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Neuropsychologia 38 (2000) 1157–1169

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

Vision and cognition in Alzheimer's disease

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Received 4 January 1999; received in revised form 6 December 1999; accepted 14 December 1999

Abstract

Alzheimer's disease (AD) is known to affect visual pathways, but potential concomitant effects on vision and cognitive performance are not well understood. We studied 43 individuals with AD of mild severity and 22 individuals without dementia on a battery of tests designed to measure multiple aspects of basic and higher-order visual perception and cognition. All subjects performed on the same visual and cognitive test batteries. The results showed no differences between groups on tests of static visual acuity, stereoacuity, dynamic visual acuity or motion direction discrimination. However, individuals with AD performed significantly worse on tests of static spatial contrast sensitivity, visual attention, shape-from-motion, color, visuospatial construction and visual memory. Correlation analyses showed strong relationships between visual and cognitive scores. The findings show that AD affects several aspects of vision and are compatible with the hypothesis that visual dysfunction in AD may contribute to performance decrements in other cognitive domains. The pattern of involvement indicates that AD affects multiple visual neural pathways and regions. It is possible that better understanding of vision-related dysfunction could aid diagnosis and interventions to improve functional capacity in patients with dementia.

Keywords: Attention; Neurodegenerative disease; Visual cortex

1. Introduction

Alzheimer's disease (AD) is the most common cause of abnormal cognitive decline in older adults [89], and neuropathological changes underlying AD involve visual pathways [61,63,111]. As sight is "the first door of the intellect" (Paccioli, ca 1445–ca 1514 [11]), it is reasonable to suspect that visual decline may contribute to intellectual deterioration in AD. AD is now reported to impair visual sensory functions including spatial contrast sensitivity [32,43,49], color, stereopsis, temporal resolution [23,25] and motion [33,103]. AD can also affect visual attention [68,74] and "higher" visual functions such as reading, route finding, object localization and recognition [24,48,60,73,101]. Better understanding of these vision-related deficits could aid diagnosis, interpretation of cognitive scores, and interventions to improve functional capacity in patients with AD [22].

The selectivity of visual deficits and relation to disease stage and locus of CNS impairment in AD remain uncertain. Recent polemic concerns selectivity of "ventral" ("what" or "temporal") vs "dorsal" ("where" or "parietal") visual pathway deficits in AD [40,48] including movement perception deficits [6,46,83,91,95,96]. Moreover, Kurylo et al. [48] suggested that visual dysfunction does not follow overall disease progression in AD but rather reflects sporadic involvement in certain cases. Visual function in

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0028-3932/00/$ - see front matter
PII: S0028-3932(00)00023-3

AD is an issue of theoretical and practical importance that requires further investigation.

The purpose of this study was to investigate visual and cognitive abilities in older individuals with and without AD. We tested the hypotheses that AD produces both ventral and dorsal visual pathway deficits while sparing basic sensory functions, and that these visual function deficits correlate with overall severity of AD.

2. Methods

2.1. Subjects

Forty-three volunteers with AD (mean age 71.9 years, SD = 8.3 years; mean education 13.2 years, SD = 3.2 years) were recruited from the Alzheimer's Disease Research Center in the Department of Neurology. The diagnosis of probable AD was based on standard criteria (NINCDS-ADRDA [58]). All participants with AD were living at home, able to attend to personal needs and were still driving or had recently quit. Group mean Clinical Dementia Rating (CDR) score was 0.69, indicating mild dementia. Twenty-eight had a CDR of 0.5, 13 had a 1.0, one had a 2.0; and one was not available.

Twenty-two control subjects were also studied (mean age 71.9 years, SD = 6.7 years; mean education 14.3 years, SD = 3.0 years). This group participated in the same screening protocols as participants with AD. These were independent, community-dwelling older individuals with no active health problems. They were not recruited from patients who sought evaluation for memory complaints. They were fully oriented, capable of self-care, able to solve everyday problems, maintain home, manage financial affairs, and function at usual levels in customary activities such as shopping, automobile driving, hobbies, and social encounters. These participants did not meet standard criteria for probable or even possible AD.

Each subject was interviewed and examined to assess for neurologic, psychiatric or ophthalmologic problems other than AD. They completed the General Health Questionnaire as well as questionnaires on visual health (the ADVS with UAB supplement) and on alcohol consumption. Alcoholism and depression were exclusion criteria. No subject had diabetes, renal disease, significant hypertension, senile macular degeneration, untreated cataract requiring surgery, ocular motor paralysis, congenital amblyopia or hereditary color blindness of retinal origin. One subject with AD had glaucoma that had been successfully treated, and none had features suggesting visual variant of AD [8,51].

The relationship between gender and disease among participants was non-significant (Fisher's exact test of 0.249). Of 65 total participants, 36 were male (55.4%) and 29 female (44.6%); of 43 with AD, 26 were male (60.5%) and 17 female (39.5%); and of the 22 controls, 10 were male (45.5%) and 12 female (54.5%). There was no significant difference between groups with respect to age ($P = 0.393$) or education level ($P = 0.119$).

Both groups participated in the same tests of visual and cognitive function. The tests were administered by trained technicians blind to experimental hypotheses. Viewing was binocular and subjects wore their glasses for all procedures. Informed consent was obtained in accord with institutional guidelines at the University of Iowa.

2.2. Visual function assessment

We assessed static and dynamic (motion-related) visual functions. The former included static visual acuity (SVA, near and far), spatial contrast sensitivity (CS), stereopsis and color. Tests with a movement component included dynamic visual acuity (DVA) motion direction discrimination and structure-from-motion (SFM). We also measured aspects of visual attention (divided, selective and sustained attention) and processing speed, as described below.

2.2.1. Static visual functions

2.2.1.1. Visual acuity. Observers viewed stationary Sloan letter shapes [98] of varying size at maximal contrast (black letters against a white background) on a Snellen card (at near) and a wall chart (at far). Shape identification performance provides an index of spatial resolution ability.

2.2.1.2. Spatial contrast sensitivity (CS). CS was assessed using a Pelli chart [75]. This test provides a measure of low to medium spatial frequency sensitivity, i.e. near peak CS function.

2.2.1.3. Stereopsis. On the Titmus Test, observers view disparate stereopairs reproduced as polarized vectographs. Polarized spectacles allow presentation of a different image to each eye. Dependent measure is stereoacuity.

2.2.1.4. Color. On the standard Pseudoisochromatic Plates, Part 2 (SPP2 [42]) subjects view 12 pseudoisochromatic plates made of colored circles of different size, hue and lightness. Consistent differences from background by color alone define a target figure such as a letter, number or shape. Red–green and blue–yellow (tritan) defects are assessed. Participants are asked to identify the target figure in each plate, or else to

trace any perceived pattern with their finger. This precludes mistaking an abnormal performance due to alexia or related defects of pattern perception for a color vision defect.

2.2.2. Movement perception

Motion perception testing demands stimuli that minimize inferences of movement from noticeable changes in the visual scene (i.e., the way we "see" the moon move across the sky). Computer-generated animation sequences, called random dot cinematograms (RDC), are ideal for this purpose. RDC present a motion signal amid spatially random background noise and allow variation of spatial displacement and temporal intervals at programmable exposure durations. We used RDC to test the perception of motion direction and structure-from-motion (SFM) as in previous studies [65,66,84]. With these stimuli, perception of motion relies on local neural mechanisms that correlate luminance displacements over time [106,108] and broader mechanisms that integrate the local motion vectors to determine an overall direction of global flow. We also measured the effects of movement on ability to identify two-dimensional target shapes [98] in a test of "dynamic acuity" (DA) where RDC were not used, and form and contour cues would be conspicuous if the shapes were stationary [83].

2.2.2.1. Motion direction discrimination. The RDC animation sequences for this task contained 13 frames depicting 150 randomly placed, small ($2' \times 2'$) black dots moving within a $4^\circ \times 4^\circ$ region upon a computer screen. To generate the apparent motion, each dot was displaced a small constant distance between frames. A proportion of dots (signal) was displaced in a single direction (up, down, left, or right). The remaining dots were given displacements from a flat distribution of directions spanning 360° to create background noise. Displacement of each signal and noise dot by a 10-min arc each 15 ms gave a stimulus velocity of approximately 11°/s. The observer was asked to indicate the perceived direction of the motion in the stimulus after viewing a 195 ms stimulus presentation. Performance was assessed by determining the minimum signal proportion necessary to generate coherent motion in a particular direction. A lower signal proportion indicates that the motion processing mechanism is better able to integrate local dot movement vectors into a coherent global flow. This task cannot be completed by scrutinizing individual dots because dots are small, frame and stimulus durations are brief, and assignment of each dot to the signal or noise distribution varies between frames. Low dot density minimizes the possibility of accidental correspondence and prevents unreliable masking of the motion signal by the noise [16,110]. Similar stimuli have been used by other investigators to study motion perception both in monkeys and in humans [2,60,69,96].

To begin each trial subjects fixated a small cross at the center of the monochrome monitor. Stimuli were presented at fixation or 5° into one of the four visual quadrants. Trials were initiated by the experimenter after the subject fixated the small central cross. The subject indicated the direction of signal motion in each stimulus, guessing if necessary. Responses were verbal or gestural and were recorded on the computer by the experimenter.

The ratio of signal to noise dots was varied within a method of constant stimuli, and used RDC stimuli ranging from 5% to 35% signal presented in a predetermined random order. Subjects completed 60 trials at each level of signal tested. Subjects who had trouble at these signal levels were tested with stimuli from 20% to 80% signals. From percent correct performance at each signal level, threshold (defined as 62.5% correct for a four-alternative forced-choice task) was determined using probit analysis. Normal, uncompromised motion perception requires about 12% for threshold performance in young observers [66], and about 40% signal (with stimulus duration of 495 ms) in "motion blind" patient LM [84].

To ensure that all participants could complete the psychophysical procedures, indicating no overt behavioral deficit to preclude subsequent testing of motion perception, an analogous static direction discrimination screening task was employed. To determine if subjects could report the uniform direction with the brief stimulus durations used in this task, stimuli were presented comprising 15 small ($24' \times 10'$), computer generated, like-oriented arrows. To ensure that subjects could perform the motion perception task with moving stimuli, a final screening procedure involved the presentation of high-signal (90–100% signal) RDC. Both screening tests used the same psychophysical procedures as the actual motion perception experiment described above.

2.2.2.2. Structure from motion. Perception of SFM or kinetic depth is a long-hypothesized real-world use of motion perception [31,64]. To quantify this ability, we used a two-alternative forced-choice shape identification task in which the observer reported the shape of the object presented in each trial. Accurate performance on this task depends on the observer's perception of the figure's structure (shape) from motion. The SFM figures were a random-dot sphere and a random-dot cube canted 45° about the x- and z- axes to stand on a corner. The figures rotated about either the horizontal or the vertical axes. The two SFM stimuli were of comparable size (about 2.8° VA in diameter) but could be easily distinguished by the SFM cues. Random dot movement (noise) was added to a square

background region surrounding the target, both to prevent shape identification from non-motion cues (e.g., edges or dot density) and to index the difficulty of the task. The background comprised 1000 small (2′ × 2′) white dots moving about randomly at 3°/s within an 8° square region. To this background were added the "signal" dots, which, when in motion, depicted a rotating SFM figure. For instance, 10% signal would mean that the SFM stimulus was depicted by 100 dots moving amongst the 1000 background dots. Initial testing showed that all participants could perceive 3D-SFM in these stimuli and make the discriminations required in this task with 100% signal and 0% background noise. In the subsequent experiment, the signal was varied between 5% and 35% using the method of constant stimuli. Each subject completed 24 trials at each signal level. In each trial, the subject viewed one complete revolution of the figure, lasting 5.4 s. From the percent correct performance at each signal level, threshold (defined as 75% correct for a two-alternative forced-choice task) was determined using probit analysis. In cerebral akinetopsic subject LM, this threshold (25–30% signal) is greatly elevated compared to controls [84].

2.2.2.3. Dynamic visual acuity (DVA). The ability to resolve detail in moving objects is an important ability in daily life that differs from the ability to perceive global structure from independent local motion vectors (as in the SFM task implemented in Experiment 2). The former ability is termed dynamic visual acuity and can be measured by procedures similar to static visual acuity testing [18,41,54,57,62]. Static visual acuity is measured by presenting stationary shapes of varying size at maximal contrast, generally black letters against a white background, as on a Snellen chart. Observers identify these stationary shapes to obtain an index of spatial resolution ability. We implemented a dynamic version of this task on the Macintosh computer, presenting moving Sloan letter stimuli [1,30,98]. These high (100%) contrast letters were viewed from 4 m with stimulus size ranging from 20/125 to 20/5. Letters moved across the screen from left to right and back again. Stimulus duration was 1.0 sec and velocity was 5.2°/s. Subjects were seated to view the computer screen with both eyes open as in Experiments 1 and 2. Testing started at 20/50. As on a static acuity test, a subject correctly identifying five letters proceeded to the next acuity level (20/45). This procedure was repeated until the subject could no longer get five letters correct. If a subject could not get five letters correct on the starting 20/50 line, the procedure was repeated at increasing letter sizes (as occurred in 1 person with AD). Acuity was expressed in terms of best level at which five letters were correctly identified (e.g., 20/25) as on Snellen testing. Group acuity scores were similarly expressed with a fixed numerator (of 20) and a variable denominator (means [SD]).

2.2.3. Visual attention

2.2.3.1. Useful field of view (UFOV). UFOV was assessed with the Visual Attention Analyzer, Model 2000 (Visual Resources, Inc.). This microprocessor-based instrument uses three subtests to provide a reliable measure of UFOV size, expressed in terms of percent of reduction (0–90%) of a maximum 35° radius field [4,5]. The first subtest assesses speed of visual processing (SP) by identifying the stimulus duration corresponding to the 75% correct identification of a target (the silhouette of a car or a truck) presented at fixation. The second subtest assesses the ability to divide attention (DA) and requires identification of the central target as well as localization of a simultaneously presented peripheral target at three eccentricities (10, 20 and 30°). The third subtest assesses selective attention (SA) ability and requires these same two responses (also at different stimulus durations), but the peripheral target is embedded among distracters (triangles). All three subtests are presented on a large video monitor at a viewing distance of 23.5 cm. Targets are presented at high contrast (99%), and subtend 5.1° × 3.2°. For subtest 1, minimum duration that subjects can perform the task with 75% correct is noted. For subtests 2 and 3, the best fitting line reflecting the relationship between eccentricity and localization errors is computed for each test duration, and UFOV size is defined as the eccentricity at which a subject can localize the peripheral target 50% of the time. Performance in the subtests is combined to arrive at three scores representing extent of difficulty with regard to speed of processing, divided attention, and selective attention. These scores range from 0 (no problem) to 30 (great difficulty). Deficits in each of these abilities have been shown to be additive in their effect on UFOV size [4]. Therefore, to summarize UFOV performance, the three scores are combined to yield a score between 0 and 90 that represents % reduction of a maximum 35° radius field.

2.2.3.2. Starry Night task. This procedure tests a subject's ability to detect transient "on" and "off" signals presented to both hemifields [85,86]. Performance depends on an observer's visual sensory function and ability over time to sustain visual attention across a spatial array. Target events comprise the onset (appearance, A) or offset (disappearance, D) of a small (0.44 mm) white light target presented against a black background at maximal contrast on a 14″ diagonal monitor. The target is embedded among many identical and spatially random distracter elements, creating a display that resembles a starry night. To start the pro-

cedure, the observer (seated 30 cm away from the monitor) fixates on a small cross located in the center of the monitor. A trial begins after the observer indicates that he or she is ready. Each trial consisted of 200 consecutive target events that occurred one at a time, at unpredictable intervals and locations throughout the display. Observers are asked to respond as quickly as possible to these events by pressing a key. This response triggers a computer clock for determinations of reaction time (RT) and accuracy of the responses. The Starry Night display contains 1000 elements (''stars''). The occurrence of A and D events is unpredictable to the observer, and is designed to keep the total number of elements in the display within ± 3 elements during each trial. Each trial lasts approximately 5–10 min, depending on the response pattern of the observer. Any response between 100 and 2000 ms after an event is regarded as a hit. If there is no response within 2000 ms it is regarded as a miss. Any response following a hit or miss in the absence of a new event is a false positive (FP). Any response within 100 ms after an event is also an FP as that response was probably initiated prior to the sensory event. Signal detection theory is used to analyze the pattern of responses [100]. This provides the most reliable index of observer accuracy, independent of bias to respond. The d' measure assesses the difference between the probability that an observer will report an event given signal-plus-noise (present in the environment and in the nervous system) vs noise alone. The higher the d' measure, the greater the ability to detect signal. d' is derived from % correct (hits) and % FP responses using the Elliott tables [27].

2.3. Cognitive assessment

All subjects participated in a battery of standardized neuropsychological tests assessing a range of cognitive functions [28,29,102]:

2.3.1. Temporal Orientation (TO)

Identify the current date, day of week, and time of day. Deviation from the correct answer is quantified (raw score) [10].

2.3.2. WAIS-R Information (INFO)

Answer questions from one's fund of general knowledge (e.g., history, geography) [109] (age-scaled score).

2.3.3. Controlled Oral Word Association (COWA)

In a brief period of time, generate as many words as possible in response to a specific letter cue. This places demands on language, memory, executive functions, and processing speed [9] (scores corrected for age and education).

2.3.4. WAIS-R Digit Span (DIGIT)

Repeat aurally presented digit strings of increasing length, placing demands on immediate memory. In the second part, the digits are repeated in reverse order, placing demands on working memory [109] (age-scaled score).

2.3.5. Complex Figure Test (CFT) — Copy

Using paper and pencil, copy a complex geometric figure. This places demands on visuospatial and visuoconstructional abilities [52] (raw score).

2.3.6. Facial Recognition Test (FRT)

With no time constraints, match complex visual stimuli (black and white images of partially masked unfamiliar faces) in the context of highly similar foils. This places demands on perceptual discrimination ability [10] (scores corrected for age and education).

2.3.7. Benton Visual Retention Test (BVRT) — Revised

View simple geometric figures for 10 seconds, then draw those figures after they are removed from sight. The figures become increasingly complex, placing demands on immediate visual memory and working memory [97] (number correct, raw score).

2.3.8. WAIS-R Block Design (BLOCK)

Under a time constraint, analyze a visual display and reproduce a pattern with blocks [109]. This task tests visuoconstructional ability and provides a reliable measure of nonverbal intellectual capacity that is highly correlated with Performance IQ [52,99] (age-scaled score).

2.3.9. Trail Making Test (TMT)

Part A: draw a continuous line sequentially connecting the numbers 1–25 in a random array on a page. Part B: draw a continuous line alternating between numbers and letters (e.g., 1–A–2–B, etc). These tasks place demands on visual search, speed of processing, and divided attention, and require cognitive flexibility and planning [80] (scaled score equivalent of raw score).

2.3.10. Overall cognitive impairment

To gauge overall cognitive impairment, a composite score was developed [83]. Standard T-scores (mean = 50, SD = 10) were assigned to each of nine tests from the neuropsychological assessment battery (part B was used from the TMT). Standardization of the scores allowed us to generate an equally weighted composite score due to homogeneity of variance of each test score. These nine standard scores were combined into a composite variable called ADSTAT.

3. Results

3.1. Visual function assessment

3.1.1. Static visual functions

There were no significant differences (Wilcoxon 2-Sample Test) between participants with AD and control subjects in static visual acuity measured at near (20/27.3 [11.7] vs 20/26.6 [8.4], $P = 0.69$) and at far (20/27.7 [16.7] vs 20/26.1 [10.3], $P = 0.91$). CS was slightly lower in the AD group (1.75 [0.22] vs 1.84 [0.21], $P = 0.04$). There was also no significant difference in stereoacuity between the AD and control groups (150.2 [230.4] vs 71.4 [78.0], $P = 0.31$). Individuals with AD performed worse than controls on the SPP2 color plates (18.4 [6.2] vs 20.8 [6.7]; $P = 0.009$).

3.1.2. Movement perception

The control subjects required 17.6% (median) signal (mean = 20.6%, SD = 8.3) to correctly determine the direction of signal dot movement at threshold. The 43 AD subjects varied widely in their abilities and required 22% (median) signal (mean = 24.7%, SD = 20.4) at threshold. Some AD subjects performed well and others poorly, as reflected in the high SD, but as a group they did not perform significantly worse than the controls (Wilcoxon 2-Sample Test, $P = 0.19$).

The 43 participants with AD tested with the SFM task required 18.1% signal (mean) at threshold (median = 13.6, SD = 15.4). The 21 controls tested required 9.3% signal (mean) at threshold (median = 9.2, SD = 3.1; Wilcoxon 2-Sample Test, $P < 0.001$).

Introduction of motion into the visual acuity task produced similar effects in both study groups. Consequently, there is no significant difference in dynamic acuity between the AD and control group (20/33.5 [17.3] vs 20/30.7 [9.8]; Wilcoxon 2-Sample Test, $P = 0.69$), just as there was no difference between these groups in static acuity (see above).

3.1.3. Visual attention

The group with AD showed more than twice the total UFOV loss (UFOVTOT) compared with controls (69.9% [SD = 22.2%] vs 31.9% loss [SD = 9.3%]). The difference is highly significant (Wilcoxon 2-Sample Test, $P < 0.001$). This included worse performance on SP (17.5 [13.3] vs 1.6 [4.7]), DA (23.1 [9.6] vs 5.0 [6.0]), and SA (29.4 [1.9] vs 25.3 [4.1]) subscores (Wilcoxon 2-Sample Test, $P < 0.001$, all cases). Participants with AD showed lower true sensitivity than control subjects on the Starry Night test ($d' = 0.53$ [1.62] vs 1.97 [1.20]; Wilcoxon 2-Sample Test, $P < 0.001$). Observers with AD also had longer RT for hits (541.6 [203.6] vs 498.0 [113.3]), but this was not significant ($P = 0.10$). They also had more FP responses (21.8 [28.4] vs 7.0 [10.4]; Wilcoxon 2-Sample Test, $P = 0.044$).

3.2. Cognitive assessment

Subjects with AD performed significantly worse than the controls on all indices and showed greater variability of performance, as anticipated on a battery of tasks sensitive to cognitive decline in AD (Figs. 1 and 2). Mean scores in the AD group fell in the range of mild to moderate impairment [52,99], including defective performance on tests with substantial visuoperceptual demands such as the CFT, FRT, VRT, WAIS-R Block Design, and TMT. As expected, the group with AD had worse overall cognitive status, indicated by significantly lower ADSTAT scores ($P < 0.001$).

When adjusted for gender, all but one of the comparisons represented in the Figure retained P-values < 0.05. (The exception was DIGIT, which went from $P = 0.014$ to the borderline value of $P = 0.050$.) The only significant interaction between gender and disease status occurred for COWA ($P = 0.013$), where AD status was predictive for males (AD mean [SD] of 26.4 [11.0] vs 43.6 [10.0] for controls), but not for females (AD and control group means [SDs] of 37.7 [13.9] and 39.7 [8.1]), respectively. So, overall, gender was not an important factor in our results.

3.3. Relationships between vision and cognition

To assess relationships between visual and cognitive decline, we examined correlations between vision and cognitive variables in the 43 participants with AD. We found a number of significant ($P < 0.05$) correlations

Table 1
Spearman correlation coefficients: ADSTAT by visual functions in observers with AD and in all subjects

	AD group	All subjects
Static		
SVA(N)	−0.40	−0.26
SVA(F)	−0.41	−0.28
CS	0.35	0.44
Stereo	−0.42	−0.37
Color	0.39	0.46
Dynamic		
MDD	−0.34	−0.39
SFM	−0.44	−0.53
DA	−0.34	−0.31
Attentional		
SP	−0.67	−0.75
DA	−0.55	−0.76
SA	−0.37	−0.61
UFOVTOT	−0.73	−0.82
d'	0.52	0.60
RT	−0.10	−0.25
FP	−0.24	−0.36

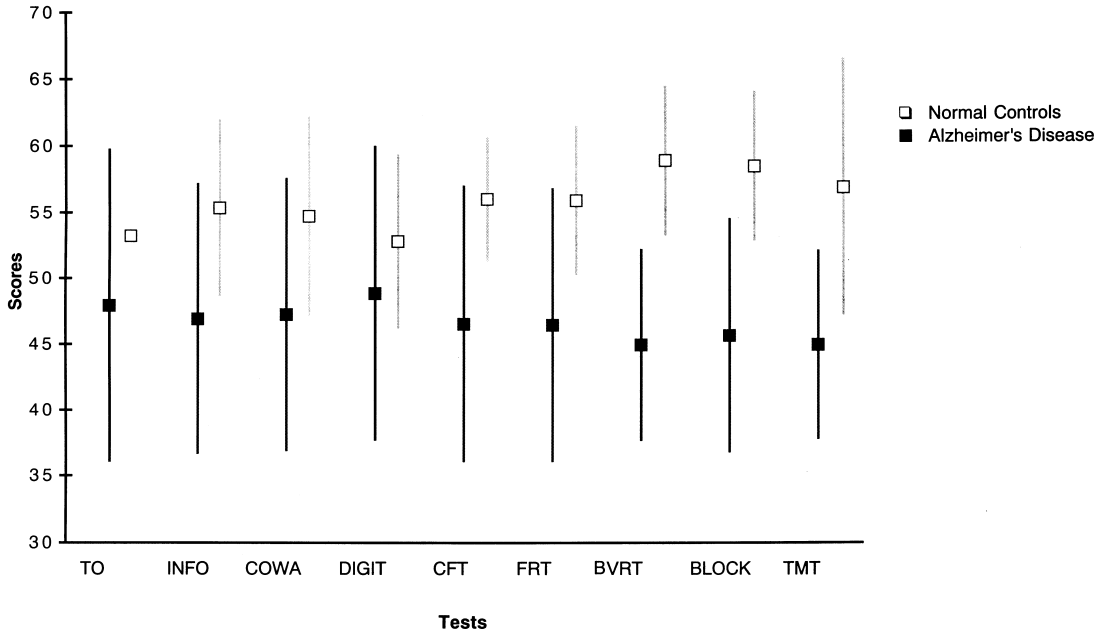

Fig. 1. Performance (T-scores) on a battery of standardized cognitive tests is shown in the group with Alzheimer's disease (AD, open squares) and in participants without dementia (closed squares). Bars denote 1 SD above and below the means. The AD group performed worse on all tests ($P < 0.001$ all cases, except Digit $P = 0.014$). Scores for the AD group fell in the range of mild to moderate impairment.

between visual function impairments and overall cognitive function (ADSTAT) in participants with AD (see Table 1). For example, a strong correlation was found between ADSTAT and SFM ($r_s = -0.53$). That is, the amount of signal needed for threshold discrimination of SFM increases with cognitive decline. Perception of motion direction also correlated with overall cognitive impairment ($r_s = -0.34$), although as a group, the par-

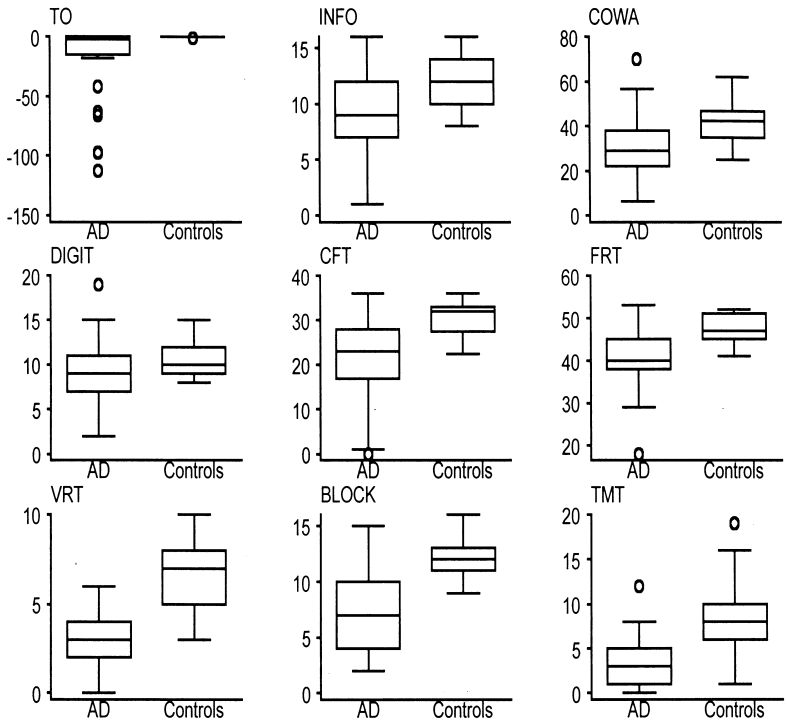

Fig. 2. Boxplots illustrating distribution of cognitive tests in AD and control groups.

ticipants with mild AD performed similarly to the normal controls on this task ($P = 0.19$). UFOVTOT was also strongly correlated with ADSTAT ($r_s = -0.73$) (and with SFM, $r_s = 0.47$). Thus, UFOV size decreases in conjunction with overall cognitive decline in AD due to reductions in speed of processing, divided attention and selective attention. Similarly, overall cognitive decline was well correlated with reduction in true sensitivity (d') on the Starry Night Test ($r_s = 0.52$). Overall, the findings are compatible with the report of Cronin-Golomb et al. [22] that visual dysfunction occurs in conjunction with progressive cognitive deficits in AD.

4. Discussion

In line with our hypothesis, the findings indicate that AD affects visual functions while sparing several basic visual sensory functions. Compared to controls, participants with mild AD showed significant impairments of visuospatial construction, higher visual perception and memory (WAIS-R Block Design, CFT-copy, FRT, VRT, TMT) and processing of complex motion (SFM). They also showed significant reductions on multiple measures of attention. On measures of static visual acuity, stereoacuity or DVA, however, there were no significant differences between participants with AD and controls ($P > 0.05$). One static visual sensory score that differed significantly was color, assessed with the SPP2 plates, compatible with Cronin-Golomb et al. [25] who demonstrated color deficiencies in AD on the City University Color test. There was also a small decrease in static CS that was marginally significant. Motion direction discrimination showed greater variability, but the performance of participants with AD as a group did not differ significantly from that of the controls, compatible with the report by Mendola et al. [60]. These findings can be interpreted in light of current evidence on the organization of the visual system and the neuropathology of AD.

4.1. Visual pathway pathology in AD

4.1.1. Subcortical deficits

Previous studies of AD have emphasized degeneration of optic nerve fibers arising from "broad band" retinal ganglion cells [39]. These cells have large receptive fields and are thought to contribute to a psychophysical "transient" channel [44] or M-pathway that conveys motion signals to the visual cortex via magnocellular layers of lateral geniculate body (LGB). However, a "broad band" pathway deficit alone does not explain the impairments we measured in observers with AD on tasks that require processing of stationary patterns and color. The latter functions are thought to rely upon a "sustained" or P-pathway that arises from small retinal cells (P-cells) with color-opponent properties and slow conducting axons, and connects with the visual cortex via parvocellular (P) layers of the LGB [53,92]. Also, it is unclear how a retinal "broad band" deficit can explain relative sparing of motion direction discrimination compared with SFM in AD. Kurylo et al. [48] and Mendola et al. [60] described perceptual profiles in AD that also could not be adequately explained by a retinal broad band defect. This is not surprising, given the range of visual system neuropathology now described in AD.

4.1.2. Cerebral pathways

AD causes multi-focal neuronal degeneration affecting visual areas in the occipital, temporal and parietal lobes [7,17,19,50,61,63,68,77]. Subcortical regions such as pulvinar [45] that process visual information [70,76,87,88] are also affected. Resulting patterns of visual dysfunction can be interpreted within the heuristic framework of "2 visual systems" [104].

Impairments of color and pattern processing and identification found in this study of AD conform to lesions of a "ventral" or "what" pathway thought to depend on ventromesial structures in the occipital lobe and adjacent temporal areas [26,81]. Cronin-Golomb et al. [22] suggested that AD predominantly affects ventral visual pathways from post-hoc analyses showing more performance variance on tests of object recognition (Gollin Incomplete Pictures, Stroop Test, Picture Arrangement, copying complex Geometric Figures, Raven's Matrices) than of spatial localization (Mental Rotation and Road Map tests) [22,173].

Kurylo et al. [48] drew similar conclusions in AD using eight tests with "specificity in measuring functions either of the dorsal stream" (Mental Rotation task, Money-Road-Map Test, Stick Test, Discrimination of Spatial Position test) "or ventral visual stream" (FRT, Mooney Closure Faces, WAIS-R Picture Arrangement, Discrimination of Complex Pictures test). Eleven observers with AD showed greater variability and worse performance on all except the Money Road-Map and Spatial Position tests. Kurylo et al. [48] also asserted that the pattern of visuoperceptual impairment "does not support the notion of parietal hypoperfusion" in AD, yet they did not assess cerebral blood flow or metabolism, and parietal hypoactivity has been repeatedly demonstrated in studies applying functional neuroimaging in AD [17,68,74,77]. Also, the assignment of tests to dorsal and ventral pathway categories in the Kurylo and Cronin-Golomb studies can be questioned.

The results of this study are compatible with the hypothesis that mild AD produces both ventral and dorsal visual pathway deficits, not just one or the other. Decline of visuospatial processing, visuomotor coordi-

nation (e.g., BLOCK, CFT-copy, TMT) and SFM found in the current study of AD supports dysfunction in a "dorsal" or "where" pathway. This pathway includes portions of visual association areas 18 and 19 above the calcarine fissure and extends onto dorsal and lateral surfaces of the hemispheres including a human homolog of the area MT (V5) complex and portions of the parietal lobe. Note that SFM is thought to involve occipital and parietal cortices and to be encoded by area MT neurons in primates [15,112,113]. Visual motion regions (including MT and parietal regions) in humans respond more to 3D motion than to simpler motion stimuli [71]; lesions in these areas can impair SFM [79,84,105], as measured in this study of AD, and possibly optic flow perception, as measured in AD by Tetewsky and Duffy [101].

4.2. Visual function and cognition decline in AD

We found that impairments of visual functions correlate with overall severity of cognitive impairment in AD. For example, good correlations with cognitive impairment were observed for SFM and color. Overall severity of AD was also strongly correlated with shrinkage in the useful field of view due to reduced speed of processing, divided attention and selective attention, and also with reduced true sensitivity (d') on the Starry Night Test. Of note, we found only a weak correlation between RT on the Starry Night task (which depends strongly on motor speed) and ADSTAT ($r = -0.10$). Gordon and Carson [34] suggested that RT slowing was sensitive to early AD due to changes in sensorimotor and decision components, whereas our data suggest that motor slowing plays a lesser role. Also, SFM and UFOVTOT, which were highly correlated with overall cognitive status, were also correlated with each other and compatible with hypothesized relationships between motion, attention and feature processing in human vision [55,56].

Our findings resemble those of Cronin-Golomb et al. [22] who assessed the relation between vision and cognitive performance in 72 subjects with AD, although missing data posed a problem in that study. Rather than entering raw data into a correlation matrix for regression analysis, the investigators constructed a correlation matrix where each number was based on available data on a given pair of variables and used this matrix as input to a regression procedure. They warned that "because this procedure did not use raw data ... interpretation of results in terms of statistical significance was problematic" [22, p. 171].

Kéri et al. [43] suggested that "early" visual impairment (of static and dynamic CS) in AD is independent of visuocognitive and memory disturbances ($n = 20$, mean age = 72.8, mean MMSE = 21.6, SD = 6.3). In that study, vision testing was limited and the investigators administered just one cognitive task (the Enhanced Cued Recall Test) outside the MMSE screen. Similarly, Kurylo et al. [48] found that the scores of the AD patients on their eight "vision" tests did not correlate significantly with information obtained from patients and relatives on a questionnaire tool aimed at defining changes in capacity, habits and personality (the Blessed Dementia Rating Scale, mean score 11.9, range 0–21). From these findings they suggested that "visual dysfunction does not follow overall disease progression but instead reflects the heterogeneous nature of the pathological change" in AD. This differs from Cronin-Golomb et al. [22] and the current findings, perhaps because Kurylo et al. [48] performed no assessment of cognitive function outside this brief screening tool, and because of small sample size ($n = 11$). We think that differences between patients probably do reflect variable distribution of neurodegenerative changes in occipital, temporal and parietal cortices in AD.

Our results are broadly compatible with those of Pietrini et al. [77], who studied cerebral glucose metabolism using PET in 32 patients with AD, 10 with marked visual symptoms. Compared to 25 healthy controls, both AD types showed reduced metabolism in parietal and temporal (middle and superior) regions. Patients without visual symptoms also showed metabolic reductions in inferior temporal, frontal and limbic structures. Patients with visual symptoms had greater deficits than those without in the parietal and occipital lobes (including primary visual cortex) and showed relative sparing of inferior temporal, frontal and limbic regions. Both AD groups performed worse than the controls on visuospatial functioning (Extended Range Drawing Test, Block Tapping Span) and visual perception (FRT). In general, patients with visual symptoms performed worse on these tasks than those without, but had better memory. The investigators concluded that AD patients with visuospatial deficits "have a distinctive regional distribution of cerebral metabolic impairment that is related to specific cognitive deficits."

4.3. Mechanisms

A few basic mechanisms can help explain the links found between visual and cognitive decline in AD: impaired separation of signal-from-noise, undersampling and generalized slowing. Normal signal perception relies on cerebral mechanisms to filter out background noise arising from scenes, eye jitter and neurons. Lesions in visual association cortex can impair these operations [1,79,84,105]. Kurylo, Corkin and Growdon [47] found abnormal sensitivity to background noise in 16 subjects with AD performing on a shape discrimination task and inferred higher visual

dysfunction at the level of global perceptual organization; we found similar effects in AD of background noise upon SFM. Another mechanism that could reduce signal-to-noise ratios in AD is "undersampling," where loss of receptors or neurons allows processing of only a portion of available signals without necessarily reducing background noise, as hypothesized by Hess and Anderson [38] in congenital amblyopia. Slowing is a simple mechanism that can alter information processing at multiple levels in the CNS [13] and cause adverse effects on complex tasks [20,21,36,90]. Decline in visual temporal resolution is a type of slowing reported in aging [14,94] and AD [23] and can affect perception of movement. Slowing can also be regarded as a decline in "energetic" aspects of attention [67], and together with other deficits of attention found in this study of AD, it can shrink the UFOV, hamper visual search, and increase the risk of injury in activities of daily life [3,72,107]. Finally, visual decline could be a factor in the cognitive performance of aged adults who do not meet criteria for dementia. Berry et al. [12] found that improvement in visual acuity (after cataract surgery or treatment of refractive error) was associated with improved scores on the MOMSSE (short version of the Dementia Rating Scale) when adjusted for depression, age and general health.

5. Conclusions

Vision impairment is the presenting complaint in a small minority of patients who later manifest neurodegenerative disease [8,78,82,93]. A "visual variant" of AD [51] is reported in a small proportion of cases and is well known since its description in the late 1980s [8]. This uncommon subtype of AD (aka posterior cortical atrophy) presents with severe visuoperceptual and visuomotor impairments [35,40,59] resembling the "minor forms of Bálint syndrome" described by Hécaen and Ajurriaguerra [37] in patients with stroke or tumor. These patients may represent the extreme end of a continuum of involvement in visual cortical areas, with most AD patients showing less but still significant visual dysfunction. We describe here the general occurrence of deficits in visual functions in patients who meet standard criteria for probable AD who are not presenting with visual complaints.

The data in our study group suggest that visual dysfunction is a regular finding in the general population of older patients with mild to moderate intellectual decline due to AD. We cannot exclude the possibility that decreased cognitive ability may contribute to reduced performance on visual function tests. The non-visual cognitive demands of these tasks are minimal, however, and participants with AD performed similarly to normal controls on several tests of basic sensory function with comparable demands on language and memory.

Cronin-Golomb et al. [22] indicated that visual dysfunction is a "significant predictor of cognitive dysfunction in AD" and "may have a strong functional impact on cognitive domains." This study provides confirmation and further detail in terms of the range of visual function deficits identified. A better understanding of visual function deficits in AD could help clarify the basis of functional deficits in some activities of daily life and suggest practical solutions for optimizing the visual environment in patients with different stages of the disease.

Acknowledgements

This work was supported by NIH PO NS19632 and CDC R49/CCR710136.

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