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ORIGINAL ARTICLE

Neuropsychological Performance, Brain Imaging, and Driving Violations in Multiple Sclerosis

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Abstract

Objective: To examine the relationship between third ventricular width, a measure of thalamic brain atrophy, and motor vehicle violation type and frequency in a cohort of patients with multiple sclerosis (MS).

Design: Retrospective cohort study.

Setting: Tertiary care university hospital.

Participants: Thirty-five individuals with clinically confirmed relapsing-remitting multiple sclerosis and 35 age-, sex-, and education-matched community-dwelling healthy comparisons (N = 70). Participants were aged between 25 and 65 years.

Interventions: Not applicable.

Main Outcome Measures: Data on motor vehicle violations were obtained from an online database (Iowa Courts Online). The violations were categorized as follows: (1) speeding, (2) nonmoving safety, (3) administrative, (4) alcohol-related offense, (5) moving safety, and (6) total violations. Neuropsychological performance in all major cognitive domains was obtained. Thalamic atrophy for the patients with MS was determined via third ventricular width measurement.

Results: The MS group had a greater number of overall violations, administrative violations, and nonmoving safety violations. The groups differed on neuropsychological tasks measuring visuospatial skills, speeded language, learning, and executive functioning, after controlling for affective symptoms. Third ventricular width was associated with total violations as well as moving safety violations. Finally, third ventricular width accounted for a significant variance in driving violation frequency above and beyond demographic variables and neuropsychological factors.

Conclusions: There is an increased frequency of motor vehicle violations among patients with multiple sclerosis, and the number of violations can be predicted by thalamic brain atrophy.

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Multiple sclerosis (MS) results in physical and cognitive deterioration and can affect driving performance. A registry-based study demonstrated that patients with MS had a crash rate per 1000 person-years 3.4 times that of controls.[1] The increased rate of motor vehicle crashes and violations in the MS population portends a need for a clinically accessible means of assessing this population. Despite the need for such a measure, there is a dearth of investigation in MS relative to other neurologically impaired populations (eg, dementia).[2-5] Such neurological populations have higher incidences of accidents and violations, and neuropsychological testing has been used to predict future on-road events.[6,7] Despite the established link between neuropsychological profiles and magnetic resonance imaging (MRI) evidence of disease, there is little literature exploring the relationship between MRI and driving violations. Thus, additional characterization of driving ability in the 2.5 million people diagnosed with MS[8] worldwide is needed.

A seminal study from 2001[9] compared patients with MS with cognitive decline, patients without cognitive decline, and healthy controls. Findings suggested that information processing speed played a significant role in declining driving ability. However, the study was limited by the heterogeneity of the sample, consisting of patients with relapsing-remitting and secondary-progressive MS, as well as uncategorized patients. Little was added to the literature until 2008, when a group examined whether neuropsychological

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measures could be used as predictors of on-road driving ability. On-road driving performance was dichotomized as "safe" or "unsafe" ("safety" being determined by a driving instructor approved by the Department of Transportation; the drivers were deemed "safe" or "unsafe" on the basis of performance on 25 maneuvers), and relations with measures of memory, information processing speed, and executive functions were identified.[10] Interestingly, to date, no study has examined the association between driving ability and brain MRI, despite MRI evaluation being the standard of care and there being a robust relation between MRI and cognition. For example, Rovaris et al[11] indicated that frontal lobe lesion load was associated with problem-solving and verbal fluency. In assessing the relation between MRI and cognitive decline, imaging researchers have adopted sophisticated methods (eg, functional MRI)[12]; however, such methods typically demand time-consuming image acquisition and complex interpretation of results; thus, they are not easily integrated into routine clinical practice. In contrast, third ventricular width measurement (a surrogate marker of thalamic gray matter atrophy[13,14]) has been shown to be a simple, yet valid and clinically useful predictor of cognitive dysfunction.

Recent literature has suggested that gray matter atrophy plays a greater role in MS pathology than previously believed. Gray matter atrophy has been shown to progress at a greater rate and is independent of white matter volume loss.[15,16] It is therefore important to note the pertinence of the thalamus.[14,17,18] Houtchens et al[19] found that thalamic volume was 16.8% lower among patients with MS than among healthy controls and found a robust relation between thalamic volume and cognition ($r=.51-.72$).

We aimed to (1) examine whether patients with MS have an increased incidence of driving violations relative to healthy comparisons; (2) explore whether the clinically useful MRI variable involving third ventricular width was associated with driving behavior in MS; and (3) explore whether specific cognitive domains and MRI measures were predictive of the total number of driving violations.

Methods

Participants

Multiple sclerosis

With ethical approval from the University of Iowa's Institutional Review Board, 2 unique databanks housed within a large Midwestern tertiary care center (the University of Iowa Hospitals and Clinics) were queried to identify participants. The first databank, the Multiple Sclerosis Registry, is directed by one of our authors (E.T.). Patients within the registry were evaluated by the University of Iowa Hospitals and Clinics staff neurologists and diagnosed with MS after consensus review and according to the McDonald Criteria (see Poser and Brinar[20]). The second databank, the Benton Neuropsychology Laboratory Database, contains data on all participants clinically referred and evaluated in the Benton Neuropsychology Laboratory for neuropsychological examination. The following were deemed exclusionary: (1) primary psychiatric disorder; (2) history of drug/alcohol abuse; and/or (3) administering neuropsychologist deemed the testing results invalid (through the inclusion of symptom validity tests[21]). The sample was limited to individuals with an Expanded Disability Status Scale score of <6, an education level of at least eighth grade, and individuals aged between 18 and 70 years. To create a homogeneous sample, only individuals with relapsing-remitting type were included. Additional exclusionary criteria included active exacerbation (diagnosed by a clinical neurologist specializing in MS) and diagnosis within 6 months. Forty-one patients with relapsing-remitting MS remained (MS group). MRIs were obtained from the University of Iowa Hospitals and Clinics's electronic medical record; 3 MRIs were unobtainable because they predated EPIC, and 3 participants did not undergo MRI for unclear reasons, leaving the final sample at 35 patients.

List of abbreviations:

BDI-II Beck Depression Inventory, Second Edition
MRI magnetic resonance imaging
MS multiple sclerosis

Healthy comparisons

An age-, sex-, and education-matched non-MS comparison sample of 35 individuals was gleaned from an ongoing research study, directed by one of our authors (N.L.D.). The healthy comparison sample was previously recruited via advertisements posted locally; only healthy, community-dwelling adults were included. Exclusionary criteria included neurological and/or psychiatric illness determined by a comprehensive clinical interview (after Tranel et al[22]).

On-road driving

Iowa Courts Online Database[23] (a free, public access service) was searched for records of driving violations in the MS group and the healthy comparison group. In an effort to generate additional texture in the data, we divided driving violations into 5 classes, in addition to total violations. We based selection of the 5 categories on several empirical studies from the driving literature.[24,25] Violations were divided into 5 categories: speeding, nonmoving safety (eg, failure to maintain safety belts), administrative (eg, failure to have valid registration), alcohol-related, and moving safety (eg, failure to yield). No violations were placed into >1 category; that is, a speeding violation was also not included in the moving safety category. The total number of violations in each category was summed. In addition, the violations were summed to create "total violations," a commonly used metric.[26,27]

Neuropsychological measures

The neuropsychological battery included the following and represented all cognitive domains. Attention and working memory (Digit Span),[28] psychomotor speed (Grooved Pegboard and Trails A),[29,30] language (Controlled Oral Word Association Test),[28,31] visuospatial (Block Design and Rey-Osterrieth Copy),[32] anterograde memory (Rey-Osterrieth Delay and Rey Auditory-Verbal Learning Test),[33] information processing (Digit Symbol/Coding),[28] executive functioning (Trails B),[30] and mood (Beck Depression Inventory).[34] Instruments were administered by technicians in the Benton Neuropsychology Laboratory (patients with MS) or research assistants in the Denburg laboratory (healthy comparison participants).

Brain MRI and analysis

Thirty-five brain MRIs were measured using EPIC. Selected scans were chronologically proximal to the neuropsychological and clinical evaluation dates (the modal amount of time between the

acquisition of the scan and the neuropsychological data was <1y). The emergence of gray matter atrophy as a key contributor to MS pathology, in addition to one's ability to measure from clinical MRI the width of the third ventricle, led us to select third ventricular width as our marker of gray matter disease. To obtain the third ventricular width, a representative axial slice, at which the anterior commissure and columns of fornix were visible, was selected. Next, a line was drawn through the long axis of the third ventricle parallel to the interhemispheric fissure. A second line was drawn perpendicular to the midpoint of this line and its length recorded after the method described by Benedict et al.[35]

Data analysis

Because this study is exploratory, no adjustment was made for multiple testing and .05 was used as the level of significance. To analyze the background characteristics of the groups, independent samples *t* tests and chi-square analyses were used. Multivariate analysis of covariance was computed using each of the 12 neuropsychological variables as the dependent variables, participant group (ie, MS vs healthy comparison) as the independent variable, and mood (Beck Depression Inventory, Second Edition [BDI-II]) score as the covariate. Multivariate analysis of variance was computed using each of the driving violation class as the dependent variables and participant group as the independent variable. Correlations between the different classes of driving violations and brain MRI measurement were examined. Finally, hierarchical regressions were conducted to examine the relation between neuropsychological performances and brain MRI to total driving violations, with attention to their contributions over and above the effects of demographic characteristics and mood. In the first step, demographic variables and BDI-II were entered into the regression equation. Neuropsychological performances relevant to driving performance based on past empirical literature[36-39] were entered into the second step. In the last step, third ventricular width was entered into the model to determine whether the unique contribution of the third ventricular width remained significant after accounting for the variance predicted by demographic characteristics, neuropsychological factors, and mood. Analyses were conducted with SPSS 19.0.0.1.[40,a]

Results

A total of 86% of the participants were white, and 89% were women. No participants were experiencing an active exacerbation at the time of MRI and neuropsychological testing; 66% were prescribed an MS disease-modifying medication (eg, beta interferon). Mean Expanded Disability Status Scale score at time of neuropsychological testing and MRI was 2.87±1.21 (range, 0−6). The mean time from the diagnosis of MS to neuropsychological evaluation and MRI was 5.8±6.78 years. Participants had a minimal visual acuity of 20/50 based on Snellen[41] chart testing.

Demographic and neuropsychological variables of MS and healthy comparison groups

Independent samples *t* tests and chi-square analyses revealed that the MS and healthy comparison groups were indistinguishable with regard to age, education, sex, handedness, and race. The 2 groups differed in terms of self-reported depression (as measured by the BDI-II)[42] (table 1), as is commonly reported in the literature.[43]

We contrasted the neuropsychological performances of the MS and healthy comparison groups while using self-reported depression (BDI-II) as a covariate. The multivariate analysis of covariance resulted in a significant multivariate effect of group ($F_{12,56}=2.37$; $P<.015$), with the healthy comparison group outperforming the MS group. Group differences were observed on several of the neuropsychological measures: Block Design ($F_{1,67}=12.46$; $P=.001$), Auditory Verbal Learning Test Learning ($F_{1,67}=5.40$; $P=.02$), Controlled Oral Word Association Test ($F_{1,67}=5.39$; $P=.02$), and Trail Making B ($F_{1,67}=4.86$; $P=.03$). The group differences were statistically insignificant ($P>.05$) on the remaining neuropsychological instruments, namely, Digit Span, Auditory Verbal Learning Test Recall, Rey-Osterrieth Copy, Rey-Osterrieth Delay (trend, $P=.07$), and Trail Making A time, Coding (trend, $P=.09$), and Grooved Pegboard (trend, $P=.09$) (table 2).

Driving violations in MS and healthy comparison groups

The multivariate analysis of variance resulted in a significant multivariate effect of group ($F_{6,63}=2.68$; $P=.02$), with the MS group demonstrating a higher rate of driving violations than did the healthy comparison group (table 3). Group differences were observed for nonmoving safety violations ($F_{1,68}=8.81$; $P=.004$), administrative violations ($F_{1,68}=5.56$; $P=.02$), and total violations ($F_{1,68}=5.93$; $P=.02$). In contrast, the number of speeding violations, alcohol-related violations, and moving safety violations were not significantly different between the groups ($P>.05$).

Driving violations and brain MRI in MS

Within our MS group, third ventricular width was associated with several driving violation outcomes. Using bivariate correlations, third ventricular width was significantly associated with total violations ($r=.48$; $P=.004$) and moving safety violations ($r=.51$; $P=.002$).

Neuropsychological performance, brain MRI, and driving violations in MS

The first step of the regression analysis revealed that age, education, sex, and mood accounted for a nonsignificant 10.1%

Table 1 Demographic and clinical characteristics by group

	Participant Group		
Characteristic	MS (n=35)	HC (n=35)	Significance
Age (y)	43.83±9.61	45.83±10.94	.42
Sex: female	83	83	.62
Education (y)	13.66±1.89	14.11±1.57	.28
Handedness: right handed	89	89	.52
Race: white	86	97	.09
EDSS score	2.87±1.21	NA	NT
BDI-II score	17.83±11.38	3.80±3.20	*P*<.0001

NOTE. Values are mean ± SD or %. The significance of continuous measures was tested with independent samples *t* tests. The categorical variables, sex, handedness, and ethnicity, were tested by using the chi-square test.
Abbreviations: EDSS, Expanded Disability Status Scale; HC, healthy comparison; NA, not applicable/available; NT, not tested.

Table 2 MANCOVA results for neuropsychological data by group

	Participant Group*		Significance	
Neuropsychological Test	MS (n=35)	HC (n=35)	F	*P*
WAIS-III Digit Span (working memory)	9.74±2.99	10.63±2.54	.07	.79
Grooved Pegs (DH) (psychomotor speed)	80.43±19.13	86.86±22.76	2.88	.09
Trail Making A (psychomotor speed)	31.37±11.17	27.31±7.49	.50	.48
COWAT (verbal fluency)	36.4±12.07	45.51±8.86	5.39	.02
WAIS-III Block Design (visuospatial)	9.23±2.20	12.11±2.22	12.46	.001
Rey-Osterrieth Copy (visuospatial)	29.79±2.57	31.81±3.92	2.98	.09
Rey-Osterrieth Recall (anterograde memory)	15.86±5.49	19.53±5.71	1.54	.22
AVLT Learning (anterograde memory)	47.26±7.99	55.69±10.50	5.40	.02
AVLT 30min Delay (anterograde memory)	10.03±3.57	12.23±2.78	3.48	.07
WAIS-III Coding (information processing)	10.26±3.04	12.74±2.77	3.53	.06
Trail Making B (executive functioning)	83.63±34.99	55.11±14.68	4.86	.03

NOTE. Raw scores are provided for each of the neuropsychological variables, with the exception of those noted. WAIS-III (in standard scores); Grooved Pegboard Test—Dominant Hand (in seconds); Trail Making Tests (in seconds); COWAT; Benton Facial Recognition Test (Benton Faces); Rey Auditory—Verbal Learning Test sum of trials 1 to 5 and 30-min delayed recall (AVLT Learning and AVLT 30min Delay).
Abbreviations: AVLT, Auditory Verbal Learning Test; COWAT, Controlled Oral Word Association Test; DH, dominant hand; HC, healthy comparison; MANCOVA, multivariate analysis of covariance; WAIS-III, Wechsler Adult Intelligence Scale—Third Edition.
* Data are presented as mean ± SD.

(*P*=.128) of the variance in total driving violations. In the second step, neuropsychological variables added a nonsignificant 8.4% (*P*=.553) of the variance in total driving violations. After accounting for the variance predicted by these variables, adding third ventricular width to the predictive model increased the amount of total driving violations variance accounted for by a significant 24.1% (adjusted), *P*=.001 (table 4).

Discussion

Our study demonstrated that patients with MS have an increased frequency of total, nonmoving safety, and administrative driving violations relative to a demographically matched healthy comparison group. Consistent with the existing literature, we also showed that the MS group performed inferiorly to the healthy comparison group on several measures of cognition, including verbal list-learning, speeded verbal fluency, and executive functioning (information processing speed approached significance; *P*=.06). We also identified a meaningful relationship between the frequency of driving violations and third ventricular width. In addition, third ventricular width predicted a significant portion of unique variance in total driving violations after taking into account demographic (including mood) and neuropsychological variables.

Table 3 MANOVA results for driving violations by group

	Participant Groups		
Variable	MS (n=35)	HC (n=35)	Significance
Speeding	0.49±1.01	0.31±0.63	.40
Nonmoving safety	0.34±0.68	0.00±0.00	.004
Administrative	0.37±0.84	0.03±0.17	.02
Alcohol-related	0.11±0.68	0.00±0.00	.32
Moving safety	0.34±0.94	0.09±0.28	.13
Total violations	1.57±2.63	0.46±0.66	.02

NOTE. Data are presented as mean ± SD.
Abbreviations: HC, healthy comparison; MANOVA, multivariate analysis of variance.

To our knowledge, we are the first group to analyze driving violation frequency in relation to thalamic atrophy. Third ventricular width was strongly associated with moving safety violations and total number of driving violations, suggesting that this measurement may provide evidence-based means for recommendations regarding the need for additional testing (eg, over-the-road evaluation). These results are particularly exciting because gray matter atrophy has emerged as a prominent aspect of MS pathology, in addition to the thalamus being subject to injury in MS, supporting the utility of third ventricle width measurement in this population.[44]

This study is particularly relevant to practicing clinicians because our study population and design are reflective of a typical population with relapsing-remitting MS. We restricted the participants to the relapsing-remitting subtype because those with secondary-progressive MS are by definition at a later point in the disease course; similarly, those with primary-progressive MS exhibit a different natural history. Previous studies exploring the relationship between cognitive decline and driving violations have excluded individuals with greater physical dysfunction.[23] In contrast, we chose to include a spectrum of Expanded Disability Status Scale scores to ease extrapolation of data to community patient populations. We note that we are the first to separate driving violations into categories. The result of this categorization allowed for a more fine-grained MS driving profile than simply "total violations." This information provides clinicians with a greater ability to describe to their patients the potential dangers of continued driving operation. Our findings suggest that thalamic atrophy, an increasingly prominent region of study in MS, may serve as a means of assessing driving safety, particularly in the absence of other forms of assessment (eg, on-road driving examination). Although studies have suggested that thalamic atrophy is due to axonal loss,[13] future prospective studies should obtain imaging at multiple time points to better establish the relation between thalamic volume loss and driving behaviors. We also successfully demonstrated that third ventricular width is a potentially viable means of predicting the increased risk of driving violations.

Table 4 Hierarchical regression of demographic characteristics, mood, neuropsychological performance, and TVW to total driving violations

	R^2	Adjusted R^2	R^2 Change	F Change	F Change Significance	b	*t* Value	b Significance
Step 1	.206	.101	.206	1.951	.128			
Demographic and mood*								
Step 2	.291	.072	.084	.770	.554			
Demographic and mood*								
Neuropsychological performance†								
Step 3	.532	.363	.241	12.883	.001			
Age						−.332	−1.931	.065
Sex						.089	.559	.581
Education						−.304	−1.788	.086
Mood						.143	.932	.360
Trails A						−.280	−1.215	.236
Trails B						−.134	−.623	.539
AVLT 30min Delay						.012	.079	.938
WAIS Coding						−.097	−.536	.597
TVW						.566	3.589	.001

Abbreviations: AVLT, Auditory Verbal Learning Test; TVW, third ventricular width; WAIS, Wechsler Adult Intelligence Scale.

* Age, sex, education, mood.

† Trails A, Trails B, AVLT 30min Delay, WAIS Coding.

Study limitations

This study is not without its limitations. Because the study is retrospective, we were unable to obtain data regarding the participants' driving habits (eg, days per week driving) relative to their driving violation frequency. An additional limitation of this study is that we did not adjust for multiple testing to control for type I errors. Given that the study is exploratory in nature, we felt that it was important to highlight the contributions of various factors (eg, neuropsychological performance and third ventricular width) to driving behavior in MS. Our findings should be viewed as forming a basis for future investigations.

Conclusions

The demonstration of a relation between the frequency of driving violations and thalamic atrophy suggests an additional clinical role for brain MRI. This is particularly exciting because MRI has become the standard of care in the evaluation of the patient with MS; thus, obtaining third ventricular width measurement would not require acquisition of additional imaging. The increasing interest in gray matter involvement, specifically the thalamus, also supports the utility of this measure because it taps into an additional component of MS pathology. Finally, the neuropsychological profile seen in our sample is consistent with the existing literature,[13] demonstrating the generalizability of our results to other populations. We believe that the third ventricular width measure has the potential to provide patients and physicians with additional advice regarding patients' ability to drive safely—a clinically and socially important finding.

Supplier

a. SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

Keywords

Automobile driving; Multiple sclerosis; Neuropsychology; Rehabilitation

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