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Brain amyloid in preclinical Alzheimer's disease is associated with increased driving risk

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Abstract

Introduction: Postmortem studies suggest that fibrillar brain amyloid places people at higher risk for hazardous driving in the preclinical stage of Alzheimer's disease (AD).

Methods: We administered driving questionnaires to 104 older drivers (19 AD, 24 mild cognitive impairment, and 61 cognitive normal) who had a recent ^{18}F-florbetapir positron emission tomography scan. We examined associations of amyloid standardized uptake value ratios with driving behaviors: traffic violations or accidents in the past 3 years.

Results: The frequency of violations or accidents was curvilinear with respect to standardized uptake value ratios, peaking around a value of 1.1 (model $r^2 = 0.10$, $P = .002$); moreover, this relationship was evident for the cognitively normal participants.

Discussion: We found that driving risk is strongly related to accumulating amyloid on positron emission tomography, and that this trend is evident in the preclinical stage of AD. Brain amyloid burden may in part explain the increased crash risk reported in older adults.

Keywords: Alzheimer's disease; Cognitive aging; Assessment of cognitive disorders/dementia MCI (mild cognitive impairment)

1. Introduction

Postmortem studies of the brains of older drivers who were killed in motor vehicle accidents (MVAs) have found that many had the neuropathologic changes of Alzheimer's disease (AD), although they may have never been diagnosed to have the disease [1–4]. Since then, advances in biomarker technology have fostered new research criteria for the "preclinical" stage of AD [5] preceding the intermediate stage of mild cognitive impairment (MCI) or "prodromal" AD [6], during which time amyloid pathology may be present before any noticeable symptoms of cognitive or functional impairments exist. These criteria are leading to an increasing body of knowledge about the very earliest signs and symptoms of AD as well as an impetus to identify sensitive clinical markers of underlying AD pathology such as amyloid plaque deposition.

Abnormal levels of AD biomarkers using the Pittsburgh compound amyloid positron emission tomography (PET) ligand were recently reported to predict performance on a standardized road test by cognitively normal older individuals, raising concern that amyloid deposition during the preclinical phase of AD could indicate an increased risk for

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hazardous driving [7]. Therefore, we examined whether the presence of increased amyloid on PET places an older person at risk for unsafe driving as evidenced by actual traffic violations or MVAs in the preclinical and the symptomatic stages of the disease. Because recent models of AD pathophysiology suggest that amyloid pathology rises during the preclinical stage and then plateaus in the symptomatic stage [8], we hypothesized that this relationship, if it exists, may be more evident in preclinical disease than in AD or MCI.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

The institutional review board of Rhode Island Hospital approved the research protocol, and all participants or their legally authorized representative provided informed consent to participate.

2.2. Study design and participants

We selected a convenience sample of people attending an outpatient memory clinic and included 19 AD, 24 MCI, and 61 cognitively normal elders. Inclusion criteria included attendance to the memory clinic and amyloid PET done as part of other observational or clinical trial research studies within the past 6 months. Clinical diagnoses of AD [9] and MCI [6] were made by a neurologist based on research criteria of the National Institute on Aging and the Alzheimer's Association. Cognitively normal elders all had a Clinical Dementia Rating [10] of 0 (see Table 1). The age range for participants was 51 to 85 years, standardized uptake value ratio (SUVR) range was 0.7 to 1.8, driving avoidance range of ratings was 1 to 5, and the number of miles driven per week range was 5 to 600.

2.3. Driving behavior

We administered a driving questionnaire, developed by the American Academy of Neurology as part of its most recent practice parameter on driving and dementia [11]. Questionnaire versions are available for drivers and family informants. The questionnaire includes three initial questions: (1) "How many times have you been stopped or ticketed for a traffic violation in the last three years?" (2) "How many accidents have you been in, or caused, within the last three years?" and (3) "In how many accidents were you at fault in the last three years?" The answers were circled on paper with the choices being 1, 2, 3, or 4 or more. We defined a positive response to *any violation or accident in the past 3 years* from the participant or their family informant as our primary outcome measure (see Table 2). Ten additional questions were about current driving behaviors that were generally regarded as risk factors for MVAs. These were anchored by a 5-point Likert scale ranging from "strongly disagree" to "strongly agree." We defined a *driving avoidance* outcome variable as the mean across four of these items: limited amount of time driving, avoiding driving at night, avoiding driving in the rain, and avoiding driving in busy traffic. We used the maximum of the mean rating from driver and family informant in analytic models. Finally,

Table 1
Participant characteristics by cognitive impairment group

Characteristic	Total (N = 104)	Normal (N = 61)	MCI (N = 24)	Dementia (N = 19)
Sex [N (%)]				
Women	69 (66)	43 (71)	13 (54)	13 (68)
Men	35 (34)	18 (30)	11 (46)	6 (32)
Age [M (SD)]	67 (8)	64 (7)	72 (8)	68 (11)
SUVR [M (SD)]	1.1 (0.3)	1.0 (0.2)	1.2 (0.3)	1.3 (0.3)
SUVR class [N (%)]				
<1.1; Negative	64 (62)	49 (80)	9 (38)	6 (32)
1.1–1.2; Intermediate	5 (5)	3 (5)	1 (4)	1 (5)
>1.2; Positive	35 (34)	9 (15)	14 (58)	12 (63)
Consensus reading [N (%)]				
Negative	68 (65)	50 (82)	11 (46)	7 (37)
Positive	36 (35)	11 (18)	13 (54)	12 (63)
No violation or accident				
In past 3 years [N (%)]	70 (67)	38 (62)	17 (71)	15 (79)
Any violation or accident				
In past 3 years [N (%)]	34 (33)	23 (38)	7 (29)	4 (21)
Accident, family report	21 (20)	11 (21)	6 (26)	4 (21)
Violation, self report	17 (16)	14 (23)	2 (9)	1 (6)
Accident, self-report	17 (16)	11 (18)	4 (17)	2 (12)
Violation, family report	9 (9)	6 (11)	2 (9)	1 (5)
Driving avoidance [M (SD)]				
Self-report	1.5 (0.8)	1.4 (0.8)	1.5 (0.9)	1.7 (1.0)
Family report	1.7 (0.9)	1.4 (0.8)	1.9 (1.1)	2.3 (0.9)
Miles driven per week [M (SD)]	118 (111)	147 (119)	92 (104)	58 (49)

Abbreviations: M, mean; MCI, mild cognitive impairment; SD, standard deviation; SUVR, standard uptake value ratio.

*Mean of reports of limiting the amount of nighttime, rain, and busy traffic driving on a scale of 1 (strongly agree) to 5 (strongly disagree). Q6

Table 2
Association of standard uptake value ratio (SUVR) and driving behavior within regions of SUVR

	SUVR		Model
Driving behavior	≤1.1	>1.1	r^2
Any violation or accident	0.56*	−0.57 †	0.38
Miles driven	−0.07	0.02	0.22
Driving avoidance ratings	0.13	−0.29 †	0.20

NOTE. Table entries are standardized regression coefficients (on the scale of correlation coefficients) describing the linear relationship of driving behavior and SUVR within two regions of SUVR. The model includes adjustment for age, sex, and diagnostic group. Driving avoidance ratings refer to the maximum of self- and family-reported mean ratings on four driving avoidance patterns (amount, nighttime, rain, and busy traffic). Items are rated on a 1 to 5 scale, where higher ratings indicate greater agreement with avoidance patterns. A negative coefficient between SUVR and driving avoidance ratings implies that the *more* Alzheimer's disease–like amyloid burden, driving avoidance behaviors are *less or fewer*.

‡$P < .001$. Q7

*$P < .01$.

†$P < .05$.