# The Sex Specificity of Navigational Strategies in Alzheimer Disease

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**Abstract:** Alzheimer disease (AD) is associated with navigational impairments that limit functional independence. We have now examined the role of cognitive and perceptual mechanisms in the navigational impairment of AD to test the hypothesis that men and women with AD may focus on different navigational cues. We conducted navigational, neuropsychologic, and psychophysical testing in men and women from 3 groups: older normal controls, patients with mild cognitive impairment, and patients with AD. Men and women showed parallel declines in navigational capacities from the older normal control, to the mild cognitive impairment, to the AD groups with men and women making similar numbers of errors but different types of errors. There were small sex differences in neuropsychologic and psychophysical performance but large sex differences in how those measures related to navigational capacity: men showed strong links between visual motion processing and navigation. Women showed strong links between verbal capacities and navigation. The findings of these cross-sectional comparisons suggest that there may be sex differences in the progressive navigational decline of AD: men and women who are impaired to the same degree may suffer somewhat different patterns of decline with men relying more on visuospatial processing and women relying more on verbal mediation.

**Key Words:** aging, Alzheimer disease, navigation, sex, spatial cognition

(*Alzheimer Dis Assoc Disord* 2007;21:122–129)

Navigational impairment limits driving and independent living in Alzheimer disease (AD).[1,2] AD patients are at higher risk of automobile accidents[3] and may get lost while driving, even in familiar environments.[4] The navigational difficulties of AD patients may also put them at risk for wandering.[5]

Women are sometimes said to show less robust navigational capacity than men.[6] However, this may reflect differences in their navigational strategies.[7] Men tend to access geometric cues about the movement space, whereas women tend to focus on their position relative to named landmarks that identify their location in the movement space.

In previous studies, we identified a selective deficit of visual motion processing in AD patients[8] and in some patients with mild cognitive impairment (MCI).[9] This deficit limits the patient's ability to perceive the large-scale radial patterns of optic flow that normally provide information about the observer's direction of self-movement.[10] We also found evidence linking this deficit of optic flow analysis to impairments of both ambulatory[8] and vehicular[11] navigation.

We previously used the structured exploration of our hospital lobby to provide a more detailed characterization of navigational impairment in AD.[12] We included the MCI subject group to test the hypothesis that these subjects are intermediate between older normal control (ONC) and AD levels of impairment. Including the MCI group also served to determine whether characterizing MCI as verbal memory impairment without other cognitive impairments might include the absence of navigational incapacities seen in AD, possibly supporting the view that MCI represents an earlier stage of AD.

In a new series of studies, we have now compared navigational performance in men and women from 3 relevant groups[13]: ONCs, MCI patients, and AD patients. We find parallel impairments in navigational capacity in men and women with AD, but substantial differences in the nature of the mechanisms supporting their residual navigational capacity.

## METHODS

### Subject Groups

We studied 3 groups: ONCs, mild cognitively impaired (MCI), and AD (Table 1). Just over half of the subjects (52%) were women, with no significant group differences in age. There was a lower proportion of women in the AD group ($\chi^2$, $P = 0.03$). All subjects were free of neurologic, ophthalmologic, or psychiatric illness other than the defining illness. Corrected binocular visual acuity of 20/40 and a Mini-Mental State Examination (MMSE) score $> 17$ were required.

Received for publication June 19, 2006; accepted January 24, 2007.
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TABLE 1. Test Subject Demographics by Group

| Subject Group | n | Age Mean (± SD) | MMSE Score Mean (± SD) | Percentage Women* |
|---|---|---|---|---|
| ONC | 68 | 73.2 (7.2) | 28.82 (1.19) | 54.4 |
| MCI | 31 | 73.4 (7.2) | 27.55 (1.65) | 51.6 |
| AD | 34 | 74.4 (7.1) | 24.03 (3.99) | 34.5 |

*Chi-square $P = 0.03$.

AD and MCI patients were recruited from outpatient programs affiliated with the University of Rochester Medical Center and were diagnosed by a geriatric neurologist or psychiatrist specializing in dementia as meeting NINCDS-ADRDA criteria for AD[14] or meeting the AAN criteria for MCI.[15] We operationalized diagnostic criteria for AD emphasizing impairment of verbal memory, measured by subtests of the Wechsler Memory Scale, and clinically confirmed impairment affecting patient or caregiver report of capacity in at least one other functional domain from the realms of: aphasia, agnosia, apraxia, and attentional, organizational, or executive incapacity. Our criteria for MCI relied on the presence of a decline in verbal memory, judged by less than normal-for-age scores on the immediate or delayed verbal paired associates tests, with no evidence of significant impairments or loss of functional capacity in other domains including social or occupational activities. ONC subjects were mainly the significant others of effected patients (78%, 53/68), with the remainder being volunteers at the Strong Memorial Hospital. All ONC subjects were independently functioning in the community without evidence of neurologic or psychiatric disease. Each subject gave informed consent at recruitment. The Institutional Human Subjects Review Board approved all procedures and protocols.

## Navigation Testing

The real-world navigational battery has been described extensively.[12] Briefly, we use the lobby of Strong Memorial Hospital as a test environment in a 90 minutes test that begins with an experimenter-directed tour of the lobby on a fixed path with subjects seated in a wheelchair. Subjects were instructed to attend to the route, as they would later be asked to retrace the route and undergo testing related to it. Their wheelchair was then pushed along the 1000-ft path over approximately 4 minutes. On completion of the route, 8 subtests were administered to assess navigational capacity; each subtest consisted of 10 questions. *Route Learning*: subject-directed repetition of the tour; *Free Recall*: naming objects along the path; *Self Orientation*: pointing toward unseen landmarks; *Route Drawing*: tracing route on a map of the lobby; *Landmark Recall*: naming objects used to navigate; *Photo Recognition*: identifying photos as being from the route; *Photo Location*: matching photos to labeled sites on map; and *Video Location*: matching video-clips to a route map. All navigational testing in this study was conducted by 1 of 2 researchers. Our previous use of this navigational test battery yielded high retest reliability in comparable groups of subjects ($r = 0.90$; $P < 0.0001$).

## Neuropsychologic Tests

The neuropsychologic battery assessed aspects of general cognition, visual-perceptual skills, and memory. Categorical Name Retrieval (for animal names) was chosen as an index of verbal fluency. The Money Road Map test[16] assesses topographic orientation through a simulated village route, using a pencil to trace a predrawn path and reporting whether turns are to the traveler's left or right. Judgment of Line Orientation[17] tested aspects of spatial perception. Two tests were taken from the Wechsler Memory Scale—Revised[18]: Figural Memory uses designs in an immediate visual recognition task; Verbal Paired-Associates Tests I and II accesses immediate and delayed recall for a list of word pairs. The MMSE[19] was part of the diagnostic assessment.

## Visual Psychophysics

Subjects underwent psychophysical threshold determination for 3 types of motion coherence stimuli in a 2-alternative forced choice paradigm controlled by an adaptive staircase algorithm. Visual motion coherence stimuli consisted of 500 white dots (2.69 $cd/m^2$) on a black background generated by a personal computer driving a projector television in an animated sequence of frames presented at 60 Hz. All stimuli had the same dot density, luminance, contrast, and average dot speed. Thresholds were determined by varying the number of randomly moving dots that were intermixed with dots moving in a fixed pattern of either: (a) leftward or rightward horizontal motion, (b) left or right (± 15 degrees) center of motion outward radial optic flow, and (c) left or right (± 15 degrees) center of motion interleaved outward and inward radial optic flow. Subjects sat in front of a large-screen computer display and were required to press 1 of 2 buttons on every trial. Centered visual fixation was maintained on white cross (2 degrees). Eye position (electro-oculogram) and head position were monitored during all trials so that gaze shifts beyond the central 20 degrees of the screen aborted that trial. Subjects were trained on each stimulus set by presenting high coherence stimuli without superimposed random dots. Each subject's threshold on the 3 visual motion coherence tests represented the percent of dot coherence required to achieve 82% correct responses. For each visual motion stimulus, each subject was first tested with 20 trials to obtain a preliminary threshold. That value was then used to seed the algorithm for the independent running of an additional 50 trials. Each subject's final coherence threshold was reported by the algorithm after 50 trials.

## Data Analysis

The total navigation score was the numeric sum of all 8 subtests (maximum score = 80). Other dependent measures included the 3 specific psychophysical thresholds and the 6 neuropsychologic test scores. Results from the navigational, psychophysical, and neuropsychologic tests were analyzed using multivariate analyses of variance in mixed-designs with subject sex (or group) as the between-subject factor and various tests as within-subject factors. All significant effects were followed-up by post hoc analyses using the Games Howell Test maintaining $\alpha$ levels at $P = 0.05$ without the assumption of equal variances between groups.

Multiple linear regression (MLR) was used to model variability in overall navigation test scores by stepwise attribution to the variability in other measures. This approach was applied to data from all groups and sexes considered separately and together. Significant $\beta$ weights for specific variables were used to describe the relative contributions of those variables to significant MLR fits. All statistical analyses were run using SPSS 12.0 statistical software.[20]

# RESULTS

## Sex Differences in Navigational Strategy

We found successively poorer total navigational performance across subject groups ($F_{2,109} = 50.33$, $P < 0.001$): ONC did better than MCI, and MCI did better than AD (Fig. 1). Our cross-sectional design does not allow us to infer the occurrence of changes in individual subjects that might represent progressive losses of cognitive abilities. We infer disease effects based on the principle that group differences distinguishing normal subjects from otherwise matched subjects with cognitive disorders reflect those disorders. This perspective is supported by the intermediate position of MCI patients between the ONC and AD groups: in the multivariate analysis all 8 subtests showed significant declines in performance from the ONC, to the MCI, to the AD groups [Games-Howell (GH) post hoc comparisons yield the largest $P$ value of 0.02].

Overall navigational scores showed no significant sex differences ($F_{1,109} = 0.595$, $P = 0.442$) or group-by-sex interactions ($F_{2,109} = 0.204$, $P = 0.815$). The multivariate analysis of navigational subtest scores (Table 2) showed significant group ($F_{16,194} = 6.80$, $P < 0.001$) and sex ($F_{8,97} = 3.31$, $P = 0.002$) effects but not group-by-sex interactions ($F_{16,194} = 0.747$, $P = 0.743$). Considered separately, all of the navigational subtests revealed significant group effects (GH post hoc largest $P = 0.007$) and 2 subtests revealed significant sex effects with women performing better than men in recognizing photographs of the lobby ($F_{1,109} = 5.46$, $P = 0.02$) and in the free recall of object names from the path ($F_{1,109} = 5.70$, $P = 0.02$). None of the subtests showed significant group-by-sex interaction effects.

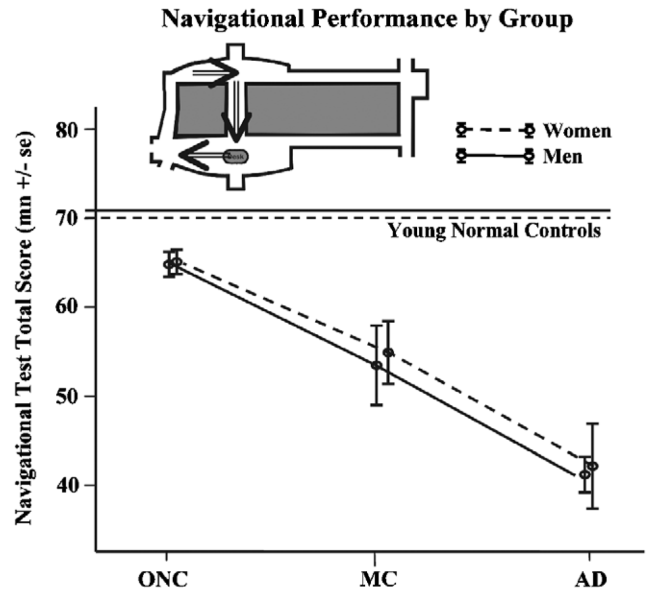


**FIGURE 1.** Navigational test scores across subject groups. Overall navigational test performance showed parallel decline in men (solid line) and women (dashed line) across the 3 subject groups. Performance was compared across older adult subjects, AD patients, and the intermediate group of patients with MCI. Significant group differences were not accompanied by sex or group-by-sex interactions effects. Comparison data from young normal subjects was derived from earlier studies of navigational performance. Inset shows a schematic top-down survey view of the hospital lobby test environment with arrows indicating the first 3 of the 10 route segments.

Group differences in total navigational test scores are also evident in the distribution of scores for all subjects tested (Fig. 2). ONC subjects showed uniformly high scores with only 24% of the subjects scoring less than 60 out of 80 points. The MCI patients showed substantially poorer performance with a broad distribution of scores and 73% of the patients scoring fewer than 60 points. The AD patients showed still poorer performance with 96% of the patients scoring fewer than 60 points. Thus, the distribution of scores for the 3 subject groups reinforces the strong tendency for both MCI and

**TABLE 2.** Navigational Subtest Scores by Subject Group

| Navigational Subtest | ONC Mean (SD) | MCI Mean (SD) | AD Mean (SD) |
|---|---|---|---|
| Route Learning | 9.57 (0.78) | 9.06 (1.3) | 7.47 (1.5) |
| Self Orientation | 8.13 (1.7) | 7.22 (2.3) | 5.09 (2.0) |
| Route Drawing | 9.40 (1.2) | 8.83 (1.6) | 6.70 (1.8) |
| Photo Recognition | 7.76 (1.3) | 7.33 (1.6) | 6.84 (1.3) |
| Photo Location | 7.15 (2.4) | 4.89 (3.0) | 2.84 (2.2) |
| Video Location | 5.82 (2.5) | 4.67 (3.2) | 1.59 (1.6) |
| Free Recall | 9.32 (1.2) | 7.72 (2.6) | 5.75 (2.6) |
| Object Recall | 6.66 (2.8) | 5.83 (3.4) | 4.16 (3.0) |

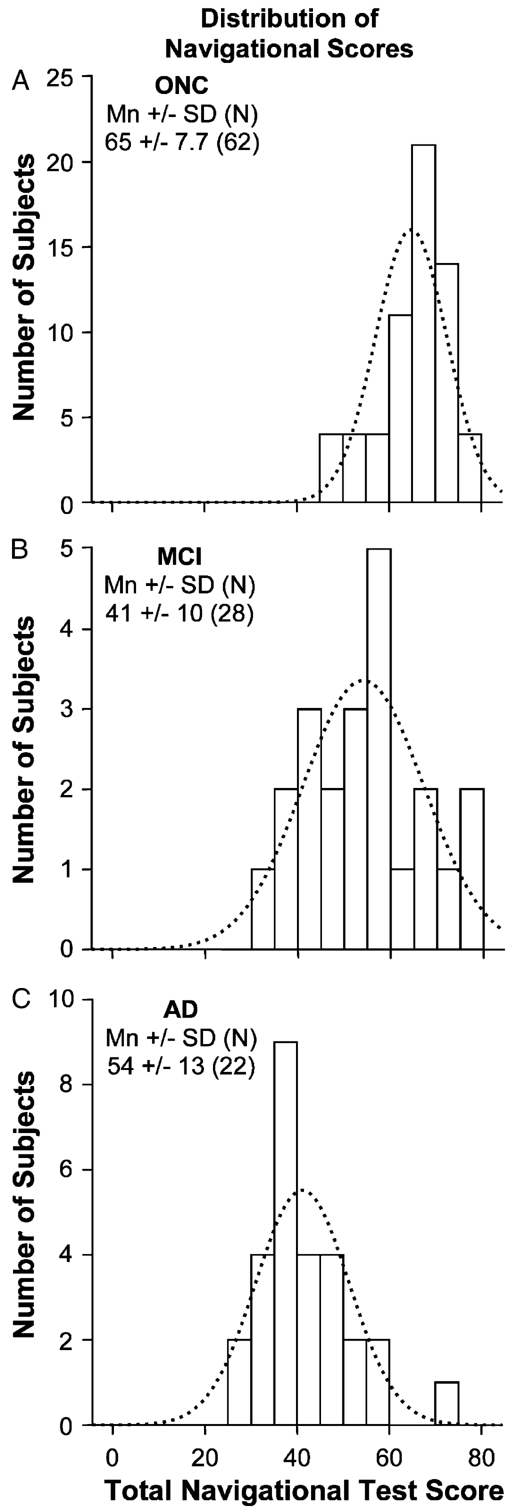


**FIGURE 2.** Bar graphs showing the distribution of subjects in each group who obtained the indicated scores on the navigational test battery. A, ONC subjects showed consistently high scores. B, MCI patients showed a broader distribution of lower scores. C, AD patients showed a broad distribution of substantially lower scores. The Gaussian curve overlapping each bar graph shows the best fit to that distribution.

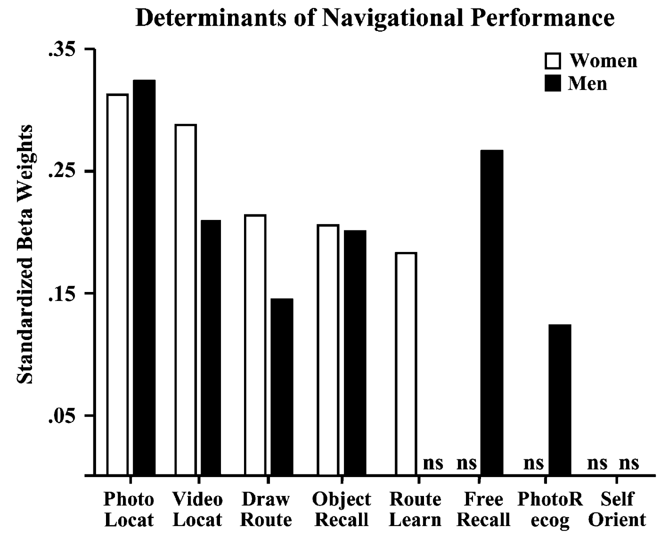


**FIGURE 3.** Standardized β weights from MLR show the relative contributions of the 8 subtests to navigational performance in men and women. Free Recall and Photograph Recognition scores contributed significantly to performance in men but not women. Route learning contributed significantly in women but not men. Thus, men and women showed similar overall performance but made different types of errors.

AD patients to score substantially more poorly on the navigational test battery.

Correlational analyses revealed substantial differences in how various navigational cues were used by men and women. Several navigational subtests showed differences in their relative contributions to the overall navigational scores of men and women. Men's scores were not significantly influenced by route learning performance, whereas women's scores were not significantly influenced by free recall or photo recognition (Fig. 3).

These results lead us to several points. First, we observe a successive decline in navigational performance from ONC subjects, to MCI patients, and then to AD patients. Second, men and women have similar abilities to derive a variety of navigational cues from real-world environments. Third, men and women differ in the way that they use various navigational cues, with men relying on cues that may be all but ignored by women and vice versa.

## Sex Differences in Cognition and Perception

We used neuropsychologic and perceptual tests to determine whether more fundamental cognitive or sensory deficits might underlie sex differences in navigational impairment. Neuropsychologic tests were used to measure spatial and verbal cognitive capacities. Perceptual capacities were measured by determining psychophysical thresholds for the visual motion seen during self-movement. Taken together, the multivariate analysis on all of these tests showed significant group differences ($F_{18,202} = 7.80$, $P < 0.001$) without significant sex effects ($F_{9,101} = 1.52$, $P = 0.153$) but with borderline group-by-sex interactions ($F_{18,202} = 1.68$, $P = 0.046$).

 

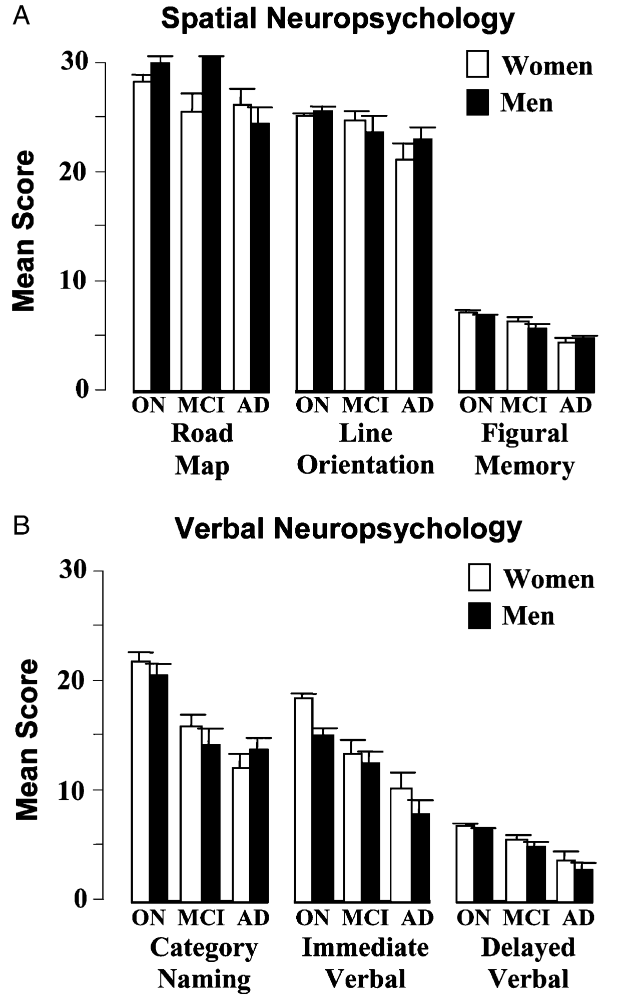


**FIGURE 4.** Six neuropsychologic tests are divided into those that focus on (A) spatial capacities and those that focus on (B) verbal capacities. All of these tests showed significant differences between ONC, MCI, and AD subjects. Error bars represent the standard error of the mean. Some tests showed small, but significant, main effects of sex: men did better on the road map spatial test and women did better on verbal memory tests. There were no significant group-by-sex interaction effects.

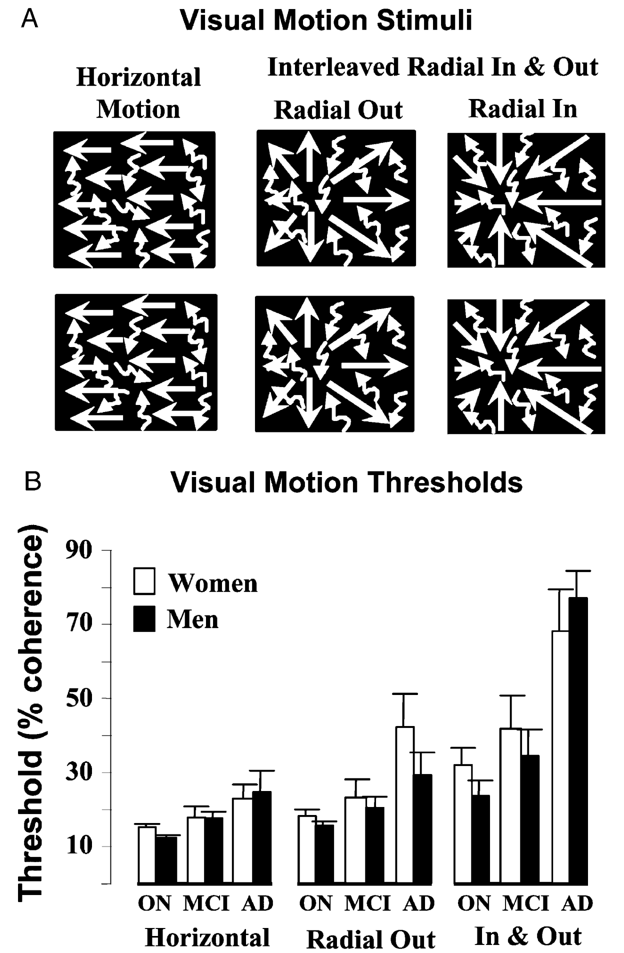


**FIGURE 5.** A, Three visual motion psychophysical tests measured thresholds for left/right horizontal motion, outward radial optic flow, and interleaved inward and outward radial optic flow. B, All 3 types of visual motion showed significant differences between ONC, MCI, and AD groups. Error bars represent the standard error of the mean. There were no significant main effects of sex or group-by-sex interaction effects. The psychophysical thresholds are the percentage of dots moving in the specified pattern, coherent motion, required for 82% correct responses.

The multivariate analysis of the neuropsychologic battery revealed cognitive differences between subject groups on all 6 tests (largest $P = 0.007$) with AD subjects scoring worse than ONC on all 6 tests (GH post hoc largest $P = 0.007$) and worse than MCI on figural (GH $P = 0.004$), immediate verbal (GH $P = 0.002$), and delayed verbal memory tests (GH $P = 0.001$). The multivariate analysis also revealed a small but significant group-by-sex interaction effect ($F_{2,114} = 4.25$, $P = 0.017$) with men doing better on the Road Map spatial test (Fig. 4).

The multivariate analysis of visual motion perceptual tests confirmed the previously recognized differences between subject groups (largest $P = 0.001$): small differences with horizontal motion ($P = 0.001$) with AD subjects scoring worse than MCI on all 3 tests (GH post hoc largest $P = 0.034$)[21]; larger differences with outward radial optic flow (GH $P = 0.005$)[8] and still larger differences with combined inward and outward radial optic flow (GH $P < 0.001$).[9] There were no significant group-by-sex interactions in visual motion perceptual measures (Fig. 5).

Thus, neuropsychologic and psychophysical test results make 2 points: first, differences between ONC, MCI, and AD subjects are consistent with greater cognitive and perceptual impairment across those groups. Second, men and women show similar functioning except that women do better on verbal memory tests.

## Linking Navigation, Cognition, and Perception

Our experience finding more substantial sex effects in the relationships between navigational subtests and total scores prompted a parallel approach with the neuropsychologic and psychophysical data. Here again we found a different perspective on sex differences by examining the relationships between specific cognitive and perceptual capacities and navigational performance.

There were strong correlations between cognitive and perceptual measures and the total navigational performance score that were seen across subject groups. Although cognitive and perceptual tests were correlated with navigational performance in both men ($R^2 = 0.58$) and women ($R^2 = 0.69$) (Fig. 6), there were clear sex differences in which tests supported this correlation.

The stepwise MLR of navigational performance in men selected 2 variables: in/out radial optic flow perceptual thresholds ($\beta = -0.50$, $P < 0.001$) and delayed verbal recall ($\beta = 0.36$, $P = 0.001$), neither of which contributed significantly to the model that emerged for women. The stepwise MLR of navigational performance in women selected 4 variables: figural ($\beta = 0.34$, $P = 0.001$) and immediate verbal ($\beta = 0.28$, $P = 0.013$) memory, Road Map scores ($\beta = 0.27$, $P = 0.003$), and category naming ($\beta = 0.26$, $P = 0.022$), none of which contributed significantly to the model that emerged for men.

The role of various neuropsychologic and psychophysical mechanisms in navigational performance may be seen as the percentage of variance in navigational performance that is explained by neuropsychologic and perceptual test scores. Most of the explained variance in men's navigational performance was attributable to in/out radial optic flow perceptual thresholds (84%) (Fig. 7A). In contrast, the majority of explained variance in women's navigational performance was attributable to category naming (55%) and figural memory (26%) (Fig. 7B). This pattern of sex differences was also present when the ONC, MCI, and AD groups were considered separately.

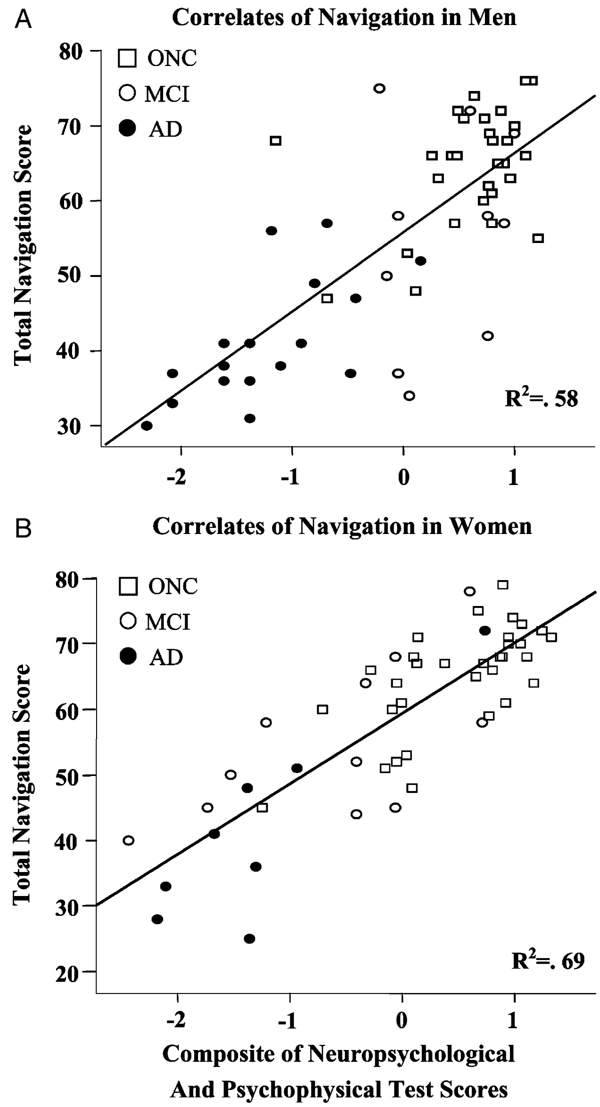


**FIGURE 6.** Scatter plots of total navigational test scores (ordinate) versus composite factor representing the prediction of MLR. Separate regressions for men (A) and women (B) were based on neuropsychologic and psychophysical tests scores (abscissas). Least squares fits show that the composite regression factors predicted navigation in both men and women. Sample sizes are smaller (men = 54, women = 49) because this analysis required that subjects complete every test.

## DISCUSSION

Men and women show the same levels of relative navigational impairment from ONC, to MCI, to AD (Fig. 1). These findings are consistent with previous reports of navigational impairment in AD and extend those results to MCI patients. The finding of navigational impairments in MCI patients raises the issue of whether these patients should be recognized as having deficits outside of the realm of verbal memory. These patients might be considered to meet diagnostic criteria for AD in that they exhibit both a memory disorder and impairments in more than 1 cognitive domain.[22]

The case for reclassifying navigationally impaired MCI patients as having AD is buttressed by the fact that the tests used in this study are based on real-world navigational tasks. These tests include both route learning and recognition measures that reflect whether a patient might become lost when trying to replicate a previously traveled route. The significance of such impairments for safe functional independence justifies their emphasis in clinical evaluations.

We also observed small declines in navigational performance in ONC subjects compared with our previous data on young controls. However, because these data were obtained in separate studies we cannot determine if the differences between younger and older normal subjects represent significant effects. Nevertheless, our earlier findings suggest that some ONC subjects have poorer navigational abilities than young normal

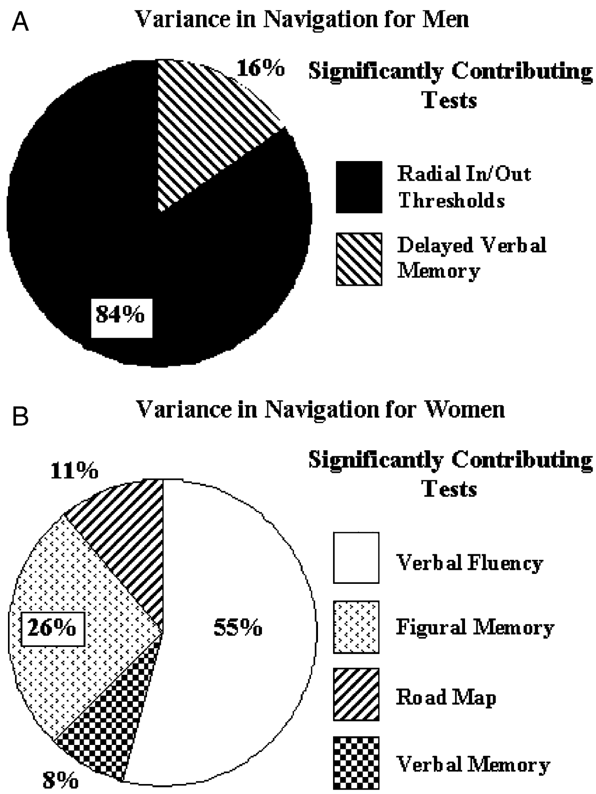


**FIGURE 7.** Pie plots showing the total amount of variance in navigational capacity that is explained by the 6 neuropsychologic and 3 psychophysical test scores in men (A) and women (B). In men, perceptual thresholds for in/out radial optic flow contribute the great majority of explained variance. In women, verbal fluency (animal naming) contributes the majority of explained variance.

subjects.[12] Considering the findings of both studies, and the potential importance of navigational testing for the early diagnosis of functional decline, we must consider that these impairments should be the subject of future research.

We compared the navigational abilities of men and women and found nearly identical patterns of relative impairment across subject groups and no significant group-by-sex interaction effects. Our cross-sectional design does not allow us to infer similar patterns of progressive impairment in men and women. However, we can conclude that the net differences between groups were the same for men and women.

Neuropsychologic (Fig. 3A) and psychophysical (Fig. 3B) tests revealed small sex differences in cognitive and perceptual abilities. Nevertheless, there were large sex differences in how those abilities related to navigational performance. In men, navigation was linked to radial optic flow perception, suggesting that they might rely on the visual analysis of their self-movement along a path. In women, navigation was linked to name retrieval, suggesting that they might rely on verbally mediated memory for named landmarks along the path (Figs. 5, 6).

These findings are consistent with the hypothesis that the reported navigational superiority of men[23] reflects an emphasis on spatial strategies that are favored by men in those studies.[24,25] This view is supported by the observation that men and women show similar performance when compared on navigational tests that do not emphasize the mental rotation of spatial information.[26] The net conclusion might be that men and women use different navigational strategies with women relying more on the verbal mediation of navigational tasks[27] and men relying more on spatial cues.

Sex dimorphisms in navigation may reflect the effects of reproductive hormones on brain mechanisms of cognition. The distinctly different hormonal milieu in which the brains of men and women develop are thought to have widespread ramifications on cortical microarchitecture.[28] Alternatively, reproductive hormonal effects may be linked to the sex-specific protective effects of reproductive hormones on cognitive aging with estrogen benefiting women[29–31] and testosterone benefiting men.[32–35] However, this picture was complicated by the results of the Women's Health Initiative Memory Study that found an increased risk of cognitive decline in elderly women given estrogen and progestin.[36]

The apparently conflicting findings regarding reproductive hormonal effects on cognitive aging may be reconciled by recognizing the potential role of gonadotropins as more direct mediators of cognitive protection in aging men and women.[37] In particular, luteinizing hormone (LH) is a likely mechanism of reproductive hormonal effects on neuronal viability with LH receptors concentrated on neurons that are vulnerable to AD pathology[38] and LH playing a role in modulating amyloid precursor metabolism.[39]

We should highlight the fact that we do not see extensive differences in the abilities of men and women in spatial cognition, verbal cognition, or perceptual domains. The sex effects seen in our studies emphasize differences in how men and women apply their cognitive and perceptual abilities to real-world navigational tasks. Our findings suggest that a full understanding of sex dimorphisms in cognitive function must include an assessment of how various capabilities are used by men and women in naturalistic behavior.

## ACKNOWLEDGMENTS

*The authors gratefully acknowledge the assistance of Teresa Steffenella and William Vaughn. They thank Drs Roberto Fernandez-Romero, Voyko Kavcic, Mark Mapstone, William K. Page, and Nobuya Sato, as well as Sarita Kishore for comments on the manuscript.*

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