will help to isolate structural pathology closely related to TBI (WM)
- Some TBI-AD risk biomarkers may be measurable in biospecimens such as blood, CSF or urine (exosomes)
Steps taken thus far

- Wrote scripts to collect subgroups:
  - NC-TBI-, NC-TBI+, SMC-TBI-, SMC-TBI+, EMCI-TBI-, EMCI-TBI+, LMCI-TBI-, LMCI-TBI+, AD-TBI- and AD-TBI+
- Installed analysis software and data on Clemson University’s supercomputer (Palmetto Cluster)
- Initiated Structural and DTI analysis with collaborative team

Next Steps

1. Single subjects over time
2. Groups over time
3. Between groups snapshot (cross-sectional)
4. Between groups long-term (longitudinal)
5. Correlational/exploratory
6. Modeling/machine learning
7. Validation in other studies
8. Validation in biospecimens
Acknowledgements

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Thank you!
Questions/Suggestions