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Tau and Amyloid Positron Emission Tomography Imaging Predict Driving Performance Among Older Adults with and without Preclinical Alzheimer's Disease

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Abstract

Abnormal levels of Alzheimer's disease (AD) biomarkers, measured by positron emission tomography imaging using amyloid-based radiotracers and cerebrospinal fluid, are associated with impaired driving performance in older adults. We examined whether preclinical AD staging, defined using amyloid imaging and tau imaging using the radiotracer T807 (AKA flortaucipir or AV-1451), was associated with receiving a marginal/fail rating on a standardized road test ($n = 42$). Participants at Stage 2 (positive amyloid and tau scans) of preclinical AD were more likely to receive a marginal/fail rating compared to participants at Stage 0 or 1. Stage 2 preclinical AD may manifest in worse driving performance.

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Keywords

Alzheimer's disease; amyloid; driving performance; imaging; noncognitive outcomes; tau

INTRODUCTION

The population of older adults will continue to grow, resulting in a projected estimate of 69 million licensed drivers aged 65 years and older by 2050 [1, 2]. Recent studies of older drivers indicate an increase in annual average miles driven, along with an associated higher number of crashes, injuries, and deaths and annual lifetime costs estimated at $80 billion [3, 4]. Compared to older drivers generally, those with symptomatic Alzheimer's disease (AD) have an increased risk of injury and mortality from crashes [4]. Autopsy studies suggested that driving impairment may be associated with the long preclinical stage preceding symptomatic AD [5].

Development of molecular biomarkers has allowed for *in vivo* detection of plaques and tangles, both hallmarks of symptomatic AD. These AD biomarkers include imaging of fibrillar amyloid using positron emission tomography (PET) with radiotracers such as Pittsburgh compound B (PiB) or florbetapir [^{18}F-AV-45] [6–9]. Our prior studies have shown that cognitively normal older adult drivers with more abnormal molecular AD biomarkers (cerebrospinal fluid (CSF) and amyloid imaging) make more errors on a standardized road test, report a greater history of traffic violations and crashes, and are more likely to fail a road test over time, compared to those with normal biomarker levels [10–12]. These observations suggest that preclinical AD may be sufficient to impair functional performance, and hence may not be entirely asymptomatic.

The hypothetical staging of preclinical AD using biomarkers suggests several stages, including Stage 0 which presents with no abnormal biomarkers, Stage 1 which presents with amyloid+ (PET or CSF) and Stage 2 which presents with amyloid and neuronal injury (CSF tau or phosphorylated tau) [13, 14]. The recent development of tau radiotracers, such as T807 (also known as ^{18}F-AV-1451 or flortaucipir), has enabled *in vivo* imaging of tau topography [15, 16]. Studies using Tau-PET imaging have examined differences between symptomatic AD and cognitively normal adults, correlations between CSF tau and tau PET, and preclinical AD staging and cognitive performance [17–22]. Additionally, tau pathology is more strongly related to concurrent cognition than amyloid-β [23]. To our knowledge, no study has used Tau-PET imaging to examine functional outcomes like driving. We examined whether preclinical AD Stages 0–2 are associated with driving performance among cognitively normal older adults.

METHODS

Design

Data from participants with normal cognition (Clinical Dementia Rating (CDR) [24] = 0), 65 years or older, with a valid driver's license, who drove at least once per week, had both tau PET and amyloid PET imaging, and who met criteria for pre-clinical AD Stages 0, 1,

and 2 were used. These participants were a subsample of individuals participating in a larger study on preclinical AD and driving, and were recruited from the pool of individuals already participating in longitudinal studies at the Knight Alzheimer's Disease Research Center. Participants also completed clinical and neuropsychological testing, and a standardized on-road test. The Washington University Human Research Protection Office approved study protocols along with written informed consents from participants.

Clinical assessment

A CDR score was derived by experienced clinicians who synthesize information obtained from interviews with the participant and a collateral source who is well acquainted with the participant [24]. CDRs are derived in accordance with a standard scoring algorithm; CDR 0 = no dementia, CDR 0.5 = very mild, CDR 1 = mild, CDR 2 = moderate, and CDR 3 = severe dementia.

Road test

The 12-mile, modified Washington University Road Test, takes approximately one hour to complete. Participants begin the course in a closed parking lot and progress into traffic routes which includes unprotected left hand turns, complex intersections and lane merges [25]. The examiner sits in the front seat and gives verbal directions to the participant while scoring their performance. A global rating of pass (no problems/errors), marginal (some errors and safety concerns), or fail (numerous errors and high safety risk) is derived at the end of the road test.

Biomarker measurement

Data were processed using a region of interest approach using FreeSurfer segmentations (http://freesurfer.net/) of magnetization-prepared rapid gradient-echo (MPRAGE) images [26]. Amyloid imaging data were obtained on a Biograph mMR scanner (Siemens Medical Solutions, Erlangen, Germany) [18]. Participants received a single intravenous injection of 7.4–11.3 mCi of florbetapir (F-AV-45) [19]. Data from the 50–70-min post IV window were converted to standardized uptake value ratios (SUVRs) using the cerebellar cortex as a reference [17, 18]. A summary measure of amyloid deposition was obtained by taking the mean from regions known to have high uptake among AD participants (pre-frontal cortex, gyrus rectus, lateral temporal cortex, and precuneus) [26]. Partial volume correction was also performed using a regional spread function technique [27]. Tau imaging data were obtained in a separate session on a Biograph 40 PET/CT scanner. Participants received a single IV injection of 7.2–10.7 mCi of flortaucipir (F-AV-1451). Data from the 80–100-min post injection window were converted to SUVRs using the cerebellar cortex as a reference and underwent partial volume correction [17, 18]. A summary measure of tau was created by averaging four regions (amygdala, entorhinal cortex, inferior temporal, and lateral occipital cortex) [28]. Established cutoffs were used for both tau (1.230) and amyloid (1.219) imaging SUVRs indicating positive versus negative [26, 28].

Statistical analyses

Driving test performance yields a global rating of pass, marginal, or fail. Since a fail rating is relatively rare in a cognitively normal sample (all CDR = 0) and marginal ratings do identify concerning driving behaviors, the overall rating was dichotomized into pass versus marginal/fail [10]. Based on the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria, a three-level biomarker variable was constructed based on Stages 0–2 [29]. Chi-square analysis examined the unadjusted association between driving performance and the three-level variable. Given the results of the three-level analysis, a dichotomous variable was also created to compare driving performance for persons with Stage 2 preclinical AD to those with Stages 0 and 1 combined. Logistic regression was then used to test the association of driving rating and the dichotomous variable while controlling for age. Secondary analyses examined differences in memory scores between participants who received a pass and marginal/fail rating using the free-recall portion of the Free and Cued Selective Reminding Test [30], Verbal Fluency (animal naming task) [31] and Trail Making Test (tasks A and B) [32], while adjusting for age. For each of the four psychometric tests, longitudinal data (when available) were used to calculate a slope of change score reflecting annualized change in psychometric test performance in the years prior to the driving test. General linear models examined whether slope of change across time, while adjusting for age, on each test differed for participants who received a pass and marginal/fail rating. Data were analyzed using SPSS Statistics version 24 (IBM Corp., Armonk, NY).

RESULTS

Data were available from 42 participants with ages ranging from 65 to 90 years (Table 1). Across the three groups, there were only five participants who received a marginal/fail rating (11.9%): – Stage 0 = 1/21; Stage 1 = 0/9; Stage 2 = 4/12 ($\chi^2 = 7.49$, df = 2, $p = 0.02$). Because of this, the major analyses examined differences between the Stage 2 (4/12, 33.3%) and Stages 0 and 1 combined (1/30, 3.3%; $\chi^2 = 7.36$, df = 1, $p = 0.007$). In the logistic regression analysis, participants classified as Stage 2 were more likely (OR: 11.4; CI: 1.03–125.8; $p = 0.047$) to receive a marginal/fail rating on a road test compared to participants classified as Stage 0 or 1. Age was not a statistically significant predictor in this model. In secondary analyses, there were no cross-sectional differences in neuropsychological performance on the Free and Cued Selective Reminding Test (F: 1.92; $p = 0.174$), Animal Fluency (F: 0.87; $p = 0.359$), or Trail Making A (F: 2.76; $p = 0.106$) and B (F: 1.30; $p = 0.265$) between participants who received a pass and marginal/fail rating. Similarly, there were no statistically significant group differences in slopes of change on Free and Cued Selective Reminding Test (F: 0.10; $p = 0.758$), Animal Fluency (F: 0.26; $p = 0.616$) or Trail Making A (F: 0.48; $p = 0.827$) and B (F: 0.94; $p = 0.341$). Age was not a statistically significant predictor in any of these models.

DISCUSSION

High levels of both tau and amyloid as ascertained via PET imaging were able to predict driving performance in a sample of cognitively normal older adults. Prior work suggests that higher stages (2 and 3) of preclinical AD are associated with greater cognitive decline and

mortality [33]. We found that participants classified at Stage 2 (positive tau and amyloid scans) were 11 times more likely to receive a marginal/fail rating on a road test compared to those at Stage 0 and 1, although the confidence interval for this point estimate was wide. Similar to cognitive testing, driving is complex activity that is dynamic and requires multisystem engagement. In this small sample, the combination of tau-PET and amyloid-PET positivity was associated with higher driving risk as reflected on a road test, supporting the hypothesis that preclinical AD is not benign. When we examined performance on four neuropsychological tests, we found no differences between participants who received a marginal/fail rating and a pass rating. This suggests that decline in driving performance likely precedes other psychometric measures of objective decline in cognitive performance. This finding is consistent with our prior work in cognitively normal older adults and driving performance [10].

There are some limitations to our study. Participants were well educated, predominately Caucasian, willing to undergo PET imaging and thus may not be representative of the larger population. Results obtained from the standardized road test may not generalize to day-to-day driving. Research using naturalistic methodologies [34–36] that collect data on a daily basis from a participant's vehicle in the actual environment they drive may be more sensitive in detecting difficulties in driving behavior. Given the small sample, these analyses should be interpreted as preliminary findings. Despite these limitations, our results suggest that Stage 2 preclinical AD may interfere with driving skills, and that tau-PET imaging can help to predict driving difficulties in participants with and without preclinical AD.

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Table 1

Baseline demographics (n = 42)*

Age, y	**72.4 ± 5.7**
Education, y	16.9 ± 2.2
Women, n	15 (35.7%)
Race, Caucasian, n	39 (92.9%)
APOE4+, n	11 (26.2%)
Interval between tau and amyloid imaging, d	3.6 ± 2.7
Interval between tau imaging and clinical assessment, d	3.0 ± 2.1
Interval between tau imaging and driving assessment, d	90 ± 197.6
PET Imaging	
Florbetapir SUVR	1.4 ± 0.7
Flortaucipir SUVR	1.2 ± 0.2
Amyloid (+)	21 (44.7%)
Tau (+)	12 (28.6%)
Imaging Groups	
Preclinical Stage 0: – amyloid – tau	21 (44.7%)
Preclinical Stage 1: +amyloid – tau	9 (19.1%)
Preclinical Stage 2: +amyloid + tau	12 (25.5%)
MMSE	29.3 ± 1.02
Road Test Rating (Pass)	37 (88.1%)

APOE, apolipoprotein ε; PET, positron emission tomography; SUVR, standardized uptake value ratio; MMSE, Mini-Mental State Examination.

*Mean or number ± SD or percentage.