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A SPECT Imaging Study Of Driving Impairment In Patients With Alzheimer's Disease

Brian R. Ott, MD^{*}, William C. Heindel, PhD^{**}, William M. Whelihan, PhD^{***}, Mark D. Caron, PhD^{***}, Andrea L. Piatt, MA^{***}, and Richard B. Noto, MD^{****}

^{*} the Neurology Division at Memorial Hospital, Brown University School of Medicine

^{**} the Department of Psychology at Brown University

^{***} the Neuropsychology Division at Roger Williams Medical Center

^{****} the Department of Diagnostic Imaging at Rhode Island Hospital.

Abstract

Single photon emission computed tomography (SPECT) was used in this study to examine the neurophysiologic basis of driving impairment in 79 subjects with dementia. Driving impairment, as measured by caregiver ratings, was significantly related to regional reduction of right hemisphere cortical perfusion on SPECT, particularly in the temporo-occipital area. With increased severity of driving impairment, frontal cortical perfusion was also reduced. Clock drawing was more significantly related to driving impairment than the Mini-Mental State Examination. Driving impairment in Alzheimer's disease is related to changes in cortical function which vary according to severity of disease. Cognitive tests of visuo-perceptual and executive functions may be more useful screening tools for identifying those at greatest risk for driving problems than examinations like the Mini-Mental State Examination, that are weighted toward left hemisphere based verbal tasks.

Keywords

SPECT; driving; Alzheimer's disease; dementia

Dementia is a well-recognized risk factor for hazardous driving, which may contribute substantially to the problem of motor vehicle accidents among the elderly. A number of editorials and review articles have addressed the issue of driving and dementia.[1-10]

In one retrospective study covering three years, drivers with Alzheimer's disease (AD) had 26.6 motor vehicle accidents per million vehicle miles of travel, compared to 8.5 for normal elderly controls.[11] Another retrospective study, based on review of driving records of 165 dementia cases and 165 controls, found that demented drivers are approximately 2.5 times more likely to be involved in motor vehicle crashes than age matched non-demented drivers. [12] In this same study, over 80% in the dementia group continued to drive over the three years following a crash, with over one-third of cases subsequently having another accident. [13] Another earlier pilot study which employed a driving history questionnaire, found that 30% of persons attending an outpatient dementia research clinic had at least one accident since the onset of their illness.[14] Friedland and coworkers[15] found a 47% prevalence rate of crashes among 30 persons with AD compared to 10% of 20 age-matched controls in

a retrospective survey over five years. Overall, there is probably a two-to-eightfold greater crash risk for elderly drivers with mild to moderate dementia compared to those not demented.[16]

If one assumes that not all demented persons are incompetent drivers, then it becomes particularly important to determine the most important cognitive or functional factors that contribute to driving impairment. Examination of neurophysiological variables that govern driving ability may extend our knowledge of these issues. Studies of the anatomic or physiologic cortical brain abnormalities that result in driving impairment in dementia, however, have not been done to our knowledge. Since cortical metabolism is directly linked to cerebral blood flow, single photon computed tomography (SPECT) provides a suitable tool for this purpose of investigation.

The present study examined the relationship of regional changes in cerebral perfusion on SPECT to reports of driving competence by caregivers of dementia patients. We chose caregiver assessment of driving ability as the dependent variable because of its face validity and practical availability. The advantage of caregiver assessments are 1) that they are based on a large period of observation time under different driving circumstances, 2) change from premorbid skills can be accounted for, and 3) misleading effects of anxiety or best behavior in the situation of a formal road test are not factors.

Whether or not caregivers can reliably assess driving skills, though, compared to other approaches such as standard road tests and road simulation tests is relatively unknown. It has been established that caregiver ratings of memory performance are valid predictors of performance on neuropsychological tests.[17] One study which examined the validity of caregiver reports on driving performance found that motor vehicle accidents were associated with lower ratings of dementia patients' driving ability by caregivers.[18]

The purpose of the present study was to define the neurophysiologic substrate for driving impairment in dementia. In a secondary analysis measures of daily functional abilities, as well as general cognitive, executive, and visuospatial ability were examined as correlates of driving impairment.

METHODS

Subjects

All patients were drawn from the Alzheimer's Disease and Memory Disorders Unit at Roger Williams Medical Center -- an outpatient diagnostic and treatment clinic in Providence, Rhode Island. Subjects selected for this study were all those patients who had undergone SPECT imaging as part of their diagnostic evaluation for suspected Alzheimer's disease or other type degenerative dementia. Patients who had never driven were excluded. There were 79 demented drivers with SPECT images, including 39 men and 40 women. The mean age was 74.7 ± 7.9 years; mean educational level was 11.6 ± 3.5 years; mean duration of illness was 2.7 ± 1.6 years. Clinical Dementia Ratings (CDR)[19] for the subjects were: questionable or very mild in 35, mild in 28, and moderate in 16. The mean Mini-Mental State Examination (MMSE)[20] score was 19.6 ± 4.9 . Based on NINCDS-ADRDA diagnostic criteria,[21] 52 subjects were classified as probable and 27 were classified as possible Alzheimer's disease. All subjects underwent computed tomography or magnetic resonance imaging as well as a battery of laboratory tests (cobalamin, thyroid function, chemistry profile, syphilis serology, complete blood count) to exclude other treatable causes of dementia.

SPECT studies

SPECT scans were performed at the Rhode Island Hospital Department of Diagnostic Imaging using a Picker Prism 2000 dual head camera. The procedures have been described in detail elsewhere.[22] While lying supine in a quiet room with eyes closed, patients received an intravenous injection of 20 mCi (740 MBq) of [^{99m}Tc]HMPAO (Ceretek, Amersham, Arlington Heights, IL). Scanning took place approximately one hour after injection using a rotating gamma camera. SPECT scanning was performed with a 360° rotation around the patient, with 64 images acquired at 5.6° intervals. A high-resolution collimator was employed. Raw data was prefiltered and reconstructed using standard back-projection techniques into transaxial, coronal, and sagittal planes.

For the semiquantitative analysis, multiple contiguous transaxial slices were reconstructed, each 4.7 mm. in thickness, and oriented parallel to the canthomeatal line. Bilateral 19 mm. X 19 mm. regions of interest (ROI) were sampled from the transaxial slices involving the cerebellum and six bilateral areas of association cortex: superior prefrontal, inferior prefrontal, anterior temporal, posterior temporal, parietal, and lateral occipital.

The slice that best displayed the fourth ventricle and cerebellum was chosen as baseline, and cerebellar ROI's were placed on this slice. Other ROI's were sampled from the six areas of association cortex. Superior prefrontal ROI's were placed 15 slices superior to baseline. Inferior prefrontal ROI's were placed eight slices superior to baseline. Anterior and posterior temporal ROI's were placed at a level two slices above the baseline. Parietal ROI's were placed at a level 12 slices above the baseline. Lateral occipital ROI's were placed at a level seven slices above the baseline. In each case, the ROI was placed in what was felt to represent the center of the particular cortical region displayed on that slice.

Localization for the ROI's was confirmed by comparison of the SPECT image slices with neuroanatomical templates from the same orientation and levels.[23] SPECT data were measured as radioactive counts per pixel normalized to average cerebellum counts per pixel (ROI/cerebellum). SPECT images were not corrected for atrophy, since co-registration with magnetic resonance images was not performed.

Clinical measures

A modification of a caregiver-rated driving ability scale was administered.[24] Driving ability of all subjects was rated by their caregivers on a four-point scale: 1) is unable to drive due to dementia; 2) Drives when someone is present to give directions (weaves from side to side, is slow in stopping for red lights and at stop signs for example); drives very slowly and cautiously; 3) drives alone, but has some tendency to lose way and get lost; has some problems driving such as occasionally driving too close to cars on either side or overshooting a traffic light or stop sign; 4) drives alone; has good sense of direction and driving skills.

A modification of the Lawton and Brody Instrumental Activities of Daily Living (IADL) scale[25] was also administered. The eight items on this scale included ability to use a telephone, shopping, food preparation, housekeeping, laundry, responsibility for own medication, ability to handle finances, and ability to perform household repairs or chores. The score for the IADL was taken as the score of items that were felt applicable to the subject divided by the total maximum applicable item score for each subject.

Other clinical measures that were performed included the Mini-Mental State Examination and clock drawing to command and to copy. The clock drawings were specifically chosen as a study variable to examine executive and nonverbal visuoconstruction abilities. The subject was asked to draw a clock on a blank sheet of paper and set the hands to 11:10. If the subject

had any difficulty with the clock to command, he or she was asked to copy a clock drawing. Each clock was scored on a five point scale based on a modification of the scoring system proposed by Henderson et al.[26] One point was allotted for each of the following: 1) all numbers present and in correct order; 2) numbers drawn on an imaginary circle within an outline; 3) hands clearly of different lengths; 4) origin of hands near center of the numbers; and 5) time correctly set. Subjects who drew a normal clock to command were assumed to draw a normal clock to copy and given a score of five for both tasks.

RESULTS

Table 1 shows the psychometric and demographic characteristics of the 79 subjects used in the present study, grouped according to their level of driving ability. One-way analyses of variance (ANOVA) indicated that the four groups of patients did not differ significantly in terms of age, education, duration of illness, or MMSE score. However, there was a highly significant difference among the four groups in terms of IADL score [$F(3,75)=18.65$; $p<.0001$]. Pair-wise comparisons, using the Newman-Keuls procedure for controlling Type I error at .05, indicated that the mean IADL score of the subjects that were unable to drive was significantly lower than the mean scores of the three less impaired groups, and that subjects with normal driving ability also displayed a significantly higher mean IADL score than those who drove poorly. Among those who had a deficit of at least 30% in their total IADL score, 27/36 (75%) were rated as unable to drive, compared to 6/43 (14%) of those who had not declined by this degree.

Inspection of Table 1 indicates that mean IADL score declined monotonically with decreasing driving ability, a finding supported by a significant Spearman rank correlation between Drive Score and IADL ($r_s = .66$, $p<.001$). Spearman rank correlation also revealed a strong monotonic relationship between Drive Score and CDR ($r_s = -.53$, $p<.001$). Taken together, these findings suggest that the 4-point driving scale used in the present study provides an ordinal measure of driving ability in AD patients.

A principal component factor analysis was performed using varimax transformation on the 12 SPECT ROI variables obtained for each subject. As shown in Table 2, each of the 12 variables loaded strongly on one of three factors: a bilateral temporoparietal factor accounting for 47% of the variance; a bilateral frontal factor accounting for 37% of the variance; and a bilateral occipital factor accounting for 15% of the variance.

The three derived factor scores obtained for each individual from the factor analysis were then used to examine whether different levels of driving impairment were associated with different patterns of regional brain perfusion. First, omnibus one-way ANOVAs were performed using Drive Score as the grouping variable and the three factor scores as dependent variables. A significant ANOVA was then followed by two planned contrasts designed to identify the locus of the significant group difference: (1) The average perfusion of the two groups of subjects who drove alone was compared to that of the two groups of subjects who did not drive alone; and (2) The average perfusion of the two groups who drove with difficulty was compared to that of the group of subjects who were unable to drive. The three one-way ANOVAs revealed significant effects of Drive Score on perfusion in the frontal [$F(3,75)=3.23$, $p<.05$] and temporoparietal [$F(3,75)=2.82$, $p<.05$] regions, but not in the occipital region [$F(3,75)=1.58$, $p=.20$]. The planned contrasts further revealed that: (1) Subjects who drove alone differed significantly from subjects who did not drive alone in perfusion of the temporoparietal [$t(75)=2.34$, $p=.02$] but not the frontal region (see Figure 1A); and (2) Subjects who drove with difficulty differed significantly from subjects who were unable to drive in perfusion of the frontal [$t(75)=2.92$, $p=.005$] but not the temporoparietal region (see Figure 1B). [The factor scores are standardized with a mean of

zero. Consequently, the factor scores for each individual region in Figure 1 are positively loaded for driving competence and negatively loaded for driving incompetence.]

Similar analyses were also performed on the semiquantitative counts for the 12 original SPECT ROI's listed in Table 2. First, omnibus one-way ANOVAs revealed significant effects of Drive Score on perfusion in the high frontal [$F(3,75)=2.93$, $p<.05$], low frontal [$F(3,75)=4.96$, $p<.01$], posterior temporal [$F(3,75)=2.99$, $p<.05$] and occipital [$F(3,75)=6.65$, $p<.001$] regions within the right hemisphere, and in the high frontal [$F(3,75)=3.18$, $p<.05$] and low frontal [$F(3,75)=3.09$, $p<.05$] regions within the left hemisphere. Second, planned contrasts following these six significant ANOVAs indicated that: (1) Subjects who drove alone differed significantly from subjects who did not drive alone in perfusion of the right posterior temporal [$t(75)=2.2$, $p=.03$] and right occipital [$t(75)=2.33$, $p=.02$] regions, but not in perfusion of the four frontal regions (See Figure 2A); and (2) Subjects who drove with difficulty differed significantly from subjects who were unable to drive in perfusion of all four frontal regions [right high frontal: $t(75)=2.86$, $p=.006$; right low frontal: $t(75)=3.26$, $p=.002$; left high frontal: $t(75)=2.90$, $p=.005$; left low frontal: $t(75)=2.93$, $p=.005$] plus the right occipital region [$t(75)=3.68$, $p<.001$], but not in perfusion of the right posterior temporal region (see Figure 2B). Using a more conservative estimate of significance at $p<.004$ as a Bonferroni correction for multiple comparisons, the difference in the right low frontal and right occipital regions in the second contrast were still statistically significant.

In a secondary analysis, scores for clock drawing to command and clock drawing to copy were examined for their relationship to driving ability. Omnibus one-way ANOVAs revealed a significant effect of Drive Score on both drawing to command [$F(3,64)=4.22$, $p<.01$] and drawing to copy [$F(3,60)=2.96$, $p<.05$]. Planned contrasts further revealed that: (1) Subjects who drove alone differed significantly from subjects who did not drive alone on drawing to copy [$t(60)=2.10$, $p<.05$] but not on drawing to command; and (2) Subjects who drove with difficulty differed significantly from subjects who were unable to drive on both drawing to copy [$t(60)=2.01$, $p<.05$] and drawing to command [$t(64)=2.29$, $p<.05$].

Spearman rank order correlations were also performed to assess the relationship of SPECT and clock drawing scores to overall ratings of driving ability. Driving Score was significantly correlated with right hemisphere perfusion in the low frontal, temporal and occipital regions, and with left hemisphere perfusion in the occipital region (all $r_s>.30$, and all $p's<.05$). Using a Bonferroni correction, driving score was still significantly related to right low frontal ($r_s=.30$, $p=.002$) and right occipital ($r_s=.40$, $p=.001$) perfusion. A significant correlation was also observed between Driving Score and clock drawing to copy ($r_s=.32$, $p=.009$), but not between Driving Score and clock drawing to command ($r_s=.19$, $p=.114$).

DISCUSSION

This study demonstrates that severity of driving impairment is correlated with severity of dementia as measured by the CDR and IADL, but not by global cognitive function as measured by the MMSE. More importantly the SPECT data on cortical perfusion extend our knowledge about the neurophysiologic basis of driving impairment in dementia by demonstrating a significant relationship between the severity of driving impairment and regional changes in cortical perfusion. In particular, these results suggest that there is a shift in the critical brain regions that are associated with different degrees of driving impairment. Changes in temporoparietal regions were found to be associated with milder driving impairment (i.e., between patients who drive alone vs. those who drive with difficulty), whereas changes in frontal regions were associated with more severe driving difficulty (i.e., between patients who drove with difficulty vs. those unable to drive). Comparisons of the

original 12 SPECT ROI's from which the factor scores were derived similarly indicated a shift from greater temporoparietal differences in the milder stages of driving impairment to greater frontal differences with more severe driving impairment. Moreover, these results also indicate a strong right posterior hemisphere contribution to driving impairment in dementia patients, with no significant left hemisphere perfusion differences in the milder stages of driving impairment, and only left frontal involvement in the more impaired stages. In the future, psychometric instruments that are most sensitive to changes in cortical function of these areas should be more extensively examined as potentially useful predictors of driving impairment.

The neurophysiological findings obtained in the present study are also generally consistent with findings from previous studies investigating the cognitive correlates of driving ability. Previous neuropsychological studies have demonstrated a significant relationship between driving performance and tests of visual performance, including visual tracking,[27] visuoception,[28,29] visual memory,[30] and visuospatial constructions.[23] Taken together these studies strongly suggest a relationship between driving impairment and visuo-perceptual ability, a finding consistent with our observation of greatest reduction of cortical perfusion in the posterior temporoparietal and right occipital association cortex. These are regions most severely affected early in the course of AD, and indeed our patient sample consisted of patients who likely had AD. Autopsy studies have shown that the majority of patients classified as possible AD as well as probable AD by NINCDS-ADRDA criteria have Alzheimer type pathology.[31,32] Since co-registration with MRI was not performed in this study, it is unknown whether the regional changes related to driving are due to cortical dysfunction of existing cells and their connections or to actual death and atrophy of the involved tissue.

The finding in the present study of a significant association between more severe driving impairment and frontal dysfunction is consistent with a previous report by Brown et al[33] indicating a posterior to anterior progression of reduced cortical perfusion on serial SPECT over time in patients with AD. Although our data is cross-sectional in nature, the temporal progression of regional pathology provides a plausible explanation for why this shift occurs. Thus, while the major underlying physiological and psychological changes that relate to driving impairment are likely to be visuo-perceptual problems from right temporo-occipital lobe dysfunction, as AD progresses and involves the frontal regions more severely, executive dysfunction may be the additional factor that finally leads to driving incompetence to the degree that safe driving is no longer possible.

Consistent with previous findings, the present study also demonstrated a significant association between effect of stage of driving impairment and daily functional ability (as measured by IADL) but not between driving impairment and general cognitive functioning (as measured by the MMSE). Hill and coworkers[34] previously found that tests of visuo-perception ability contributed significantly to ADL and IADL. The contribution to driving specifically was not addressed in that study; however, Odenheimer[3] reported that function in IADL's was a significant predictor of driving status among 162 demented persons.

In contrast, while some previous studies of demented subjects have shown a correlation between global measures of cognitive impairment and driving impairment,[24,26-30,35,36] our findings support others that failed to find a clear correlation between general cognitive impairment and driving ability. For example, Friedland et al.[15] previously found that patients with AD who had crashes were not more cognitively impaired on the MMSE score. Similarly, Trobe and coworkers[37] found that neither neuropsychological test scores nor the MMSE predicted future crashes or violations. In another dementia clinic sample from

the United Kingdom, ADL but not MMSE scores, discriminated impaired from unimpaired drivers.[38]

Taken together, both the present findings and previous studies suggest a strong influence of right posterior hemispheric cortical dysfunction in demented patients on visuoperceptual skills and secondarily on IADL's, of which driving may be considered an integral part. Therefore, IADL measures are likely to be more practical and accurate clinical predictors of driving impairment than global cognitive screening tests such as the MMSE that are weighted toward assessment of left hemispheric language function. Furthermore, IADL's may be the most appropriate single clinical predictor of driving impairment in dementia since they are closely related to problems of both executive and visuoperceptual abilities that are important at varying stages of disease progression in AD.

The pattern of performance of patients with different degrees of driving impairment on the clock drawing test are also consistent with the present neurophysiological findings as well as previous neuropsychological studies. First, performance on drawing to copy (which is presumably dependent upon visuoperceptual processes) was significantly impaired in the earlier stages of driving impairment, whereas drawing to command (which presumably is additionally dependent upon conceptual/executive processes) was also impaired in the later stages of driving impairment. Again, these findings suggest that the early stages of driving impairment are primarily associated with right occipital/visuospatial dysfunction, whereas the later stages of impairment are additionally associated with frontal/executive dysfunction.

One caveat regarding the interpretation of the present study should be noted. Although one previous study found that motor vehicle accidents were associated with lower ratings of dementia patients' driving ability by caregivers,[18] Hunt et al.[28] found, that self-report was unreliable and family assessments were equivocal in predicting driving performance on a road test. Due to variations in familiarity and complexity of driving environments for different drivers, the use of a standardized road test may produce more valid estimates of driving ability among those with dementia. Thus, the reliance on caregiver reports of driving ability may have weakened the significance of our findings if indeed their assessments were partially inaccurate.

In summary, the results of the present study indicate that severity of driving impairment in patients with AD is related to regional changes in cortical function. The contribution of such regional changes to driving impairment should be considered in future investigations of driving and dementia and in the development of screening examinations for driving impairment among this population. Our investigation provides a neurophysiological basis for previous observations demonstrating a relationship between driving impairment and visuoperceptual dysfunction.

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A. Comparison of drivers able to drive alone vs those not able to drive alone.

B. Comparison of drivers able to drive with difficulty to those completely unable to drive.

Figure 1.
Brain region factor scores derived from factor analysis:

A. Comparison of drivers able to drive alone vs those not able to drive alone.

Abbreviations: hf = high frontal; lf = low frontal; at = anterior temporal; pt = posterior temporal; p = parietal; o = occipital

B. Comparison of drivers able to drive with difficulty to those completely unable to drive.

Abbreviations: hf = high frontal; lf = low frontal; at = anterior temporal; pt = posterior temporal; p = parietal; o = occipital

Figure 2.

Cortical perfusion as SPECT region of interest counts for 12 individual brain regions:

Table 1

Psychometric and demographic characteristics of the subjects, grouped according to driving ability.

	<u>Drives alone</u>	<u>Drives alone with difficulty</u>	<u>Drives poorly</u>	<u>Unable to drive</u>
Sample size	13	25	9	33
Percent male	46	63	67	36
Age	73.4 (6.4)	73.2 (8.9)	76.0 (4.3)	75.8 (8.3)
Education	12.7 (2.9)	11.4 (3.8)	12.1 (4.3)	11.2 (3.3)
Duration	2.4 (0.9)	2.5 (1.6)	2.4 (1.1)	3.1 (2.2)
IADL	.83 (.13)	.78 (.15)	.67 (.14)	.54 (.14)
MMSE	20.2 (5.6)	20.9 (4.4)	19.8 (4.4)	18.5 (4.9)

Table 2

Factor loadings for 12 SPECT regions of interest in the principal component factor analysis using varimax rotation with orthogonal transformation.

	<u>Factor 1</u>	<u>Factor 2</u>	<u>Factor 3</u>
Right anterior temporal	.46	.09	-.06
Left anterior temporal	.56	-.07	-.02
Right posterior temporal	.55	.03	-.12
Left posterior temporal	.69	-.33	.02
Right parietal	.48	.02	.04
Left parietal	.59	-.21	.16
Right high frontal	-.27	.66	.20
Left high frontal	-.30	.63	.26
Right low frontal	.00	.66	.26
Left low frontal	-.02	.65	-.15
Right occipital	-.01	.10	.62
Left occipital	.02	-.13	.79