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

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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 (R^2 adj = 0.41, $P = 0.001$) whereas, in Alzheimer's disease patients, it was largely attributable to deficits of visual motion perception (R^2 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

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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 (Cauller and Cauller, 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 (Kavcic *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.*, 1991). 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.*, 2003).

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 females, 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

Group	N (% female)	Age	Years of education	Contrast sensitivity (cycles/degree)
YAC	26 (63)	26.5* (7.0)	16.9** (2.0)	20 (5.0)
OAC	21 (67)	72.4 (6.3)	15.1 (2.5)	28.8 (13.6)
EAD	18 (55)	75.3 (7.2)	16.1 (2.6)	33.1 (16.5)

*YAC group significantly younger than OAC and EAD groups (P's < 0.001).
**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 ± 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 $2.4 \times 2.4 \times 1.8\,\mathrm{m}^3$ enclosure, the front wall of which was a $2.4 \times 1.8\,\mathrm{m}^2$ rear-projection tangent screen. The display covered the central $90^\circ \times 60^\circ$ 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 2 Cognitive test performance: means and SDs

Group	MMSE	WMS-R Verbal Paired Associates Immediate	WMS-R Verbal Paired Associates Delayed	WMS-R Figural Memory	Category Fluency (Animals)	Letter fluency (FAS)	Benton Judgment of Line Orientation	Benton Facial Recognition	Money Road Map
YAC	29.3 (1.2)	20.7 (3.0)	7.8 (0.5)	8.3 (1.5)	25.7 (6.9)	43.7 (17.1)	27.3 (2.7)	46.7 (3.1)	31.2 (2.3)
OAC	28.7 (1.3)	17.7† (3.5)	6.6† (1.3)	6.7† (1.3)	21.9 (6.1)	39.9 (14.0)	24.1† (4.0)	46.6 (3.6)	28.4 (3.6)
EAD	27.3* (2.2)	11.6** (3.9)	4.1** (1.8)	6.0 (1.4)	14.7** (5.2)	28.7 (10.9)	22.3 (4.1)	42.6* (6.7)	26.7 (5.3)

†OAC significantly worse than YAC $P < 0.05$.
*EAD significantly worse than OAC $P < 0.05$.
**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 {[(coherently moving dots)/(coherently moving dots + random dots)] × 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/outward motion (Fig. 5B).

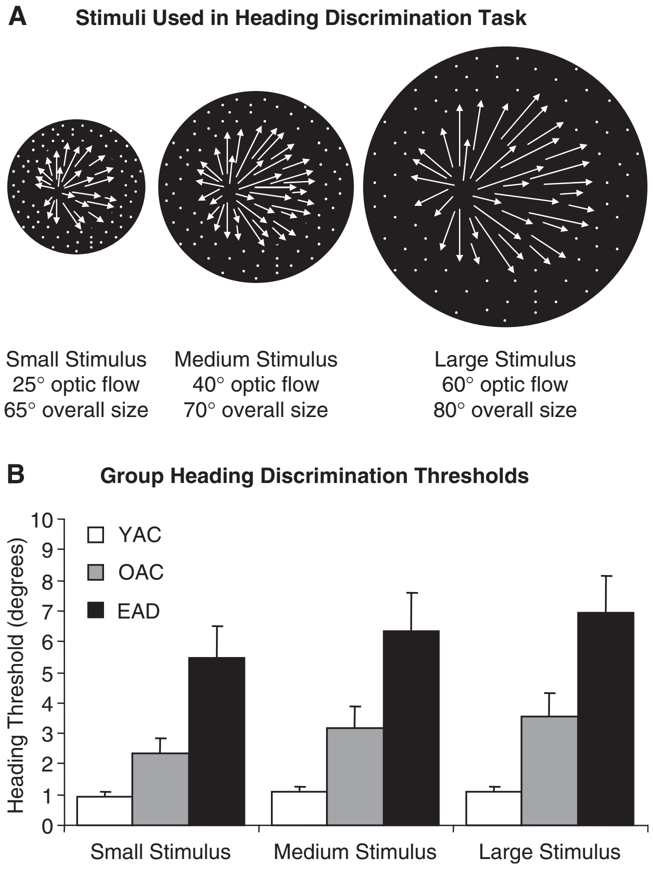

Fig. 1 Stimuli used in the heading discrimination task consisted of an optic flow field at one of the three sizes with an annulus of either task-irrelevant information; moving or static dots. (**A**) Outward radial optic flow patterns consisting of white dots on a black background were presented with 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 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 parafoveal 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.

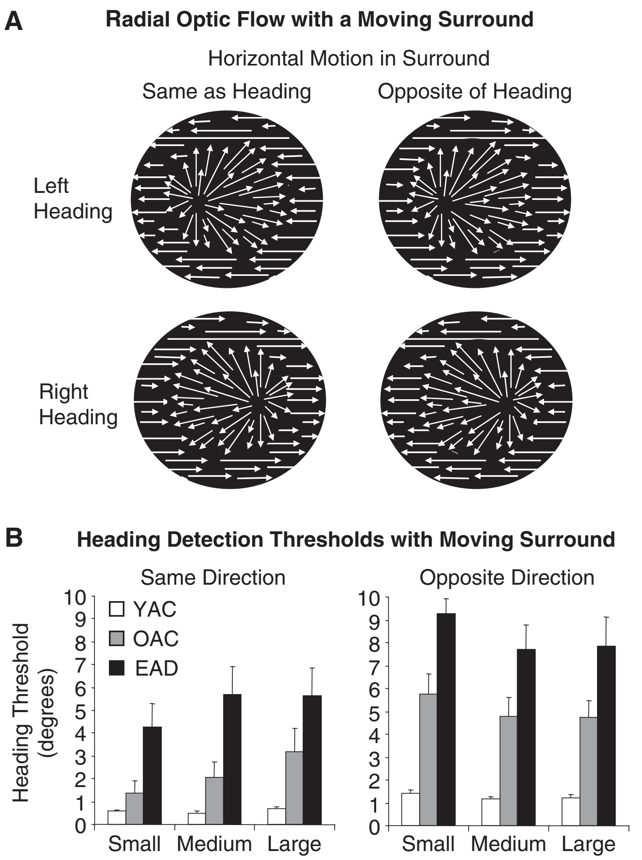

Fig. 2 Optic flow heading discrimination stimuli at the three stimulus sizes was presented with left- or right-ward motion in the annular surround. (**A**) The left- or right-ward eccentricity of FOEs in the radial optic flow was randomly combined with left- or right-ward horizontal motion in the surround. The surrounding horizontal motion was used to induce an illusory shift of the FOE in optic flow. (**B**) At all stimulus sizes motion in the surround influenced heading discrimination thresholds in all groups. Bar graphs show heading discrimination thresholds for each stimulus size and participant group, as in Fig. 1B. Surround motion in the same direction as the FOE eccentricity (left) lowered heading thresholds ($P < 0.001$), whereas surround motion in the opposite direction as the FOE eccentricity (right) raised heading thresholds ($P < 0.001$). Stimulus size effects (same $P = 0.022$, opposite $P = 0.011$) were similar to those seen in the static surround condition.

Each presentation lasted 1.5 s and the first 108 trials were non-adaptive, practice trials to allow the subject to become accustomed to the experimental task and stimuli. The total duration of each trial was determined by the response time of each individual subject. The time between the subject's response and the next presentation was ~0.5 s. In total, 540 adaptive trials were recorded, 60 trials for each of the nine conditions (all combinations of three peripheral motion conditions and three optic flow sizes). The participants' responses were recorded by pushing one of the two buttons. The subject pushed the button on the left if the centre of motion was on the left and pushed a button on the right if the centre of motion was on the right. The participants were encouraged to guess if they were unsure of an answer. The participants were asked if they would like to take a break at 180 trials and 360 trials. Some participants chose to rest while others chose to complete the task with no breaks.

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 $\leqslant 0.05$ with probability to remove set to $\geqslant 0.10$. 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 (stationary, leftward motion, rightward motion) as well as their interactions using MANOVA with follow-up ANOVA and pair-wise *post hoc* tests using Tukey's HSD. The omnibus MANOVA was significant [$F(26,584) = 13.0$, $P < 0.001$], with significant main effects of subject group [$F(2,584) = 136.4$, $P < 0.001$] and direction of peripheral planar motion [$F(2,584) = 22.5$, $P < 0.001$] and a significant interaction between subject group and direction of peripheral planar motion [$F(4,584) = 3.3$, $P = 0.01$]. These findings indicate that heading discrimination thresholds differed depending on subject group and peripheral planar motion with no overall effect of stimulus size.

We first focused on heading discrimination with stationary surrounds, further analysing main effects of subject group, stimulus size and their interactions. There was a significant group effect [$F(2,194) = 40.5$, $P < 0.001$] with the highest heading discrimination thresholds in the EAD group, the lowest in the YAC group and intermediate thresholds in the OAC group (all P's < 0.05). Again, we found no main effect of stimulus size or interaction between group and stimulus size suggesting that the larger optic flow fields did not lead to better heading discrimination in any group. Indeed all groups showed a small non-significant trend towards higher heading discrimination thresholds (poorer performance) with increasing stimulus size (Fig. 1B).

We examined the effect of peripheral planar motion on optic flow heading discrimination using a three-way ANOVA with main effects of subject group, stimulus size and the direction of peripheral planar motion (same as left/right heading direction or its opposite). Again we found a significant group effect [$F(2,389) = 96.5$, $P < 0.001$] with the EAD group showing higher heading discrimination thresholds than both control groups ($P < 0.05$ each). There was also a significant main effect of peripheral motion direction [$F(1,389) = 42.8$, $P < 0.001$] with planar motion opposite the heading offset increasing heading detection thresholds and planar motion in the same direction as the heading offset decreasing heading detection thresholds (Fig. 2B), again without an effect of stimulus size.

Stimulus size and the direction of peripheral motion interacted to yield a significant impact on heading discrimination [$F(2,389) = 3.3$, $P = 0.04$] with substantially increased thresholds with opposite direction peripheral motion surrounding the smaller stimuli (Fig. 3). There was also a significant interaction between subject group and the direction of peripheral planar motion [$F(2,389) = 5.7$, $P = 0.004$] with substantial effects in both older groups (OAC and EAD). Thus, the most robust effects of peripheral motion were seen in older subjects viewing small optic flow stimuli surrounded by oppositely directed planar motion; the three-way interaction was not significant.

Overall, our findings indicate that greater stimulus area does not improve heading discrimination in any subject group. However, peripheral visual motion can strongly influence heading discrimination in older subjects. 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.

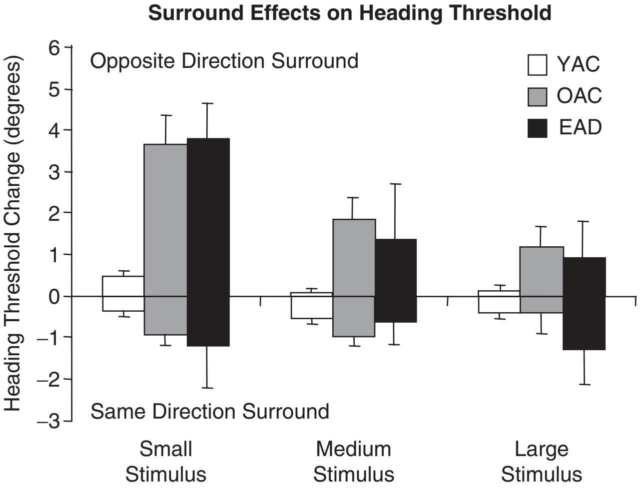

Fig. 3 Heading discrimination thresholds were changed by planar motion surrounding the central radial optic flow stimulus. At each stimulus size, thresholds obtained with stationary dot surrounds were subtracted from those obtained when surrounding planar motion was in the opposite or same direction as the left/right heading offset. Opposite direction planar motion evoked larger thresholds in OAC and EAD subjects, greatly with small stimuli and much less so with the medium and large sizes. Same direction planar motion had substantially less effect on heading discrimination thresholds.

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

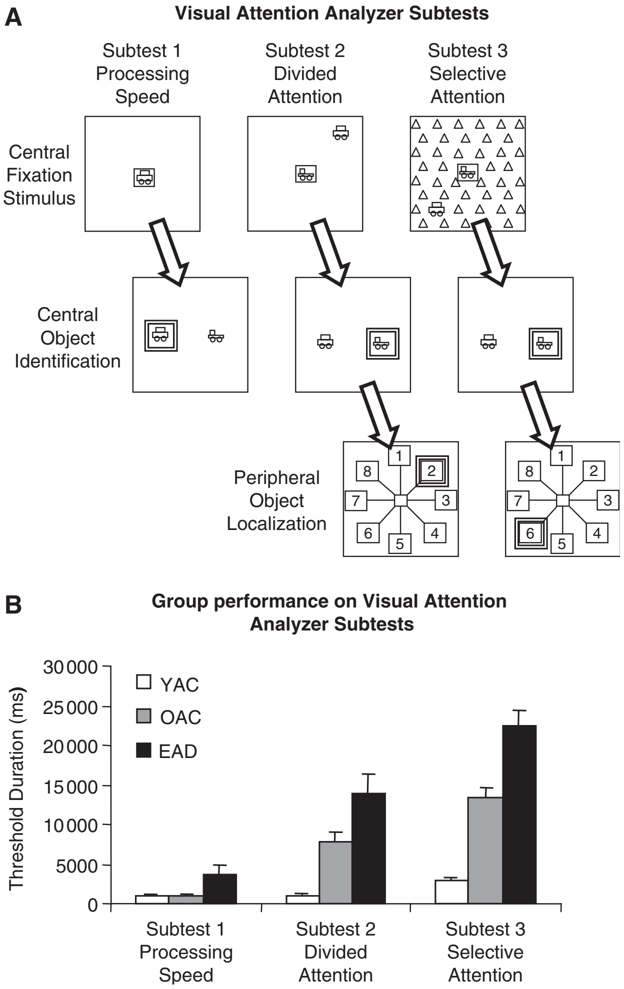

Fig. 4 To assess attentional contributions to heading discrimination impairments we used the Visual Attention Analyzer (Visual Awareness, Inc.). (**A**) The Visual Attention Analyzer consists of three reaction time (RT) subtests presented on a 17 in. touch-screen monitor at a distance of 24 in. Subtest 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 paired with a car figure presented at one of the eight peripheral locations arranged at 45° intervals and 10° displacement around the centre and was again followed by paired car and truck figures. This test required that participants first touch the figure that was previously presented in the centre and then the location of the figure that was previously presented in the periphery. 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 ($P < 0.001$). The EAD group performed worse than the YAC and OAC groups on all three subtests, including processing speed. The OAC group showed performance like that of the YAC in the processing speed subtest and showed performance that was intermediate between the YAC and EAD on subtests 2 and 3 (all *P*-values <0.01).

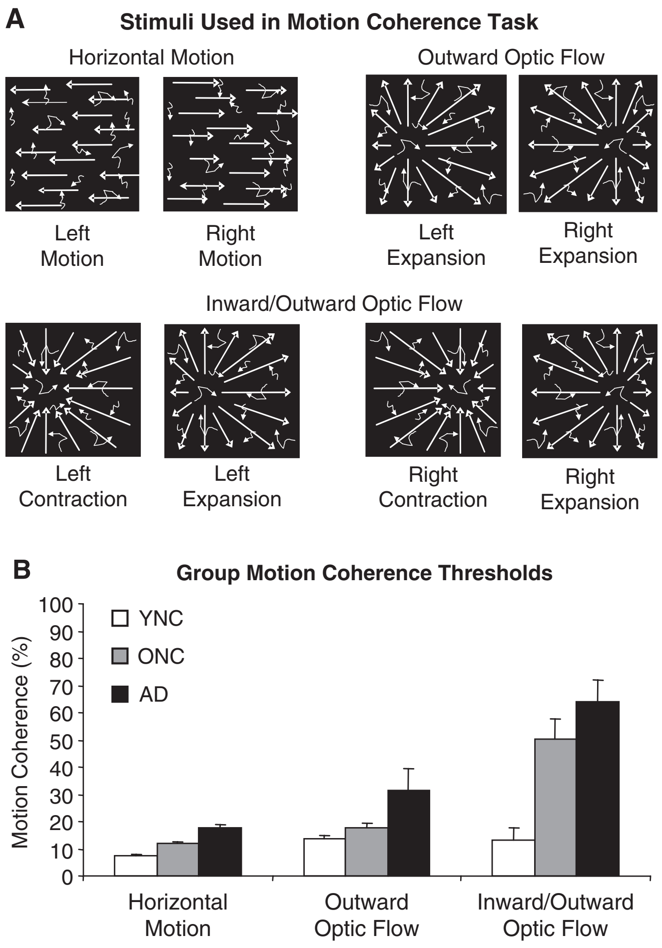

Fig. 5 Visual stimuli used for motion coherence perceptual testing in these studies. (**A**) Horizontal motion and radial optic flow perception was assessed by varying motion coherence from 100% (all dots undergoing patterned motion) to 1% (nearly all dots undergoing random motion) using an algorithm 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, $P < 0.001$).

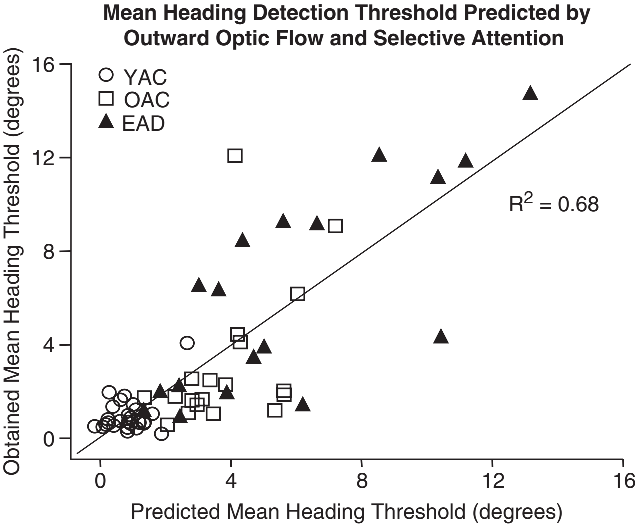

Fig. 6 The relationship between heading discrimination thresholds and performance on the Visual Attention Analyzer and visual motion psychophysical tests. Step-wise multiple linear regression model developed for all participants yielded a significant fit ($R^2 = 0.68$, $P < 0.001$) attributable to the inclusion of Visual Attention Analyzer subtest 3, selective attention ($\beta = 0.53$) and outward radial motion coherence thresholds ($\beta = 0.40$). Subject groups are indicated by corresponding symbols; the regression line reflects the least squares fit.

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 divided attention and selective attention appear similarly and significantly impaired in OAC subjects, although the latter predominates in the correlational analysis linking it to impaired heading discrimination.

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 (Betts *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 (Betts *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 hyperexcitability. 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.

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