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Review

Improving Our Understanding of Driving Changes in Preclinical and Early Symptomatic Alzheimer's Disease: The Role of Naturalistic Driving Studies

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Abstract. Research on how preclinical and early symptomatic Alzheimer's disease (AD) impacts driving behavior is in its infancy, with several important research areas yet to be explored. This paper identifies research gaps and suggests priorities for driving studies over the next few years among those at the earliest stages of AD. These priorities include how individual differences in demographic and biomarker measures of AD pathology, as well as differences in the in-vehicle and external driving environment, affect driving behavior. Understanding these differences is important to developing future interventions to increase driving safety among those at the earliest stages of AD.

Keywords: biomarkers, driving, early Alzheimer's disease, mild cognitive impairment, preclinical Alzheimer's disease

INTRODUCTION

The detrimental effects of symptomatic Alzheimer disease (AD) on driving are well known, with higher crash risks [1, 2] and greater morbidity and mortality [3]. Since the cause of most dementia conditions is underlying Alzheimer's disease (AD) [4], much dementia and driving research focuses on how AD, specifically, effects driving behavior. Newer assessment techniques over the past few decades have seen earlier and earlier diagnosis of symptomatic AD, including at the mild cognitive impairment [5–7] (MCI)/very mild dementia stage, allowing examination of driving at the earliest onset of clinical symptoms. These studies indicate that persons with very mild dementia show a restricted driving space, making fewer trips, traveling shorter distances, and visiting fewer unique destinations; drive slower; and are less likely to drive at night, compared to cognitively normal persons [8, 9]. Longitudinal studies indicate that having very mild dementia versus cognitive normality predicts a faster time to failing a road test in the future [10].

More recently, the advent of molecular biomarkers has enabled examination of the effect of driving in preclinical AD, when AD neuropathology is present but the individual is cognitively normal [11–13]. The

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most commonly-used biomarkers to date reflect the presence of lesions and/or abnormal protein levels characteristic of biological AD, amyloid and tau. These biomarkers can be obtained via cerebrospinal fluid (CSF), positron emission tomography (PET) imaging using specialized radiotracers, and plasma [14–18]. Preclinical AD may begin up to 20 years before AD dementia symptoms occur [19–22]. Studies indicate that persons with preclinical AD already show a pattern of driving restriction similar to, albeit to a lesser degree, those with very early AD dementia [23, 24]. Further, persons with preclinical AD also show more errors on an on-road driving test [25] and have a more rapid time to failing a road test in the future [26, 27].

Ultimately most driving research in early AD has a long-term goal of contributing to improved safety for older drivers and others on the road. Although road tests and simulators were previously considered to be the "gold standard" in assessing driving skills, the extent to which these measures represent driving as it occurs in everyday life is unclear. Rapid advances in technology have led to the increasing use of sensors to study naturalistic driving, as people drive in their own vehicles and their own environments, where and when they choose [28–30] (see Singh and Kathura, [30] for a review of naturalistic driving work). Although naturalistic driving studies reflect actual driving behavior, they may not be as informative as other methodologies regarding all aspects of an individual's ability to drive, particularly when visual information regarding the driving environment is not captured. For example, simulator studies may be better at assessing reaction time to threatening stimuli when faced with emergency situations. Several large, longitudinal studies of naturalistic driving behavior, such as the Strategic Highway Research Program (SHRP 2) [31] and the 100-Car Naturalistic Driving Study [32, 33], have been completed or are underway. Some of these studies concentrate specifically on driving among older adults, including those who may have/develop cognitive impairment or dementia due to any cause, such as the Candrive II/Ozcandrive [34] and the American Automobile Association's LongROAD study [35]. Sensors used in these studies provide data about where and when an individual drives on an essentially continuous basis (e.g., every 1 second). Some sensor systems include cameras which record visual and sound information from both inside and outside the vehicle [29]. Sensor data can be transmitted wirelessly from the vehicle to cell phone towers, and then to servers for storage.

Given the widespread availability of these sensor-based methods, and the rich data that they yield on an ongoing basis, this position paper primarily concentrates on recommendations for future research on naturalistic driving. Future driving research needs for those at the earliest stages of AD can broadly be categorized as study of the effects of individual differences among drivers, as well as interactions between the driver, the vehicle, and the driving environment.

INDIVIDUAL DIFFERENCES AMONG DRIVERS: AD BIOMARKERS

Research examining relationships between molecular biomarkers of AD and cognition has intensified in the previous few years. Indeed, the research framework proposed by the National Institute on Aging—Alzheimer's Association for defining AD is based solely on the abnormality of AD biomarkers (amyloid, tau, neurodegeneration) [13], and much research has been devoted to examining how these biomarkers are associated with global cognitive performance as well as different domains of cognition, including executive functioning, memory, attention, and processing speed [17, 36, 37]. However, research examining links between biomarkers and driving behavior is only beginning.

First, there is little research to date on associations between driving behaviors in early symptomatic AD and molecular biomarkers. Examination of biomarker levels in studies among persons with early AD dementia symptoms is important to ensure that sample participants actually have AD, as opposed to some other condition that may impact cognition and driving behavior, such as medication-related effects, depression, frontotemporal dementia, or Lewy body disease. Second, research is needed to compare whether the extent to which the emerging AD-biomarker relationships in preclinical AD are similar to, and differ from, those in early symptomatic AD. And third, several models of biological AD evolution, as they relate to biomarker changes and the appearance of symptoms with time, have been proposed. These models generally suggest that decline in CSF amyloid levels is among the earliest changes, and is followed by increases in amyloid plaques, then by increased CSF tau levels, then by increased tangles in the brain, followed by neurodegeneration, and then cognitive symptoms [11–13, 38].

More research is needed to determine where to place complex functional activities like driving,

which involve physical, cognitive, and behavioral components, on this AD development timeline. The earliest existing driving research using molecular AD biomarkers suggests that, within a single sample of cognitively normal older adults, driving errors are unrelated to low CSF amyloid levels alone (i.e., at the very early stages of the AD pathological process), but occur when the ratio of CSF tau to amyloid is high, indicating increased tau levels in the presence of decreased amyloid [25], and when imaging indicates that substantial fibrillar amyloid plaques are present [25]. Relatedly, high levels of imaged fibrillar plaques are associated with risky driving behaviors (self-reported traffic violations and accidents) [39]. Other cross-sectional and longitudinal research indicates that driving difficulties, defined as receiving a Marginal Pass or Fail rating on a standardized road test, are most associated with abnormality of both amyloid and tau pathology, rather than amyloid alone [26, 40]. However, naturalistic and self-reported driving research indicates that AD-associated differences in driving behavior, namely driving restriction, occur even when amyloid abnormalities alone are considered [24].

Recent work using sensors indicates that, in addition to driving restriction behaviors, the amount of "jerk" in driving style is a feature of amyloid abnormality among cognitively normal persons [41]. Jerk, i.e., sudden changes in acceleration, increases the likelihood of being involved in safety critical events such as roadway departures, rear end collisions, and sideswipes [42]. Since associations between jerk in driving style and early or preclinical AD do not appear to have been previously reported, this new work suggests that naturalistic driving methodologies may reveal novel driving variables important at early stages in the AD continuum. Taken together, this work supports the hypothesis that subtle changes in driving behavior are present at the earliest stages of preclinical AD when amyloid levels are abnormal, with more salient changes associated with road safety (e.g., failing a driving test) occurring when tau abnormalities are also present. Future research aimed at testing this hypothesis is needed.

As noted earlier, the few studies that exist show clear associations between driving behaviors and preclinical AD defined using traditional AD biomarkers: CSF and imaging measures of amyloid and tau pathology. However, newer biomarkers that reflect other AD-related pathologies are being developed and tested at a rapid pace. These include markers of neurodegeneration such as neurofilament light polypeptide (NFL) [43], neurogranin, visinin-like protein 1 (VILIP-1); markers of neuroinflammation reflected in β2-microglobulin, progranulin, and soluble triggering receptor expressed on myeloid cells 2 (sTREM2) levels; and proteins related to the degradation and removal of pathologic Aβ and pathologic tau proteins such as clusterin. As science uncovers the increasingly-important role of these additional pathophysiological mechanisms, incorporation of some of these novel biomarkers into the current research framework for defining AD are being proposed [44]. Future research should examine how these newer biomarkers relate to different driving behaviors among cognitively normal persons as well as those with early AD dementia symptoms.

One long-sought-after objective of AD research, the development of sensitive, specific, and accurate blood biomarkers has become a reality over the last few years [14, 45]. These plasma biomarkers are a welcome new research tool, as they are likely to be more accessible than CSF and imaging biomarkers which typically must be obtained at specialized research centers. They are also likely to be more acceptable to participants than the more invasive traditional biomarkers, and although currently expensive, are expected to become more affordable in the future. Since late 2020, amyloid-based plasma biomarkers have been commercially available to physicians for clinical use to help detect biological AD, and tau-based commercial blood biomarkers are under development [45–47]. However, plasma biomarkers are not currently in clinical use in most places in the world. A literature search indicates that there are no published studies examining whether, and to what extent, these plasma biomarkers are related to driving behavior. Likewise, studies are needed that compare plasma AD biomarkers with CSF and imaging measures in predicting driving behavior. This is an important and unexplored area of research.

INDIVIDUAL DIFFERENCES IN DRIVING BEHAVIOR: DEMOGRAPHICS

Because past research has shown that preclinical and very mild AD dementia predict cross-sectional and longitudinal driving behavior, researchers are beginning to explore whether driving behavior can be used to identify the earliest stages of AD. Early studies indicate that statistical models made up of combinations of naturalistic driving behaviors

can accurately identify which participants have preclinical AD (measured via CSF amyloid levels in cognitively normal participants) [41, 48] and distinguish older adult participants with and without AD dementia [49]. No studies have yet used driving behavior to predict the onset of incident symptomatic AD.

For purposes of identifying preclinical and early AD, the predictive value of these driving behavior models could possibly be enhanced by including variables reflecting individual differences between older drivers. For example, the addition of age in predictive models is known to significantly enhance the ability to identify biological AD captured via imaging in both molecular biomarkers [50] (e.g., CSF, plasma) and driving behavior [41] models. However, the main and interactive effects of demographic variables such as gender, race, place (e.g., rural versus urban, New York versus Kentucky) and number and type of comorbidities (e.g., diabetes, depression) with AD biomarkers on driving behavior are largely unknown.

INTERACTIONS BETWEEN DRIVER CHARACTERISTICS AND THE IN-VEHICLE ENVIRONMENT

The higher rates of crashes among older adult drivers compared to younger adults are thought to be at least partially influenced by physical and cognitive changes that accompany aging, such as vision, reaction time, and attention [51–53]. These changes are even more pronounced among persons with early symptomatic [54] and preclinical [36, 55–58] AD and may interact with the increasingly complex in-vehicle environment.

This environment includes advanced driver assistance systems (ADAS) which are abundant in modern vehicles. ADAS systems are designed to increase safety and decrease crashes by alerting the driver via sound, visual, and/or vibrotactile stimuli, and include lane keeping assist, emergency braking, and pedestrian and blind spot detection. Although ADAS systems may decrease crash risk generally across adults, there is sparse research as to how individual driver characteristics that accompany aging and early AD may influence the effectiveness of these warning systems [51]. It is possible that instead of improving safety, they may startle and distract drivers who need to devote more attentional resources to driving than others, slow driver responses, and unintentionally reduce road safety [59]. Research is needed to determine how sound type, duration, and level; and differences in visual images (e.g., placement of images, contrast, color) of ADAS systems interact with demographic characteristics and AD pathology. This may help in increasing the effectiveness of ADAS symptoms in preventing crashes. For example, Saito et al. (2021) report substantial differences in driver behaviors across older and younger age groups and driving conditions when investigating the effects of an ADAS system in approaching blind intersections. Since the type and timing of warning signals can be manipulated (although not currently a standard feature on most vehicles) a simple intervention to increase ADAS effectiveness may be to set the signal type according to the driver's age.

In addition to ADAS systems, other characteristics of newer vehicles add to the complexity of the in-vehicle environment. The number of controls on the steering wheel and column has increased from a simple horn press and turn signals to now allow for manipulation of windshield wipers and fluid, cruise control, telephone, and radio. Smart, in-dash touch screens can also be used to perform these features and may also allow changing of the in-vehicle temperature and lighting levels as well as access to infotainment options such as audiobooks, news, and weather reports. Although in-dash screens allow a multitude of functions to be accessed easily, they also require that that the driver divide their attention, at least for a brief time, between the road and the screen. The ability to divide attention between the roadway and the in-vehicle environment declines with older adult age, particularly when a motor response (as is needed to operate a touch-screen) is required [60].

Most in-dash touch screens include a navigational system. GPS navigation may prove helpful in wayfinding and preventing getting lost, which is more likely to occur in the later stages of AD, but more research is needed as to how these systems impact driving in the preclinical and early AD/MCI stages. Existing studies suggest that GPS-based navigation may aid in finding the destination among persons with early AD/MCI, especially when auditory-only directions are used, with driving performance declining as reliance visual GPS output increases [61]. Smart phone-based GPS navigational systems are also widely used and offer similar advantages to touch-screen based systems. However, there has been great concern about the detrimental effects of distracted driving that occurs with cell phone use [62, 63]. Although much of this research has focused

on cell phone use among younger adults [64], there is some evidence that, like teenagers, the driving of adults aged 65+ may be especially affected by concomitant cell phone use [65]. Simulator studies suggest that older adults with MCI have slower reaction times and a greater probability of being in an accident when distracted by cell phone use compared to those with normal cognition [66, 67]. Some research has found that conversation with a passenger impairs simulated driving among older adults with MCI and mild AD [68], although other studies have not [66]. Whether these greater driving effects due to cell phone use and passenger conversation shown in MCI occur during the preclinical AD stage is an open question.

INTERACTIONS BETWEEN DRIVER CHARACTERISTICS AND THE EXTERNAL DRIVING ENVIRONMENT

There are a few existing studies that have examined how early AD interacts with aspects of the external driving environment such as weather. Naturalistic driving data suggest that persons with questionable/very mild and mild AD are less likely to drive in inclement weather, and more likely to drive in sunny weather, compared to nondemented controls [69]. However, two studies using self-report data indicate that individuals with MCI do not differ from those with normal cognition with regard to driving in rain or "bad weather" [70, 71]. Additionally, seasonality research indicates that the highest likelihood of US crash deaths occurs June through October, months with generally good weather [72].

Research is needed to determine whether the disparate findings are due to the different presumed etiologies of the clinical groups studied (AD specifically versus MCI generally), or to the different methodologies (naturalistic driving versus self-report). Driving in other types of weather conditions in early symptomatic AD such as snow, ice, glare, fog, etc. should also be explored. Data derived from in-vehicle sensors to monitor naturalistic driving can be linked together with large weather databases to indicate the type of weather condition at the time that an individual is driving in an area and capture their driving behavior under those particular weather conditions. This would presumably generate more accurate data compared to self-report and allow for exploration of driving during different weather types. No studies could be found that looked at weather and seasonality effects on driving among persons with preclinical AD.

Much research is needed to understand how preclinical and early symptomatic AD interact with other external driving factors, such as road type (e.g., interstate versus two-lane highway), traffic density (e.g., rush hour), intersection behavior, and awareness of objects (e.g., pedestrians, other vehicles) in the driving environment. Driving behavior is known to differ from city to city as well as in rural compared to urban environments [73, 74]. Examining how the presence of preclinical and early AD changes driving behavior in these different types of geographic locations is also a fruitful area of enquiry.

CONCLUSIONS

Research on how preclinical and early symptomatic AD impact driving behavior is in its infancy, with several important research areas yet to be explored. These include how individual differences in demographic and biomarker measures of AD pathology, as well as differences in the in-vehicle and external driving environment, affect driving behavior. Understanding these differences is important to developing future interventions to increase driving safety among those at the earliest stages of AD.

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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