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Lower Hippocampal Volume Predicts Decrements in Lane Control among Drivers with Amnesic MCI

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Abstract

Objectives—There are few methods to discern driving risks in patients with early dementia and Mild Cognitive Impairment (MCI). We aimed to determine whether structural MRI of the hippocampus – a biomarker of probable Alzheimer pathology and a measure of disease severity in those affected – is linked to objective ratings of on-road driving performance in older adults with and without amnesic MCI.

Methods—49 consensus-diagnosed participants from an Alzheimer's Disease Research Center (15 diagnosed with amnesic MCI and 34 demographically similar controls) underwent structural MRI and on-road driving assessments.

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Drs. Griffith, Okonkwo, Stewart, Stoeckel, den Hollander, Harrell, Brockington, Clark, Ball, Owsley, Marson and Wadley, as well as Ms. Elgin, report no conflicts of interest related to the content of this manuscript.

Results—Mild atrophy of the left hippocampus was associated with less-than-optimal ratings in lane control but not with other discrete driving skills. Decrements in left hippocampal volume conferred higher risk for less-than-optimal lane control ratings in the MCI patients ($B = -1.63$, $SE = .74$, $Wald = 4.85$, $P = .028$), but not in controls ($B = 0.13$, $SE = .415$, $Wald = 0.10$, $P = .752$). The odds ratio (OR) and 95% confidence interval (CI) for below optimal lane control in the MCI group was 4.41 (1.18, 16.36), which was attenuated to 3.46 (0.88, 13.60) after accounting for the contribution of left hippocampal volume.

Conclusion—These findings suggest that there may be a link between hippocampal atrophy and difficulties with lane control in persons with amnesic MCI. Further study appears warranted to better discern patterns of brain atrophy in MCI and AD and whether these could be early markers of clinically meaningful driving risk.

Keywords

MCI (mild cognitive impairment); Volumetric MRI; Driving performance

Introduction

Interest in assessing risk of driving in older adults has grown as the driver population over age 65 grows. While many factors may put older drivers at risk¹, few are as compelling as the effects of neurological² and cognitive impairment³. Persons with Alzheimer's disease (AD) are at risk for motor vehicle crashes^{4,5}, and this risk may relate to both structural and functional brain changes^{6,7} and associated cognitive deficits in AD^{8,9}. Our group previously reported on subtle changes in driving skills of persons with amnesic mild cognitive impairment (MCI)¹⁰. These patients showed greater odds of suboptimal performance compared to healthy older adults during an on-road driving evaluation observed by a driving rehabilitation specialist who was masked to participants' diagnoses and cognitive status. Given that persons with amnesic MCI are at high risk for developing AD¹¹, small changes in driving skills and other instrumental activities of daily living (IADLs) may be the earliest harbingers of progression to dementia¹². However, clinical office visits do not routinely identify risk for driving difficulties¹³ and are insufficient to be used as sole predictors of present or future risk¹⁴.

A recent review of 120 simulated driving studies using functional magnetic resonance imaging (fMRI) reported that the parietal-occipital and frontal brain regions are most consistently activated during driving simulation tasks¹⁵. The authors suggest that functional connectivity networks may more fully account for the dynamics involved in the complex demands of driving¹⁵. Disruption in functional connectivity between the hippocampus and the rest of the brain is a hallmark of AD⁷. Neuroimaging methods used to study brain changes in patients with amnesic MCI indicate that reduction in volumes of the hippocampus is observed in MCI, is a robust predictor of progression to AD 2 or more years later¹⁶, progressively worsens as patients approach clinical AD¹⁷, and corresponds to postmortem neuropathology^{18,19}. MRI volumetrics of the hippocampus is a promising marker of neurodegenerative disease in MCI and can be quantified with structural MRI techniques that are more widely available than fMRI. In addition, structural MRI findings can be linked with findings obtained in the more naturalistic context of on-road driving

rather than driving simulation tasks inherent to most fMRI studies. We therefore aimed to examine hippocampal volumes in MCI patients in relation to on-road driving assessments. We hypothesized that those with lower hippocampal volumes would have lower ratings on driving skills that have been shown to be less than optimal in patients with MCI: turning, lane control, gap judgment, steering steadiness, and speed maintenance¹⁰.

Methods

Participants

Forty-nine participants were included in this study (15 with amnesic MCI and 34 age-similar healthy controls). Participants with MCI were community-dwelling older adults who presented for clinical evaluation at the University of Alabama at Birmingham (UAB) Memory Disorders Clinic. They were recruited between June 2004 and October 2009 by the UAB Alzheimer's Disease Research Center (ADRC) and two associated studies of functional change in MCI: the Cognitive Observations in Seniors, or "COINS" study, and the Measuring Independent Living in the Elderly Study, or "MILES". All participants underwent research assessments consisting of neurological, neuropsychological, and functional capacity testing, as well as blood work. The diagnosis of amnesic MCI was made during consensus diagnostic conferences using original Mayo criteria²⁰. Subjective memory impairment was determined through self-report, clinical examination, and informant interview. Neuropsychological tests included the Wechsler Memory Scale-Revised Edition (WMS-R) Logical Memory²¹, the California Verbal Learning Test II (CVLT-II)²², Dementia Rating Scale-2 (DRS-2)²³ Memory, and 10/36 Spatial Recall. Impairment was determined by ADRC neuropsychologists in reference to appropriate age-based norms and change from prior/premorbidity level of function. Overall cognition was assessed with the DDRS-2 and the Mini-Mental State Examination (MMSE)²⁴. Activities of daily living were assessed by informant report using a standardized interview format relevant to MCI and early AD. According to revised MCI criteria²⁵, approximately 2/3 of the participants met criteria for amnesic MCI - multiple cognitive domains involved.

All participants were current licensed drivers and had adequate corrected vision for driving (Snellen score range 20/30 to 20/13), as evaluated in the MILES study.

Exclusion criteria for the amnesic MCI group included a diagnosis of exclusively non-amnesic MCI, evidence or history of another neurodegenerative disease, stroke, severe organ disease, autoimmune disease, cancer (except skin cancer), alcoholism, untreated major depression or severe psychiatric disorder, or life-limiting illness.

Control participants were volunteers recruited from the community into the ADRC, its funded MILES project, and the COINS R01 project through newspaper advertisements and health fairs. Controls underwent ADRC neurological evaluation and neuropsychological testing and were characterized as cognitively normal in ADRC diagnostic consensus conferences. They also were subject to the exclusion criteria used for MCI participants.

This research was conducted in compliance with the ethical rules for human experimentation that are stated in the Declaration of Helsinki. The UAB Institutional Review Board approved the use of human subjects for this study. All participants gave written informed consent.

Driving Evaluation

The driving evaluation conducted during the MILES study visits has been described elsewhere¹⁰; we briefly summarize the procedures here. We used a research-standardized driving route in Birmingham, Alabama in clear weather conditions between 12:30 and 4:00 PM. Each participant drove a 1998 Chevy Lumina with dual controls under the supervision of a certified driving rehabilitation specialist (CDRS) who was masked to participant group status (i.e. MCI or normal control). The CDRS coded each participant's performance on specific driving skills that were sampled across varying contexts, including crossing intersections, merging, turning at intersections, exiting the interstate, changing lanes, driving on straight stretches, and taking curves.

Coding of each skill was done on a five-point Likert scale: *1 = evaluator took control of the car; 2 = unsafe; 3 = unsatisfactory; 4 = not optimal; and 5 = optimal*. At the end of the drive, the CDRS also rated the participant's overall driving skills on the same 5-point scale. Consistent with our prior report¹⁰, we used a data reduction strategy that involved a-priori selection of driving skills judged to be critical for safe operation of a motor vehicle: right and left turns, lane control, gap judgment, steering steadiness, and maintaining proper speed. The global driving rating was also included. We then created composite variables by averaging the participant's ratings on each occasion of the selected driving skills (e.g., each drive contained 5 left turns, each left turn maneuver was rated, and these ratings were averaged to create a left turn composite rating). Lastly, given that data on driving skills in this research sample were subject to ceiling effects¹⁰, we recoded each variable into dichotomous variables with 0 indicating "less than optimal driving" (mean score less than 5 across all occasions of a given driving behavior) and 1 indicating "optimal driving" (mean score of 5 across all occasions).

MRI Acquisition and Data Processing

MRI images were obtained using a Philips Intera 3 Tesla MRI system with a quadrature TR head coil to measure gray matter volumes from our regions of interest (ROI). These imaging sequences consisted of 1) multi-slice sagittal, axial, and coronal T1 FFE scout sequences acquired using TR/TE=11.1/4.6 ms, 256 × 128 resolution, and 10 mm slice thickness (for the purpose of image alignment) and 2) multi-slice sagittal T1 FFE acquired using TR/TE=9.3/4.6 ms, 240 × 240 resolution, and 2 mm slice thickness.

The MRI images were transferred to a workstation running SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5). Tissue segmentation derived in SPM5 involved segmentation/normalization/modulation of the brain and smoothing of the resulting gray and white matter images²⁶. The T1 image set was first skull stripped and the origin of each scan manually set to the anterior commissure. Next, a combined normalization/segmentation process was implemented on the scan using the prior probability templates provided with the SPM5 program (modified versions of the ICBM Tissue Probabilistic Atlases). The resulting

gray matter, white matter, and CSF images for each subject were normalized to the same stereotactic space²⁶. Gray and white matter images were smoothed using an 8 mm Gaussian kernel.

The ROI for volumetric analyses were identified using an SPM5 automated pickatlas routine based on an anatomical parcellation of the MNI MRI Single-subject brain²⁷. This method requires no trained user interface to reliably obtain volumetric masks from any of 45 cortical and subcortical ROI per hemisphere after modulated MRI images are segmented and normalized in SPM5. Similar methods have been shown to have good reliability with manual traces of the hippocampus in patients with dementia²⁸. Based upon this method, we derived volumes of the hippocampus for both hemispheres, consisting of the gray matter in the region of the temporal ventricular horns including the dentate gyrus, uncus, and hippocampus proper, limited caudally by the parahippocampal ramus of the collateral fissure²⁷. We adjusted for the influence of sex and age on MRI volumes using multiple regression analyses based on the control participants²⁹ and applied to the volumes of MCI participants, with the predicted variance removed from the observed volumes. The result is a residual score with variance due to body size and aging removed. We then computed z-score transformations of adjusted volumes based upon the control group's mean adjusted volumes.

Statistical Analyses

Demographic data were compared using independent samples *t* tests or Chi-square, as appropriate. Group differences on neuropsychological and MRI measures were tested using independent samples *t* tests, and on driving skill ratings using Chi-square. Point biserial correlations were examined between hippocampal volumes and the driving assessment variables in the full sample (MCI patients and controls). Logistic regression was subsequently performed to test for group differences in the relationship of hippocampal volumes to significantly correlated driving skills. We estimated odds ratios with 95% confidence intervals (CIs) for less than optimal driving and hippocampal volume only for those variables on which the correlations between driving and hippocampal volumes were significant. We used a threshold of $< .05$ for statistical significance without correction for multiple comparisons because we were interested a priori in discrete driving behaviors and their relation to hippocampal volumes. We limited the number of total comparisons by (1) reducing the data to essential skills, and (2) examining volumes of the right and left hippocampus only (out of a possible 90 regions).

Results

Sample characteristics

Demographics, dementia staging, and clinical characteristics are presented in Table 1. Our samples showed no significant differences in terms of age, education, race, or gender. The MMSE score was significantly lower in the MCI patients compared to controls. All MCI patients had Clinical Dementia Rating (CDR)³⁰ scale scores of 0.5; all controls had CDR of 0.0. Over half of the MCI patients were taking a cholinesterase inhibitor.

Driving ratings

Table 1 includes the dichotomous ratings for driving skills and overall global rating for the MCI patients and controls. There were significantly lower proportions of optimal ratings for the MCI participants compared to controls on the driving ratings of lane control, gap judgment, steer steadiness, maintaining speed, and the global rating. Contrary to prior research¹⁰, there was no difference observed between the proportion of optimal and less than optimal ratings between controls and amnesic MCI patients on the left turn ratings in this subsample of MILES participants who also had MRI data.

Hippocampal volumes

MRI volumes from the left and right hippocampus are displayed in Table 2. Z-score corrected volumes of both the left and right hippocampi tended to be smaller in the MCI patients. Cohen's effect sizes for the volume difference between groups were medium for the right ($P = .126$), and medium-to-large for the left hippocampus ($P = .057$).

Correlations between driving and hippocampal volumes

Table 3 shows the correlations between driving measures and hippocampal volumes in the full sample. As expected, most driving ratings were correlated with each other, as were left and right hippocampus volumes. There was a modest but significant correlation between the lane control rating and the left hippocampus ($r = .30$, $P < .05$). No other significant correlations were observed between driving measures and hippocampal volumes.

Logistic regression

Logistic regression models tested whether the relationship of lane control with the left hippocampus differed between the study groups. The interaction term of group $\times$ hippocampal volume demonstrated that the relationship of left hippocampal volume with lane control rating differed between groups ($B = 1.76$, $SE = .85$, $Wald = 4.32$, $P = .038$). For the MCI patients, decreases in left hippocampal volume conferred increased risk for less-than-optimal lane control ratings ($B = -1.63$, $SE = .74$, $Wald = 4.85$, $P = .028$). For the controls, there was no evident relationship of left hippocampal volume to lane control ratings ($B = 0.13$, $SE = .415$, $Wald = 0.10$, $P = .752$).

Odds ratios

For less than optimal ratings on lane control are presented in Table 4. Persons with amnesic MCI were 4.41 times more likely than controls to have less-than-optimal lane control ratings. After accounting for left hippocampal volumes, these odds fell to 3.46 (n.s.). Figure 1 demonstrates the relationship of the lane control ratings with left hippocampal volume z score in the amnesic MCI patients.

Discussion

The results of this study offer preliminary evidence that mild decrements in driving skills in persons with amnesic MCI are associated with reduced left hippocampus volumes. For patients with amnesic MCI within this dataset, risk for less-than-optimal ratings of lane

control increased as the adjusted volume of the left hippocampus decreased. No other driving maneuvers were associated with hippocampal volume. These findings expand our previous work linking brain volumes with laboratory-based IADL assessments³¹ and extend this linkage to driving in a real-world setting. This investigation demonstrates that neuroimaging measures can afford better understanding of how neuropathological changes affect daily activities essential to independent function. The findings of this study suggest that changes in the medial temporal lobes within the course of amnesic MCI are tied to subtle decrements in driving skills. Early volume loss is known to occur in mild AD¹⁷, amnesic MCI¹⁷, and prior to symptoms of memory loss³², and progressive medial temporal lobe atrophy corresponds strongly to the course of clinical decline in AD³³. MRI volumetric loss has been tied to post-mortem measures of amyloid plaques and neurofibrillary tangles in both AD and MCI^{18,19}. It is thus not surprising that there is an association between MRI volumes and differences in driving skills. What is surprising is that this finding was detected in patients with amnesic MCI who are clinically not demented, and also that these differences occur in a specific driving skill: lane control.

The specificity of the relationship of the hippocampus to lane control is not completely unexpected. This study of structural neuroimaging and driving is a subsample drawn from a prior study of driving with a larger sample of amnesic MCI patients and controls. That study revealed that lane control was the most robust performance anomaly¹⁰. Thus, lane control may be the most sensitive indicator of less-than-optimal driving in amnesic MCI. While in our sample other skills were also suboptimal in the amnesic MCI group (i.e., gap judgment, steer steadiness, and maintaining speed), there may be different underlying neurocognitive determinants of these driving skills that are not associated with hippocampal volumes. It is also possible that a greater degree of hippocampal atrophy than was present in this sample may be necessary before associations with deficits in other driving skills can be detected.

The relationship of hippocampal volumes to driving ratings likely is not directly linked to the strong association of the hippocampus with declarative memory and amnesia³⁴, as these neurocognitive processes are not central to deficits in driving performance^{9,35}. Although memory impairment was associated with poor driving in a meta-analytic study of dementia patients, visuospatial skills were found to be more important³⁶. Furthermore, the few studies that have looked at hippocampal volumes and driving skills have focused on spatial navigation³⁷⁻³⁹, consistent with animal studies showing that spatial navigation is highly tied to function and dysfunction of the hippocampus^{40,41}. However, two alternative hypotheses may be considered to explain this study's finding. One is that the hippocampus, as a biomarker of AD, simply identifies persons who are further along in the AD process and consequently are developing more changes in IADLs, such as driving. An alternative hypothesis is that the hippocampus plays a role in neurocognitive processes that directly influence lane control. One potential neurocognitive skill that has been identified with driving is visuospatial attention^{7,42,43}. There are studies that support a role for the hippocampus in modulating spatial attention processes as well as spatial memory^{41,44,45}. Given the limitations of sample size within the current study, we currently cannot provide evidence to support or refute either of these hypotheses.

Although our data imply that the left hippocampus is preferentially associated with lane control, this finding could be attributable to asymmetries in the hippocampal volumes of normal adults⁴⁶ as well as asymmetries in the temporal course of hippocampal atrophy in MCI and early AD⁴⁷ rather than hemispheric specialization for lane control. Hippocampal volume loss is known to occur prior to the earliest cognitive symptoms in preclinical AD³², and left hippocampal volumes and microstructures differ significantly between MCI patients whose diagnoses remain stable for 3 or more years versus those who progress to AD 2 or more years later¹⁶. Other structural changes—including those that may occur in brain regions that have been implicated in functional neuroimaging studies of driving—are likely not robust at the preclinical AD stage.

Functional MRI and near-infrared spectroscopy studies of neural correlates of driving have produced varying patterns of regional brain activations depending upon the characteristics of the study sample (e.g., Alzheimer's disease versus normal controls⁴⁸) and the nature of the driving challenge (e.g., hazardous versus non-hazardous conditions⁴⁹). A study using single photon emission computed tomography found perfusion differences in the frontal, temporo-parietal, and occipital regions of Alzheimer's disease patients who drove alone versus those who did not, as well as those who drove with difficulty versus those who were unable to drive, according to caregiver reports⁵⁰. In our study, it is possible that hippocampal volume reductions serve as a marker of broader network dysfunction in MCI, including disruptions involving these previously identified brain regions.

Limitations of the current study include the relatively small sample of persons with amnesic MCI. Although we lacked power to demonstrate group differences in the volumes of the hippocampus, we did find clear-cut group differences in driving ratings, and the regression findings were robust. Having a larger sample would allow for investigation of neurocognitive correlates of driving abilities and further examination of possible laterality effects, as well as consideration of medication use effects. Although the educational attainment of our control participants did not differ from that of our MCI participants, this sample generally had attended some college and therefore may not be representative of all community dwelling older adults. Furthermore, although our statistical comparisons were planned and data reduction techniques were used to minimize experimentwise error, we cannot rule out the possibility that our findings could be due to Type I error. Furthermore, while our use of a validated ROI approach was guided by our *a priori* interest in understanding how hippocampal atrophy influences functional abilities, such approaches preclude the detection of potential effects that lie outside of the chosen ROI. The use of whole-brain voxel-wise analyses and other evolving approaches in the future may amplify upon these findings.

Better discernment of risks associated with declines in driving in early dementia and mild cognitive impairment is of high importance. This study is a preliminary attempt to link ratings of driving skills with structural MRI of the hippocampus in persons with amnesic MCI. Although tentative, these findings suggest that there is a link between hippocampal atrophy and diminished lane control performance in persons with amnesic MCI. However, our data should not be interpreted as raising concerns regarding driving safety in MCI. Indeed, as we reported in our previous study among the larger sample of MCI participants

and controls¹⁰, ratings of unsatisfactory or unsafe driving performance were infrequent (occurring in 10 of 105 participants in that study), were isolated to instances of turning and lane control, and did not occur exclusively among participants with MCI.

Further study appears warranted to better discern patterns of brain atrophy in MCI and AD and whether these could identify risk for changes in driving skills and safety. In particular, research is needed which examines resting state functional activity in brain regions previously implicated in driving task performance, and functional connectivity patterns, in relation to hippocampal volume loss and naturalistic driving in MCI.

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Figure 1. Scatterplot of left hippocampal volume by lane control performance in patients with amnesic MCI.

Table 1
Demographics and Study Measures in Controls and MCI Patients

Variable	Controls <i>N</i> = 34	Amnesic MCI <i>N</i> = 15	<i>P</i> Value
Age mean (SD)	66.85 (7.68)	68.73 (7.07)	.410
Sex (males / females)	10 / 24	7 / 8	.242
Race (Caucasian / African-American)	30 / 4	11 / 4	.193
Education mean (SD)	15.44 (2.22)	14.67 (2.50)	.284
Mini-Mental State Exam score mean (SD)	29.48 (1.06)	28.47 (1.41)	.008
CDR Staging (0 / 0.5)	34 / 0	0 / 15	<.001
Cholinesterase Inhibitor (yes / no)	----	8 / 7	----
Right Turn (optimal / less than optimal)	27 / 7	9 / 6	.156
Left Turn (optimal / less than optimal)	22 / 12	7 / 8	.236
Lane Control (optimal / less than optimal)	27 / 7	7 / 8	.022
Gap Judgment (optimal / less than optimal)	18 / 16	3 / 12	.032
Steer Steadiness (optimal / less than optimal)	18 / 16	3 / 12	.032
Maintain Speed (optimal / less than optimal)	24 / 10	4 / 11	.004
Global Rating (optimal / less than optimal)	28 / 6	7 / 8	.011

Table 2

Volumes of Regions of Interest in Controls and MCI Patients^a

Measure	Controls N = 34 Mean (SD)	Amnesic MCI N = 15 Mean (SD)	Difference of mean Z Scores	P Value ^b	Number of MCI Patients below -1.0 SD	Effect Size d
Left Hippocampus	3.11 (0.31)	2.89 (0.36)	-.67	.057	6 / 15	.66
Right Hippocampus	2.91 (0.28)	2.75 (0.22)	-.49	.126	4 / 15	.58

^a observed values are in cm³

^b statistical test performed on Z score adjusted values

Table 3

Correlations among MRI Volume Regions of Interest and Driving Ratings

	Right Turn	Left Turn	Lane Control	Gap Judgment	Steer Steadiness	Maintain Speed	Global Rating	Left Hippocampus
Left Turn	.16	---						
Lane Control	.50**	.26	---					
Gap Judgment	.43**	.13	.31*	---				
Steer Steadiness	.43**	.22	.40**	.50**	---			
Maintain Speed	.60**	.29*	.59**	.42**	.58**	---		
Global Rating	.54**	.49**	.56**	.37**	.46**	.64**	---	
Left Hippocampus	.14	.09	.30*	.08	.04	.16	.16	---
Right Hippocampus	-.01	.04	.18	.00	.07	.08	.02	.89**

*

p < .05

**

p < .01

Table 4

Odds Ratios and 95% CIs for Less-than-optimal Lane Control

	B	SE	OR	CI	P Value
amnesic MCI	1.48	0.67	4.41	1.18, 16.36	.027
amnesic MCI ^a	1.24	0.70	3.46	0.88, 13.60	.076
Left hippocampal z score ^b	-1.63	0.74	0.20	0.05, 0.84	.028

^a adjusted for left hippocampus^b performed in amnesic MCI only