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Cue integration for the perception and control of self-movement in ageing and Alzheimer's disease

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The perception and control of self-movement relies on visual cues derived from the radial patterns of optic flow and from the relative motion of objects within view. Optic flow and object motion processing impairments might limit independent self-movement in a manner like that seen in ageing and in Alzheimer's disease. We used optic flow and object motion stimuli to simulate aspects of the self-movement scene. Stimulus salience was individualized to present comparable stimuli to young [*n* = 18; mean age = 25.6, standard error of measurement (SEM) = 1.4], middle-aged (*n* = 17; mean age = 53.9, SEM = 0.9), older adult (*n* = 30; mean age = 72.4, SEM = 1.4) and Alzheimer's disease (*n* = 15; mean age 75.2, SEM = 1.6) subjects. All groups were tested in two tasks: pointing towards the simulated direction of self-movement and steering the simulated self-movement towards a straight-ahead direction. We found that young and middle-aged subjects show similar pointing accuracy using either optic flow or object motion, but steer better with object motion than with optic flow. Older adult subjects show better performance with optic flow than object cues for pointing (*P* < 0.001), but their performance improves when both cues are combined in the pointing (*P* = 0.012) and steering (*P* = 0.02) tasks. Alzheimer's disease patients show poorer performance with optic flow and object motion than all other groups and do not benefit from the combined presentation of cues for either pointing or steering. We conclude that ageing and Alzheimer's disease are associated with distinct profiles of visual processing deficits that limit the ability to use optic flow and object motion to perceive and control self-movement.

Keywords: ageing; Alzheimer's disease; optic flow; pointing; steering

Abbreviations: MMSE = Mini-Mental State Examination; MNC = middle-age normal control; ONC = older normal control; SEM = standard error of measurement; THSD = Tukey's honestly significant difference; YNC = younger normal control

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Introduction

Self-movement is guided by the expanding radial pattern of background motion in optic flow and by the relative visual motion of discrete objects (Gibson, 1950). Earth-fixed landmark objects are generally regarded as the dominant visual cue for independent navigation (O'Keefe and Nadel, 1978). However, the patterned motion in optic flow can guide self-movement in the absence of recognized landmarks and can link sequential visual scenes into a cognitive map of the environment (Golledge, 1999).

The co-occurrence of optic flow and object motion cues during self-movement belies their separate processing in extrastriate visual cortex (Mishkin *et al.*, 1983). Object processing occurs in the ventral visual pathway extending from occipital to temporal lobe areas (Haxby *et al.*, 1991; Kobatake and Tanaka, 1994). Optic flow processing occurs in the dorsal visual pathway extending from occipital to parietal lobe areas (Duffy and Page, 2004; Warren, 2004). These separate cues might be integrated in superior temporal cortical regions that respond to both optic flow (Saito *et al.*, 1986) and to object motion (Tanaka *et al.*, 1993), along with other visual cues (Oostende *et al.*, 1997), as well as non-visual (vestibular) cues about self-movement (Duffy, 1998). Alternatively, optic flow and object motion cues about self-movement may be integrated by interactions between neural centres that dynamically bind self-movement cues into a unified perceptual experience (Friedman-Hill *et al.*, 1995; Singer and Gray, 1995).

We hypothesize that the visual analysis of self-movement depends on both dorsal and ventral extrastriate specialization for the processing of particular cues (Ungerleider and Haxby, 1994) and interactions between cortical systems (Merigan and Maunsell, 1993) in a manner that is sensitive to the different demands of behavioural tasks that emphasize localization and active motor control (Goodale and Milner, 1992). Just as focal cortical syndromes revealed distinctions between dorsal and ventral centres (Kleist, 1935), the visual impairments of ageing and Alzheimer's disease (Cronin-Golomb *et al.*, 1995) (Mendola *et al.*, 1995) can elucidate aspects of perceptual organization for self-movement analysis (Mapstone *et al.*, 2003). Specifically, we predict that the posterior cortical degeneration of Alzheimer's disease (Braak and Braak, 1991), which is particularly disruptive of cortico-cortical connectivity (Hof *et al.*, 1997), results in poorer integration of multiple visual cues related to heading perception.

We have now examined the effects of ageing and Alzheimer's disease on the use of optic flow and object motion to perceive and control the simulated direction of self-movement. We find that optic flow and object motion are used differently in pointing and steering and that ageing and Alzheimer's disease have different effects on cue use and task performance.

Material and methods

Subjects

We enrolled 80 subjects in this study: 15 with Alzheimer's disease (40% female) and 65 neurologically normal (47% female). To study the effects of ageing, we separated the neurologically normal subjects into three age groups. A younger normal control (YNC) group consisted of 18 subjects (39% female) between the ages of 20 and 40. A middle-age normal control (MNC) group consisted of 17 subjects (65% female) between the ages of 40 and 60. An older normal control (ONC) group consisted of 30 subjects (43% female) between the ages of 60 and 88. As defined, the three control groups differed significantly in age, but the ONC and Alzheimer's disease groups did not. The MNC group had significantly lower education than the ONC group (Table 1).

All subjects had Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) scores of 18 or higher, and were free from ophthalmic, neurological and psychiatric disease other than Alzheimer's disease. Our experience testing Alzheimer's disease patients in psychophysical experiments suggests that patients scoring <18 on the MMSE might have some difficulty understanding the task instructions; thus we excluded patients scoring <18 on the MMSE. Our Alzheimer's disease patients typically did not require more explanation or practice than our ONC subjects, a fact that we attribute to our having made every effort to develop straightforward stimulus–response compatibility using the familiar response manipulandum of a steering wheel. Alzheimer's disease subjects were recruited from the Geriatric Neurology and Psychiatry Clinic at the University of Rochester. A neurologist or psychiatrist specializing in dementia made a clinical diagnosis of all Alzheimer's disease subjects using NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke, Alzheimer's Disease and Related Disorders Association) criteria for probable Alzheimer's disease (McKhann *et al.*, 1984). Normal control subjects included patients' spouses or caregivers, volunteers from the University of Rochester community and undergraduate or graduate students at the University of Rochester.

Procedure

All subjects were tested in the Visual Orientation Laboratory at the University of Rochester Medical Center in four, 2 h sessions. Subjects completed two experimental tasks using simulated self-movement stimuli. The tasks consisted of pointing to a simulated self-movement heading and steering a self-movement heading. The headings consisted of optic flow or a moving object, either alone or combined together and were presented at several lateral eccentricities. All self-movement stimuli in the pointing and steering tasks were presented at two confidence intervals above individually determined perceptual thresholds for optic flow and object movement in an attempt to make the stimuli equi-salient across groups, using the confidence intervals derived from that subject's threshold data. In addition, the pointing and steering tasks were preceded by identical visuomotor control tasks without headings to adjust for visuomotor aspects of the tasks. Basic visual capacities and cognitive function were also assessed. The protocol was explained to all subjects in advance, and informed consent was obtained. All protocols were approved by the University of Rochester Human Subjects Review Board.

Basic visual function

Visual acuity at 6 m was measured with the standard Snellen acuity chart. All subjects demonstrated corrected binocular acuity of 20/40 or better. Visual field testing to confrontation demonstrated intact visual fields in all subjects. Visual contrast sensitivity testing at five spatial frequencies (0.5–18 cycles/°, VisTech Consultants, Inc.) showed normal profiles in all groups. However, the Alzheimer's disease group had significantly worse contrast sensitivity than all other groups ($P < 0.01$ each), while the control groups did not differ from each other (Table 1).

Cognitive testing

The cognitive battery was designed to assess general cognitive ability, visuospatial abilities, language, and verbal and non-verbal memory independent of the diagnostic process. The MMSE provided an index of overall cognitive ability (Folstein *et al.*, 1975). The Money Road Map Test was used to assess topographic orientation (Money, 1976). In this pencil and paper test, subjects follow a route outlined on a city map and indicate left and right turns at each intersection. The Judgement of Line Orientation and Face Recognition Tests (Benton *et al.*, 1978) were used to assess dorsal and ventral stream processing, respectively. In the line orientation task, subjects are shown two lines that create an angle and are asked to identify from a fan-shaped array of 13 lines two lines that would create the same angle as the sample. In the face recognition test, subjects must match unfamiliar faces in different lighting and orientations to a sample face. Language abilities were assessed with the category fluency test (Rosen, 1980). In this task, subjects name as many animals as possible in 1 min. Non-verbal memory was assessed with the Figural Memory subtest of the Wechsler Memory Scale—Revised (Wechsler, 1987). This test uses geometric patterns to test immediate visual memory. The Verbal

Paired Associates subtest of the Wechsler Memory Scale—Revised (Wechsler, 1987) was used to assess immediate and delayed verbal memory using pairs of unrelated words.

As expected, there were significant group differences on all cognitive tests [$F(24, 197) = 7.3$, $P < 0.001$], with the Alzheimer's disease group significantly worse than the other groups on almost all tests (Table 2). The YNC group performed better than the ONC group on the memory tasks and better than the MNC group on the non-verbal memory task, suggesting the possibility that some ageing effects on mnemonic capacities might be common even in middle life.

Experimental set-up

Apparatus

Subjects sat near the centre of a darkened 2.4 × 2.4 × 1.8 m enclosure, the front wall of which was a 2.4 × 1.8 m 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. Subjects wore an eye patch over the weaker or non-preferred eye to eliminate binocular disparity cues. Subjects maintained fixation on the centre of the screen in all tasks, with eye position monitored by infrared oculography (ASL, Inc.). Deviation of central fixation by >5° during heading stimulus presentation caused that trial to be terminated and re-presented later; <3% of all trials were re-presented for this reason. All visual stimuli were generated on a personal computer using proprietary software and projected onto the screen by a TV projector (Electrohome, Inc.). Subjects responded by rotating a steering wheel mounted at a comfortable height that did not obstruct vision of the display (Fig. 1A, left). All stimulus parameters, gaze and response cursor position were recorded in real time using the Real-time Experimental control system (Hays *et al.*, 1982).

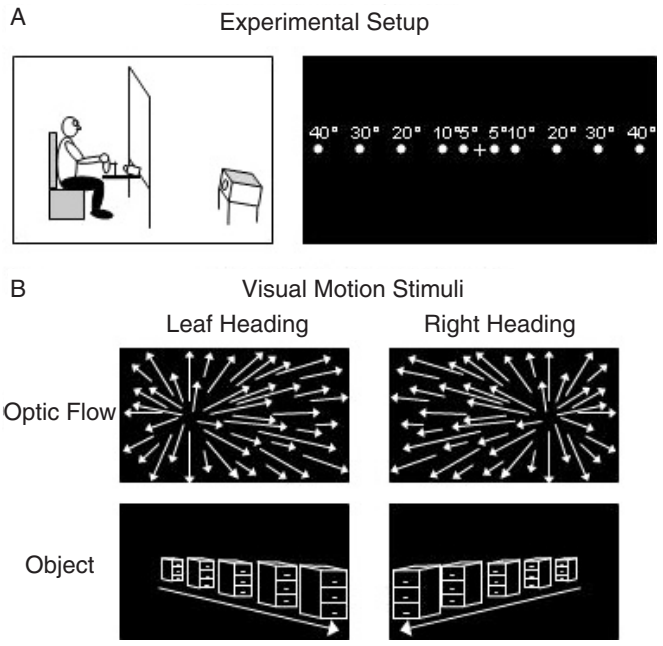

Fig. 1 Perceptual testing paradigm used throughout these studies. (**A**) Subjects sat in a light-tight booth facing a 2.4 × 1.8 m rear-projection screen that subtended a 60° × 90° stimulus area. Subjects maintained centred fixation that was monitored by infrared oculometry (*left*). In the pointing and steering tasks the stimuli simulated one of the 10 headings along the horizontal meridian (*right*). (**B**) Visual motion stimuli used to determine perceptual thresholds and in the pointing and steering tasks consisted of white dots on a black background.

Basic visual psychophysics

Simulated heading stimuli

We used the same visual motion stimuli for both the experimental pointing and steering tasks and individual motion perceptual threshold determination (Fig. 1B). The stimuli simulated observer self-movement into the plane of the projection screen and consisted of an optic flow pattern or a moving object. The optic flow stimuli consisted of animated sequences of 1000 white dots (2.69 cd/m^2) presented on a dark background at a 60 Hz frame rate (O'Brien *et al.*, 2001) (Fig. 1B, top). The object stimulus was a wire frame, three-dimensional representation of a standard three-drawer file cabinet. The object stimulus moved on the screen with constant geometric transformation simulating a stable observer perspective relative to the cabinet (Fig. 1B, bottom). Before the experimental tasks, each subject was pushed in a wheeled desk chair with normal room illumination to illustrate the visual motion in optic flow. They were also moved past a three-drawer file cabinet with luminous taped edges in an otherwise dark room to demonstrate how movement past an earth-fixed object can provide heading cues. All subjects indicated understanding of how these self-movement cues could provide heading information and expressed their readiness to begin testing after a few practice trials in each task.

Perceptual threshold determination

We used a two-alternative, forced-choice paradigm to obtain each subject's perceptual threshold for horizontal motion, radial optic flow and object motion. The three threshold tasks required that subjects choose whether the stimulus was directed towards the left or right (horizontal motion), or simulated self-movement heading towards the left or right of midline (optic flow and object motion). Thresholds for horizontal motion (30°/s) and radial optic flow (heading +/−30°) were determined by varying the percentage of moving dots that were part of the specified pattern with the remainder undergoing random motion (Tetewsky and Duffy, 1999). Thresholds for object motion were determined by varying the exposure duty cycle of the stimulus as the percentage of the cabinet's simulated path that was presented during a left/right (±30°) heading discrimination trial (Fig. 2A, bottom). At every exposure duty cycle level the object was always present on the screen: at a low exposure duty cycle it repeatedly covered only the middle segment of its potential path; at a high exposure duty cycle it repeatedly covered a greater portion of its potential path. Motion coherence and exposure duty cycles were selected for each trial using threshold parameter estimation by sequential testing (Pentland, 1980; Harvey, 1997). The resulting direction threshold for horizontal motion and heading discrimination threshold for both optic flow and the moving object was the coherence or exposure duty cycle yielding 82.5% correct left/right discriminations, conventionally used to accommodate the Weibul function used to fit the data.

With the exception of one Alzheimer's disease and one MNC subject, all subjects showed horizontal motion coherence thresholds of <30%, demonstrating the capacity to discriminate the direction of moving dots under these viewing conditions. The Alzheimer's disease group had significantly higher horizontal motion coherence

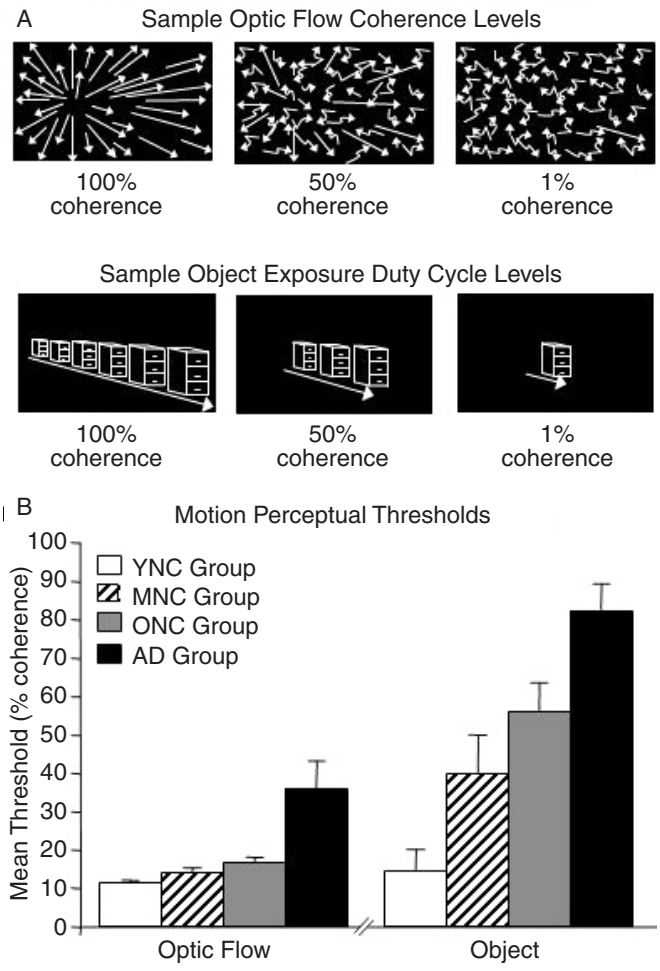

Fig. 2 Visual perceptual thresholds for the stimuli used throughout these studies. (**A**) Perceptual thresholds were obtained in a left–right 2AFC paradigm using push-button responses. Horizontal motion and radial optic flow thresholds were obtained by varying motion coherence from 100% fully patterned motion to 1% nearly random motion (*top*). Object motion thresholds were obtained by varying the length of the object's path from a short segment to a longer exposure; in all cases, when the object reached the end of the segment, it reappeared at its origin in the next frame (*bottom*). (**B**) Perceptual thresholds ± SEM (ordinate) for optic flow and object stimuli (abscissa) averaged for each subject group. Alzheimer's disease subjects showed large and significantly elevated thresholds for radial optic flow. There were substantial increases in object motion thresholds across groups from YNC to MNC, to ONC and to Alzheimer's disease. Radial optic flow and object motion thresholds were used to standardize stimuli across groups in all subsequent tasks.

thresholds than the YNC group [Tukey's honestly significant difference (THSD) $P < 0.01$], but there were no other significant differences between subject groups (Table 1).

Each individual's heading discrimination threshold for optic flow and object motion was used to adjust the coherence of the simulated heading in the pointing and steering experiments. All self-movement stimuli used in the pointing and steering tasks were presented at the individual's threshold plus twice the 95% confidence interval of that threshold. This resulted in the presentation of self-movement stimuli having equivalent visual salience across all subjects.

Experimental tasks

In each subject, we first administered a visuomotor task to test for relevant coordinated skills and then tasks of heading localization (pointing) and heading control (steering). To minimize the impact of group and individual motion perceptual differences, we presented the optic flow and object motion stimuli at each subject's perceptual threshold plus two times their 95% confidence interval. A third stimulus condition in both heading tasks consisted of presenting both an optic flow pattern and a moving object depicting the same heading presented using individual thresholds for each stimulus simultaneously.

Subjects were required to maintain centred visual fixation throughout the presentation of all visual test stimuli. In all of the tasks the test trials began after the subject positioned the onscreen cursor over a central fixation point using the steering wheel with continued maintenance of central fixation for 0.5 s. The cursor then disappeared with the onset of the heading stimulus. Testing times and stimulus eccentricities were the same in the visuomotor coordination tasks and the pointing and steering heading tasks. Error on the visuomotor coordination tasks was subtracted from the appropriate experimental task to adjust for group and individual differences in visuomotor control.

Controlling for visuomotor coordination

Before the pointing and steering tasks, subjects completed two visuomotor coordination tasks to assess their ability to properly control the response steering wheel in the experimental tasks. These visuomotor coordination tasks were identical to the pointing and steering tasks described above, except that a 2° square location target was used instead of a simulated heading.

Visuomotor aspects of the pointing task were assessed by presenting a 2° square target at one of the 10 eccentric positions (+/−5°, +/−10°, +/−20°, +/−30° and +/−40°) flashed along the horizontal meridian for 1.5 s during centred fixation. The subject then used the steering wheel to place a small cross at the location of the preceding square target (Fig. 3A, top). Visuomotor aspects of the steering task were assessed by presenting a 2° square target at one of the 10 eccentric positions along the horizontal meridian (+/−5°, +/−10°, +/−20°, +/−30° and +/−40°). The subject then used the steering wheel to move the square to the centre of the screen over a period of up to 8 s (Fig. 3A, bottom).

Pointing at the heading direction

In the pointing task, an optic flow field, the moving object or both stimuli appeared on the screen, indicating observer self-movement to one of the 10 heading directions: 5, 10, 20, 30 or 40° to the left or right of central fixation (Fig. 1A, right). The stimulus remained on the screen for 1.5 s while subjects maintained centred gaze (+/−5°). The heading stimulus was then extinguished and subjects were free to shift their gaze. Within 1 s after the stimulus was extinguished, subjects were required to rotate the steering wheel to move the cursor (clockwise for rightward displacement) to indicate the perceived heading direction simulated in the preceding stimulus. The trial ended after 8 s or when the subject indicated a final position by holding the cursor in a 1° area for 1 s (Fig. 4).

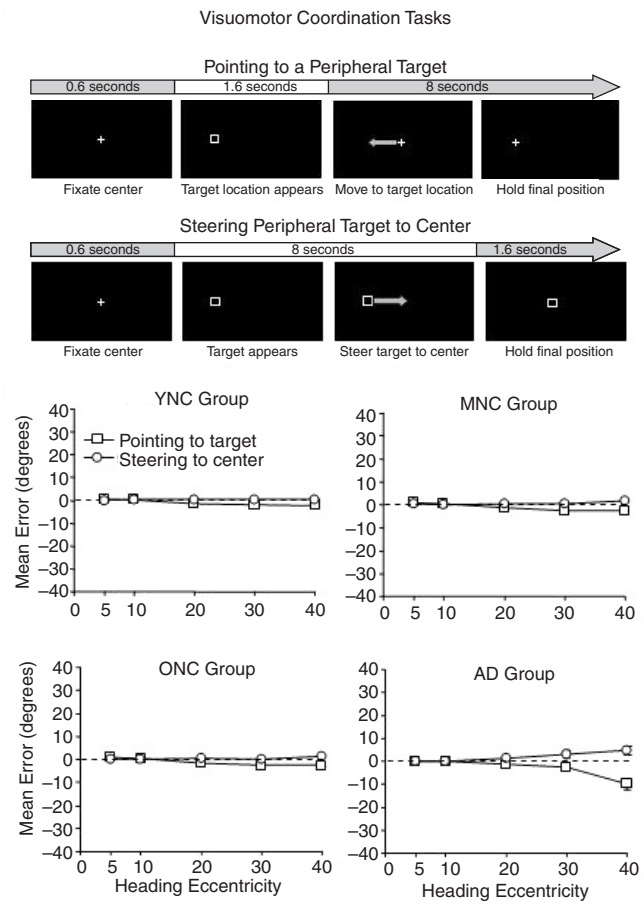

Fig. 3 Controlling for visuomotor coordination aspects of the pointing and steering tasks. (**A**) *Top*: visuomotor coordination for the pointing task consisted of maintaining centred fixation during the 1.5 s presentation of a 2° square stimulus at one of the 10 eccentric locations. They then used the steering wheel to move a marker to indicate the remembered location of the square. *Bottom*: Visuomotor coordination for the steering task consisted of maintaining centred fixation during the presentation of a 2° square stimulus having its initial position at one of the 10 eccentric locations. They then used the steering wheel to move the square into the centre of the screen. (**B**) Mean error ± SEM (ordinate) for each location eccentricity (abscissa) for each task (lines) averaged within each subject group. The YNC, MNC and ONC groups all showed similar performance, doing well in both the pointing and steering visuomotor coordination tasks. The Alzheimer's disease group showed larger errors at peripheral eccentricities in both tasks. Each individual's performance on the experimental pointing and steering heading tasks were adjusted for their performance on these visuomotor coordination control tasks.

Subjects completed three randomly presented trials at each of the 10 heading directions for a total of 30 trials. Each subject completed three blocks of 30 such trials, one block for each stimulus condition: optic flow, object motion and combined optic flow and object motion. The order of the stimulus presentation was randomized by subject. The final position of the cursor was recorded at the end of the trial, and pointing error in visual angle from the heading direction simulated by the stimulus was determined. We determined pointing error relative to the target location ([−] medial to the target, [+] lateral to the target)

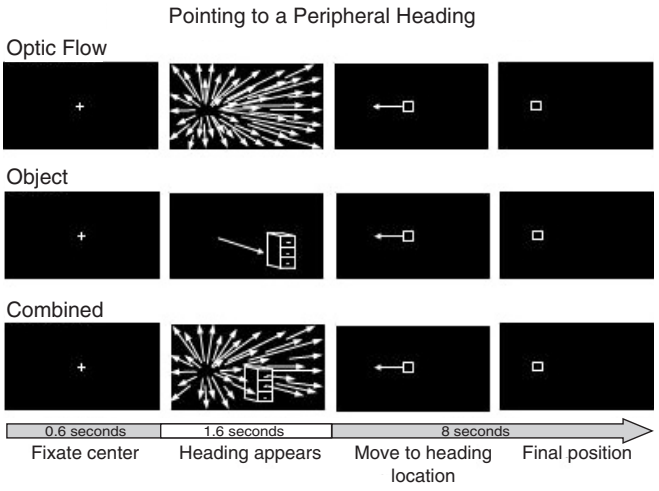

Fig. 4 Pointing task used with optic flow, object motion and combined stimuli. The pointing task consisted of maintaining centred fixation during the 1.5 s presentation of visual stimuli simulating observer self-movement on an eccentric heading. After the stimulus was extinguished, subjects responded by rotating the steering wheel to move an onscreen marker to their perceived location of the simulated heading direction. Ten heading directions along the horizontal meridian were simulated by radial optic flow (*top*), object motion (*middle*) and combined optic flow and object motion stimuli. Each stimulus type was tested in a counterbalanced sequence of block-wise presentation.

to measure response undershoot (−) or overshoot (+) of the subject's moving the cursor from the centre starting position to the eccentric heading direction.

Steering toward a centred heading direction

In the steering task, after subjects established central fixation and centred the cursor, a heading stimulus appeared. The heading stimuli consisted of an optic flow field, object motion or both stimuli presented together at one of the 10 eccentric, initial heading directions: 5, 10, 20, 30 or 40° to the left or right of central fixation. The stimulus remained on the screen, and the subjects maintained centred fixation, while they rotated the steering wheel (clockwise for rightward displacement) to bring the heading to centre of the screen. The trial ended after 8 s or when the subject held the cursor within a 1° area for 1 s to indicate a final response. None of the subjects were limited by the maximum 8 s stimulus duration, typically completing all trials in 5–6 s.

Subjects completed three trials at each of the 10 initial heading directions. Each subject completed three blocks of 30 trials, one block for each stimulus condition: optic flow, object motion, and combined optic flow and object motion. The final heading direction was recorded at the end of the trial, and steering error was determined in degrees from the centred, straight-ahead heading direction. We determined steering error relative to the centre location ([−] medial to the target, [+] lateral to the target) to measure response undershoot (+) or overshoot (−) of the subject's moving the simulated heading from its eccentric initial heading direction to the centred, straight-ahead heading direction.

Data analysis

Separate multivariate analysis of variance (MANOVA) procedures were used to test for group differences in basic visual and cognitive

abilities, and visual motion perceptual thresholds. A repeated-measures analysis of variance (ANOVA) with subject group (YNC, MNC, ONC, Alzheimer's disease) as the between-subjects factor and task (pointing, steering) and target eccentricity (+/−5°, +/−10°, +/−20°, +/−30°, +/−40°) as within-subjects measures was used to examine performance on the visuomotor control task.

Before analysing error obtained from the pointing and steering tasks, we subtracted each individual's mean error at each of the eccentricities obtained from the visuomotor control task from their mean pointing or steering error at each eccentricity to minimize the effect of individual differences in visuomotor performance on the experimental tasks.

Preliminary analyses of hemi-spatial lateralization effects revealed no difference in performance for targets on the left side of the screen compared with the right side of the screen in either task or for any of the stimulus conditions. Since no group showed evidence of a hemi-spatial bias, we folded the left and right hemi-fields along the vertical meridian such that pointing or steering error at each eccentricity reflects the average error at that eccentricity for both left and right hemi-fields. This reduced the number of target locations to five and doubled the number of trials at each eccentricity.

We then used separate repeated-measures ANOVAs with subject group (YNC, MNC, ONC, Alzheimer's disease) as the between-subjects factor and eccentricity (5, 10, 20, 30 and 40°) and heading stimulus type (optic flow, object, combined) as within-subjects factors to analyse error from the pointing and steering tasks. For all analyses, significant main effects were followed up with one-way ANOVA and *post hoc* tests using THSD as indicated.

Finally, we computed mean error across all heading eccentricities by stimulus type (optic flow, object, combined) and task (pointing, steering) for each individual subject. We used correlation and step-wise multiple linear regression analyses to examine relationships between stimulus conditions and the contributions of independent stimulus cues to performance with combined stimulus cues across groups and individuals. These data were also used in regression analysis to explore for relationships between performance on the pointing and steering tasks and performance on the cognitive tests and perceptual thresholds for visual motion stimuli. Alpha levels for statistical significance on all tests were set at $P < 0.05$. All statistical analyses were run using SPSS statistical software (SPSS Inc., 2005).

Results

Basic perceptual and visuomotor capacities

Each subject's motion coherence threshold for radial optic flow and their exposure threshold for object motion were obtained to characterize their basic visual motion perceptual capacities (Fig. 2A). These thresholds were used to adjust the coherence and exposure of the heading stimuli in the pointing and steering tasks, so all subjects saw equally salient heading stimuli. The optic flow and object motion perceptual thresholds showed significant interaction effects across tests and subject groups [$F(3, 76) = 4.57$ $P < 0.01$] (Fig. 2B). There was a significant main effect of group for the optic flow threshold [$F(3, 76) = 10.3$, $P < 0.001$]. The Alzheimer's disease group showed substantially higher radial optic flow thresholds than all other groups (THSDs, $P < 0.01$: AD > ONC = MNC = YNC) who did not differ from each other, suggesting impaired optic flow processing due to Alzheimer's disease and not due to ageing.

There was a main effect of subject group for the object motion exposure duration threshold [$F(3, 76) = 10.3$, $P < 0.001$] as well with the Alzheimer's disease group showing elevated thresholds compared with the YNC and MNC groups (THSDs, $P < 0.01$), but they did not differ from the ONC group. The YNC group showed the lowest object motion thresholds, differing significantly from both the ONC and Alzheimer's disease groups (THSDs, $P < 0.01$), whereas the MNC group differed only from the Alzheimer's disease group (THSD, $P < 0.01$). Thus, exposure duration thresholds for the object reveal increasing impairment in using a moving object to estimate heading across the groups, suggesting an effect primarily due to ageing and not disease.

All subjects completed visuomotor coordination tasks to assess the potential influence of impairments in basic visuomotor coordination on performance in the pointing and steering heading tasks (Fig. 3A). The visuomotor tasks were the same as the heading tasks but presented a square box stimulus instead of a heading stimulus. Subjects in all groups showed good use of the steering wheel to control the square in the pointing and steering control tasks; there were no main effects of subject group (Fig. 3B). There was a main effect of target eccentricity with greater error at greater target eccentricities [$F(9, 64) = 6.83$, $P < 0.001$]. This was attributable to Alzheimer's disease subjects having difficulty with the extreme target eccentricity as reflected in a significant group-by-eccentricity interaction [$F(27, 188) = 1.92$, $P = 0.006$]. Directional error in these tests was used to adjust the results of the corresponding heading task in each subject; visuomotor error was subtracted from heading error in the pointing and steering tasks.

Pointing at the heading direction

In the pointing task, subjects pointed to the heading direction in the preceding self-movement stimulus that contained optic flow, object motion, or both (Fig. 4).

Types of pointing error

Pointing error (Fig. 5A–D) showed that all subject groups undershot the target heading direction by failing to move the response cursor far enough laterally to match peripheral heading directions. There were no response differences for left- versus right-sided stimuli, so data were grouped by stimulus eccentricity. These effects yielded significant group × stimulus × eccentricity interactions [$F(24, 183) = 2.49$, $P < 0.001$]. There were no differences between the groups when using optic flow to localize heading location ($P > 0.05$), with all groups showing the same patterns of increasing error linked to increasing heading eccentricity. Pointing error using object motion showed significant group effects [$F(3, 73) = 5.07$, $P = 0.003$] attributable to differences

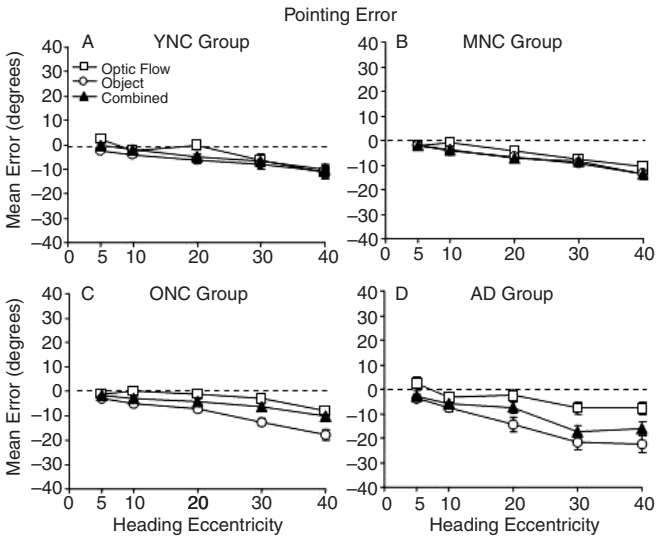

Fig. 5 Pointing error for each subject group and stimulus type. Graphs show pointing error ± SEM (ordinate) for each heading eccentricity (abscissa), type of stimulus (lines) and subject group (**A**–**D**). Pointing error is plotted as average medial–lateral position relative to the target heading eccentricity. Practically all of the pointing inaccuracy in all groups consisted of a tendency to point towards a position that was less eccentric than that presented in the heading stimulus; subjects underestimated heading eccentricity. There was no substantial leftward or rightward bias in the pointing responses of any group.

between the Alzheimer's disease group and both the YNC ($P < 0.01$) and MNC ($P < 0.01$) groups; the ONC and Alzheimer's disease groups did not differ from each other and the YNC and MNC groups did not differ from each other. Thus, younger subjects (YNC and MNC) perform the pointing task well with either optic flow or object motion stimuli, whereas older subjects (ONC and AD) showed poorer performance with object motion but preserved performance with optic flow.

Cue interactions in pointing

Pointing responses based on combined optic flow and object motion also showed significant group differences [$F(3, 72) = 4.01$, $P < 0.01$]. The YNC and MNC groups showed the same pattern of good performance with combined stimuli as they showed with object motion and optic flow alone (Fig. 5A and B). The ONC group's good performance with combined stimuli (Fig. 5C) was similar to their performance with optic flow alone ($P > 0.05$), differing from their poorer performance with object motion alone ($P = 0.012$).

The Alzheimer's disease group's performance with combined stimuli was intermediate between their poor performance with object motion alone and better performance with optic flow alone. All three stimulus conditions yielded comparable results at the 30 and 40° heading eccentricities, suggesting that Alzheimer's disease subjects' performance might be limited by floor effects. This is not supported by our finding different limits in the three stimulus conditions. Further, response floor effects should show increasing error with increasing target eccentricity, but that was not the case.

Thus, the ONC group showed a winner-take-all strategy that yielded performance with combined cues matching their better performance with object motion and showed no evidence of interference by their poorer performance with optic flow. In contrast, the Alzheimer's disease group did not show a winner-take-all strategy yielding performance with combined cues that was intermediate between their better performance with object motion and their poorer performance with optic flow.

The range of relationships between performance with combined stimuli and interference by object motion is seen across the spectrum of ONC subjects (Fig. 6). ONC Subject 7 showed a clear winner-take-all effect with performance using combined stimuli matching good performance with optic flow in spite of poor performance with object motion (Fig. 6A). ONC Subject 14 performed similarly with combined stimuli performance mirroring poorer performance with object motion responses at small heading eccentricities but switching over to the better performance with optic flow at greater heading eccentricities (Fig. 6B). Finally, ONC Subject 22 showed responses to combined stimuli that matched the poorer performance with object motion in spite of the better performance seen with optic flow (Fig. 6C).

The results of the pointing task suggest that in ageing and Alzheimer's disease there is a progressive deterioration of the ability to use object motion to point at the simulated heading. In ONC subjects, good performance with combined stimuli can be maintained by using optic flow in the face of poorer performance with object motion. In Alzheimer's disease subjects, there is an apparent loss of this compensatory capacity with increasing object motion error interfering with performance using combined stimuli.

Steering straight ahead

In the steering task, subjects moved the simulated heading from an initially eccentric direction to a straight-ahead direction using self-movement stimuli that contained optic flow, object motion, or both stimuli (Fig. 7).

Types of steering error

There were significant group differences in the steering task [$F(3, 75) = 5.67$, $P < 0.001$] attributable to the Alzheimer's disease differing from all other groups ($P < 0.05$). Steering with optic flow differed significantly across groups [$F(3, 75) = 4.07$, $P < 0.01$]: All groups made similar magnitudes of increasing errors with increasing initial eccentricity. This reflects steering undershoot with a final heading direction that is too eccentric because the subject did not bring the heading all the way into the centre of the screen (Fig. 8).

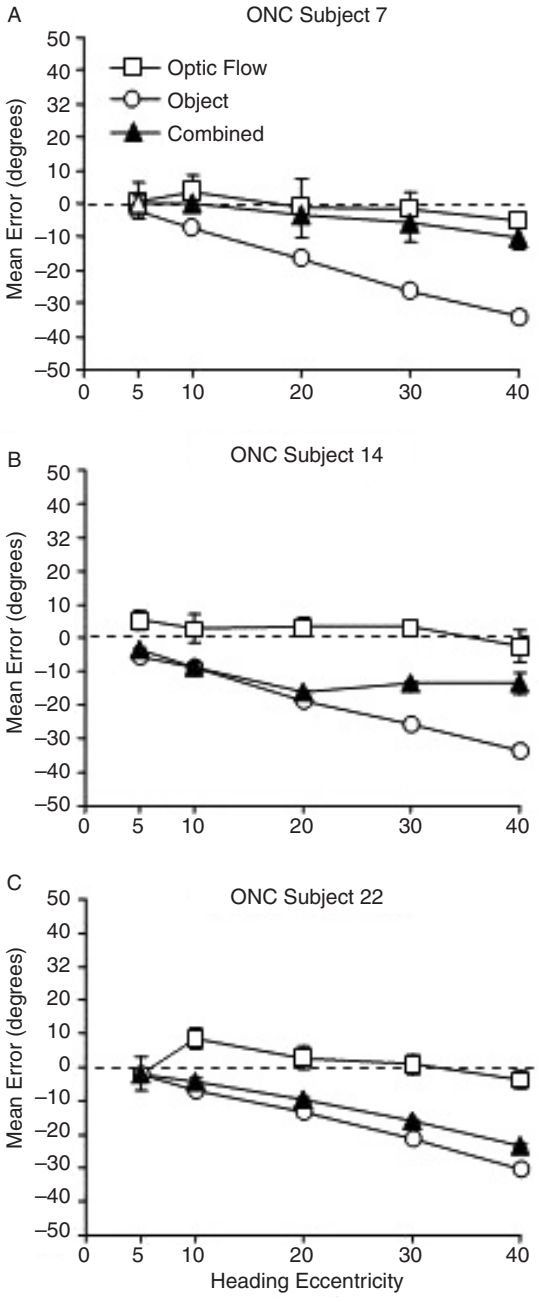

Fig. 6 Individual differences in pointing error with optic flow and object motion. Pointing error +/− SEM (ordinate) across heading eccentricity (abscissa) in three ONC subjects. (**A**) ONC Subject 7 showed an isolated increase in object motion error with increasing target eccentricity with excellent performance using optic flow and combined stimuli. (**B**) ONC Subject 14 showed large errors with object motion, excellent performance with optic flow and eccentricity-dependent effects with combined stimuli. Combined stimuli yielded errors like those seen with object motion for the more central headings, and errors that are increasingly like those seen with optic flow for the more peripheral headings. (**C**) ONC Subject 22 showed large errors with object motion, excellent performance with optic flow and errors with combined stimuli that were like those seen with object motion. Thus, individual ONC subjects show a range of reliance on optic flow in combined stimuli with increasing heading errors based on object motion.

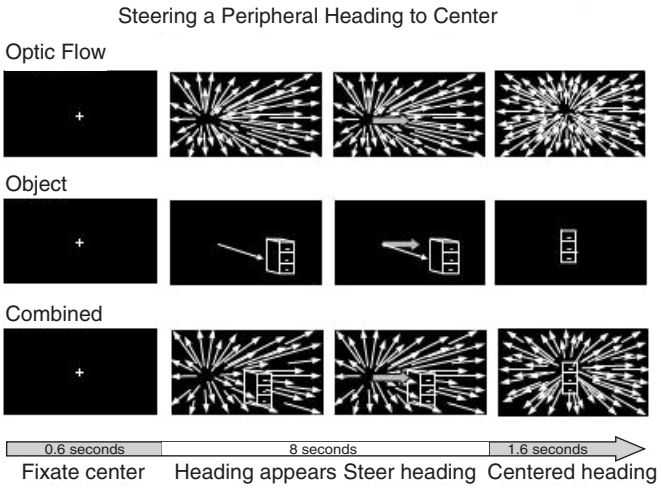

Fig. 7 Steering task used with optic flow, object motion and combined stimuli. The steering tasks consisted of maintaining centred fixation during the presentation of visual stimuli simulating observer self-movement. At the beginning of each trial the simulated heading was at one of the 10 eccentric positions. Subjects then used a steering wheel to steer the simulated heading towards the straight-ahead direction. Radial optic flow (*top*), object motion (*middle*) and combined optic flow and object motion stimuli were tested in a counterbalanced block-wise design.

However, the Alzheimer's disease group showed greater error compared with the YNC ($P < 0.05$) and ONC ($P < 0.01$) groups who did not differ from each other. There was relatively little error when subjects from all groups steered using object motion. However, the groups differed when steering with combined stimuli in a manner similar to that seen when steering with optic flow alone [$F(3, 75) = 3.95$, $P < 0.01$]. Again, this was attributable to the Alzheimer's disease group differing from the YNC ($P < 0.05$) and ONC ($P < 0.01$) groups.

The YNC and MNC groups showed nearly perfect performance in the steering task using either the object motion alone or the combined cues (Fig. 8A and B). In contrast, the ONC group showed poorer performance with object motion, much as with optic flow. However, they maintained good performance with the combined object motion and optic flow stimuli (Fig. 8C). This resulted in significant stimulus effects within the ONC group [$F(2, 87) = 3.75$, $P < 0.05$] attributable to differences between the combined and optic flow stimuli (THSD, $P < 0.05$).

The Alzheimer's disease group showed somewhat worse performance than the ONC using both optic flow and object motion, but the greater distinction was that the Alzheimer's disease also showed significantly poorer performance with combined stimuli [$F(3, 75) = 3.95$, $P < 0.01$; THSD, $P = 0.009$] (Fig. 8C and D). The optic flow stimulus condition yielded comparable results at the 30 and 40° heading eccentricities. This did not appear to reflect response floor effects because the other stimulus conditions yielded different results and floor effects should yield increasing error relative to target eccentricity.

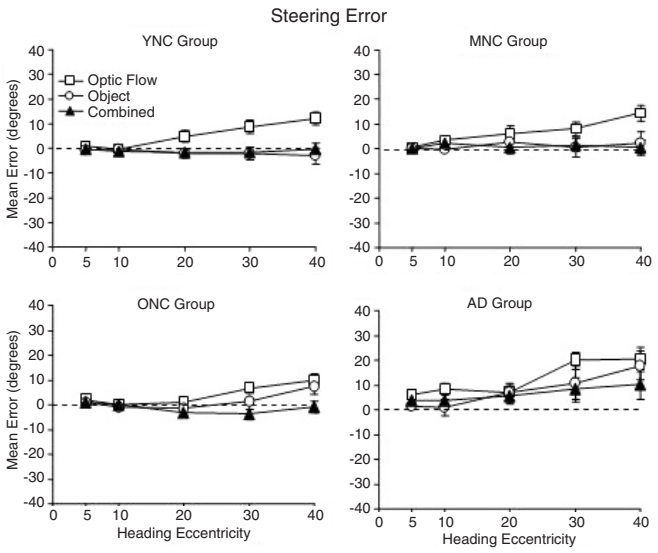

Fig. 8 Steering error for each subject group and stimulus type. Graphs show steering error +/− SEM (ordinate) for each heading eccentricity (abscissa), type of stimulus (lines) and subject group (**A**–**D**). Steering error is plotted as average final heading position relative to the centre of the screen. In all groups, error with optic flow stimuli was attributable to bias that reflected a failure to bring the simulated heading all the way into the centre of the screen; subjects underestimated the distance between the final heading and the centre of the screen. Object motion showed substantial bias only in the older groups, ONC and Alzheimer's disease. Combined stimuli resulted in substantial bias only in the Alzheimer's disease group.

Cue interactions in steering

The ONC group included individuals with a selective loss of capacity to steer either by optic flow or by object motion, but with preserved steering capacity by the other stimulus (Fig. 9). ONC Subject 9 did poorly with object motion but did well with optic flow (Fig. 9A, left), while ONC Subject 3 did poorly with optic flow but did well with object motion (Fig. 9A, right). In both cases, performance with combined cues was preserved, apparently matching that seen with the unaffected cue presented alone. Thus, the ONC group's better performance with combined stimuli than with either stimulus presented alone did not reflect synergistic cue interactions but rather a winner-take-all strategy favouring the more effective cue.

The Alzheimer's disease group also included individuals with greater steering impairments with one stimulus or the other. Alzheimer's disease Subject 10 did poorly with object motion and much better with optic flow (Fig. 9B, left), whereas Alzheimer's disease Subject 15 did poorly with optic flow and much better with object motion (Fig. 9B, right). In both cases, performance with combined cues was worse than that with the better of the two cues presented alone. In contrast to the ONC, these Alzheimer's disease subjects showed greater interference by the less accurate stimulus in steering by combined stimuli. Alzheimer's disease subjects did not show consistent winner-take-all strategies; instead they showed eccentricity-dependent alternation between cues.

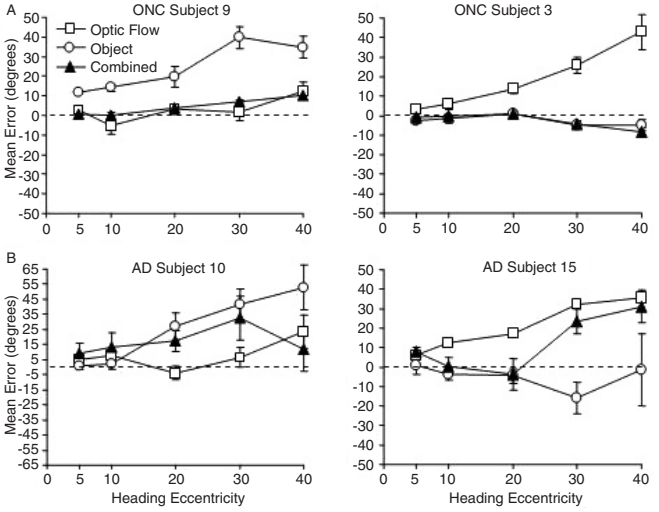

Fig. 9 Differences between ONC and Alzheimer's disease in the steering task. Mean steering error +/− SEM (ordinates) across heading eccentricity (abscissas) in two ONC subjects and two Alzheimer's disease subjects. (**A**) ONC Subject 9 showed an isolated increase in object error with excellent performance using optic flow and combined stimuli. ONC Subject 3 showed an isolated increase in optic flow error with excellent performance using object motion and combined stimuli. Thus, individual ONC subjects showed isolated impairments of object motion or optic flow-based performance with apparently full reliance on the alternative cue when presented with combined stimuli. (**B**) Alzheimer's disease Subject 10 showed an isolated increase in object motion error with correspondingly poor performance using combined stimuli that improves to approximate object motion performance at eccentric headings. Alzheimer's disease Subject 15 showed an isolated increase in optic flow error with correspondingly poor performance using combined stimuli, particularly at eccentric headings. Thus, individual Alzheimer's disease subjects showed isolated impairments of object motion or optic flow-based performance with incomplete reliance on the preserved cue that yields poorer performance with combined stimuli.

Thus, the steering task was performed better using object motion than optic flow. All groups showed increasing steering error with increasing optic flow heading eccentricity. In YNC and MNC subjects, this optic flow error did not interfere with good performance using combined cues. The ONC group's preserved performance with combined stimuli appeared to reflect winner-take-all cue selection without synergistic interactions between cues. Alzheimer's disease subjects showed still worse performance with both optic flow and object motion and also showed an inability to support performance with combined cues using winner-take-all cue integration.

Optic flow and object motion in pointing and steering errors

To explore relationships between the individual cues and the independent contributions of the cues in the combined condition, we computed mean error across all heading eccentricities by stimulus type (optic flow, object, combined)

and task (pointing, steering) for each subject. Correlational analyses showed independence of errors with each cue and task. Across all subjects, error with optic flow and object motion were not correlated in either the pointing ($r = 0.08$, $P = 0.52$) or the steering ($r = 0.14$, $P = 0.22$) tasks. In addition, there were no significant correlations between error on the two tasks for optic flow ($r = -0.03$, $P = 0.83$), object motion ($r = -0.20$, $P = 0.08$) or combined stimuli ($r = -0.11$, $P = 0.35$). Thus, error using optic flow and object motion are not linked in either task. Furthermore, performance in the pointing and steering tasks is not linked in any of the stimulus conditions. That is, the errors made by individual subjects revealed selective declines in the use of optic flow or object motion in either the pointing or the steering tasks.

This point must be distinguished from the fact that errors with both optic flow and object motion contributed substantially to errors with combined stimuli. In the pointing task, error using object motion was significantly correlated with error using combined stimuli ($r = 0.74$, $P < 0.001$). However, in pointing, the generally smaller error using optic flow was not correlated with error using combined stimuli ($r = 0.16$, $P < 0.16$). In the steering task, error using optic flow ($r = 0.39$, $P < 0.001$) and object motion ($r = 0.57$, $P < 0.001$) were both significantly correlated with error using combined stimuli. These findings suggest that object motion error was the larger source of pointing error with combined stimuli, whereas both optic flow and object motion error contributed similarly to steering error with combined stimuli.

Multiple linear regression analysis was used to explore the relative contributions of each stimulus to the combined condition. In the pointing task, multiple linear regression yielded good fits ($R^2 > 0.5$) in 87% of the subjects, without substantial differences across subject groups. There were generally higher β-weights for object motion with proportionately lower β-weights for optic flow (Fig. 10A). There was no evident partitioning of subjects by group along either the $\beta_{\text{object motion}}$ or $\beta_{\text{optic flow}}$ axes, or in the 2-D distribution. This suggests that the relative influence of optic flow and object motion on pointing with combined stimuli varies more as a matter of individual idiosyncrasy rather than group tendency.

In the steering task, multiple linear regression yielded good fits ($R^2 > 0.5$) in 60% of the subjects, again without substantial differences across subject groups. In this task there was less of a systematic relationship between error with combined stimuli and with optic flow or object motion (Fig. 10B). The wide scatter of all groups implies that an additional factor, other than optic flow and object motion performance, accounts for much of the variance in steering with combined cues.

We sought relationships between pointing and steering error, used as dependent measures, and neuropsychological test scores, optic flow and object motion perceptual thresholds, used as independent variables. Neither pointing nor steering were significantly linked to neuropsychological or perceptual measures, considered separately or together, in any of the subject groups. Thus, pointing and steering by equi-salient visual cues is not simply related to neuropsychological or perceptual capacities.

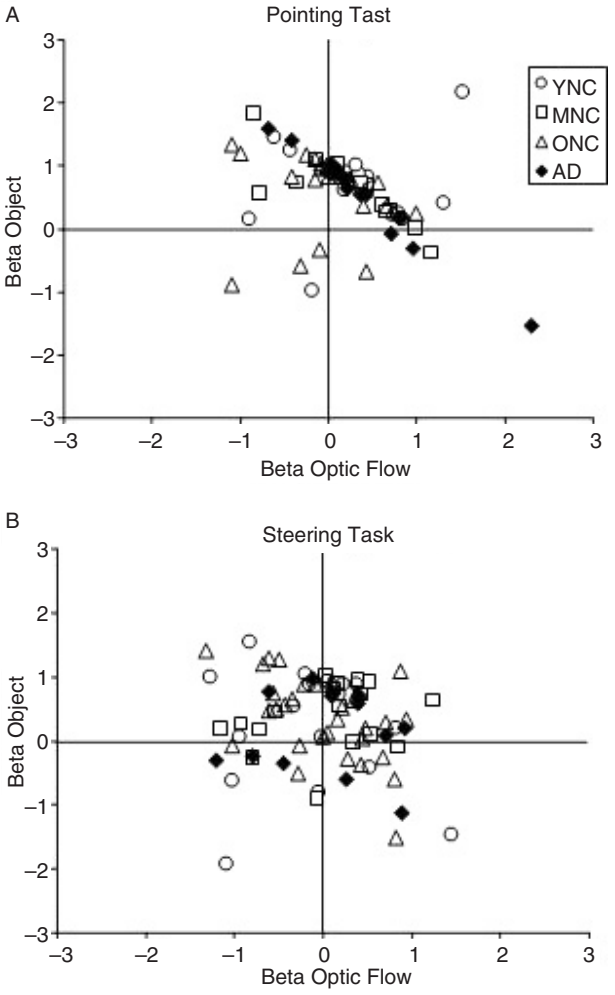

Fig. 10 Contributions of optic flow and object motion error in combined condition for pointing and steering tasks. Multiple linear regression was used to determine the influence of optic flow and object cues on combined cue performance in each subject in all groups. The influence of each cue is shown as the β-weights for object motion (ordinates) and optic flow (abscissas). (**A**) Object motion and optic flow effects in the pointing task show an apparently reciprocal relationship: subjects with the greatest influence of object motion showed the least influence of optic flow. (**B**) Object motion and optic flow effects in the steering task show a wide range of effects including a substantial number of subjects with apparently inverse relationship: a substantial number of subjects showed negative β-weights for object motion or optic flow.

Discussion

Perceptual impairment in ageing and Alzheimer's disease

We have found perceptual impairments in ageing and Alzheimer's disease with elevated visual motion

discrimination thresholds for navigational stimuli. Ageing impairs the perception of heading from object motion cues with further impairment in Alzheimer's disease. Alzheimer's disease also impairs the perception of heading from optic flow, with little effect of ageing in our data, although ageing may adversely affect other aspects of optic flow analysis (Atchley and Andersen, 1998).

Impaired horizontal motion perception in Alzheimer's disease seen here and reported previously (Trick and Silverman, 1991) is independent of the common loss of contrast sensitivity associated with ageing and Alzheimer's disease (Gilmore *et al.*, 1994). Likewise, impaired horizontal motion perception in Alzheimer's disease does not affect the lower-order visual processing of those stimuli that induce optokinetic nystagmus (Silverman *et al.*, 1994). These findings support the notion that Alzheimer's disease is characterized by a higher-order visual motion processing deficit.

Alzheimer's disease is accompanied by a large increase in discrimination thresholds for headings represented by the radial patterns of visual motion in optic flow. The finding that the ONC and younger groups have similar horizontal and radial thresholds suggests that the large increase in Alzheimer's disease thresholds reflects a specific impairment rather than overall task difficulty. The difference between horizontal and radial thresholds in Alzheimer's disease is consistent with evidence that Alzheimer's disease patients have specific impairments in the processing of global motion cues, with local motion analysis being less effected (O'Brien *et al.*, 2001; Mapstone *et al.*, 2003).

A unique finding in the current work is that both ageing and Alzheimer's disease increase visual object motion heading discrimination thresholds. Impaired object motion processing compared with optic flow analysis is consistent with difficulty in perceiving the structure of an object from patterned motion (Rizzo and Nawrot, 1998) and the preservation of the ability to benefit from motion parallax depth cues (Norman *et al.*, 2004) that are more prominent in optic flow than in object motion. We must also consider the possibility that adjusting the object motion exposure duty cycle does not equalize perceptual capacities across groups to the degree that optic flow motion coherence seems to achieve. The use of different stimulus manipulations was required to independently control both types of stimuli when superimposed for combined stimulation, but might also be viewed as more naturalistic manipulations of object and pattern salience in self-movement. In either case, advancing age might promote greater reliance on the use of optic flow patterns rather than object motion cues about self-movement, with the onset of Alzheimer's disease also undermining residual navigational capacity by specifically impairing optic flow perception (Warren *et al.*, 1989; Moffat *et al.*, 2001).

Cue use for pointing and steering

YNC and MNC subjects produced similar pointing responses in all stimulus conditions, suggesting that they interpret object motion and optic flow stimuli as comparable heading cues. All groups underestimated the eccentricity of peripheral headings far more than eccentrically flashed targets, possibly because of attentional shifts during stimulus presentation or gaze shifts during pointing responses (Admiraal *et al.*, 2003).

Comparison of the contributions of optic flow and object motion to performance with combined stimuli yielded different results for the pointing and steering tasks. Pointing showed a trade-off of optic flow and object motion so that individuals in all groups idiosyncratically used an additive combination of the two cues. In contrast, steering showed a wide range of relative contributions of optic flow and object motion stimuli across individuals in all groups.

Our findings highlight differences between the uses of optic flow and object motion for pointing and steering. This may be further evidence that the open-loop perception and action sequence of pointing attaches different weights to visual cues than the closed-loop, feedback-controlled, dynamic motor responses of steering (Knill, 2005). Different patterns of visual processing for perceptually weighted tasks and for dynamic motor responses have been seen in focal lesions and in the behaviour of intact subjects (Milner and Goodale, 1993). Steering may be typical of tasks that are supported by an iterative process, with heading perception triggering an initially ballistic response that results in heading changes that lead to further motor adjustments. This is consistent with the activation of different brain areas at the onset of simulated driving versus sustained periods of simulated driving (Calhoun *et al.*, 2002).

Effects of ageing

Ageing is associated with an increase in pointing and steering error when using object motion stimuli but not when using optic flow. This object processing impairment may be related to the loss of centre-surround antagonism in normal ageing (Betts *et al.*, 2005). Centre-surround antagonism might enhance the perception of an object's motion through the visual field, so its path can be extrapolated into a heading of relative self-motion. Centre-surround effects on object motion discrimination may also contribute to the critical impairment of object recognition, such as road signs and other vehicles, in older drivers (Uc *et al.*, 2005). Optic flow's continuous coverage of the entire visual field may protect optic flow analysis from impairments due to the loss of centre-surround antagonism.

ONC subjects overcame their difficulties using object motion when it was combined with optic flow in both the pointing and the steering tasks. Group averages suggested synergistic benefits of combined cues in ONC subjects. However, we found that these apparently synergistic effects were attributable to idiosyncratic cue selection: subjects who showed poor performance with either optic flow or object motion showed much better performance with the other cue. When those subjects viewed combined stimuli, they

performed as they did with the better of the two cues, benefiting from a winner-take-all cue selection strategy.

The observation that some subjects showed impaired performance with either optic flow or object motion, and preserved performance with the other cue, establishes the double dissociation of optic flow and object motion processing. This double dissociation suggests that optic flow and object motion processing for heading discrimination is supported by somewhat separate neural mechanisms (Teuber, 1955). The separate processing of optic flow and object motion cues about self-movement may be reflected in the lack of synergistic interactions between these stimuli when they are presented together in combined stimuli. We speculate that the separate processing of optic flow and object motion is required by the potential independence of self-movement and the motion of independently moving, animate objects in natural environments. This view is supported by evidence that independently moving objects only interfere with heading estimation from optic flow under a limited set of circumstances, particularly when the object obscures the heading point (Royden and Hildreth, 1996; Hildreth *et al.*, 2000).

Effects of Alzheimer's disease

Alzheimer's disease patients showed still greater error than ONC subjects in pointing and steering by object motion. Furthermore, Alzheimer's disease patients did not fully benefit from the addition of optic flow to the object motion when they were presented together in combined stimuli. Apparently, the winner-take-all strategy often failed in the Alzheimer's disease group. Viewed another way, only in Alzheimer's disease patients did impaired pointing by object motion interfere with pointing by superimposed optic flow.

The failure of winner-take-all cue integration in Alzheimer's disease could reflect the selective loss of cortico-cortical connection neurons (Morrison *et al.*, 1991; Hof *et al.*, 1997). The particular impact of Alzheimer's disease on cortico-cortical connectivity is consistent with both the concentration of neurofibrillary tangles in the infra- and supra-granular layers of visual association areas (Pearson *et al.*, 1985) and the marked degeneration of cortico-cortical white matter tracts measured by diffusion tensor MRI (Rose *et al.*, 2000; Bozzali *et al.*, 2002). We speculate that one functional consequence of cortico-cortical disconnection in Alzheimer's disease may be an inability to compare optic flow and object motion signals that are processed by separate neuronal populations but must be combined to support winner-take-all effects (Lumer, 2000). The loss of cortico-cortical connectivity may also impede the longer spatial range required for the global motion processing of optic flow, rather than the local motion processing of object motion (O'Brien *et al.*, 2001).

The loss of winner-take-all cue integration is consistent with the concentration of Alzheimer's disease pathology in parietotemporal association cortex (Brun and Englund, 1981; Arnold *et al.*, 1991). Parietal visual association cortex includes the medial superior temporal area in which neurons show winner-take-all interactions between opposite directions of optic flow and object motion (Logan and Duffy, 2005), as in their pursuit responses to opposite directions of motion (Recanzone and Wurtz, 1999), and the adjacent middle temporal neuronal responses to opposite directions of visual motion (Nichols and Newsome, 2002). Thus, it appears as though winner-take-all cue selection is a common mechanism in dorsal stream neuronal signal processing with robust perceptual and behavioural consequences.

We have found parallel declines in both pointing and steering performance with increasing heading eccentricity. These effects are evident in all subject groups, suggesting that all groups use similar approaches in each task: pointing is an open-loop task that prompts the weighing of each cue in an idiosyncratic manner to generate ballistic responses. Steering is a feedback-controlled task that prompts initially ballistic responses that are then adjusted during continued stimulation. Overall, we found that optic flow was used more effectively for pointing and object motion was used more effectively for steering. Ageing was associated with a decline in the capacity to perceive and use object motion as a heading cue. Alzheimer's disease was associated with impaired optic flow perception and a decline in the capacity to consistently apply a winner-take-all cue selection strategy.

Our findings support the view that some degree of functional independence is created by the separation of dorsal and ventral extrastriate neural mechanisms processing optic flow and object motion for pointing and steering. It appears that the inter-regional integration required by this functional independence may create vulnerability to the cortico-cortical disconnection of Alzheimer's disease and account for some of the functional impairments seen in these patients.

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References

Admiraal MA, Keijsers NLW, Gielen CC. Interaction between gaze and pointing toward remembered visual targets. J Neurophysiol 2003; 90: 2136–48.

Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1991; 1: 103–16.

Atchley P, Andersen GJ. The effect of age, retinal eccentricity, and speed on the detection of optic flow components. Psychol Aging 1998; 13: 297–308.

Benton AL, Varney NR, Hamsher KD. Visuospatial judgment. A clinical test. Arch Neurol 1978; 35: 364–7.

Betts LR, Taylor CP, Sekuler AB, Bennett PJ. Aging reduces center-surround antagonism in visual motion processing. Neuron 2005; 45: 361–6.

Bozzali M, Falini A, Franceschi M, Cercignani M, Zuffi M, Scotti G, et al. White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. J Neurol Neurosurg Psychiatry 2002; 72: 742–6.

Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathologica 1991; 82: 239–59.

Brun A, Englund E. Regional pattern of degeneration in Alzheimer's disease: neuronal loss and histopathological grading. Histopathology 1981; 5: 549–64.

Calhoun VD, Peker JJ, McGinty VB, Adali T, Watson TD, Pearlson GD. Different activation dynamics in multiple neural systems during simulated driving. Hum Brain Mapp 2002; 16: 158–67.

Cronin-Golomb A, Corkin S, Growdon JH. Visual dysfunction predicts cognitive deficits in Alzheimer's disease. Optom Vis Sci 1995; 72: 168–76.

Duffy CJ. MST neurons respond to optic flow and translational movement. J Neurophysiol 1998; 80: 1816–27.

Duffy CJ, Page WK. Optic flow and vestibular self-movement cues: multi-sensory interactions in cortical area MST. In: Vaina LM, Beardsley SA, Rushton SK, editors. Optic flow and beyond. : Kluwer Academic Publishers. 2004. p. 23–44.

Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Friedman-Hill SR, Robertson LC, Treisman A. Parietal contributions to visual feature binding: evidence from a patient with bilateral lesions. Science 1995; 269: 853–5.

Gibson JJ. The perception of the visual world. Boston: Houghton Mifflin; 1950.

Gilmore GC, Wenk HE, Naylor LA, Koss E. Motion perception and Alzheimer's disease. J Gerontol 1994; 49: P52–7.

Golledge RG. Wayfinding behavior: cognitive mapping and other spatial processes. Baltimore: The Johns Hopkins University Press; 1999.

Goodale MA, Milner AD. Separate visual pathways for perception and action. Trends Neurosci 1992; 15: 20–5.

Harvey LO Jr. Efficient estimation of sensory thresholds with ML-PEST. Spat Vis 1997; 11: 121–8.

Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, et al. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proc Natl Acad Sci USA 1991; 88: 1621–5.

Hays AV, Richmond BJ, Optican LM. A UNIX-based multiple process system for real-time data acquisition and control. WESCON Conf Proc 1982; 2: 1–10.

Hildreth EC, Beusmans JM, Boer ER, Royden CS. From vision to action: experiments and models of steering control during driving. J Exp Psychol Hum Percept Perform 2000; 26: 1106–32.

Hof PR, Vogt BA, Bouras C, Morrison JH. Atypical form of Alzheimer's disease with prominent posterior cortical atrophy: a review of lesion distribution and circuit disconnection in cortical visual pathways. [Review]. Vision Res 1997; 37: 3609–25.

Kleist K. Uber Form und Orstsblindheit bei Verletzungen des Hinterhaut-lappens. Dtsch Z Nervenheilk 1935; 138: 206–14.

Knill DC. Reaching for visual cues to depth: the brain combines depth cues differently for motor control and perception. J Vis 2005; 5: 103–15.

Kobatake E, Tanaka K. Neuronal selectivities to complex object features in the ventral visual pathway of the macaque cerebral cortex. J Neurophysiol 1994; 71: 856–67.

Logan DJ, Duffy CJ. Cortical area MSTd combines visual cues to represent 3-D self-movement. 2005. In press.

Lumer ED. Effects of spike timing on winner-take-all competition in model cortical circuits. Neural Comput 2000; 12: 181–94.

Mapstone M, Steffenella TM, Duffy CJ. A visuospatial variant of mild cognitive impairment: getting lost between aging and AD. Neurology 2003; 60: 802–8.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984; 34: 939–44.

Mendola JD, Cronin-Golomb A, Corkin S, Growdon JH. Prevalence of visual deficits in Alzheimer's disease. Optom Vis Sci 1995; 72: 155–67.

Merigan WH, Maunsell JHR. How parallel are the primate visual pathways? Annu Rev Neurosci 1993; 16: 369–402.

Milner AD, Goodale MA. Visual pathways to perception and action. Prog Brain Res 1993; 95: 317–37.

Mishkin M, Ungerleider LG, Macko KA. Object vision and spatial vision: two cortical pathways. Trends Neurosci 1983: 414–7.

Moffat SD, Zonderman AB, Resnick SM. Age differences in spatial memory in a virtual environment navigation task. Neurobiol Aging 2001; 22: 787–96.

Money J. A standardized road map test of direction sense. San Rafael, CA: Academic Therapy Publications; 1976.

Morrison JH, Hof PR, Bouras C. An anatomic substrate for visual disconnection in Alzheimer's disease. [Review]. Ann NY Acad Sci 1991; 640: 36–43.

Nichols MJ, Newsome WT. Middle temporal visual area microstimulation influences veridical judgments of motion direction. J Neurosci 2002; 22: 9530–40.

Norman JF, Clayton AM, Shular CF, Thompson SR. Aging and the perception of depth and 3-D shape from motion parallax. Psychol Aging 2004; 19: 506–14.

O'Brien HL, Tetewsky S, Avery LM, Cushman LA, Makous W, Duffy CJ. Visual mechanisms of spatial disorientation in Alzheimer's disease. Cereb Cortex 2001; 11: 1083–92.

O'Keefe J, Nadel L. The hippocampus as a cognitive map. Oxford: Clarendon Press; 1978.

Oostende SV, Sunaert S, Hecke PV, Marchal G, Orban GA. The kinetic occipital (KO) region in man: an fMRI study. Cereb Cortex 1997; 7: 690–701.

Pearson RC, Esiri MM, Hiorns RW, Wilcock GK, Powell TP. Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. Proc Natl Acad Sci USA 1985; 82: 4531–4.

Pentland A. Maximum likelihood estimation: the best PEST. Percept Psychophys 1980; 28: 377–9.

Recanzone GH, Wurtz RH. Shift in smooth pursuit initiation and MT and MST neuronal activity under different stimulus. J Neurophysiol 1999; 82: 1710–27.

Rizzo M, Nawrot M. Perception of movement and shape in Alzheimer's disease. Brain 1998; 121: 2259–70.

Rose SE, Chen F, Chalk JB, Zelaya FO, Strugnell WE, Benson M, et al. Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. J Neurol Neurosurg Psychiatry 2000; 69: 528–30.

Rosen RS. Verbal fluency in aging and dementia. J Clin Neuropsychol 1980; 2: 135–46.

Royden CS, Hildreth EC. Human heading judgments in the presence of moving objects. Percept Psychophys 1996; 58: 836–56.

Saito H, Yukie M, Tanaka K, Hikosaka K, Fukada Y, Iwai E. Integration of direction signals of image motion in the superior temporal sulcus of the macaque monkey. J Neurosci 1986; 6: 145–57.

Silverman SE, Tran DB, Zimmerman KM, Feldon SE. Dissociation between the detection and perception of motion in Alzheimer's disease. Neurology 1994; 44: 1814–8.

Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis. Annu Rev Neurosci 1995; 18: 555–86.

Tanaka K, Sugita Y, Moriya M, Saito H. Analysis of object motion in the ventral part of the medial superior temporal area of the macaque visual cortex. J Neurophysiol 1993; 69: 128–42.

Tetewsky S, Duffy CJ. Visual loss and getting lost in Alzheimer's disease. Neurology 1999; 52: 958–65.

Teuber HL. Physiological psychology. Annu Rev Psychol 1955; 6: 267–96.

Trick GL, Silverman SE. Visual sensitivity to motion: age-related changes and deficits in senile dementia of the Alzheimer type. Neurology 1991; 41: 1437–40.

Uc EY, Rizzo M, Anderson SW, Shi Q, Dawson JD. Driver landmark and traffic sign identification in early Alzheimer's disease. J Neurol Neurosurg Psychiatry 2005; 76: 764–8.

Ungerleider LG, Haxby JV. 'What' and 'where' in the human brain. Curr Biol 1994; 4: 157–65.

Warren WH. Optic flow. In: Chalupa LM, Werner JS, editors. The visual neurosciences. Cambridge: MIT Press; 2004. p. 1247–59.

Warren WH Jr, Blackwell AW, Morris MW. Age differences in perceiving the direction of self-motion from optical flow. J Gerontol 1989; 44: P147–53.

Wechsler D. Wechsler Memory Scale, Revised Manual. San Antonio, TX: Psychological Corporation; 1987.