Distinct mechanisms of impairment in cognitive ageing and Alzheimer’s disease

Mark Mapstone, Kathryn Dickerson and Charles J. Duffy

Departments of Neurology, Brain and Cognitive Sciences, Neurobiology and Anatomy, Ophthalmology, and the Center for Visual Science, The University of Rochester Medical Center, Rochester, NY 14642, USA

Correspondence to: Mark Mapstone, PhD, Department of Neurology, University of Rochester Medical Center, 601 Elmwood Avenue, Box 673, Rochester, NY 14642-0673, USA
E-mail: mark_mapstone@urmc.rochester.edu

Similar manifestations of functional decline in ageing and Alzheimer’s disease obscure differences in the underlying cognitive mechanisms of impairment. We sought to examine the contributions of top-down attentional and bottom-up perceptual factors to visual self-movement processing in ageing and Alzheimer’s disease. We administered a novel heading discrimination task requiring subjects to determine direction of simulated self-movement from left or right offset optic flow fields of several sizes (25°, 40° or 60° in diameter) to 18 Alzheimer’s disease subjects (mean age = 75.3, 55% female), 21 older adult control subjects (mean age = 72.4, 67% female), and 26 younger control subjects (mean age = 26.5, 63% female). We also administered computerized measures of processing speed and divided and selective attention, and psychophysical measures of visual motion perception to all subjects. Both older groups showed significant difficulty in judging the direction of virtual self-movement [F(2,194) = 40.5, P < 0.001] and optic flow stimulus size had little effect on heading discrimination for any group. Both older groups showed impairments on measures of divided [F(2,62) = 22.2, P < 0.01] and selective [F(2,62) = 63.0, P < 0.001] attention relative to the younger adult control group, while the Alzheimer’s disease group showed a selective impairment in outward optic flow perception [F(2,64) = 6.3, P = 0.003] relative to both control groups. Multiple linear regression revealed distinct attentional and perceptual contributions to heading discrimination performance for the two older groups. In older adult control subjects, poorer heading discrimination was attributable to attentional deficits (R² adj = 0.41, P = 0.001) whereas, in Alzheimer’s disease patients, it was largely attributable to deficits of visual motion perception (R² adj = 0.57, P < 0.001). These findings suggest that successive attentional and perceptual deficits play independent roles in the progressive functional impairments of ageing and Alzheimer’s disease. We speculate that the attentional deficits that dominate in older adults may promote the development of the perceptual deficits that further constrain performance in Alzheimer’s disease.

Keywords: attention; perception; vision; ageing; Alzheimer’s disease

Abbreviations: EAD = Early Alzheimer’s disease; OAC = Older adult control; YAC = Younger adult control


Introduction

Attention links sensation and action through a bidirectional network of frontal and parietal cortical regions that shape perceptual processing and guide behaviour (Mesulam, 1998). This network integrates bottom-up sensory signals from lower unimodal perceptual centres with top-down, task-related inputs from multimodal cognitive centres (Cauiller and Cauiller, 1995). The selection of the featural content or spatial distribution of perceptual stimuli for detailed processing relies on the convergence of signals in this network (Posner, 1980).

Normal ageing is associated with cognitive declines linked to anterior cortical dysfunction (Hanninen et al., 1997) that constrain the speed and selectivity of cortical information processing (Salthouse, 1996). Structural imaging studies show age-related anterior cortical tissue loss affecting both overall cortical volume (Salat et al., 2004) and subcortical white matter integrity (O’Sullivan et al., 2001).
These findings are consistent with functional imaging evidence of age-related decreases in frontal lobe metabolism and perfusion (Tumeh et al., 2007), which may be a cause or an effect of this region’s selective vulnerability to the effects of ageing (Greenwood, 2000).

In contrast, Alzheimer’s disease is associated with functional declines referable to posterior cortical dysfunction (Cummings, 2000). The memory disorder that is the commonly recognized hallmark of Alzheimer’s disease is accompanied by a variety of visual disorders including impairments of contrast sensitivity, motion perception and navigation (Kavic et al., 2006). Much of the diverse behavioural phenomenology of Alzheimer’s disease can be viewed as signs of cortical disconnection (Mesulam, 1998). This interpretation is supported by histological and imaging evidence of white matter changes that are disproportionate to neuronal pathology in Alzheimer’s disease (Arnold et al., 2006). These white matter changes may reflect the selective loss of cortico-cortical projection neurons in Alzheimer’s disease, particularly in the posterior parietal areas that are involved in fronto-parietal interactions (Braak and Braak, 1991; Morrison et al., 1991).

The posterior concentration of Alzheimer’s disease pathology, and its impact on cortico-cortical connections, is consistent with the localization and connectivity of visual motion processing mechanisms in the occipito-parietal areas that form the dorsal extrastriate visual pathway (Ungerleider and Mishkin, 1982). The large receptive fields of neurons in macaque dorsal medial superior temporal cortex (MSTd) respond selectively to the radial patterns of visual motion in optic flow (Duffy and Wurtz, 1997) that provide moving observers with information about their heading direction. The dorsal extrastriate processing stream integrates optic flow analysis with the processing of other self-movement cues that support autonomous navigation (Page and Duffy, 2003).

The posterior cortical centres that support navigation reside in the midst of the neocortical regions most affected by Alzheimer’s disease neuropathology (Brun and Englund, 1981). This is consistent with the common occurrence of optic flow perceptual deficits in Alzheimer’s disease that are linked to ambulatory and vehicular navigational failure (O’Brien et al., 2001) and are independent of memory and language impairments in Alzheimer’s disease (Mapstone et al., 2006).

In this study, we examined the contributions of top-down attentional processing and bottom-up perceptual processing on optic flow-based heading discrimination in ageing and Alzheimer’s disease. Our goal was to test the notion that both top-down attentional control and bottom-up perceptual processing contribute to heading discrimination. We hypothesize that heading discrimination declines in both ageing and Alzheimer’s disease, and that age-related attentional dysfunction underlies heading discrimination deficits in older adults, whereas disease-related perceptual dysfunction primarily impacts on heading discrimination in Alzheimer’s disease.

### Material and Methods

#### Subjects

A total of 65 individuals participated in this study. Eighteen had the recent onset of Alzheimer’s disease with symptoms recognized by the patient or family members as emerging within the preceding 4 years. A total of 47 subjects served as normal controls. Early Alzheimer’s disease (EAD) patients were referred by a geriatric neurologist or psychiatrist affiliated with the clinical programmes at the University of Rochester Medical Center. All of these patients met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer’s disease (McKhann et al., 1984). The normal control participants were divided into two groups in order to examine the effects of ageing. Older adult controls (OACs, $n = 21$) were between the ages of 60 and 84 years and younger adult controls (YACs, $n = 26$) were between the ages of 20 and 43 years. OAC participants included volunteers from the community and many were spouses or caregivers of EAD group participants. YAC participants were students or staff at the University of Rochester. All participants were free from neurological and psychiatric illness with the exception of Alzheimer’s disease in the EAD group. Of the EAD group, 55% were males, while 67% were females in the OAC group and 63% were females in the YAC group. All participants had corrected binocular visual acuity of at least 20/40 and were free from ophthalmic illness. All subjects in this study were native speakers of English. As defined, the YAC and OAC groups differed in age ($P < 0.001$), but the Alzheimer’s disease and OAC groups did not ($P > 0.05$) (Table 1).

#### Procedures

All testing was completed in the Visual Orientation laboratory at the University of Rochester Medical Center in two, 1-h sessions. The protocol was explained to all participants in advance and written consent was obtained. All participants completed the same experimental protocol. The first visit consisted of pencil and paper cognitive tests and the Visual Attention Analyzer (Visual Resources, Inc., Chicago, USA) test of spatial attention, while the second visit consisted of visual motion coherence threshold testing and a novel heading discrimination threshold task. The University of Rochester Institutional Review Board approved all protocols used.

#### Table 1 Subject characteristics: means and SDs

<table>
<thead>
<tr>
<th>Group</th>
<th>$N$ (% female)</th>
<th>Age ($\bar{x}$)</th>
<th>Years of education ($\bar{x}$)</th>
<th>Contrast sensitivity (cycles/degree)</th>
<th>$P'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>YAC</td>
<td>26 (63)</td>
<td>26.5° (70)</td>
<td>16.9° (2.0)</td>
<td>20 (5.0)</td>
<td></td>
</tr>
<tr>
<td>OAC</td>
<td>21 (67)</td>
<td>72.4 (6.3)</td>
<td>15.1 (2.5)</td>
<td>28.8 (13.6)</td>
<td></td>
</tr>
<tr>
<td>EAD</td>
<td>18 (55)</td>
<td>75.3 (7.2)</td>
<td>16.1 (2.6)</td>
<td>33.1 (16.5)</td>
<td></td>
</tr>
</tbody>
</table>

$\bar{x}$ YAC group significantly younger than OAC and EAD groups ($P’<0.001$).

$\bar{x}$ YAC group has significantly more years of education than OAC group ($P = 0.039$).
A battery of cognitive tests were administered to corroborate the diagnosis of Alzheimer’s disease in the EAD group participants and to rule out specific cognitive impairments in the normal control groups. The Mini Mental State Examination (MMSE) was used as a measure of global cognitive ability. Mean MMSE score for the EAD group was \((27.3 \pm 2.2)\) suggesting that these participants were in the earliest detectable stage of the disease (Table 2). Verbal immediate and delayed memory were assessed using the Wechsler Memory Scale-Revised (WMS-R) Paired Association Learning Test, in which participants learn novel associations between eight unrelated word pairs. Non-verbal Immediate memory was assessed using the WMS-R Figural Memory Test, in which participants study novel geometric designs and perform a three alternative forced choice recognition task for the design. Language was assessed using a category fluency test, in which participants name as many animals as possible in 1 min and a phonemic fluency task, in which participants say as many words as possible, which begin with the letters F, A and S in separate 1-min trials. Three measures of visuospatial function were administered including the Judgment of Line Orientation task that assesses the ability to judge spatial relationships between two lines. In this task, participants are shown two lines that create an angle and must identify as to which two lines create the same angle as the sample from among 13 lines arranged in a fan-shaped array. We also administered the Facial Recognition Test, in which participants match pictures of unfamiliar faces from different perspectives and under different lighting conditions (Lezak, 1995). Finally, we administered the Money Road Map Test (Money, 1976), which assesses route-following and topographic orientation. In this paper and pencil test, participants visually follow a marked route on a top-down perspective city map and indicate left or right turns at each junction.

**Attentional measures**

The dynamic range of spatial attention was measured using the Visual Attention Analyzer (Visual Resources, Inc.). The Visual Attention Analyzer measures the range over which spatial attention can be deployed using blocks of individual subtests of sustained attention, divided attention and selective attention. Participants sit at a fixed distance from a computer monitor and press a touch screen to respond to each of the three tasks. In the most difficult selective attention condition, participants identify the location of a peripherally flashed stimulus embedded in distractors and the identity of a centrally flashed stimulus. The stimuli are presented at fixed points in the periphery, but stimulus exposure time varies across trials (Fig. 4A). The software adjusts subsequent stimulus exposure duration (in milliseconds) based on whether the previous response was correct; shortening exposure for correct responses and lengthening for incorrect. The software continues to adjust stimulus exposure on a trial-wise basis until the subject reaches a stable 75% correct performance level. The number of trials required to attain this performance criterion is variable depending upon the overall performance of the subject and stability of responses across trials. The resultant measure from the Visual Attention Analyzer is a stimulus exposure duration for reliable detection of visual stimuli for each of the three subtests (sustained attention, divided attention and selective attention).

**Perceptual measures**

Participants sat near the centre of a darkened \(2.4 \times 2.4 \times 1.8 \text{ m}^3\) enclosure, the front wall of which was a \(2.4 \times 1.8 \text{ m}^2\) rear-projection tangent screen. The display covered the central 90° × 60° of the subject’s visual field while they sat in a fixed orientation facing the tangent screen. Participants maintained fixation on the centre of the screen in all tasks with eye position monitored by infrared oculography (ASL, Inc., Bedford, MA, USA). All visual stimuli were generated on a personal computer using proprietary software and projected onto the screen by a TV projector (Electrohome, Inc., Ontario, Canada). Participants turned a steering wheel left or right or pushed one of two buttons in order to respond to each stimulus (depending on the task). Neither the steering wheel nor the button box obstructed vision of the screen. All stimulus parameters, gaze and response cursor position were recorded in real time.

**Motion coherence thresholds**

The visual motion stimuli used in visual motion coherence threshold determination consisted of horizontal planar motion or an optic flow field. Animated sequences of 750 white dots were presented on a dark background by a television projector at 60 Hz. Planar motion stimuli were made up of rightward or leftward moving dots. Radial motion stimuli were dots moving in a radial pattern from a focus of expansion or contraction 15° to the right or left of the centre on the horizontal midline of the screen. Radial inward and outward motion consisted of dots moving in a radial pattern contracting into (radial in) or expanding out from (radial out) the focus of expansion. The two types of motion were presented pseudo-randomly on a trial-wise basis such that an equal number of in and out stimuli were presented during the block (Fig. 5). Random dot motion was mixed in with these coherent motion patterns. The percentage of randomly and coherently moving dots varied between trials in order to determine the

<table>
<thead>
<tr>
<th>Group</th>
<th>MMSE</th>
<th>WMS-R Verbal Fluency (Animals)</th>
<th>WMS-R Verbal Fluency (FAS)</th>
<th>WMS-R Figural Memory</th>
<th>Category Fluency (Animals)</th>
<th>Letter Fluency (FAS)</th>
<th>Benton Judgment of Line Orientation</th>
<th>Benton Facial Recognition</th>
<th>Money Road Map</th>
</tr>
</thead>
<tbody>
<tr>
<td>YAC</td>
<td>293 (1.2)</td>
<td>20.7 (3.0)</td>
<td>78 (0.5)</td>
<td>8.3 (1.5)</td>
<td>25.7 (6.9)</td>
<td>43.7 (17.1)</td>
<td>273 (2.7)</td>
<td>46.7 (3.1)</td>
<td>31.2 (2.3)</td>
</tr>
<tr>
<td>OAC</td>
<td>28.7 (1.3)</td>
<td>177 (3.5)</td>
<td>6.6 (1.3)</td>
<td>6.7 (1.3)</td>
<td>21.9 (6.1)</td>
<td>399 (140)</td>
<td>24.1 (4.0)</td>
<td>46.6 (3.6)</td>
<td>28.4 (3.6)</td>
</tr>
<tr>
<td>EAD</td>
<td>273* (2.2)</td>
<td>11.6** (3.9)</td>
<td>41** (1.8)</td>
<td>6.0 (1.4)</td>
<td>14.7** (5.2)</td>
<td>28.7 (109)</td>
<td>22.3 (4.1)</td>
<td>42.6* (6.7)</td>
<td>26.7 (5.3)</td>
</tr>
</tbody>
</table>

*OAC significantly worse than YAC \(P < 0.05\).

**EAD significantly worse than YAC \(P < 0.05\).**

**EAD significantly worse than OAC \(P < 0.001\).**
motion coherence thresholds. At each frame, dots were randomly assigned to the coherent and random groups with the appropriate proportions. All stimuli had the same luminance, contrast and density. The coherent group always had the same speed.

Visual motion coherence thresholds for planar, radial outward and radial inward/outward motion were determined in separate blocks using a one interval, two-alternative forced-choice left/right identification task (Fig. 5A). Each trial began with the subject centering a cursor, using the steering wheel, over a central fixation square on the screen for 0.5 s while fixating in the centre. Each trial started after central fixation was maintained for 0.5 s. For the planar movement trials, participants indicated whether the dots were moving to the left or to the right by moving the steering wheel in the direction of the moving dots. In the radial out and radial in/out movement conditions, participants were asked to indicate whether the centre of motion was on the left or right of the central fixation square by moving the steering wheel. Once each trial had ended a large letter L and letter R were visible on the screen and the subject moved the steering wheel towards the L if he thought left was the correct response or towards the R if he thought right was the correct response. The next trial began after the computer recorded each response. Participants were encouraged to guess if they were unsure of the answer.

Coherence discrimination thresholds for planar, radial out and radial in/out motion were determined using the parameter estimation by sequential testing (PEST) technique (Harvey, 1997). The PEST algorithm was first run for 20 practice trials, to accustom the participants to the task and the stimuli, beginning with a seed value of 100% coherence for all groups (EAD, OAC and YAC). Each subject’s threshold from these 20 practice trials was used to seed the subsequent 50-trial test phase that determined the final coherence threshold for that subject. Thus, each subject completed 20 practice and 50 test trials for each of the three types of motion: planar, radial out and radial in/out. The three tasks were presented in separate blocks with short breaks between blocks. Perceptual threshold was defined as the percentage of coherent motion in stimuli \( (\text{coherently moving dots} \times \text{random dots}) \times 100 \) that yield 82.5% correct responses, using a Weibull function as the psychometric function model. Separate thresholds were obtained for planar, radial outward and radial in/out motion (Fig. 5B).

**Heading discrimination**

The heading discrimination task is a novel task designed to examine the influence of varying eccentricities of peripheral horizontal planar motion on heading determination from a parfoveal optic flow field. In this task, participants make a left/right heading offset determination under different conditions of peripheral horizontal planar motion and of varying sizes of an optic flow field. The stimulus consisted of an optic flow field in an inner circle with a planar motion flow field in an outer annulus. The planar motion moved in the same direction of the heading offset (i.e. left of centre heading and leftward planar motion) or in the opposite direction of the heading offset (left of centre heading and rightward planar motion). In one condition, the planar motion was replaced by static dots on the screen. The circumference of the inner optic flow field was adjacent to, but did not overlap with the outer annulus (Figs 1A and 2A). The size of the inner optic flow field was one of three fixed sizes: small (25° in diameter), medium (40° in diameter) and large (60° in diameter). In order to maintain a constant area of planar motion in the outer annulus, the overall diameter of the combined stimuli (inner optic flow field plus the outer planar motion annulus) expanded from 65.8° in diameter for the small stimulus, 70.7° for the medium stimulus and 80° for the large stimulus (Fig. 5). There were two independent variables in this task: the size of the inner optic flow field (25°, 40° and 60°) and the direction of planar motion (in the same direction as the heading offset, static, and in the opposite direction from the heading offset). The trial presentation was random across all sizes of the inner optic flow field and direction of planar motion. To obtain heading distance offset thresholds, the centre of motion was presented on a logarithmic scale at 1 of 12 eccentricities from the central fixation point (0.05°–12.2°) along a horizontal plane.

**Fig. 1** Stimuli used in the heading discrimination task consisted of an optic flow field at one of the three sizes with an annulus of either task-irrelevant information: moving or static dots. (A) Outward radial optic flow patterns consisting of white dots on a black background were presented with a surrounding pattern of stationary dots. Three stimulus sizes were randomly interleaved to assess the spatial integration of simulated self-movement cues. The circular field of radial motion and annular surround of stationary dots were scaled to maintain a constant ratio. (B) Heading discrimination performance was better in YAC, than OAC, than EAD participants with an unexpected increase in thresholds with larger stimuli. Bar graphs showing heading discrimination thresholds (mean ± SEM, ordinate) for each stimulus size and subject group. ANOVA confirmed large increases in thresholds across subject groups \( (P < 0.001) \) and smaller increases with increasing stimulus size \( (P = 0.018) \) with no significant interaction.
Heading offset distance thresholds were determined simultaneously for all nine conditions (stimulus size × direction of planar motion) by using an adaptive method of constant stimuli. This method involved a Weibull function as the psychometric function model and the maximum likelihood procedure for threshold estimation. Heading distance offset threshold was defined as the minimum distance from the central fixation point where the subject could identify the centre of motion with 80% accuracy.

### Data analysis

Subject group effects on the neuropsychological tests, visual motion coherence thresholds and Visual Attention Analyzer subtests were examined in separate multivariate analysis of variance (MANOVA). Follow-up one-way analysis of variance (ANOVA) and Tukey’s HSD post hoc tests were applied where indicated.

Heading discrimination thresholds were examined for main effects of subject group (YAC, OAC, EAD), stimulus size (small, medium, large) and surrounding stimuli (stationary, leftward motion, rightward motion) as well as their interactions using MANOVA with follow-up ANOVAs and pair-wise post hoc tests using Tukey’s HSD.

Finally, multiple linear regression was used to examine the contributions of attention and perception to heading discrimination thresholds. We performed a step-wise multiple linear regression with mean heading discrimination threshold for the three stimulus sizes in the static peripheral motion condition as the dependent measure and the three visual motion coherence thresholds (horizontal, outward optic flow, interleaved inward/outward optic flow) and the Visual Attention Analyzer subtests (processing speed, divided attention, selective attention) as the independent measures. Probability of F to enter the model was set at ≤0.05 with probability to remove set to ≥0.10. Significance levels for all analyses were set at an α of 0.5. All statistical analyses were run using SPSS statistical software (SPSS, Chicago, IL, USA).

### Results

Twenty-six YACs and 21 OACs, and 18 EAD patients (Table 1) underwent a battery of visual and neuropsychological tests (Table 2) that revealed deficits by standard measures that are consistent with group assignment.

### Optic flow heading discrimination

To assess heading discrimination, subjects viewed large-field optic flow stimuli simulating headings to the left or right of their centred fixation point. We determined the minimum reliable displacement for left/right heading discrimination expressed as a perceptual threshold for each subject. Optic flow displays of three different sizes were presented with stationary surrounds to assess the impact of stimulus area (Fig. 1A). Randomly interleaved trials presented the same optic flow stimuli surrounded by left or right planar motion to assess the impact of non-overlapping visual motion on performance in the heading discrimination task.

Heading discrimination thresholds were examined for main effects of subject group (YAC, OAC, EAD), stimulus size (small, medium, large) and surrounding stimuli...
surrounded by oppositely directed planar motion were seen in older subjects viewing small stimuli and much less so with the medium and large sizes. Same direction planar motion had substantially less effect on heading discrimination thresholds.

These peripheral motion effects are consistent with illusory displacement of perceived heading direction by planar motion (Duffy and Wurtz, 1997). Our findings are surprising in that we find an asymmetry of displacement relative to heading direction and much larger illusory displacements when older subjects see planar motion in the near periphery.

### Attentional mechanisms

To examine the effects of ageing and Alzheimer’s disease on attention we used the Visual Attention Analyzer (Visual Awareness Inc, Chicago, IL, USA) to obtain stimulus duration thresholds in three tasks designed to assess: (i) processing speed, (ii) divided attention and (iii) selective attention (Fig. 4A). Our three subject groups showed a range of differences across the three tasks [two-way ANOVA: group \( F(2,189) = 83.1, P<0.001 \); task \( F(2,189) = 71.5, P<0.001 \); interaction \( F(4,189) = 15.3, P<0.001 \)]. All three subject groups showed significant task effects \( F(2,62) = 63.0, P<0.001 \) with the EAD group having the longest thresholds in all three tasks (Fig. 4B). The OAC group showed consistently better performance than the EADs on all three tasks and worse performance than the YACs on all but the processing speed task. \( Post hoc \) tests of group differences yielded: processing speed \( F(2,63) = 6.8, P=0.002 \) with YAC=OAC<EAD at \( P<0.001 \); divided attention \( F(2,62) = 22.2, P<0.001 \) with YAC<OAC<EAD at \( P<0.001 \); selective attention \( F(2,62) = 63.0, P<0.001 \) with YAC<OAC<EAD at \( P<0.001 \). Thus, the OAC and
visual attention analyzer subtests

**A**

**Visual Attention Analyzer Subtests**

- **Subtest 1** Processing Speed
- **Subtest 2** Divided Attention
- **Subtest 3** Selective Attention

**B**

**Group performance on Visual Attention Analyzer Subtests**

- YAC
- OAC
- EAD

**Fig. 4** To assess attentional contributions to heading discrimination impairments we used the Visual Attention Analyzer (Visual Awareness, Inc.) (A) The Visual Attention Analyzer consists of three reaction time (RT) subtests presented on a 17 in. touch-screen monitor at a distance of 24 in. Subtest 1 (left) is intended to measure processing speed and consists of the central presentation of a car or truck figure followed by a car and a truck on either side of the screen. This test required that participants touch the previously presented object and measured reaction time from the onset of the paired stimuli. Subtest 2 (middle) is intended to measure divided attention and consists of the presentation of a central car or truck figure followed by a car and a truck on either side of the screen. This test required that participants touch the previously presented object and measured reaction time from the onset of the paired stimuli. Subtest 3 (right) is intended to measure selective attention and follows the stimulus and response sequence of subtest 2 but includes the overlay of a grid of triangular shapes on the first stimulus screen. (B) Responses (mean + SE) of each subject group in each of the three Visual Attention Analyzer subtests reveal an age-related increase in RT with increasing attentional demands (P < 0.001).

**Stimuli Used in Motion Coherence Task**

- **Horizontal Motion**
- **Outward Optic Flow**
- **Inward/Outward Optic Flow**

**Group Motion Coherence Thresholds**

- **YNC**
- **ONC**
- **AD**

**Fig. 5** Visual stimuli used for motion coherence perceptual testing in these studies. (A) Horizontal motion and radial optic flow perception was assessed by varying motion coherence from 100% (all dots undergoing patterned motion) to 1% (nearly all dots undergoing random motion) using an algorithm for maximum likelihood threshold determination. (B) Bar graphs show significant differences between perceptual thresholds (mean + SE, ordinate) for each motion stimulus and subject group (P < 0.001) revealing both age and disease effects. OAC thresholds were higher than the YAC with inward/outward radial motion (P < 0.001). EAD participants showed higher thresholds than YACs on all tasks with higher thresholds than the OAC with outward radial motion (all P-values <0.01).

EAD groups showed the same pattern of attentional impairment, with the EAD showing more severe deficits in all three attentional tasks. This group-wise analysis of variance indicates that the groups are significantly different on the attentional measures.

**Perceptual mechanisms**

Visual motion coherence thresholds were obtained to assess the impact of ageing and Alzheimer’s disease on visual processing using three stimulus sets: (i) horizontal motion, (ii) outward radial motion and (iii) interleaved inward and outward radial motion (Fig. 5A). Our three subject groups differed across the stimulus sets [two-way ANOVA: group...
F(2,193) = 30.2, P < 0.001; stimulus F(2,193) = 37.0, P < 0.001; interaction F(4,193) = 7.8, P < 0.001]. The EAD group performed worse than the YAC group on all tests, but worse than the OAC group only with outward radial motion (Fig. 5B). The OAC group performed worse than the YAC group only with interleaved inward and outward radial motion. [Post hoc tests of group difference yielded: horizontal motion F(2,64) = 5.2, P = 0.008 with YAC<EAD at P = 0.006; outward radial F(2,64) = 6.3, P = 0.003 with YAC = OAC<EAD at P = 0.003; inward and outward radial F(2,63) = 20.1, P < 0.001 with YAC<OAC = EAD at P < 0.001.] Thus, the impairment in outward radial optic flow seen in the OAC and EAD groups, but not the YAC may be considered an age-related deficit, while the radial in/out radial optic flow impairment seen only in the EAD group may be considered a disease-specific impairment as it is not seen in the OAC group. This group-wise ANOVA indicates that the groups are significantly different on the perceptual measures.

**Attentional and perceptual contributions to heading discrimination**

We combined the results of our attentional and perceptual tests in a multiple linear regression model to predict performance on optic flow heading discrimination. We used the mean heading discrimination threshold achieved across the three stimulus sizes for the static peripheral motion condition as the dependent measure and the three perceptual thresholds (horizontal, outward, interleaved inward/outward motion) and the three Visual Attention Analyzer subtests (processing speed, divided attention, selective attention) as independent variables. We also included a separate block of variables coded for group membership. The regression model yielded a good fit to the data from all three subject groups (R^2 adj = 0.68, P < 0.001) by combining measures of selective attention and outward radial motion perception (Fig. 6). Group membership did not account for additional variance in heading discrimination performance in this regression model. This may be considered surprising given our ANOVA results indicating significant group effects on heading discrimination with the static periphery (Fig. 1B). However, we also demonstrated significant group differences via ANOVA on the attentional and perceptual variables used in this regression analysis, which may suggest independent mechanisms of attentional and perceptual effects on heading discrimination in each group. Thus, we separated the groups and conducted independent regression analyses for each.

The three subject groups showed different relationships between heading discrimination and the other measures. In the YAC group, variability in heading discrimination was predicted by slight variation in processing speed (R^2 adj = 0.64, P < 0.001), in the context of excellent performance of these subjects. In the OAC group, heading discrimination was best predicted by selective attention (R^2 adj = 0.41, P = 0.001). In the EAD group, heading discrimination was best predicted by outward radial optic flow thresholds (R^2 adj = 0.57, P < 0.001).

Finally, we explored the possibility that attentional and perceptual influences might interact in determining heading discrimination threshold performance. To do so, we created an interaction term for the multiple regression by multiplying the selective attention and outward radial thresholds. Repeating the regression analysis revealed a highly significant effect of the interaction term in the EAD group only (R^2 adj = 0.57, P < 0.001). While it is note-worthy that the regression chose this interaction factor in this group, the one group in which we might expect both the ageing and disease effects, the lack of change in the R^2 suggests that the perceptual factor may be dominant. Alternatively, the interaction between attention and perception to drive heading performance may be more complex than can be captured by the multiplicative term we created. In summary, these results suggest that attentional and perceptual measures can effectively predict heading discrimination with different measures being most relevant in YAC, OAC and EAD participants.

**Discussion**

**Mechanisms of cognitive ageing**

We find that normal ageing and Alzheimer’s disease are accompanied by impaired abilities to discriminate heading direction during simulated self-movement. Surprisingly,
heading discrimination performance in the three subject groups is limited by different factors. The YAC group’s excellent performance (Fig. 1B) is limited only by minor variation in processing speed (Fig. 4B), with all but uniformly accurate heading estimates. For YAC subjects, seeing the stimulus is tantamount to knowing the heading. In contrast, for OAC and EAD subjects there is a substantial gap between processing time and performance. Considering a multiplicative interaction accounted for no more of the variance.

The OAC’s performance was no different from that of the YACs when viewing the smaller stimuli, but the OACs were significantly worse with the largest stimuli: the OAC group’s thresholds were twice that of the YACs with the smallest stimuli and more than three times that of the YACs with the largest stimuli. Thus, healthy older adults showed much poorer heading discrimination than young subjects (Fig. 1B). Such an ageing effect has been seen in studies of more elementary visual motion processing (Trick and Silverman, 1991) and in some measures of optic flow perception (Warren et al., 1989). We have previously seen elevated motion coherence thresholds for optic flow (O’Brien et al., 2001; Mapstone et al., 2003) and now find large, age-related declines in a naturalistic heading discrimination and steering response paradigm with potentially important implications for driving in the elderly.

The OACs’ processing speed, and the variance in that measure, was about the same as that obtained in the YACs (Fig. 4B). However, in the YACs, processing speed appeared to limit heading discrimination; whereas in the OACs, processing speed did not influence heading discrimination. Instead, heading discrimination in OACs was closely related to an independent measure of selective attention. The common notion that older adults slow down, and that such slowing is responsible for their poorer performance in critical tasks, is not supported by these data. Rather, the OACs in these studies appear to be limited by failures in their attentional capacities: The capacities referred to as attentional declines in ageing have been interpreted as a failure to scale attention to the scope of relevant stimuli (Greenwood et al., 2004). This may explain our findings as reflected in the relationship between selective attention and heading discrimination change when older subjects viewed small optic flow stimuli surrounded by planar motion in the direction opposite of the heading displacement. If older subjects were unable to narrow the scope of attention to within the area of the small optic flow stimulus they would have greater illusory shifts of their perceived heading and larger heading discrimination thresholds. This model is also compatible with the link between attention and virtual navigation seen in earlier experiments (Mapstone et al., 2001).

The mechanisms distinguishing these tests of divided and selective attention are not certain, but the differences in YAC and OAC performance on both tasks are robust and the link to attention is clear. Here we identify attentional factors as the critical difference between young and older subjects in a task that may be closely related to demanding tasks of everyday significance. It is worth noting that these group differences were seen in the context of nearly identical processing speed.

**Attentional and perceptual impairments**

At all stimulus sizes the EADs’ heading discrimination thresholds were twice as large as the OACs’ and three to four times larger than the YACs’ (Fig. 1). The EADs’ significant increase over the OACs’ thresholds attests to the substantial further impairment attributable to Alzheimer’s disease. The lack of stimulus size effects in either older group suggests that peripheral visual motion did not substantially influence heading discrimination. Thus, our subjects may have used central vision in this task rather than relying on the global radial pattern of optic flow.

Heading discrimination by local motion processing relies on comparison of the direction of local dot motion to the left or right of fixation in order to judge the simulated heading direction. We have previously seen reliance on local motion cues during far left versus far right heading discrimination in patients with Alzheimer’s disease or mild cognitive impairment, and some older normal controls, who are seemingly unable to access global pattern analysis (O’Brien et al., 2001). This was revealed by these subjects showing much larger optic flow motion coherence thresholds when inward and outward patterns are interleaved to confound local motion cues. In the current studies, both OAC and EAD subjects show this effect as larger thresholds for intermixed inward and outward optic flow as compared to outward optic flow alone. This may indicate that our more exacting heading discrimination task encourages our subjects to focus on local motion near the centre of the stimulus.

The use of a local motion heading discrimination strategy may be linked to the attentional control of perceptual processing as revealed by our recent findings from monkey single neuron neurophysiology (Page and Duffy, 2007). In those experiments, we found that manipulating spatial attention by changing the details of the experimental tasks could shape the monkeys’ reliance on the local or global motion cues in optic flow. This manipulation resulted in substantial effects on the relative activation of intermixed subpopulations of MSTd’s optic flow responsive neurons in a manner like that obtained with classical attentional manipulations (Dubin and Duffy, 2007). Thus, our current findings in ageing and Alzheimer’s disease could reflect the attentional selection of local versus global motion processing strategies, which supports a dynamic view of attentional control over vision.
We probed attentional selection’s influence on visual motion processing by presenting task-irrelevant planar motion in the visual periphery and determining what influence it might have on heading discrimination based on radial optic flow (Fig. 2B). We previously showed that overlapping planar and radial motion results in an illusory shift of perceived heading direction (Duffy and Wurtz, 1993). Recently, this illusion was seen with adjacent, non-overlapping planar and radial patterns in young subjects, although the magnitude of the illusion with non-overlapping stimuli was substantially smaller than that seen with overlapping stimuli (Duijnhouwer et al., 2006). We have now obtained similar results in our YAC subjects, but find much larger effects in older subjects; effects of the magnitude seen with overlapping planar and radial stimuli in previous studies.

We see age-related increase in the effects of peripheral planar motion as a failure of motion segregation; an inability to perceptually segregate areas containing different directions of visual motion. This is supported by the largest effects of planar motion in older subjects with small stimuli in which the planar motion encroaches on central vision. Motion segregation may be served by middle temporal neurons having receptive fields with specialized centre–surround interactions (Huang et al., 2007) or comparably structured MST neurons directly involved in optic flow analysis (Komatsu and Wurtz, 1988). Our findings support the notion that ageing is accompanied by losses of centre-surround antagonism (Bets et al., 2005) but not with those authors’ conclusion that these effects are advantageous. Rather, we conclude that the loss of antagonistic surrounds favours synergistic interactions to result in stimulus-specific functional consequences that are beneficial when centre-surround integration is required (Bets et al., 2005), but detrimental when centre-surround segregation is required.

Cortical mechanisms of cognitive impairment

Processing speed limits heading discrimination in YACs (Fig. 4B) but does not cause the poorer performance of OACs whose heading discrimination is limited by attentional deficits. These findings are not consistent with the view that reductions in processing speed generally account for age-related functional decline (Salthouse, 1996). Instead, our studies suggest a predominantly frontal lobar, dysexecutive profile of cognitive ageing (Dempster, 1992) with the prominent loss of attentional filtering (West, 1996). The frontal predominance of ageing effects is suggested by frontal cortical shrinkage (Raz et al., 2005), loss of frontal cortico-cortical white matter (Pfefferbaum et al., 2005) and frontal regional hypometabolism (Tumeh et al., 2007). These changes may impact on visual function by creating fronto–parietal cortico-cortical disconnection in ageing (O’Sullivan et al., 2001).

Substantial losses of attentional control are also evident in the earliest stages of Alzheimer’s disease with particular effects on the re-direction of spatial attention (Filoteo et al., 1992) and attentionally mediated stimulus feature selectivity (Nebes and Brady, 1989). Our findings support the existence of such attentional deficits in EAD (Fig. 4B) but also suggest that perceptual (Fig. 5B), rather than attentional, factors limit functional capacity in this group (Fig. 6). The more severe declines of heading discrimination in EAD patients may reflect a coupling of an age-related attentional disorder with a distinct deficit of optic flow perception; the attentional deficits being too uniform to account for variation in heading performance that can be attributed to Alzheimer’s disease-related perceptual deficits.

The perceptual deficits of EAD are consistent with the concentration of Alzheimer’s disease pathology in posterior cortical areas with atrophy and white matter loss in both MCI and Alzheimer’s disease. This pattern of tissue loss is consistent with the posterior cortical predominance of histopathological markers of Alzheimer’s disease (Brun and Gustafon, 1976) and posterior regional hypoperfusion (Buck et al., 1997). Together with the variety of visual deficits characterized in clinical analyses of Alzheimer’s disease (Renner et al., 2004) (Tang-Wai et al., 2004), a coherent picture of posterior cortical dysfunction in Alzheimer’s disease emerges as a profile that is distinct from the frontal predominance of changes in normal ageing.

The predominantly frontal attentional deficits of OAC subjects and the predominantly posterior perceptual deficits of EAD patients might be linked not just by the superimposition of dysfunction and pathology but also as a causal sequence of cortical pathophysiology. The loss of frontal lobar inhibitory feedback on posterior cortical visual processing centres (Armstrong et al., 2006) may significantly alter the selectivity of posterior cortical activation (Tsushima et al., 2006). Alteration of antagonistic centre–surround interactions mediated by changes in GABA-ergic inhibitory feedback from frontal cognitive centres may be the mechanism for this loss of selectivity (Leventhal et al., 2003). Evidence of disinhibitory effects may be seen in our recent finding of abnormally large optic flow-evoked potentials in some Alzheimer’s disease patients (Fernandez et al., 2007) that could reflect posterior cortical hyper-excitability. From this perspective, frontal cortical deterioration could predispose posterior cortical areas to excitotoxic damage (Mamelak, 2006) from over-activity that could primarily or synergistically promote the development of Alzheimer’s disease pathology (Roberson et al., 2007). Support for this hypothesis will require more detailed analysis of the transition from normal cognitive ageing to the disabling impairments of Alzheimer’s disease.

Acknowledgements

We gratefully acknowledge the assistance of Teresa Steffenella and William Vaughn in conducting these experiments. We thank Dr William Page and Dr Voyko Kavic...
for comments on an earlier draft of the manuscript. This work was supported by NIA grants AG17596 and AG20647, NEI grant EY10287.

References


Dubin MJ, Duffy CJ. Behavioral influences on cortial neuronal responses to optic flow. Cerebral Cortex 2007; 17: 1722–32.


Page WK, Duffy CJ. Cortical neuronal responses to optic flow are shaped by visual strategies for steering. Cereb Cortex 2007 [Epub ahead of print].


West RL. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull 1996; 120: 272–92.