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Disclosures of Interest

Research Support
1. ADRC Pilot (2012)
2. R01AG043434
3. R01AG043434-03S1
4. University Research Strategic Alliance (URSA) # 2016-02
5. P50AG005681
6. P01AG003991
7. P01AG026276
8. Fred Simmons and Olga Mohan
9. The Farrell Family Research Fund
10. The Charles and Joanne Knight Alzheimer’s Research Initiative
11. Alzheimer’s Association Research Fellowship to Promote Diversity (Babulal)

Speakers Bureau
N/A

Clinical Trials
N/A

Consultant
N/A

I own no stocks or equity in any pharmaceutical company.
Preclinical AD and driving

- Symptomatic AD ↑ risk poor driving
- ~30% in U.S. aged 65y+ have preclinical AD: normal cognition & biomarker evidence\(^1,2\)

\(^1\)Morris et al., 2010.
\(^2\)Jansen et al., 2015.
Literature suggesting preclinical AD may influence driving

- **Autopsy studies**
  - 50% and 72% of drivers aged 65-75y and 75y+, respectively, had neuritic plaques\(^1\)
  - Among older drivers who died in car accidents, 47%-53% (depending on cutpoint used) had neuritic plaque scores indicating/suggesting histologic AD.\(^2\)
  - 57% drivers who died in an accident had sparse neuritic plaque pathology vs. 25% of controls who died of other causes.\(^3\)

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Is preclinical AD a risk factor for impaired driving?

- Enroll 180 participants with normal cognition from Knight ADRC
  - 65+ years old
  - Had/willing amyloid imaging and/or LP to obtain biomarkers
  - Valid driver’s license
  - Drive at least one time per week
- Follow 2y-4y

<table>
<thead>
<tr>
<th>Assessed for:</th>
<th>Baseline</th>
<th>Yearly FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid imaging</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture (CSF)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ADRC Clinical &amp; psychometric tests</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>On-road driving test</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Office testing: Driving, cognitive reserve, mood, navigation, etc. questionnaires</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Biomarker measures of preclinical AD

- Lumbar puncture for CSF
  - Abnormal levels of soluble amyloid (plaques) and tau (tangles)\(^1\)
- Amyloid imaging
  - Presence fibrillar plaques
  - Pittsburgh Compound B (PIB)\(^1,2\)
  - Positron Emission Tomography (PET) scans

\(^1\)Vlassenko et al., 2016.
Driving outcomes: Driving Habits Questionnaire (DHQ)\textsuperscript{1}

- Measures driving space and self-regulation of driving over the past year.
- Self-report
- Subscales
  - Driving space
  - Miles driven
  - # places visited
  - # trips

Driving outcomes: Modified Washington University Road Test\textsuperscript{1}

- **Standardized**
  - 60 minutes, in-traffic, ~13 miles
  - Mid-sized sedan, dual brakes

- **Outcomes**
  - # of errors
  - Pass/Marginal/Fail rating

(1) Cross-sectional associations of preclinical AD and driving

Baseline data on N=129 with processed biomarker results

<table>
<thead>
<tr>
<th>Table 1. Demographics (N=129)</th>
<th>N/Mean</th>
<th>%/SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at driving assessment, y</td>
<td>72.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Women</td>
<td>69</td>
<td>53.5%</td>
</tr>
<tr>
<td>Minority race</td>
<td>12</td>
<td>9.3%</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.1</td>
<td>2.6</td>
</tr>
<tr>
<td>APOE4+</td>
<td>38</td>
<td>29.5%</td>
</tr>
<tr>
<td>Clinical Dementia Rating = 0</td>
<td>129</td>
<td>100%</td>
</tr>
<tr>
<td>Mini-Mental State Exam score*</td>
<td>29.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Cross-sectional analyses: General linear models

- **Independent variables of interest**
  - Mean Cortical Binding Potential [MCBP] for Pittsburgh Compound B [PIB]
  - CSF Aβ42, tau, ptau181, tau/Aβ42, ptau181/Aβ42

- **Dependent variables**
  - Driving: total # of errors on road test, DHQ subscale scores
  - Cognition: psychometric composite score: results from 10 tests

- **Biomarkers treated as dichotomous**
  - ↓tertile for Aβ42, ↑tertile for others

- **Adjusted for age, education, gender, race, APOE4, driving evaluator**

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Cross-sectional results

- No assoc of biomarkers with DHQ (p>.15)
  - miles driven
  - # trips
  - # places
  - driving space

- No assoc of biomarkers with Ψometric composite (p=.68)
Conclusions

- Taken together
  - Preclinical AD may be linked to subtle systemic changes (e.g., cognitive, visual, spatial, motor function, etc.)
  - When considered alone, may go unnoticed
  - When combined, these cognitive and functional changes may impact complex behaviors such as driving
(2) Longitudinal associations of preclinical AD and driving¹

- Predicting who most risk of decline in driving abilities and when
  - Allow intervention before/at the time early decline prevent crashes, injuries, and deaths
  - Preservation of safe driving ability would also prolong the independence and enhance the well-being of elders

Driving as potential outcome in clinical trials

- Trials to prevent or slow the AD pathologic process with CN persons at high risk (genetics, biomarkers)$^{1-3}$
  - Measures of very early functional change in preclinical AD are needed for these trials$^4$
  - These measures must be relevant to the disease process as well as clinically meaningful$^5$

Can AD biomarkers predict onset of driving problems among CN adults?

- Drawn from N=129 in cross-sectional
  - Similar demographics
- One or more driving tests post baseline test (N=104)
- IVs: based on cross-sectional results
  - MCBP for PIB, CSF tau/Aβ_{42}, and CSF ptau_{181}/Aβ_{42}
Outcomes

Driving decline outcomes
- Time from baseline to receiving a rating of marginal or fail on the road test
- Self-reported decline over time on everyday driving behaviors assessed using the DHQ

Cognitive outcomes
- CDR Sum of Boxes – slope & time to 1pt ↑
- MMSE – slope & time to 2pt ↓
- Psychometric composite - slope
Time to Marginal/Fail driving rating, \textbf{CSF tau/A}^{\beta_{42}}

\[
HR (95\% CI) = 5.75 (1.70-19.53), \quad p=.005
\]

---------- Lower

-------- Higher
Time to Marginal/Fail driving rating, CSF ptau$_{181}$/Aβ$_{42}$

HR (95% CI) = 6.19 (1.75-21.88), p=.005

--- Lower

-------- Higher
Time to Marginal/Fail driving rating, MCBP for PIB

HR (95% CI) = 2.65 (.73-9.00), p=.12

--- Lower
--------- Higher
Other outcomes

- Self-reported driving (DHQ): no biomarker-linked change in miles driven, number of trips, number places visited, driving space (p>.60)

- Cognition: no association of biomarkers with changes in CDR Sum of Boxes, MMSE, and psychometric composite (p>.53)
Conclusions

- Although driving test performance problems occurred faster for those with preclinical AD, didn’t change their everyday driving behavior over same time period
  - Did not notice any change in driving skills
  - Did notice change, but did not believe warranted modification of everyday driving behavior
  - Effects of preclinical AD on driving may occur under controlled conditions of driving test, not in everyday driving
(3) New direction: To objectively measure everyday driving behavior\textsuperscript{1-3}

- As people travel in their own vehicles
- In their own environments
- Continuously over time
- Cost effective
- Minimally invasive (i.e., no vehicle modification)

Fleet Management Industry

- FedEx, Coca Cola, etc.
- Our participants make up our “fleet” (N=35 now)
Naturalistic driving: DRIVES chip workflow

Driving Real-world In-Vehicle Evaluation System
Breadcrumbs

Variables (some)

- Latitude and longitude
- Time
- # trips
- # miles
- # unique destinations
- Speeding
- Hard braking
- Sudden acceleration
- Minor or major impact as detected by accelerometer
Driving Area
Combining DRIVES chip data with other databases

- Sunrise/sunset
- US Census
  - Rural vs. urban
  - Median income
- National Weather Service
  - Precipitation
  - Snow
Acknowledgements

Preclinical AD and Driving Study
- David Carr
- Becky Fierberg
- Brad Garland
- Nupur Ghoshal
- Denise Head
- Annie Johnson
- Brian Ott
- Tammie Benzinger
- Anne Fagan
- Scot Fague
- John Morris
- Chengjie Xiong
- Dave Warren

ADRC and Neurology
- Beau Ances
- Betsy Grant
- David Holtzman
- Shruti Mishra
- Sushi Sathyan

Data/GIS Services
- Aaron Addison
- Mark Sellan
- Cindy Traub
- Mollie Webb

Former Team Members
- Peggy Barco
- Nate Lucena
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- Elizabeth Vernon