

Visual Mechanisms of Spatial Disorientation in Alzheimer's Disease

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Impaired optic flow perception may contribute to the visuospatial disorientation of Alzheimer's disease (AD). We find that 36% of AD patients have elevated perceptual thresholds for left/right outward radial optic flow discrimination. This impairment is related to independent visual motion processing deficits affecting the perception of left/right motion-defined boundaries and in/out radial motion. Elevated optic flow thresholds in AD are correlated with greater difficulty in the Road Map test of visuospatial function ($r = -0.5$) and in on-the-road driving tests ($r = -0.83$). When local motion cues are removed from optic flow, subjects must rely on the global pattern of motion. This reveals global pattern perceptual deficits that affect most AD patients (85%) and some normal elderly subjects (21%). This deficit might combine with impaired local motion processing to undermine the alternative perceptual strategies for visuospatial orientation. The greater prevalence of global pattern deficits suggests that it might precede local motion processing impairments, possibly relating to the sequence of early hippocampal and later posterior cortical damage that is typical of AD.

Introduction

Optic flow is the patterned visual motion seen by a moving observer (Gibson, 1950). It provides cues about heading direction and the three-dimensional structure of the visual environment (Warren and Hannon, 1988; Royden *et al.*, 1992). We previously showed that visuospatial disorientation in Alzheimer's disease (AD) (Cogan, 1985) is linked to impaired optic flow perception (Tetewsky and Duffy, 1999). We now find that this impairment is related to more elementary visual motion processing deficits.

Visuospatial disorientation is often attributed to the hippocampal damage (Kesner *et al.*, 1989; Carli *et al.*, 1997) that is typical of early AD (Braak and Braak, 1991). But neuro-pathological (Benson *et al.*, 1988; Hof and Morrison, 1990) and functional imaging (Kiyosawa *et al.*, 1989; Pietrini *et al.*, 1996) studies link visuospatial disorientation (Henderson *et al.*, 1989) to the later posterior cortical extension of AD (Brun and Gustafson, 1976; Brun and Englund, 1981).

Neurophysiological studies have identified posterior cortical areas for visual motion processing (Maunsell and Van Essen, 1983; Albright *et al.*, 1984; Salzman *et al.*, 1992; Pasternak and Merigan, 1994) and optic flow analysis (Saito *et al.*, 1986; Tanaka *et al.*, 1989). Neurons in the medial superior temporal area (MST) respond to optic flow (Duffy and Wurtz, 1991b; Orban *et al.*, 1992; Graziano *et al.*, 1994) with heading selectivity (Duffy and Wurtz, 1995) that is elaborated in adjacent parietal cortex (Schaafsma and Duysens, 1996; Bremmer *et al.*, 1997; Siegel and Read, 1997). Lesion studies show that these areas support the visuospatial capacities of humans (Holmes, 1918; Kleist, 1935) and monkeys (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992), suggesting a link between visual motion processing and spatial orientation.

Nevertheless, the role of the hippocampus in visuospatial orientation is well-established (O'Keefe and Nadel, 1978) with

neuronal responses to specific locations in familiar environments (Wilson and McNaughton, 1993; Muller *et al.*, 1994; Markus *et al.*, 1995). This is consistent with human hippocampal (Maguire *et al.*, 1998) and parahippocampal (Aguirre *et al.*, 1996; Epstein, 1998) activation in visuospatial tasks and suggests hippocampal-cortical interactions for visuospatial orientation (Chen *et al.*, 1994; Burgess *et al.*, 1999).

We have used psychophysical tests to analyze the perceptual mechanisms of visuospatial disorientation in AD. We find impaired global pattern recognition of optic flow in most AD patients and impaired visual motion processing of optic flow in those with visuospatial disorientation. We speculate that impaired global processing reflects hippocampal damage in early AD and impaired motion processing reflects later posterior cortical involvement in AD.

Materials and Methods

Subject Selection

Patients diagnosed with probable AD (McKhann *et al.*, 1984) were recruited from clinical programs of the University of Rochester Alzheimer's Disease Center. Elderly normal (EN) subjects were either the spouses of AD patients or participants in programs for healthy older adults. Young normal (YN) subjects were healthy students from local colleges. We tested 26 AD patients (ages 65–86 years; mean = 77), 50 EN subjects (ages 59–85 years; mean = 71) and 32 YN subjects (ages 19–30 years; mean = 22). Each subject gave informed consent in protocols approved by the University Human Subjects Review Board.

Subjects were screened for neurological and ophthalmological abnormalities other than those attributable to AD. All subjects had normal primary visual function measured by Snellen acuity [left eye, right eye (mean \pm SEM): YN = 14.9 \pm 1.1, 16.6 \pm 1.9; EN = 19.3 \pm .95, 24.7 \pm 4.0; AD = 27.6 \pm 4.5, 22.6 \pm 1.6] and full visual fields to a standard protocol for clinical confrontation testing. All subjects showed normal contrast sensitivity tested at five spatial frequencies (0.5–18 cycles/degree) spaced on a log scale (VisTech, Inc.).

Visual Discrimination Stimuli

We obtained visual discrimination thresholds for six types of motion stimuli and two types of static stimuli. All stimuli were constructed from varying numbers of white dots (2.69 cd/m²) on a black background in an animated sequence of frames presented at 60 Hz. All of the motion stimuli contained a total of 500 dots that had the same average speed. Dot positions were specified for each frame by algorithms for each type of stimulus (Duffy and Wurtz, 1991b). Random dot movement was introduced by randomly assigning each dot, in each frame, either to the patterned motion or to random repositioning. Different numbers of random dots were superimposed on a pattern of moving or stationary dots to create a family of coherence stimuli. The percentage of dots in the coherent pattern ranged from 1 to 100% on a log scale of 1–5% increments.

Subjects were tested with eight different types of stimuli that are described here in the sequence in which they are presented in Results. *Left/right horizontal motion stimuli* contained leftward or rightward moving dots superimposed on various numbers of randomly moving dots (Fig. 1A). *Left/right FOE outward radial motion stimuli* contained

outward radial motion with a focus of expansion (FOE) 30° to the left or right of center with superimposed randomly moving dots (Fig. 1B). *Left/right outward motion-defined boundary stimuli* contained leftward motion on the left side of the screen and rightward motion on the right side to create patterned movement outward from the vertically oriented motion-defined boundary 30° to either the right or left of center (Fig. 3A). *In/out centered FOE radial motion stimuli* contained radial motion either inward to or outward from the centered FOE (Fig. 4A). *Stationary square location stimuli* contained up to 48 static dots arranged to form the outline of a 20° square centered 15° to the right or left (Fig. 5A). Additional dots were randomly distributed in the central 45° × 30° of the visual field to maintain dot density equal to that in the motion stimuli. *Left/right FOE in/out radial motion stimuli* contained the same left- or right-sided radial motion FOEs described for left/right radial optic flow (Fig. 1B) but included stimuli with motion either inward to or outward from the left- and right-sided FOEs (Fig. 6A). *Stationary radial pattern stimuli* contained stationary dots arranged along radial lines that intersected at a point 15° to the right or left of center (Fig. 8A). *Left/right in/out motion-defined boundary stimuli* contained the same left- or right-sided horizontal motion-defined boundaries described above but included stimuli with motion either inward to or outward from that boundary (Fig. 9A).

These types of stimuli were presented in one of four counterbalanced sequences with equal numbers of subjects assigned to each sequence. Subjects responded by pressing one of two buttons, typically on the left or right side. They selected the button on the side that corresponded to the direction of motion, or the location of the pertinent feature, in the stimulus. For left/right outward motion-defined boundary stimuli, they were instructed not to rely on the direction of dot motion but to identify the location of the kinetic edge. For in/out centered FOE radial motion stimuli, the response box was turned 90° in the horizontal plane to enhance stimulus-response compatibility with subjects pressing the closer button for outward motion and the further button for inward motion. For left/right FOE in/out radial motion stimuli and left/right in/out motion-defined boundary stimuli we emphasized the need to respond to the left- or right-sided location of the motion-defined FOE or boundary respectively.

Psychophysical Protocol

Psychophysical tests were administered with subjects seated in a dark room, 4 ft away from an 8' × 6' screen that covered the central 90° × 74° of their visual field. Visual stimuli were generated off-line and rear-projected onto the screen by a personal computer driving a television projector (Electrohome 4100) to create a 90° × 60° image centered at eye height.

Subjects were fitted with electro-oculogram (EOG) electrodes to monitor eye movements. The EOG signals were calibrated to the position of points projected at ±20° on the horizontal and vertical axes. During stimulus presentation, centered fixation (±10°) of a red laser LED image (0.2°) was required. If the subject's eyes moved outside the fixation window during a trial, that trial was aborted and the data were deleted. Stimulus presentation, gaze monitoring and data storage were controlled by the Real-Time Experimental system (Hays *et al.*, 1982).

Test trials began with an auditory tone indicating that fixation was required within 1 s. Once fixation was established, a visual stimulus was presented for 1500 ms. The screen then went blank, two audible tones were given, and the buttons on the response box were illuminated to prompt the subject to make a decision and push a button within 8 s. Responses were not registered until the stimulus was extinguished so that all subjects viewed the stimuli for the same period of time to discourage speed-accuracy tradeoffs.

Subjects were acquainted with the apparatus in a preliminary test of response reliability. A circular figure (10° diam.) was presented 30° to the left or right of the fixation point, and subjects pressed the left or right response button to indicate the location of the figure. Twenty trials with a random sequence of locations were presented. Subjects who consistently performed the task properly were eligible for further tests.

Visual discrimination testing with visual motion and visual pattern stimuli used an adaptive staircase algorithm (Harvey, 1986) to control stimulus selection and determine psychophysical thresholds. A Weibull function fit to the data using a maximum likelihood technique deter-

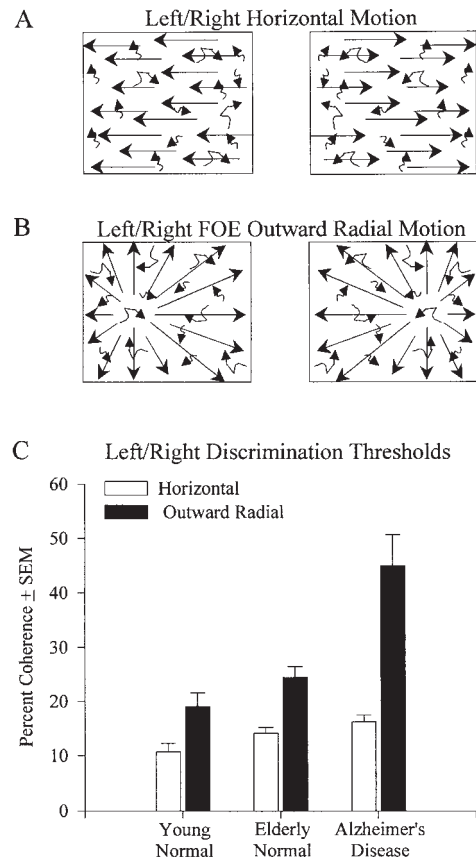


Figure 1. Selective elevation of radial motion discrimination thresholds in AD. (A) Left/right horizontal motion stimuli contained either leftward or rightward moving dots along with randomly moving dots. (B) Left/right FOE outward radial optic flow stimuli contained an FOE 30° to the left or right of center along with randomly moving dots. (C) Discrimination thresholds (ordinate) for horizontal motion (open bars) and radial optic flow (filled bars) for each subject group (abscissa): YN, young normals ($n = 29$); EN, elderly normals ($n = 48$); AD, Alzheimer's disease subjects ($n = 26$).

mined the stimulus coherence that was estimated to yield a threshold of 82.5% correct. The right or left version of the stimulus was selected randomly for each trial. Each test began at 100% coherence and continued for 20 trials to establish a preliminary estimate of the subject's threshold. That preliminary estimate was used as the starting value for a run of 50 trials to determine the final threshold.

Performance Tests

Neuropsychological Tests

Neuropsychological testing consisted of a battery of pencil-and-paper tests administered under standard conditions. The Mini-Mental State Examination (Folstein *et al.*, 1975) tests spatial and temporal orientation as well as attention, language, memory and drawing. It is widely used as a general measure of the degree of impairment in AD. The Money Road Map test (Money, 1976) assesses topographic orientation in simulated route following. Subjects use a pencil to trace a pre-drawn path on a village map and report whether turns are to the traveler's left or right. Two tests were taken from the Wechsler Memory Scale – Revised (Wechsler, 1987): the Figural Memory test uses block patterns in an immediate visual recognition task; the Verbal Paired Associates Test I has immediate and delayed recall sub-tests of memory for a list of word pairs.

On-the-Road Driving Test

AD subjects who held a valid license and had driven in the previous 6 months were eligible for the on-the-road driving tests. Each subject first completed the Written Road Signs test. They then underwent an on-the-road driving evaluation that was conducted by New York State

Left/Right Discrimination Thresholds

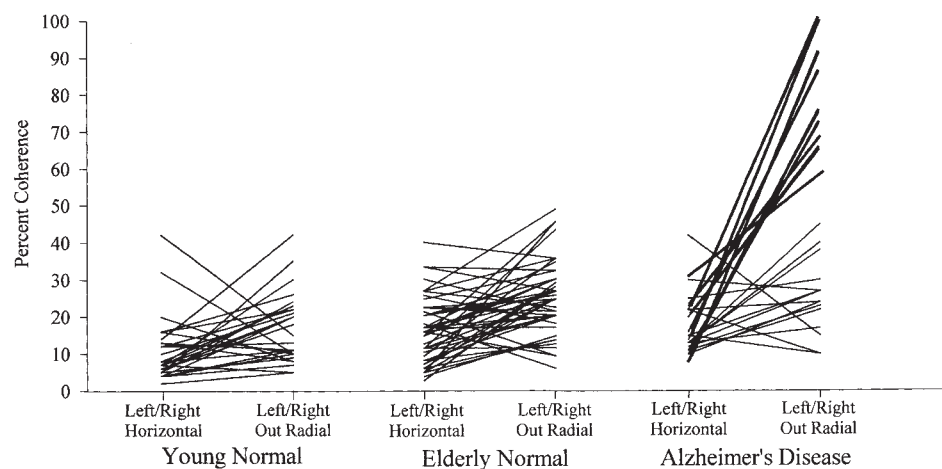


Figure 2. AD subjects with elevated radial motion thresholds. Left/right horizontal and left/right FOE outward radial motion thresholds (ordinate) are shown for subjects in each group (abscissa). One-third of the AD subjects (36%, 9/25; bold lines) had selectively elevated radial motion thresholds (>50% coherence). All other subjects showed both horizontal and radial motion thresholds <50%.

certified driving evaluators who were unaware of the subject's diagnosis or performance on other tests. Driving was scored on a scale developed by the State of New York in tests of elderly drivers.

Useful Field of View Test

The useful field of view test (Visual Resources, Inc.) measured visual attention relevant to driving (Ball *et al.*, 1993) in subjects undergoing driving testing. Subjects sat in front of a visual display and identified and localized the silhouette of a car or a truck briefly presented at the center of the screen and at one of 24 locations 20° or 30° from the center. This test yields a composite measure of functional visual field restriction.

Data Analysis

For each type of visual discrimination stimulus, a threshold level of stimulus coherence was determined using a maximum-likelihood estimation technique (Harvey, 1986). We also calculated the 95% confidence intervals for each threshold.

Data analysis relied on standard statistical packages (SAS Institute, 1993, 1996; Arbuckle and Wothke, 2000; SPSS, 2000). The threshold data were summarized using a mixed-design analysis of variance (ANOVA), with subject population as a between-group factor and stimulus type as a repeated-measure factor. The simple main effects of subject group and stimulus type were analyzed using one-way ANOVAs, along with Tukey's Honestly Significant Difference (HSD) test to protect against an inflated alpha level in the *post hoc* comparisons. Simple and multiple linear regression was used to analyze the relationships between various psychophysical performance measures.

We used path analysis to develop structural models of the significant correlations between psychophysical and neuropsychological measures. Path analysis uses data from each subject to evaluate the probability of various causal relations underlying correlations between measures (Arbuckle and Wothke, 2000; Schumaker and Lomax, 1996). The chi-squared (χ^2) statistic describes the goodness-of-fit between the structural model and the data with higher χ^2 , and higher associated *P* values, reflecting the absence of significant differences between a model and the data. Each link in a structural model has a path coefficient that ranges from -1 to 1 to reflect the strength of that link as a standardized partial correlation coefficient. Each path coefficient has an associated *P* value that reflects the significance of that link. Different models are compared using the Akaike Information Criterion (AIC) with smaller values reflecting improving fits between the data and the model.

Results

Elevated Radial Thresholds in AD

We determined visual motion coherence thresholds in young normal (YN, $n = 29$), elderly normal (EN, $n = 48$), and Alzheimer's disease (AD, $n = 26$) subjects. All subjects were tested for left/right horizontal motion discrimination (Fig. 1A) and left/right FOE outward radial motion discrimination (Fig. 1B). AD subjects showed a selective impairment of radial motion perception with greatly elevated left/right FOE outward radial motion thresholds and normal left/right horizontal motion thresholds [group-by-stimulus interaction $F(2,99) = 13.97$, $P < 0.0001$] (Fig. 1C).

Not all AD subjects showed elevated left/right FOE outward radial motion thresholds. There was a broad range of those thresholds in AD with an apparent gap in the distribution near 50% coherence (Fig. 2). Non-parametric cluster analysis confirmed that some AD subjects (36%, 9/25) had elevated radial thresholds (bold lines) when compared to other AD subjects ($P < 0.0137$) or all other subjects ($P < 0.0001$).

The comparability of thresholds across subject groups was confirmed by calculating the 95% confidence interval for each subjects' thresholds. The confidence intervals did not show the interaction effect that was seen in the threshold data [$F(2,68) = 2.82$, $P = 0.063$]. Reaction times across stimulus types and subject groups showed no significant differences across all trials or in the last five trials (near threshold). There was no bias for left or right responses across subject groups or stimuli as might have been expected if AD subjects had left hemi-neglect.

We conclude that some AD subjects show a robust and selective impairment of left/right FOE outward radial motion discrimination.

Stimulus Attributes Affecting Radial Thresholds

Left/right FOE outward radial motion and left/right horizontal motion differ in two ways: firstly, the radial stimuli present a left- or right-sided location that must be identified; secondly, the radial stimuli present a pattern combining all directions of dot motion. We tested the effects of these differences by: (i) present-

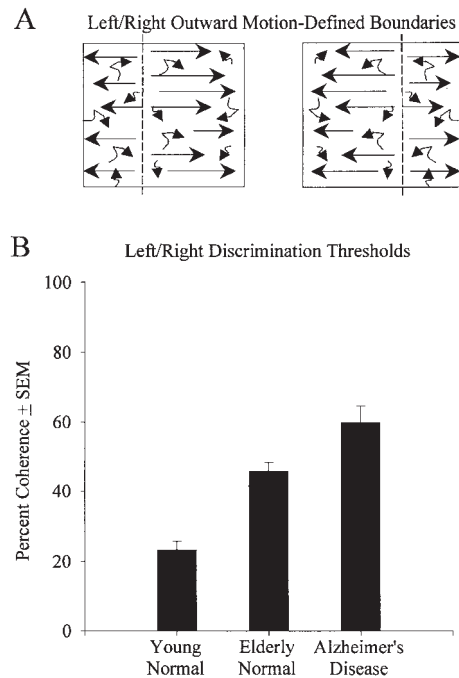


Figure 3. Higher AD thresholds for left/right outward motion-defined boundary discrimination. (A) Left/right outward motion-defined boundary stimuli contained leftward motion on the left and rightward motion on the right with randomly moving dots distributed across the screen. A vertically oriented motion-defined boundary was 30° to the left or right of center (dashed line in illustration was not in stimuli). (B) Left/right discrimination thresholds (ordinate) for each group (abscissa) showed a significant elevation in the AD group.

ing horizontal motion with a left/right location as left/right outward motion-defined boundary stimuli, and (ii) presenting radial motion without a left/right FOE location as in/out centered FOE radial motion stimuli.

The motion-defined boundary stimuli contained a vertical kinetic edge 30° to the left or right of center with leftward motion moving out from the kinetic edge on the left side and rightward motion moving out from the kinetic edge on the right side (Fig. 3A). Random dot motion was added to create motion coherence levels. These stimuli yielded left/right outward motion-defined boundary discrimination thresholds that were elevated in both EN and AD subjects [group $F(2,98) = 28.51, P < 0.001$] with the highest thresholds from AD subjects (Tukey's HSD: $YN < EN < AD$) (Fig. 3B).

The in/out centered FOE radial motion stimuli presented either inward radial motion toward the center or outward radial motion from the center (Fig. 4A). Random dot motion was added to create motion coherence levels. These stimuli yielded in/out centered FOE radial motion discrimination thresholds that were elevated only in AD subjects [group $F(2,97) = 22.69, P < 0.0001$]. The YN and EN thresholds were not significantly different (Tukey's HSD: $YN = EN < AD$) (Fig. 4B).

Regression analysis showed that elevated left/right FOE outward radial thresholds in AD subjects were correlated with both the left/right outward motion-defined boundary thresholds ($r = 0.58, P = 0.004$) and the in/out centered FOE radial thresholds ($r = 0.62, P = 0.002$), but the latter two effects were not correlated with each other ($r = 0.17, P = 0.47$). In AD subjects, multiple regression showed that combining left/right outward motion-defined boundary and in/out centered FOE radial thresholds produced a significant fit ($r = 0.78, P < 0.001$)

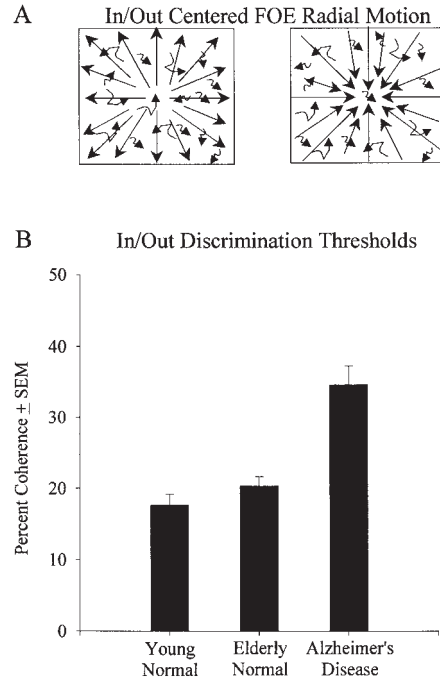


Figure 4. Higher AD thresholds for in/out centered FOE radial motion discrimination. (A) Inward or outward radial motion with centered foci-of-expansion or -contraction (FOE). (B) In/out discrimination thresholds (ordinate) for each group (abscissa) showed significant elevations in the AD group.

to left/right FOE outward radial thresholds with significant contributions from both. EN and YN subjects showed no significant correlations between their thresholds on any of these tests. Thus, in AD subjects only, the combination of impaired left/right outward motion-defined boundary discrimination and impaired in/out centered FOE radial motion discrimination provides the best explanation for impairments in left/right FOE outward radial motion discrimination.

We considered that impaired left/right outward motion-defined boundary perception might simply reflect impaired left/right visual localization. To test this hypothesis we presented stationary dot stimuli with a percentage of the dots forming a 20° square centered 15° to the left or right and the remaining dots evenly distributed throughout the 45° × 30° stimulus (Fig. 5A). EN and AD subjects showed small but significant elevations of left/right stationary square discrimination thresholds [$F(3,99) = 10.42, P < 0.001$; Tukey's HSD: $YN < EN = AD$; Fig. 5C] that did not significantly affect the multiple regression model of left/right FOE outward radial motion discrimination.

We conclude that impaired left/right FOE outward radial motion discrimination in AD is associated with impaired perception of motion-defined boundaries and multi-directional radial motion. These effects are independent of each other and do not reflect impaired left/right location discrimination.

Local versus Global Motion Processing

Left/right FOE outward radial motion can be identified by either the global pattern of radial motion or by local motion at a selected point in the stimulus. That is, the left/right FOE outward radial motion stimuli might be discriminated based only on the direction of motion at the center of the stimuli. We tested whether our subjects could use global motion by removing the utility of local motion. Left/right FOE in/out radial motion stimuli contained inward or outward radial motion with either a left- or

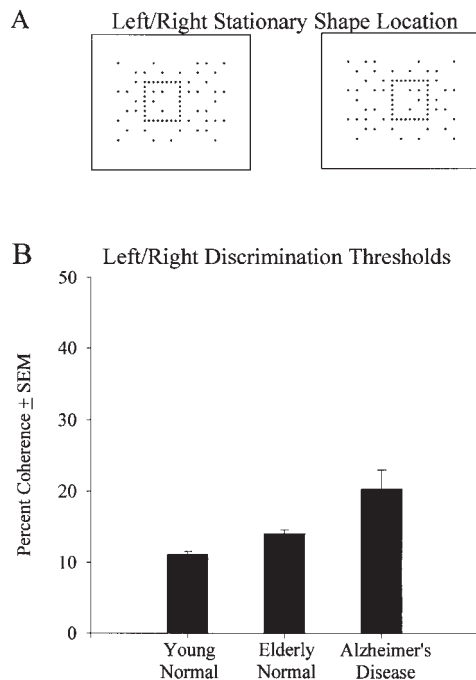


Figure 5. Left/right stationary square location thresholds were similar across groups. (A) Stationary dot stimuli contained small square patterns ($20^{\circ 2}$) centered 15° to the left or right of center within a $45^{\circ} \times 30^{\circ}$ area of evenly distributed stationary dots. (B) Coherence thresholds (square pattern/total dots) for left/right square location discrimination (ordinate) were similarly elevated in both the EN and AD groups (abscissa).

right-sided FOE (Fig. 6A). In these stimuli, local motion in a given direction might be from a left- or right-sided FOE and cannot aid left/right FOE discrimination. Random dot motion was added to create motion coherence levels.

Left/right FOE in/out radial motion thresholds (without local motion cues) were much higher than left/right FOE outward radial motion thresholds (with local motion cues) in AD and somewhat higher in EN (Fig. 6B). This is reflected in a significant group-by-stimulus interaction effect [$F(2,93) = 12.81, P < 0.001$] comparing thresholds to left/right FOE outward radial motion and left/right FOE in-out radial motion across the three subject groups. Individual subject thresholds showed a reliance on local motion cues in almost all AD subjects (85%, 17/20), and some EN subjects (32%, 12/38), seen as thresholds above 50% when local motion cues were removed (Fig. 7). YN subjects showed a significant correlation between left/right FOE outward radial motion thresholds and left/right FOE in-out radial motion thresholds ($r = 0.55, P < 0.001$); EN and AD subjects did not.

Another way of testing radial pattern perception without local motion cues is by presenting stationary dots arrayed along radial lines. We created stationary radial dot patterns with intersections 30° to the left or right. These were superimposed on various numbers of evenly distributed stationary dots to create stationary radial pattern coherence stimuli (Fig. 8A). Stationary radial pattern stimuli yielded significantly higher left/right discrimination thresholds across groups [$F(2,110) = 28.97, P < 0.001$]. The profile of group differences was the same as that seen with left/right FOE in/out radial motion stimuli (Tukey's HSD: YN < EN < AD) but the radial motion thresholds were 2–3 times higher than the stationary radial thresholds (Fig. 8B).

We considered that left/right FOE in/out radial motion thresholds might be higher in the EN and AD groups because of

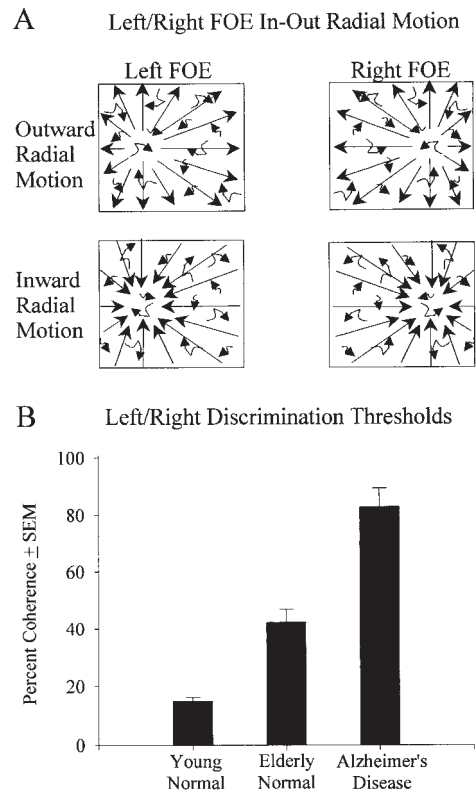


Figure 6. Global pattern radial motion perception was impaired in EN and AD. (A) Left/right FOE in/out radial motion stimuli were created to remove the utility of local motion cues by interleaving stimuli having radial motion outward from (upper) or inward to (lower) left- or right-sided FOEs. (B) Left/right discrimination thresholds (ordinate) for left/right FOE in/out radial motion stimuli for each group (abscissa) showed an elevation in both the EN and AD groups.

task effects; left- and right-sided responses were each needed for two different stimulus patterns, inward and outward radial motion. To assess task effects, we used the same task with left/right in/out horizontal motion-defined boundary stimuli having horizontal motion either inward to or outward from left- or right-sided kinetic edges (Fig. 9A). Left/right in/out motion-defined boundary stimuli yielded the same pattern of discrimination thresholds across groups as was seen with left/right outward-only motion-defined boundary stimuli [$F(2,109) = 32.94, P < 0.001$; Tukey's HSD: YN < EN < AD; Fig. 9B]. In fact, the group values were almost identical in the two tasks (compare to Fig. 3B). We conclude that task effects did not cause higher EN and AD thresholds for left/right FOE in/out radial motion.

Thus, almost all AD and some EN subjects show selectively impaired use of global pattern cues for radial optic flow perception. All subjects with elevated thresholds for discriminating left/right FOE outward radial motion also had elevated thresholds for discriminating left/right FOE in/out radial motion, but the converse was not true. This implies that impaired global pattern radial motion perception is necessary, but not sufficient, for the development of impaired left/right FOE outward radial motion perception.

Links to Spatial Cognition

Neuropsychological tests yielded normal scores in the YN and EN groups and revealed impairments in the AD group consistent with their diagnosis (Table 1). We used Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) scores to assess the

Left/Right FOE Radial Motion Thresholds

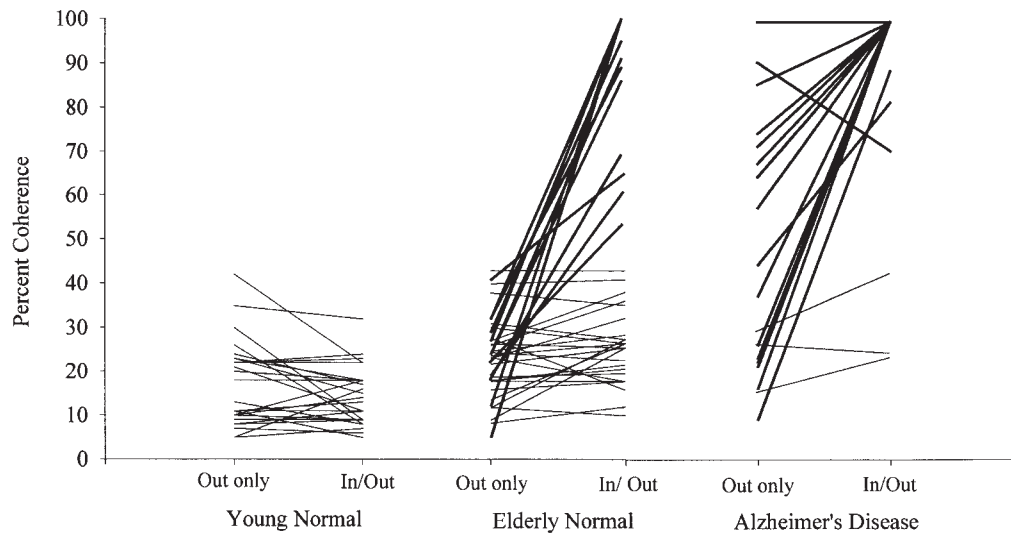


Figure 7. Subjects with elevated left/right FOE in/out radial motion thresholds. Left/right FOE radial motion discrimination thresholds for subjects (ordinate) in each group (abscissa) are shown for left/right FOE outward radial motion stimuli (left side for each subject group) and for left/right FOE in/out radial motion stimuli (right side for each subject group). Almost all AD ($n = 20$) subjects (85%, 17/20), and some EN ($n = 38$) subjects (32%, 12/38), showed thresholds $>50\%$ coherence when local motion cues were removed by interleaving in and out radial motion.

Table 1

Results of neuropsychological testing for each group

Subject group	MMSE (30)	Road Map (32)	Figural (10)	Verbal (24)	Delayed (8)
YN	29.8 ± 0.09	31.6 ± 0.15	8.6 ± 0.13	22.2 ± 0.30	8.0 ± 0.03
EN	29.5 ± 0.14	29.5 ± 0.43	7.3 ± 0.19	18.7 ± 0.55	7.2 ± 0.19
AD	29.5 ± 0.14	29.5 ± 0.43	7.3 ± 0.19	18.7 ± 0.55	7.2 ± 0.19

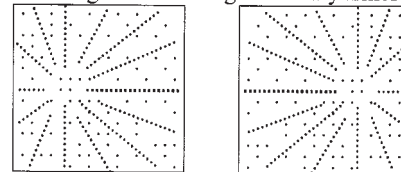
Data are mean \pm SEM. AD subjects had the lowest scores on all neuropsychological tests. Neuropsychological tests: MMSE, mini-mental state exam; Road Map, Money road map test; Figural memory, verbal immediate memory, and verbal delayed memory from the Wechsler memory scale. (Values in parentheses are maximum scores.) YN, young normals ($n = 32$); EN, elderly normals ($n = 50$); AD, Alzheimer's disease subjects ($n = 26$).

impact of disease severity on left/right FOE outward radial motion thresholds. Analysis of group differences, with MMSE as a covariate, again showed elevated left/right FOE outward radial thresholds in AD [$F(2,101) = 19.05, P < 0.001$].

Four neuropsychological tests of specific cognitive capacities were conducted to identify deficits that might help to explain the selective impairment of left/right FOE outward radial motion discrimination. Only the Road Map test scores were significantly correlated with left/right FOE outward radial motion thresholds in AD subjects ($r = -0.50, P < 0.01$). The only other significant correlations were between stationary visual stimulus thresholds and scores on tests of figural and verbal memory. These findings suggest left/right FOE outward radial motion discrimination is linked to spatial cognition.

This conclusion was supported by the results of on-the-road driving tests in 11 AD subjects who met New York State qualifications for testing by having a valid driver's license and having driven in the previous 6 months. The keep-in-lane score, measuring the ability to respect lane boundaries during sustained driving, was correlated with left/right FOE outward radial thresholds ($r = -0.83, P < 0.003$). There were no significant correlations between any psychophysical measure and on-the-road driving tests of vehicular control or road safety measures, nor were there any significant correlations with the

A Left/Right Intersecting Stationary Lines



B Left/Right Discrimination Thresholds

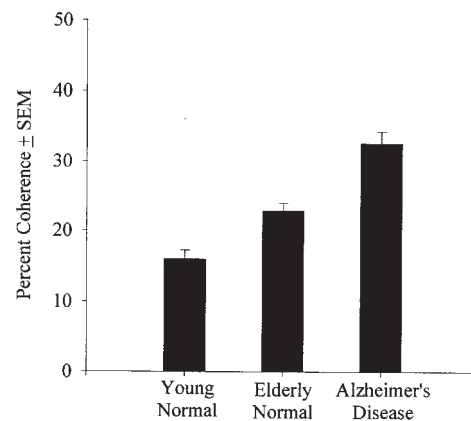


Figure 8. Stationary radial pattern thresholds were higher in EN and AD. (A) Stationary dots arrayed along radial lines extended from a 5° open area that was 30° to the left or right of center. The $90^\circ \times 60^\circ$ stimulus area also containing randomly distributed stationary dots. (B) Coherence thresholds (radial pattern/total dots) for discriminating left/right radial intersections (ordinate) were higher in the EN and AD groups (abscissa).

Useful Field of View test of attentional function relevant to driving (Ball *et al.*, 1993).

We evaluated structural models of the significant correlations found in AD subjects by applying path analysis. Path analysis uses a set of correlations to make causal inferences about the

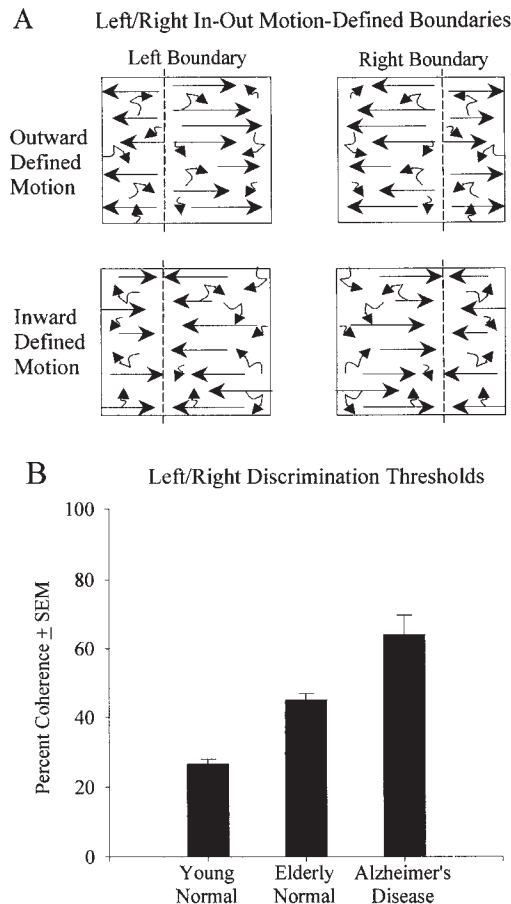


Figure 9. Global pattern motion-defined boundaries yielded thresholds like those for outward-only motion-defined boundaries. (A) Left/right in/out motion-defined boundary stimuli removed the utility of local motion cues by interleaving horizontal motion outward from (upper) or inward to (lower) left- or right-sided kinetic edges. Subjects responded to the side of the kinetic edge so the task was the same as that used with left/right in/out radial motion stimuli. (B) Left/right discrimination thresholds (ordinate) for left/right in/out motion-defined each group (abscissa) showed a significant elevation only in the AD group.

direction of influence between observed variables. We began with left/right outward motion-defined boundary and in/out centered FOE radial thresholds influencing left/right FOE outward radial thresholds that then influence Road Map scores (Fig. 10A). This model fit the data with high χ^2 P values reflecting no significant differences between the data and the model and significant path coefficients (standardized semi-partial correlation coefficients).

We considered the possibility that the correlation between left/right FOE outward radial motion perception and Road Map scores might reflect spatial cognition providing a top-down influence on optic flow perception. We tested this by reversing the path on the right in the model (Fig. 10B). This worsened the fit to the data and caused that path coefficient to become smaller and non-significant. Thus, we conclude that left/right FOE outward radial motion perception influences Road Map performance.

We also tested the possibility that left/right FOE outward radial motion perception is the foundation for, not a consequence of, left/right outward motion-defined boundary and in/out centered FOE radial motion perception. We tested this by reversing the paths on the left in the model (Fig. 10C) and found

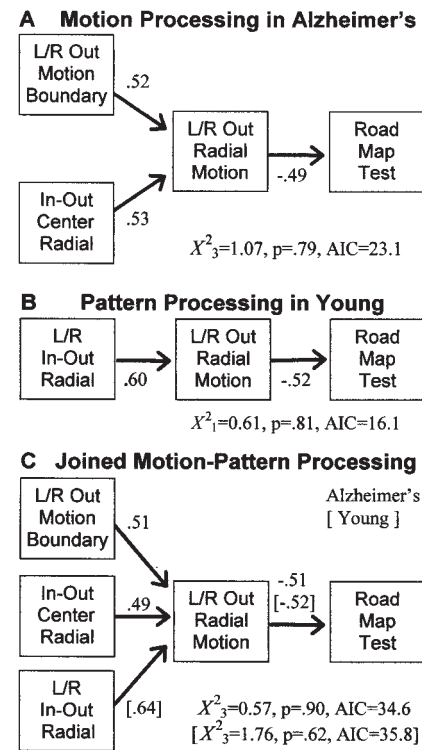


Figure 10. Path analysis tested structural models of possible causal links between the four psychophysical and neuropsychological measures identified by significant correlations in the preceding regression analyses. (A) Bottom-up processing with left/right outward motion-defined boundary thresholds and in/out centered FOE radial motion thresholds influencing left/right FOE outward radial motion thresholds which, in turn, influence Road Map test scores. This model fit the data (χ^2 P value showed no significant difference between the data and model) with significant path coefficients for each link. (B) Top-down spatial cognition model reversed the link on the right so that Road Map test scores influence left/right FOE outward radial motion thresholds. This model barely fit the data and the path coefficient of the top-down link was smaller and non-significant. (C) Top-down visual processing model reversed the links on the left so that left/right FOE outward radial motion thresholds influence left/right outward motion-defined boundary thresholds and in/out centered FOE radial motion thresholds. This model fits the data and yielded significant path coefficients so that neither it nor the model in (A) should clearly be preferred. Path coefficients, and their associated P values, are adjacent to each arrow. The corresponding χ^2 's, P values, and the Akaike Information Coefficients (AIC) are shown for each model.

that this model fits the data and shows significant path coefficients. In spite of a higher Akaike Information Criterion (AIC), the fit to this model may not be significantly different from that of the model shown in Figure 10A; an explicitly reciprocal model was no better. Thus, we cannot determine whether left/right FOE outward radial motion perception drives, or is driven by, left/right outward motion-defined boundary and in/out centered FOE radial perception.

Discussion

Impaired Radial Motion Perception in AD

We have found a selective impairment of radial motion discrimination in AD. One-third of the AD subjects (8/24) had left/right FOE outward radial motion coherence thresholds that were more than three times that of the other AD or EN subjects (Figs 1–2). We have also confirmed earlier reports of small, AD-related impairments in horizontal motion perception (Trick and Silverman, 1991; Gilmore *et al.*, 1992) and a trend supporting

the earlier report of age-related impairments in radial motion perception (Warren *et al.*, 1989).

Horizontal and radial motion stimuli differ in the number of directions of motion they contain and in the presence of left- or right-sided motion-defined FOEs. We assessed the effects of these differences by creating more complex horizontal motion stimuli, with left- or right-sided motion-defined boundaries, and by creating in/out centered FOE radial motion with no lateralizing cue. These stimuli revealed independent perceptual impairments that were significantly related to impaired left/right FOE outward radial motion discrimination in AD ($r = 0.78$, $P = 0.001$) (Figs 3–5).

These findings suggest that complex radial patterns and motion-defined FOEs are not only structural features of optic flow but are also separate perceptual cues. These cues may be processed in separate motion-defined feature (Regan *et al.*, 1992; Schenk and Zihl, 1997; Van Oostende *et al.*, 1997; Cornette *et al.*, 1998) and radial motion pattern (de Jong *et al.*, 1994; Rutschmann *et al.*, 2000; Peuskens *et al.*, 2001) areas in dorsal stream extrastriate visual cortex, even within the superior temporal sulcus (Lauwers *et al.*, 2000). Alternatively, they may be processed in different neuronal subpopulations within a single cortical area. The medial superior temporal area (MST) contains such subpopulations with planar motion selective neurons, modeled as motion-defined boundary detectors (Lappe and Rauschecker, 1993) and radial selective neurons (Duffy and Wurtz, 1991a,b), both of which contribute to optic flow analysis (Duffy and Wurtz, 1995).

Global Motion Processing Impairments

Radial patterns contain local motion cues that betray the location of the FOE from the direction of motion at the center of the screen. We created left/right radial optic flow stimuli using inward and outward radial motion to test the use of local motion cues versus global radial pattern discrimination. Almost all AD (85%), and many EN (32%), subjects were impaired in the use of global radial patterns (Figs 6 and 7) with much smaller impairments in stationary pattern discrimination (Fig. 8) and no comparable effects when the same task was used with left/right in/out motion-defined boundary stimuli (Fig. 9). Thus, local motion was used for radial pattern discrimination but not motion-defined boundary discrimination, possibly explaining the independence of their effects in the regression model of left/right FOE radial motion discrimination.

Young subjects showed no effect of being forced to rely on the global radial pattern, suggesting that they were using global pattern recognition all along. Some EN and AD subjects were impaired on global radial pattern discrimination alone, whereas all AD subjects who were impaired on left/right FOE outward radial motion discrimination were also impaired on the global radial pattern discrimination of left/right FOE in-out radial motion stimuli. Thus, impaired global radial pattern discrimination in AD may precede impaired left/right FOE outward radial motion perception as a matter of disease progression.

This suggests that there are two stages in the development of impaired optic flow perception. First, the global pattern recognition strategy used by YN subjects is impaired before clinically evident AD appears. This forces some elderly and almost all AD subjects to rely on local motion processing. Second, clinically evident AD is associated with the progressive impairment of local motion processing. This means that both global and local processing strategies are lost and only then does left/right FOE outward radial motion perception fail.

Impaired global radial pattern discrimination might reflect

the effect that AD has in narrowing spatial attention within the visual field (Parasuraman *et al.*, 1995; Starck *et al.*, 1997; Mapstone *et al.*, 2001), or the damage that AD causes to cortico-cortical connections (Hof and Morrison, 1990) that mediate local versus long-range interactions in extrastriate visual cortex (Xiao *et al.*, 1997; Berezovskii and Born, 2000). Alternatively, impaired global radial pattern discrimination in EN and AD subjects might suggest a link to the hippocampal damage that is evident in the earliest stages of AD (Brun and Gustafson, 1976). This damage could impede direct hippocampal contributions to optic flow analysis (Wylie *et al.*, 1999) or undermine hippocampal spatial memory for optic flow (Suzuki *et al.*, 1997). The latter mechanism might support the temporal integration of optic flow during sustained observer movement along a path through the environment (McNaughton *et al.*, 1996) to create context-dependent hippocampal place responses (Knierim and McNaughton, 2001). Hippocampal damage might also impede visual memory feedback (Beason-Held *et al.*, 1999) to cortical optic flow analyzers for template-matching pattern recognition strategies of heading estimation (Perrone and Stone, 1994).

Perceptual Mechanisms of Visuospatial Orientation

Left/right FOE outward radial motion thresholds were elevated in AD independent of disease severity as measured by the MMSE. These thresholds were correlated with impaired spatial cognition in the Road Map test ($r = -0.50$, $P < 0.01$) and impaired navigation in the on-the-road driving test's keep-in-lane score ($r = -0.83$, $P < 0.003$).

This link might reflect the damage that AD causes to optic flow areas in cortex (Duffy and Wurtz, 1995; Schaafsma and Duysens, 1996; Siegel and Read, 1997). Such damage could elevate radial motion discrimination thresholds in simulated optic flow and also impede self-movement perception based on the optic flow fields encountered in driving (Lee, 1974; Warren and Hannon, 1988). These same areas might also be involved in performance on the Road Map test of spatial cognition by supporting the visual imagery needed to interpret the direction of imagined self-movement required in that test (Mast *et al.*, 1999).

Path analysis showed that left/right FOE outward radial motion discrimination influences Road Map scores, not the other way around (Fig. 10A,B). This is consistent with the long-held impression that visual perceptual processes in dorsal extrastriate areas are the foundation for spatial cognitive mechanisms attributed to posterior parietal cortex (Kleist, 1935; Mountcastle and Edelman, 1978; Ungerleider and Mishkin, 1982; Goodale and Milner, 1992).

Path analysis could not resolve the causal direction of the link between left/right FOE outward radial motion discrimination and left/right outward motion-defined boundary or in/out centered FOE radial motion thresholds (Fig. 10A,C). In either direction, path coefficients between left/right radial thresholds and left/right boundary or in/out radial motion thresholds are ~ 0.5 . Regression analysis showed, and path analysis confirmed, that the latter two measures were not correlated. One interpretation of these observations is that left/right boundary and in/out radial discrimination reflect separate aspects of the processes serving left/right FOE outward radial motion discrimination.

The context of previous findings, discussed above, leads us to suggest that planar motion-defined boundary neurons and radial optic flow neurons that are intermingled in macaque MST may be in different areas in human cerebral cortex. This separation

might account for the independent vulnerability of these functions.

Notes

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