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We examined performance of healthy older and younger adults and individuals with Alzheimer's disease (AD) and Parkinson's disease (PD) on digit cancellation, a task putatively sensitive to cognitive impairment, but possibly affected by visual impairment, particularly in contrast sensitivity. Critical contrast thresholds were established to create custom stimulus arrays that were proximally matched across individuals. Age- and PD-related differences in search were fully accounted for by the sensory deficit. Increased contrast benefited AD patients, but could not override cognitive impairment. We conclude that visually fair neuropsychological testing can effectively compensate for normal age- and PD-related visual changes that affect cognitive performance.

Keywords: vision, contrast sensitivity, aging, Alzheimer, Parkinson

Neuropsychological evaluations are administered to a large extent visually, but assessments of the visual capacities of the person whose cognition is being evaluated are rarely performed. Many older individuals undergoing cognitive assessment may have concomitant visual dysfunction, some of it related to normal aging (Carman, 1997; Jackson & Owsley, 2003; Owsley, 2011; Spear, 1993) and some of it to specific age-related disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). Because impairments in basic vision can predict deficits in visual cognition (Cronin-Golomb, 1995; Cronin-Golomb, Corkin, & Growdon, 1995; Cronin-Golomb, Gilmore, Neargarder, Morrison & Laudate, 2007; Gilmore, Cronin-Golomb, Neargarder, & Morrison, 2005; Mapstone, Steffenella, & Duffy, 2003; Mendez, Tomsak, & Remler, 1990; Rizzo, Anderson, Dawson, Myers, & Ball, 2000), visual deficits should be considered when administering assessments dependent on vision and visual cognition.

The need to conduct neuropsychological assessment of domains such as cognition and especially memory in individuals with possible or probable AD is obvious. Patients with PD also may present with impaired cognitive function even at the early stages of the disease. When compared with the general population, their risk of dementia is five to six times higher (Ibarretxe-Bilbao, Tolosa, Jungue, & Marti, 2009). Currently, a number of standard neuropsychological tests are used to examine cognitive functioning in AD and PD and are sensitive to cognitive decline. One test that is often used to assess visual attention and concentration, and is instrumental in the diagnosis of AD, is digit cancellation.

Mohs and colleagues (1997) conducted a large multisite study to identify tests for the Alzheimer's Disease Assessment Scale (ADAS) that would be useful in measuring early signs of cognitive impairment. The only test that met their criteria for reliability and sensitivity to cognitive change over time was digit cancellation. While overtly simple, the task requires effective employment of multiple information-processing components such as encoding, memory, visual search, concentration, and visual attention (Neisser, 1964; Lezak, 1984). Mohs and colleagues reported that the test

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was quite sensitive to dementia status and therefore was a valuable addition to the ADAS, which is widely used in studies evaluating cognitive performance in AD (Knopman, 2008; Mielke et al., 2009; Schneider et al., 2009). What was unknown was the extent to which basic visual deficits accounted for performance on the digit-cancellation task and hence, to what extent the task assesses visual dysfunction rather than, or in addition to, cognition.

One of the strongest predictors of dysfunctional visual cognition is a decrease in contrast sensitivity, as occurs in AD (Cronin-Golomb et al., 1991; Cronin-Golomb, Corkin, & Growdon, 1995; Cronin-Golomb et al., 2007; Gilmore et al., 2005; Gilmore & Levy, 1991; Neargarder, Stone, Cronin-Golomb & Oross, 2003) and PD (Amick et al., 2003; Bodis-Wollner et al., 1987; Davidsdottir, Cronin-Golomb, & Lee, 2005; Davidsdottir, Wagenaar, Young, & Cronin-Golomb, 2008; Seichepine et al., 2011; Uc et al., 2005). We have shown that the speed of letter identification by AD, PD and healthy older adults is strongly related to stimulus contrast (Amick et al., 2003; Cronin-Golomb et al., 2007; Gilmore, Thomas, Klitz, Persanyi, & Tomsak, 1996) and that contrast sensitivity is related to dementia severity (Cronin-Golomb et al., 1991; Cronin-Golomb et al., 2007). It is reasonable to assert that persons with deficits in contrast sensitivity would be challenged on a cancellation task. Indeed, it may be hypothesized that the poor performance of AD and PD patients on cancellation tasks may be due to their visual deficits rather than or in addition to higher-order, visual information-processing problems. To test this hypothesis, we examined a digit-cancellation task under several levels of stimulus contrast to ascertain the extent to which the test's sensitivity to cognitive dysfunction is related to the participant's contrast sensitivity. The approach was to evaluate performance under two extreme levels of contrast to determine if contrast affected digit cancellation. A method was established to test task performance at a contrast level that was set for each individual participant in order to match individuals on the proximal strength of the stimuli. If differences among groups in digit-cancellation performance are due to differences in contrast sensitivity, then in the proximally matched condition, the groups should perform equivalently.

Method

This project was part of a dual-site study of vision and cognition in aging and neurodegenerative disorders. Recruitment and test procedures and analytic methods were standard across the two sites of the study, Boston University and Case Western Reserve University.

Participants

Participants included 12 individuals with probable AD (6 men, 6 women), 12 healthy older control participants matched to the AD group for age (OC-AD, 5 men, 7 women), 14 individuals with PD without dementia (8 men, 6 women), 14 older control participants matched to the PD group for age (OC-PD, 8 men, 6 women), and 12 younger adult control participants (YC, 6 men, 6 women). The AD patients were recruited from the Boston University Alzheimer's Disease Center and day health centers in Lowell and Medford, MA, and from University Hospitals' Alzheimer Center in Cleveland, OH. These individuals met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann et al., 1984). We recruited participants with idiopathic PD from the Parkinson's Disease and Movement Disorders Center of the Department of Neurology of Boston Medical Center, and from local PD support groups. The OC-AD and OC-PD participants were from the general communities surrounding Boston and Cleveland. The YC participants were students at Boston University and Case Western Reserve University.

Analyses (t test for homogeneous variances) revealed that the AD and OC-AD groups were comparable in age, $t(22) = -.22$, $p = .83$, and that the OC-PD and PD groups were comparable in age, $t(26) = .03$, $p = .976$. Mean age, M_{age} (standard deviation, *SD*) was 75.3 (8.3) years for AD, 74.6 (6.6) for OC-AD, 64.1 (5.4) years for PD, 64.1 (7.1) for OC-PD, and 19.8 (1.4) for YC. There were group differences in education, $F(4, 59) = 5.59$, $p = .001$. Follow-up analysis indicated that the OC-AD group had a higher education level ($M = 15.8$, $SD = 1.6$) than the YC group ($M = 14.1$, $SD = 1.4$) and the AD group ($M = 13.5$, $SD = 2.9$). The OC-PD group had a significantly higher education level ($M = 16.6$, $SD = 1.7$) than the YC group only. We note that the YC group was composed of current college students who are expected to have a higher terminal than current education level. Current education correlated with performance on digit cancellation at the 69% contrast level for AD participants ($r = -.58$, $p < .05$) and was included as a covariate in subsequent analyses.

OC-PD, OC-AD, AD, and PD participants were given the Modified Mini-Mental State Examination (MMSE) (Teng & Chui, 1987) to assess overall mental status, except for one OC-PD and three OC-AD, who had the standard MMSE (Folstein, Folstein, & McHugh, 1975). Modified MMSE scores were converted to the standard MMSE scale ranging from 0–30, with lower scores reflecting more severe cognitive impairment. The range for OC-PD, OC-AD and PD was 26–30, and the range for AD was 11–22. The mean score for the OC-AD group was 28.4 ($SD = 1.5$), for the OC-PD group was 29.1 ($SD = 1.4$), for the PD group was 28.0 ($SD = 1.3$) and for the AD group was 18.7 ($SD = 4.6$).

Participants were administered a health-history questionnaire to establish that they were free of medical abnormalities. No participant met or exceeded predetermined cutoff scores on measures of depression, including the Beck Depression Inventory II (cutoff = 14; Beck, Steer, & Brown, 1996) for YC, and the Geriatric Depression Scale (cutoff = 17; Yesavage, 1988) for the other groups. All were free of any psychiatric disorders as determined from medical reports. Motor-symptom severity of PD was quantified using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr (H & Y) staging (Hoehn & Yahr, 1967). UPDRS mean total score was 23.5 ($SD = 8.2$). Median H & Y stage was 2. OC-PD, OC-AD, AD, and PD received a detailed neuro-ophthalmological examination to rule out visual disorders arising from dysfunction of the anterior pathways, including cataracts, glaucoma, and macular degeneration. All participants of these groups received this examination except for one OC-AD, one OC-PD, one PD, and three AD who had scheduling difficulties. There was no difference in participant characteristics between those who did and did not receive the eye examination. YC reported no history of significant abnormalities in vision or eye health.

Study methods were reviewed and approved by the Institutional Review Boards of Boston University, Case Western Reserve University, and the University Hospitals Case Medical Center. All individuals gave informed consent. Exclusion criteria included: (a) being a non-native speaker of English; (b) presence of any serious, uncorrected eye condition such as glaucoma, cataracts, or double vision; (c) coexisting, serious, chronic medical illnesses (including psychiatric or neurological), (d) use of psychoactive medication besides antidepressants and anxiolytics in the PD or AD groups; (e) use of any psychoactive medications in the control groups; (f) history of intracranial surgery; (g) head trauma resulting in loss of consciousness; (h) history of drug and alcohol abuse, and (i) dementia (for all groups except AD).

Participant characteristics are provided in Table 1.

Procedures

Testing was conducted in a room with controlled lighting, illuminated by two lamps, each with a 150-W General Electric light-bulb, connected to a voltage regulator to minimize variability. The lighting in the room was approximately 90 cd/m^2 at eight inches from the center of the monitor, halfway between the participant and the monitor.

A digit masking task was used to identify the critical contrast level (CC) necessary to identify a very briefly presented digit with 80% accuracy. The task permitted the assessment of the contrast needed to identify the specific stimuli used in the digit-cancellation task. Participants were seated 16 in from a computer monitor and a chin rest was used to minimize movement. Two horizontal fixation points (16 mm in length) were presented in the center of the computer screen. A number between 1 and 9 appeared between the two fixation points for 35.5 ms and participants orally identified the number. The examiner recorded the verbal responses by keyboard. The first number displayed was at a high contrast. Correct responses decreased the contrast of subsequent numbers, while incorrect responses increased the contrast. A parameter estimation method (Xue & Wilson, 1998) was used to obtain a threshold. This threshold is considered the individual's CC for identifying a digit. Stimuli presented at each person's CC provided proximal matching across individuals.

In the digit-cancellation test, after practice tasks the touch screen displayed eight rows of digits, with digits ranging from 1 to 9. Participants searched for the target digits 4 and 9 and touched each target with their preferred hand. There were three to seven targets in each row. Sixty seconds were allowed for the search. The total number of possible targets was 40 with twenty 4s and twenty 9s per trial. One trial was given for each contrast condition. Scores were calculated by subtracting total incorrect responses and as-needed task reminders from total correct responses. A task reminder consisted of reminding the participant of the correct target numbers they should be looking for and selecting.

The task was administered under three contrast conditions: 22%, 69%, and the proximal match condition. In the latter condition, the CC obtained for the individual was used. The digits appeared as gray elements on a black background. To control for order effects, the conditions administered were randomized across participants.

Results

Contrast Sensitivity for Digit Identification

The CC is a direct measure of the stimulus-specific contrast sensitivity for identifying digits. CC values obtained during the masking task were significantly different between groups, $F(4, 59) = 13.7$, $p < .001$. AD participants required a mean contrast of 60.7% (*SD* 19.3). PD participants required a mean contrast of 47.9% (*SD* 21.1) The OC-PD, OC-AD and YC groups required mean contrasts of 31.7% (*SD* 12.8), 42.1% (*SD* 22.0) and 12.1% (*SD* 5.1), respectively. Paired comparisons with Bonferroni correction for multiple comparisons demonstrated significant differences between groups. The range of contrast sensitivities among the groups illustrates the challenge faced by PD, OC-PD, OC-AD and AD participants in identifying digits relative to the YC. The CC value obtained from an individual was used as the contrast for that person in the proximal match condition of the digit cancellation task.

Digit Cancellation

Contrast effects. The effects of contrast and group membership were analyzed with a mixed-model ANOVA. Contrast (22% and 69%) affected performance on the digit-cancellation task for each group. As shown in Figure 1, each group yielded better performance under the high contrast (69%) condition than the lower contrast (22%) condition, $F(1, 59) = 10.7$, $p = .002$. The groups differed in their level of performance, following the expected pattern of superior performance by the YC with their mean performance of 32.4 digits at 22% contrast and 34.7 digits at 69% contrast, and poorest scores among the AD group with mean performance of 13.0 digits at 22% contrast and 17.3 digits at 69%

Table 1
Participant Characteristics

	Age in years, mean (*SD*)	Male : Female	Education in years, mean (*SD*)	MMSE, mean score (*SD*)	Beck Depression Inventory, mean score (*SD*)	Geriatric Depression Scale, mean score (*SD*)
YC ($n = 12$)	19.8 (1.4)	6 : 6	14.1 (1.4)	N/A	1.9 (2.7)	N/A
OC-AD ($n = 12$)	74.6 (6.6)	5 : 7	15.8 (1.6)	28.4 (1.5)	N/A	1.9 (1.7)
AD ($n = 12$)	75.3 (8.3)	6 : 6	13.5 (2.9)	18.7 (4.6)	N/A	7.8 (4.4)
OC-PD ($n = 14$)	64.1 (7.1)	8 : 6	16.6 (1.7)	29.1 (1.4)	N/A	4.9 (5.0)
PD ($n = 14$)	64.1 (5.4)	8 : 6	16.6 (1.7)	28.0 (1.3)	N/A	5.6 (3.1)

Note. MMSE = Modified Mini-Mental State Examination scores, converted to standard Mini-Mental State Exam equivalent; YC = Younger adult control participants; OC-AD = Older control adults, matched to AD; AD = Alzheimer's disease participants; OC-PD = Older control adults, matched to PD; PD = Parkinson's disease participants. *SD* = standard deviation.

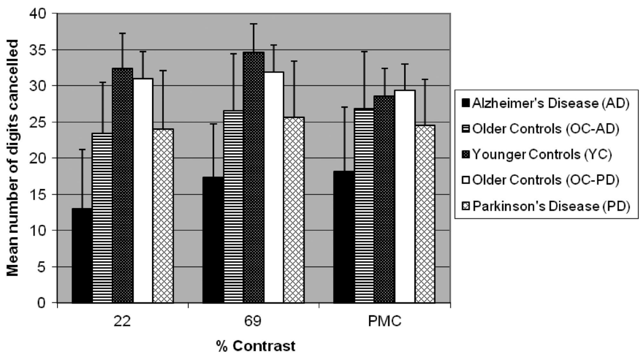

Figure 1. Mean number of digits cancelled in 60 seconds in the three conditions. Error bars show standard deviations. PMC = Proximal Match Condition, in which stimuli were presented at the critical contrast measured for each individual to yield 80% accuracy for a briefly presented digit. OC-AD = Older control adults, matched to those with Alzheimer's disease; OC-PD = Older control adults, matched to those with Parkinson's disease.

contrast (each out of a maximum of 40 digits), $F(4, 59) = 19.0$, $p < .001$. There was no interaction between contrast and group, $F(4, 59) = 0.7$. The null effect suggests that the five groups were affected equally by the contrast manipulation.

Post hoc tests with Bonferroni adjustment demonstrated an interesting age effect among the YC and both healthy older control groups. The older OC-AD group, which was 10.5 years older than the OC-PD group, yielded fewer digit cancellations. By contrast, the younger OC-PD group had a performance level that was not significantly different from the YC group. This pattern of age effects suggests that marked slowing in digit cancellation appears in healthy individuals late in life. In evaluating the clinical groups, we found that the PD group (which was younger than the AD group) had a significantly higher cancellation score than the AD group. Beyond age effects, the results demonstrated that the clinical groups showed additional impairment in performance. When the AD and PD groups were compared with their respective older control groups that were matched for age, each clinical group exhibited significantly poorer performance.

Proximal match effect. A between-group ANOVA was used to analyze performance in the proximal match condition where groups were matched for proximal stimulus strength. While there was a significant effect of group, $F(4, 59) = 6.2$, $p < .001$, a comparison of groups with Bonferroni correction demonstrated that the YC, OC-PD, OC-AD and PD groups yielded cancellation scores that were not different. The PD group's score was not significantly different from that of their age-matched comparison group. It was the AD group whose performance was different from the other groups. Proximally matching the stimuli across individuals eliminated the age effect on digit cancellation but not the impact of AD (see Figure 1).

Discussion

Implicit in the design of the study was the assertion that the strength of a stimulus will affect performance on a visual-search task. The finding was very clear that the distal contrast level of the digits affected the speed with which the targets could be found.

Given this result, it is reasonable to expect that persons who have a deficit in contrast sensitivity will perform more poorly on the digit-cancellation task because the proximal strength of the stimuli is reduced by their vision deficit. Indeed, the pattern of performance among the groups in both digit cancellation and contrast sensitivity, as assessed with the digit-masking task, was the same. YC had the best performance on both measures and the AD group had the poorest performance. Of course, this simple, monotonic relation does not demonstrate a causal relation between poor contrast sensitivity and digit cancellation, but it is consistent with such a relation.

The use of proximally matched stimuli provided a strong test of the hypothesis that poor performance on digit cancellation is related directly to the contrast sensitivity deficit of the participants. The stimuli were shown to each participant at the contrast level determined for him or her to yield a criterion level of performance when viewing briefly presented stimuli. The use of this criterion-based contrast level was expected to produce stimuli that were matched for proximal strength across participants. The proximal match condition was designed to compensate for the contrast-sensitivity deficit of each individual and to make the task equally challenging for each participant. The extent to which group differences were modified by the use of proximally matched stimuli would indicate the role of contrast sensitivity in driving group differences on the digit-cancellation task.

In the proximal match condition, the difference between the age groups (YC, OC-PD, OC-AD) was not significant. It was striking that the age effect, which was so apparent in the comparisons of the groups when the 22% and 69% conditions were used, was absent under this condition, as was the effect of PD relative to its control group. This finding suggests that the poorer digit cancellation by the older control adults and PD participants was due in large part to their weaker contrast sensitivity and not to a deficiency in organizing an efficient visual search of the array. The AD participants, however, continued to perform more poorly than all control groups and the PD group even when the stimuli were proximally matched. It appears that the poorer performance of the AD group must be linked to their inefficient visual-search ability.

It has been suggested that testing participants at a high contrast level should compensate for their contrast-sensitivity deficit. The present study demonstrates the limitation of such an approach. A fixed, distal, high-contrast stimulus processed by a visual system that is deficient will still result in a lower proximal contrast than that stimulus processed by an intact system. Consequently, if the efficient processing of the stimulus in the task is affected by the contrast of the stimulus, as in digit cancellation, then there will still be performance differences among groups in both high- and low-contrast conditions, as illustrated in this study. This is why there was no interaction between the group and contrast (22% and 69%) conditions.

One may postulate that a certain level of proximal contrast is required for efficient stimulus processing in a task. Beyond that level there would be no gain in performance by increasing the stimulus contrast. The present study did not attempt to determine that point of asymptote in the contrast by task-performance relation. A goal of the present study was to show simply that the strength of a stimulus affects performance on a speeded visual-search task. A weaker stimulus may require more time to encode, or may result in a feature representation that is poorer for efficient visual search. Gilmore, Spinks, and Thomas (2006), in evaluating age differences on performance of a coding task, also reported that degradation of stimuli hampered visual search. In assessing PD patients on performance of a backward masking task of letter identification, we found that performance improved when the contrast level of the target stimulus was enhanced (Amick et al., 2003; Davidsdottir et al., 2008). The impact of a sensory deficit in contrast sensitivity needs to be taken into account when evaluating performance on cognitive tests. While the proximal match condition did not eliminate the digit-cancellation performance deficit of the AD participants, performance of the healthy older adults and PD patients with reduced contrast sensitivity was normalized relative to younger adult performance by compensating for the visual deficit. PD patients have been shown to have deficits in contrast sensitivity when compared to age-matched control participants and nevertheless were able to overcome this deficit and perform comparably to the control groups in the proximal-match condition. By contrast, the AD patient is burdened by the sensory deficit in addition to the impact of the illness on their more cognitive information-processing abilities, as we have further demonstrated recently with a more naturalistic task (playing Bingo) on which AD patients improved in performance when stimulus contrast was enhanced (Laudate et al., 2011).

Our findings indicate that it is necessary to take into account the sensory capability of individuals in order to validly evaluate their cognitive ability. Further, it is important to recognize that in healthy older adults and individuals with PD without dementia, putative cognitive deficiency may in fact be accounted for by correctable sensory impairment. Conversely, the use of cognitive assessments that are visually easy to process may mask age-group or neurological-group differences that are apparent under normal, more visually challenging conditions (Seichepine et al., in press). Our findings provide new information about the sensory and perceptual deficits of healthy older adults and individuals with AD and PD, and also direct attention to possible nonpharmacological methods of visual intervention to improve cognition. A next step in the development of visually fair neuropsychological testing will be to determine the point of asymptote in the contrast by performance relation, as described above—that is, the level of proximal contrast that is required for efficient stimulus processing, beyond which contrast level there would be no further improvement in performance. The ultimate goal is to enable older adults, clinicians, researchers, and patient caregivers to identify visual deficits that may be ameliorated through vision-based interventions, which in turn may boost memory, cognition, and daily function.

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