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Amyloid Imaging, Cerebrospinal Fluid Biomarkers Predict Driving Performance among Cognitively Normal Individuals

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Introduction

Seventeen percent (36.8 million) of licensed United States (U.S.) drivers are aged 65 years and above, and the number of older adults in the U.S. is expected to double within the next 40 years. It is well known that people with symptomatic Alzheimer disease (AD) are at increased risk for impaired driving and motor vehicle accidents; therefore, it is expected that the number of drivers with AD will rise dramatically. Moreover, driving skills decline with advancing age even among cognitively normal individuals.^{1,2}

There is a long preclinical stage of AD, during which AD neuropathology is present without detectable cognitive or functional impairment. Preclinical AD may have subtle cognitive and functional effects, which could combine to impair complex behaviors such as driving. Consistent with this idea, postmortem studies of the brains of older drivers who were killed in car accidents found that many had underlying AD neuropathological changes.³

Cerebral cortical plaques and tangles are the signature lesions of AD. *In vivo* imaging of fibrillar amyloid plaques can be obtained using positron emission tomography (PET) with amyloid tracers such as Pittsburgh Compound B (PIB). Cerebrospinal fluid (CSF) biomarkers are based on assays of proteins that are integral to the pathological hallmarks of AD, including soluble levels of brain beta-amyloid ($A\beta_{42}$); and tau and phosphorylated tau (ptau₁₈₁), the principal components of neurofibrillary tangles. We examined whether these biomarkers are related to driving performance among cognitively normal older adults.

Methods

Design

Participants with normal cognition (Clinical Dementia Rating [CDR] = 0),⁴ aged 65 years and older, a valid driver's license, and who were driving at least once per week, were recruited for this study from the pool of individuals already participating in longitudinal studies at the Knight Alzheimer's Disease Research Center (ADRC). Participants took part in clinical and psychometric assessments, a performance-based driving test, and completed PET PIB and/or CSF collection. The study was approved by the Washington University Human Research Protection Office, and written informed consent was obtained from all participants.

Clinical assessments

A CDR is derived by experienced clinicians who synthesize information obtained from interviews with the participant and separately with a collateral source who knows the

participant well. The clinician's judgment about the presence of dementia is based on the principle of intra-individual change where the individual is used as his or her own control.⁴ The clinical assessment battery also includes the Mini-Mental State Examination.⁵

Measurement of AD biomarkers

Imaging—PET-PIB imaging was used to determine brain amyloid burden. Detailed information on our PET-PIB methodology is available.⁶ The Freesurfer image analysis suite (version 5.3) was used to obtain estimates of total brain volume and intracranial volume.

CSF biomarkers—We measured CSF analytes ($A\beta_{42}$, tau and ptau₁₈₁) using sensitive and quantitative enzyme-linked immunosorbent assays (INNOTEST, Fujirebio [formerly Innogenetics], Ghent, Belgium). CSF levels of $A\beta_{42}$ have consistently been reported to be reduced in AD, whereas levels of tau and ptau₁₈₁ (and the ratios of tau/ $A\beta_{42}$ and ptau₁₈₁/ $A\beta_{42}$) are elevated.⁷ CSF was obtained by neurologists via standard lumbar puncture using a 22-gauge Sprotte spinal needle to draw 20–30 mL of CSF at 8:00 AM following an overnight fast. CSF samples were gently inverted and centrifuged at low speed to avoid possible gradient effects and frozen at -84°C after aliquoting into polypropylene tubes. All biomarker assays included a common reference standard, within-plate sample randomization and strict standardized protocol adherence. Samples were re-analyzed if coefficients of variability (CV) exceed 25% or if the pooled common CSF sample yielded widely discrepant values.

APOE genotyping—Briefly, all DNA samples underwent stringent quality control before genotyping with the Illumina 610 or the Omniexpress chip.⁸ Detailed information regarding *APOE* genotyping has been published.⁸

Driving test

The 12-mile, modified Washington University Road Test (mWURT), takes about an hour to complete and the Record of Driving Errors⁹ was used to obtain the total number of driving errors made during the test. The course begins in a closed parking lot so that the participant becomes familiar with the study car, a 4-door sedan, then proceeds to a community in-traffic route which includes unprotected left hand turns, in addition to complex intersections and merges.⁹ Following directions delivered by an occupational therapy/driving rehabilitation specialist (OTR/DRS) sitting in the front seat, the participant drives through the entire mWURT route. The front-seat OTR/DRS can take control of the wheel if needed, and can apply a second, passenger-side brake if necessary.

Statistical analyses

General linear models (adjusted for age, education, gender, race, *APOE4*, error rater) were used to test whether the number of driving errors differed as a function of each of the biomarker variables (MCBP for PIB, and CSF $A\beta_{42}$, tau, ptau₁₈₁, tau/ $A\beta_{42}$, ptau₁₈₁/ $A\beta_{42}$). Due to concerns with variability among CSF assay performance and no consensus on specific biomarker levels that characterize AD, we did not use a predetermined cutoff value for dichotomization. Rather, we examined the frequency distributions of each biomarker variable, and divided each distribution into tertiles. Lower values of $A\beta_{42}$, and higher values of all other biomarkers studied here, are associated with preclinical AD. In the statistical

analyses, therefore, we compared the lowest tertile for $A\beta_{42}$, and highest tertile for the other biomarker variables, to the remaining tertiles combined. We also used an adjusted general linear model to examine whether a psychometric composite score comprised of results from 10 psychometric tests¹⁰ was associated with number of driving errors. The composite score was dichotomized such that scores in the highest tertile were considered “better performance” compared to the remaining scores.

Results

Individuals aged 64.9 years to 88.2 years (N=129) met inclusion criteria and had processed amyloid brain imaging (N=113) and/or CSF biomarker (N=123) data available for analyses (Table 1). Higher ratios of CSF tau/ $A\beta_{42}$ and ptau₁₈₁/ $A\beta_{42}$, in addition to PIB MCBP, were associated with increased numbers of driving errors (Table 2). Lower levels of CSF $A\beta_{42}$ were also associated with increases in the number of driving errors, but this did not reach statistical significance ($p=0.06$). The psychometric composite score was also not associated with number of driving errors ($p=.68$).

Discussion

AD biomarker patterns consistent with the presence of underlying AD pathology were associated with an increased number of errors on a road test among cognitively normal older adults, indicating that in addition to cognitive outcomes, AD biomarkers can predict functional outcomes. However, a composite score reflecting psychometric functioning was unassociated with number of driving errors. Together, these results suggest that preclinical AD may have subtle cognitive and functional effects, which alone may go unnoticed. However, when combined, these cognitive and functional changes may impact complex behaviors such as driving.

As with the prediction of cognitive outcomes,⁷ we found that CSF biomarkers that combine elements of amyloid and tau are better predictors of on-road driving behavior than biomarkers reflecting either component alone.

Because new diagnostic guidelines advocate the use of biomarkers to help identify both mild cognitive impairment due to AD and AD dementia, and are under investigation for clinical use to identify preclinical AD, biomarkers may soon be used routinely in the clinical setting to make diagnostic decisions. Further, multiple clinical trials are now underway to evaluate new drugs designed to prevent, stop, or slow the AD pathologic process. Current AD therapies administered during the symptomatic stage may only slightly improve clinical symptoms and their progression, leading researchers to conclude that interventions must start earlier in the pathologic process, among individuals who are still asymptomatic. Consequently, identifying sensitive tools to measure cognitive and functional changes in the early stages is an urgent priority. Although some have cautioned that it may not be feasible to assess functional impairment at the earliest stages of the disease, the present results suggest that on-the-road driving tests, or driving simulation, may eventually provide such a measure.

Our study has limitations. We used a one-hour road test to assess driving performance, which may be an inadequate time to capture significant driving errors. Additionally, a driving simulation test might provide more detailed information on the types and importance of driving errors and could be repeated in other settings and with other samples. Further, it is unclear the extent to which road tests reflect day-to-day driving in the participant's own environment. Future research should examine associations between AD biomarker levels among cognitively normal participants and day-to-day driving in the participant's own environment.

Despite these limitations, our results suggest that even among cognitively normal individuals, abnormal levels of AD biomarkers can be used to predict performance in driving, a task which involves multiple complex functional and cognitive processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Ducheck JM, Carr DB, Hunt L, et al. Longitudinal driving performance in early-stage dementia of the Alzheimer type. *J Am Geriatr Soc.* 2003; 51:1342–1347. [PubMed: 14511152]
2. Ott BR, Heindel WC, Papandonatos GD, et al. A longitudinal study of drivers with Alzheimer disease. *Neurology.* 2008; 70:1171–1178. [PubMed: 18216302]
3. Gorrie CA, Rodriguez M, Sachdev P, Duflou J, Waite PM. Mild neuritic changes are increased in the brains of fatally injured older motor vehicle drivers. *Accid Anal Prev.* 2007; 39:1114–1120. [PubMed: 17920833]
4. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993; 43:2412–2414.
5. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res Nov.* 1975; 12:189–198.
6. Mintun MA, Larossa GN, Sheline YI, et al. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology.* 2006; 67:446–452. [PubMed: 16894106]
7. Blennow K, Zetterberg H, Fagan AM. Fluid biomarkers in Alzheimer disease. *Cold Spring Harb Perspect Med.* 2012 Sep 1.2(9):a006221.doi: 10.1101/cshperspect.a006221 [PubMed: 22951438]
8. Cruchaga C, Kauwe JS, Nowotny P, et al. Cerebrospinal fluid APOE levels: An endophenotype for genetic studies for Alzheimer's disease. *Human Molecular Genetics.* 2012; 21:4558–4571. [PubMed: 22821396]
9. Barco PP, Baum CM, Ott BR, Ice S, Johnson A, Wallendorf M, Carr DB. Driving errors in persons with dementia. *J Am Geriatr Soc.* 2015; 63:1373–1380. [PubMed: 26140521]
10. Obermann KR, Morris JC, Roe CM. Exploration of 100 commonly used drugs and supplements on cognition in older adults. *Alzheimers Dement.* 2013; 9:724–732. [PubMed: 23954027]

Demographics (N=129)**Table 1**

Age at driving assessment, mean (SD), y	72.9 (4.9)
Women, No. (%)	69 (53.5)
African American, * No. (%)	12 (9.3)
Education, mean (SD), y	16.1 (2.59)
<i>APOE4</i> +, No.(%)	38 (29.5)
MMSE, mean (SD) [†]	29.4 (0.9)
Time from clinical assessment to driving assessment, mean (SD), y	0.35 (0.19)
Time from CSF collection to driving assessment, mean (SD), y	0.50 (0.57)
Time from amyloid imaging to driving assessment, mean (SD), y	0.39 (0.49)

Abbreviations: *APOE4*=apolipoprotein E ε4; CSF=cerebrospinal fluid, MMSE, Mini-Mental State Examination

* All remaining participants reported their race as Caucasian

[†] MMSE scores range from 0 (worst performance) to 30 (best performance)

Table 2
Total number of errors on the road test for persons with lower and higher Alzheimer disease biomarker values.*

	Least-Square Means [†] for Biomarker Groups (95% CI)		P-value
	Lower	Higher	
MCBP for PIB	7.1 (5.6-8.6)	9.5 (7.8-11.2)	0.007
CSF A β ₄₂	8.7 (7.1-10.3)	7.1 (5.7-8.6)	0.06
CSF tau	7.6 (6.2-9.0)	8.2 (6.6-9.9)	0.43
CSF ptau ₁₈₁	7.5 (6.2-8.9)	8.4 (6.7-10.1)	0.28
CSF tau/A β ₄₂	6.9 (5.6-8.3)	9.4 (7.8-11.0)	0.002
CSF ptau ₁₈₁ /A β ₄₂	7.0 (5.6-8.4)	9.1 (7.5-10.8)	0.01

Abbreviations: A β ₄₂, amyloid- β ₁₋₄₂; MCBP=mean cortical binding potential; PIB=Pittsburgh Compound B; CSF=cerebrospinal fluid.

* Values were dichotomized by tertiles, lower tertile vs. upper two tertiles for CSF A β ₄₂ and upper tertile vs. lower two tertiles for PIB MCBP and the tau-related biomarkers. Lower values of A β ₄₂, and higher values of all other biomarkers, are associated with preclinical AD.

[†] Analyses adjusted for age, gender, race, education, *APOE4* status, and driving error rate.