Original Research Article

Saccular Impairment in Alzheimer's Disease Is Associated with Driving Difficulty

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Keywords

Alzheimer's disease · Vestibular system · Automobile driving · Spatial cognition · Saccule and utricle

Abstract

Background/Aims: Patients with Alzheimer's disease (AD) experience increased rates of vestibular loss. Recent studies suggest that saccular impairment in mild cognitive impairment (MCI) and AD patients is associated with impaired spatial cognitive function. However, the impact of saccular impairment on everyday behaviors that rely on spatial cognitive function is unknown. **Methods:** We recruited 60 patients (21 MCI and 39 AD) from an interdisciplinary Memory Clinic. Saccular function was measured, and a visuospatial questionnaire was administered to assess whether participants experienced impairments in terms of driving difficulty, losing objects, falls, and fear of falling. **Results:** In multiple logistic regression analyses, MCI and AD patients with bilateral saccular impairment had a significant, greater than 12-fold odds of driving difficulty (OR 12.1, 95% CI 1.2, 117.7) compared to MCI and AD patients with normal saccular function, and the association appears to be mediated by spatial cognition as measured by the Money Road Map Test. **Conclusion:** This study suggests a novel link between saccular impairment and driving difficulty in MCI and AD patients and demonstrates that driving difficulty may be a real-world manifestation of impaired spatial cognition associated with saccular impairment.

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This work was conducted at Johns Hopkins University.

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Introduction

Patients with Alzheimer's disease (AD) commonly experience deficits in spatial cognition, such as spatial memory and navigation. Deficits in these skills have been shown to underlie many functional impairments in mild cognitive impairment (MCI) and AD patients. Several studies in MCI and AD patients have demonstrated that performance on spatial cognitive tests is a strong predictor of driving performance both in simulation and on-road conditions [1–3]. Additionally, spatial disorientation in MCI and AD has also been shown to contribute to falls risk [4–6], while deficits in spatial memory are thought to contribute to losing or misplacing objects [4, 7–9]. Longitudinal studies of MCI patients have shown that a subset of MCI patients develop severe visuospatial deficits [10], and this subset of MCI patients may be more likely to undergo clinical progression as determined by the Clinical Dementia Rating (CDR) scale over 2 years of follow-up [11].

The vestibular (inner ear balance) system plays an integral role in spatial memory and navigation abilities [12–16]. Vestibular ablation in rats results in impaired performance on foraging tasks requiring spatial memory and navigation [17–21]. Studies in humans have demonstrated that vestibular loss leads to impaired performance on neurocognitive tests of spatial memory and navigation tasks and also leads to hippocampal atrophy, which may mediate the link between vestibular and spatial cognitive function [16, 22, 23]. Patients with AD have been shown to have greater rates of vestibular loss compared to age-matched controls [24–26]. In recent work, we showed that AD patients with vestibular loss, specifically loss of saccular function, are significantly more likely to have spatial cognitive deficits (measured by neurocognitive tests of spatial cognition) relative to AD patients with normal vestibular function [27]. However, it is unknown whether saccular impairments may be related to real-world behaviors indicative of spatial cognitive deficits in MCI and AD patients.

In this study, we evaluated 60 patients with MCI and AD who were seen in the Johns Hopkins Memory and Alzheimer's Treatment Center (JHMATC), an interdisciplinary memory disorder clinic, and the Johns Hopkins Alzheimer's Disease Research Center (JHADRC). We assessed whether saccular impairment was associated with behavioral symptoms related to impaired spatial cognition, specifically losing objects, driving difficulty, and falls. Our study provides evidence that saccular impairment contributes to impaired driving ability and demonstrates a real-world behavioral correlate of the role of vestibular function in spatial cognition in MCI and AD patients.

Methods

Study Participants

This was a single-center prospective cross-sectional study. Participants were recruited from December 2014 until August 2017 from the JHMATC, an interdisciplinary memory disorder clinic, and the JHADRC. Inclusion criteria for the study were (1) age ≥ 55 years; (2) diagnosis of MCI or AD; (3) Mini-Mental State Examination (MMSE) score ≥ 11 ; (4) fluency in English; and (5) ability to obtain informed consent from the participant or a legally authorized representative. A diagnosis of MCI or AD was made using the National Institute on Aging-Alzheimer's Association diagnostic criteria [28, 29]. An MMSE score cutoff of ≥ 11 was used as it has been shown to correspond to the threshold between moderate and severe dementia [30]. Prior to participation, a Memory Center physician determined the participant's ability to follow examination procedures.

Patients were excluded from the study if they had a previous history of vestibular disease or were unable to understand and participate in examination procedures. Demographic characteristics (age, gender, and education) were obtained from the patients' charts. Education was classified as less than college, college, or greater than college. All participants provided written informed consent. The study was approved by the Johns Hopkins Institutional Review Board.

Saccular Function Tests

Saccular function was assessed with the sound-evoked cervical vestibular evoked myogenic potential (cVEMP). Recordings were made with a commercial electromyographic system (software version 21.1; Natus Neurology, Middletown, WI, USA), with self-adhesive electrodes from GN Otometrics (Schaumburg, IL, USA). Testing methods have been published in detail previously and are described briefly here [31–33]. Participants sat on a chair with their heads inclined at 30° from the horizontal. Trained examiners placed recording electromyographic electrodes on the sternocleidomastoid (SCM) muscle and the sternoclavicular junction bilaterally. A ground electrode was placed on the manubrium sterni. Patients were instructed to turn their heads against resistance to activate the SCM muscle. A sweep of auditory tone bursts (500 Hz, 125 dB SPL) was delivered monaurally through headphones (Viasys Healthcare, Madison, WI, USA), and inhibitory potentials were recorded from the ipsilateral SCM muscle. The presence or absence of a cVEMP response was recorded for each ear, indicating normal or impaired saccular function, respectively, as characterized by published guidelines [31–33].

Visuospatial Questionnaire

Given increasing evidence linking vestibular loss, including saccular impairment, to impairments in spatial cognition [12, 16, 23], we sought to evaluate the association between saccular function and family- and patient-reported difficulties with 3 behavioral symptoms that reflect spatial cognition: losing objects [4, 7–9], difficulty driving [1–3], and falls [4–6]. As an additional measure of fall risk, we also asked about fear of falling. At present, no validated questionnaires probing visuospatial skills in MCI/AD patients have been published; therefore, we devised 4 simple questions. Participants and/or family members were asked the following questions in person or via telephone:

1. Do you (or the care recipient) lose objects? Yes or no.
2. Do you (or the care recipient) have difficulty driving? Yes or no.
3. Have you (or the care recipient) ever fallen? Yes or no.
4. Are you (or the care recipient) afraid of falling? Yes or no.

Money Road Map Test

We administered the Money Road Map Test (MRMT), a measure of visuospatial ability [34–36], to assess whether any potential associations between saccular impairment and behavioral symptoms may be mediated by spatial cognitive impairment. We previously reported that saccular impairment in MCI and AD patients was associated with spatial cognitive impairment, as determined by errors on MRMT [27]. The procedure has been published in detail [34] and will be briefly explained here. The participant was shown a 2D representation of a small city map on a sheet of paper in a fixed orientation. The city map contains a walking path with 32 turns. The participant was asked to imagine that they were traveling along the route through the city. As the examiner traced the route, the examiner asked the participant at each turn whether a right or left turn would be required to continue along the route. The participant's responses were recorded at each turn by the examiner up until a 300-s time limit. The main outcome of interest was the number of errors (i.e., incorrect or missing responses) out of 32 turns. Among the sample of 60 participants, a subsample of 48 (19 MCI and 29 AD) were able to complete the MRMT. Twelve patients (2 MCI, 10 AD) were not able to complete the MRMT because of inability to understand the test procedures after the instructions were explained once prior to the start of testing and up to 2 additional times.

Statistical Analysis

Descriptive statistics were conducted to evaluate participant demographics, saccular function, responses to visuospatial questionnaire items, and performance on the MRMT by category of cognitive impairment (MCI and AD).

We evaluated the relationship between each visuospatial questionnaire item and saccular function in multivariable analyses. Saccular function was categorized as normal function, unilaterally absent function, or bilaterally absent function. Responses to each questionnaire item were categorized with 0 representing “no” and 1 representing “yes.” Multiple logistic regression models adjusting for demographic characteristics (age, sex, and education) were developed to explore the association between saccular impairment and each item on the visuospatial questionnaire. Furthermore, to evaluate whether the association between saccular function and driving difficulty was mediated by spatial cognition, we added the number of errors on MRMT to the regression model as a proxy for spatial cognition. All analyses were performed using STATA version 14 (College Station, TX, USA).

Table 1. Demographic characteristics of the study population, saccular function, and responses on the visuospatial questionnaire

	MCI (n = 21)	AD (n = 39)
Sex		
Male	9 (42.9)	10 (25.6)
Female	12 (57.1)	29 (74.4)
Age, years	71.5±9.7	76.3±6.5
Education		
Less than college	6 (28.6)	12 (30.8)
College	6 (28.6)	20 (51.3)
Greater than college	9 (42.9)	7 (17.9)
Saccular function		
Normal function	7 (33.3)	4 (10.3)
Unilateral loss	7 (33.3)	11 (28.2)
Bilateral loss	7 (33.3)	24 (61.5)
Visuospatial questionnaire		
Lose objects ^a	12 (57.1)	27 (69.2)
Driving difficulty ^b	5 (23.8)	20 (51.3)
Falls ^c	8 (38.1)	15 (38.5)
Fear of falling ^d	6 (28.6)	7 (17.9)
MRMT errors	4.5±6.2 ^e	11.0±6.6 ^f

Values are means ± standard deviations or n (%). MCI, mild cognitive impairment; AD, Alzheimer's disease; MRMT, Money Road Map Test.

^a Do you (or the care recipient) lose objects? ^b Do you (or the care recipient) have difficulty driving? ^c Have you (or the care recipient) ever fallen? ^d Are you (or the care recipient) afraid of falling? ^e Nineteen MCI patients completed the MRMT. ^f Twenty-nine AD patients completed the MRMT.

Results

Sixty patients (21 MCI and 39 AD) completed cVEMP testing and the visuospatial questionnaire (Table 1). AD patients (mean age of 76.3 years, SD 6.5) were slightly older than MCI patients (mean age of 71.5 years, SD 9.7). Compared to AD patients, MCI patients were less likely to report difficulty with losing objects (57.1% in MCI and 69.2% in AD), driving difficulty (23.8% in MCI and 51.3% in AD), and falls (38.1% in MCI and 38.5% in AD) but more likely to report being afraid of falls (28.6% in MCI and 17.9% in AD). AD patients made a greater number of errors on the MRMT (mean 11.0, SD 6.6) compared to MCI patients (mean 4.5, SD 6.2).

Multiple logistic regression analyses were conducted to assess the association between saccular impairment and each questionnaire item in MCI and AD patients (Table 2). Compared to patients with normal saccular function, patients with unilateral saccular impairment had a nonsignificant increased odds of experiencing driving difficulty (OR 6.9, 95% CI 0.7, 72.6), while patients with bilateral saccular impairment had a significant, over 12-fold odds of experiencing driving difficulty (OR 12.1, 95% CI 1.2, 117.7). We did not observe any significant difference in the odds of losing objects, falling, or fear of falling by level of saccular function.

To assess whether the association between saccular impairment and driving difficulty may be mediated by spatial cognitive impairment, errors on MRMT was added to the regression model for driving difficulty as a proxy for spatial cognition. The addition of MRMT performance in the model for driving difficulty substantially reduced the coefficients for unilateral and bilateral saccular impairment in the model, and bilateral saccular impairment

Table 2. Saccular impairment and visuospatial functional impairments

	Losing objects		Driving difficulty		Falls		Fear of falling	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Saccular impairment								
Normal function	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Unilateral loss	3.1 (0.6, 16.2)	0.19	6.9 (0.7, 72.6)	0.11	0.8 (0.1, 4.2)	0.79	2.9 (0.3, 32.8)	0.39
Bilateral loss	2.5 (0.6, 11.3)	0.23	<i>12.1 (1.2, 117.7)</i>	<i>0.03</i>	0.8 (0.2, 3.4)	0.71	4.1 (0.4, 41.0)	0.23
Age	1.0 (0.9, 1.1)	0.86	1.0 (0.9, 1.1)		1.0 (0.9, 1.1)	0.87	1.0 (0.9, 1.1)	0.87
Sex								
Male	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Female	0.8 (0.2, 2.9)	0.76	2.1 (0.5, 8.5)	0.28	2.6 (0.7, 9.9)	0.15	0.7 (0.2, 3.3)	0.70
Education								
Less than college	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
College	2.0 (0.5, 7.6)	0.31	2.4 (0.6, 9.5)	0.22	0.5 (0.1, 1.6)	0.23	0.7 (0.2, 2.9)	0.60
Greater than college	1.2 (0.3, 5.7)	0.80	0.4 (0.1, 2.6)	0.35	0.4 (0.1, 1.8)	0.21	0.3 (0.04, 2.1)	0.21

Italics indicate statistical significance. OR, odds ratio; CI, confidence interval.

Table 3. Association between saccular impairment and driving adjusting for spatial cognition

	Driving	
	OR (95% CI)	p value
Saccular impairment		
Normal function	1.0 (ref.)	
Unilateral loss	2.8 (0.2, 35.3)	0.42
Bilateral loss	4.0 (0.3, 48.2)	0.28
Age	1.0 (0.9, 1.1)	0.58
Sex		
Male	1.0 (ref.)	
Female	1.5 (0.3, 8.1)	0.64
Education		
Less than college	1.0 (ref.)	
College	3.1 (0.6, 16.6)	0.18
Greater than college	1.1 (0.1, 9.4)	0.91
Errors on MRMT	1.1 (0.9, 1.2)	0.30

OR, odds ratio; CI, confidence interval; MRMT, Money Road Map Test.

was no longer significantly associated with driving difficulty. Specifically, after adjusting for MRMT performance, patients with unilateral saccular impairment had a 2.8 odds (95% CI 0.2, 35.3) and patients with bilateral saccular impairment had a 4.0 odds (95% CI 0.3, 48.2) of experiencing driving difficulty relative to patients with normal saccular function (Table 3).

Discussion

In this study of MCI and AD patients, bilateral saccular impairment, as determined by bilaterally absent responses on the sound-evoked cVEMP, was significantly associated with a greater than 12-fold odds of driving difficulty, while unilateral saccular impairment had a borderline nonsignificant nearly 7-fold odds of driving difficulty. Moreover, the associations

between saccular impairment and driving difficulty appear to be mediated by performance on the MRMT, a measure of spatial cognition. These findings suggest a novel link between saccular impairment and a real-world consequence of impaired spatial cognition in MCI and AD patients: driving difficulty.

Our study in MCI and AD patients builds on prior studies that also observed a link between vestibular dysfunction and driving difficulty in cognitively intact individuals with vestibular disorders. Studies in patients with specific vestibular disorders found that 60% of patients with Ménière disease found driving to be either difficult or dangerous to perform [37], and 30% of patients with vestibular schwannomas experienced driving difficulty following surgical resection of their tumors [38]. Recently published data from the National Health and Nutrition Examination Survey (NHANES) found that individuals with symptomatic vestibular dysfunction had an over 4-fold odds of experiencing driving difficulty relative to individuals without vestibular dysfunction [39]. Furthermore, when assessing specific driving conditions, 1 study found that vestibular patients have particularly greater difficulty with driving tasks that require spatial navigation, such as changing lanes in traffic, staying in lane, and pulling into or out of parking spaces, as well as with driving tasks where vision was limited, such as driving at night or in the rain [40]. On-road studies have further demonstrated that patients with bilateral vestibular loss exhibit reduced accuracy in reading and processing signs while sitting in a car [41] and slower horizontal head movements during driving [42]. Our study builds on previous work in patients with vestibular disorders by extending the association between saccular impairment and driving difficulty to MCI and AD patients. These findings are particularly relevant given that patients with MCI and AD have long been shown to have greater impairments in driving ability and AD drivers have a 2.3-fold increased risk of crash involvement compared to age-matched controls [1, 3, 43–45].

Our finding that the association between saccular impairment and driving difficulty in MCI and AD patients appears to be mediated by spatial cognition further suggests that driving difficulty may be a consequence of the contribution of the saccule to spatial cognitive function. Neuropsychological studies have established that spatial cognitive function, as determined by measures such as the Intersecting Pentagon Copying, Clock-Face Drawing, and Block Design tests, predicts driving performance and crash involvement in MCI and AD patients, and in older adults more broadly [46–52]. Meanwhile, a growing body of literature has demonstrated that vestibular function significantly contributes to performance on spatial cognitive measures. Animal studies have shown that rodents with absent vestibular function exhibit impaired performance on behavioral tasks of spatial memory and navigation [17–20] and also exhibit loss of location-specific firing in hippocampal place cells [15, 21]. These observations were corroborated by human studies which demonstrated that vestibular input, particularly saccular function, mediates performance on static and dynamic assessments of spatial navigation and memory [12–14], including the Triangle Completion Task (TCT) [16, 22]. Moreover, we observed in recent work that MCI and AD patients with saccular impairment, as determined by cVEMP responses, were significantly more likely to have spatial cognitive impairment relative to MCI and AD patients with normal vestibular function [27]. The hippocampus is considered the anatomic locus of spatial cognition [53] and, indeed, has been shown to receive substantial input from the vestibular system. Functional neuroimaging studies have demonstrated that saccular stimulation (specifically, sound-evoked cVEMP stimulation) activates the hippocampus [54], while patients with bilateral vestibular loss exhibited reduced hippocampal volume with concomitant poorer performance on a virtual navigation task compared to age-matched controls [23]. Our study thus builds on previous work establishing that vestibular dysfunction, and specifically saccular impairment, contributes to spatial cognitive impairment, by presenting driving difficulty as a real-world behavioral correlate of this relationship in MCI and AD patients.

In our study, saccular impairment was not significantly associated with losing objects, falls, and fear of falling. Losing objects may reflect higher-order cognitive processes in addition to visuospatial skills, such as attention [4], while falls risk may represent a more complex interaction of multiple factors, such as medication use, vision, bone and muscle strength, reaction time, and general cognitive ability [5, 55–58]. Further prospective studies in larger samples will be needed to clarify the relationship between saccular function and these as well as other behavioral correlates of impaired spatial cognition in MCI and AD, such as wandering [59].

We note important limitations in our study. The study was cross-sectional and, thus, cannot support causal inferences between saccular impairment and driving difficulty in MCI and AD patients. We acknowledge the potential for reverse causality or, alternatively, that other factors, such as traumatic brain injury, hypertension, diabetes, and/or cardiovascular disease, may contribute to both saccular impairment and spatial cognitive decline [26]. Nevertheless, our findings can be interpreted in the context of previous studies that suggest a causal contribution of saccular impairment to spatial cognitive dysfunction, especially given that the association between saccular impairment and driving difficulty in this study appears to be mediated by spatial cognition. Moreover, although we elected to focus on cVEMPs in the current study, further studies employing other measures of vestibular function may be valuable. An additional limitation of the study is that we did not differentiate between subtypes of MCI, which may or may not be of likely AD cause. Further work focused on driving difficulty and spatial cognition in MCI patients could restrict the study sample to MCI patients with likely AD etiology.

In summary, in this study of MCI and AD patients, a significant association was found between bilateral saccular impairment and self-reported difficulty driving a motor vehicle, and this association appears to be mediated by spatial cognition. This finding suggests that driving difficulty may be a real-life behavioral manifestation of the role of saccular impairment on impaired spatial cognition in MCI and AD patients. This study may have important clinical implications as difficulty driving is a challenging condition in patients with MCI and AD, who as a result face driving-related morbidity and reduced autonomy. Identifying a risk factor for driving difficulty, such as saccular impairment, which is potentially modifiable through vestibular rehabilitation, could be of significant benefit to MCI and AD patients. Clinicians seeing MCI and AD patients who report a history of driving impairments or accidents should consider diagnosis and treatment of potential underlying vestibular dysfunction. Further investigations are needed to evaluate whether vestibular rehabilitation may improve driving ability in MCI and AD patients who report difficulty driving a motor vehicle.

Acknowledgments

E.X.W. was a participant in the Medical Student Training in Aging Research program, funded by the American Federation for Aging Research and the National Institute on Aging (NIA). E.S.O. was funded by a NIA/NIH K23 Award (1K23AG043504-01), the Roberts Gift Fund, and the Ossoff Family Fund. A.H. was funded by a NIH T32 Award (5T32DC000027-25) and an AAO-HNSF Core Grant (349386). Y.A. was funded by a NIH K23 Award (5K23DC013056-02). The Alzheimer's Disease Research Council is supported by an NIA award (3P50AG005146-32S1).

Disclosure Statement

The authors have no conflicts of interest to report.

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