Color Discrimination Performance in Patients with Alzheimer's Disease

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Key Words

Alzheimer's disease • Color discrimination • Cognitive impairment • Perceptive/sensory disturbance

depend upon cognitive impairment, and involvement of the primary visual cortex and/or retinal ganglionar cells may be contributory.

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Abstract

Background/Aims: Visual deficits are frequent in Alzheimer's disease (AD), yet little is known about the nature of these disturbances. The aim of the present study was to investigate color discrimination in patients with AD to determine whether impairment of this visual function is a cognitive or perceptive/sensory disturbance. **Methods:** A cross-sectional clinical study was conducted in a specialized dementia unit on 20 patients with mild/moderate AD and 21 age-matched normal controls. Color discrimination was measured by the Farnsworth-Munsell 100 hue test. Cognitive functioning was measured with the Mini-Mental State Examination (MMSE) and a comprehensive battery of neuropsychological tests. The scores obtained on the color discrimination test were compared between AD patients and controls adjusting for global and domain-specific cognitive performance. **Results:** Color discrimination performance was inversely related to MMSE score. AD patients had a higher number of errors in color discrimination than controls (mean $\pm$ SD total error score: 442.4 $\pm$ 84.5 vs. 304.1 $\pm$ 45.9). This trend persisted even after adjustment for MMSE score and cognitive performance on specific cognitive domains. **Conclusions:** A specific reduction of color discrimination capacity is present in AD patients. This deficit does not solely

Introduction

Alzheimer's disease (AD) is a degenerative disorder of the central nervous system characterized by early and prominent impairment of episodic memory followed by a reduction of other cognitive functions [1]. AD patients frequently present with visual problems, such as visual agnosia, impaired stereoacuity and disorders of visual-spatial processing [2]. In patients presenting with early and marked visual impairment, a specific profile of the disease, called the 'visual variant' of AD, has been described. Although these patients may have no ophthalmologic or retinal abnormalities, they exhibit early reading deficits, as well as blurred and reduced vision [3].

The capacity of seeing requires integrity of sensation, perception and the activation of stored memories to form conscious experiences (recognition) [4]. Sensation and perception are cortical and subcortical functions, requiring the activation of primary visual cortical areas [4]. Recognition is a purely cortical function consequent to the activation of associative areas devoted to cognition [4]. This raises the question of whether visual impairment in AD patients is due to the degeneration of the

brain areas involved in cognition [5] or to alterations in either the primary cortical areas or the subcortical regions involved in sensation and perception [6]. Some evidence supports the idea that there may be a specific involvement of the sensory visual system. A primary retinal involvement appears plausible since cholinergic and glutamatergic systems are impaired in AD [7]. In the retina, light-activated photoreceptors transmit signals to bipolar and ganglionar cells via glutamate and aspartate neural transmission. Furthermore, amacrine cells, which are specifically involved in chromatic light stimulus transmission, utilize acetylcholine as a neurochemical mediator [7].

A certain degree of cell loss in retinal ganglions and the macula and lateral geniculate nucleus is normal during aging [8], and visual disorders in the elderly might derive from damage in these structures. However, in AD patients, both visual disorders and cell loss are correlated with the severity of dementia and are more evident than in healthy elderly individuals [8–11].

Color discrimination involves the capacity to distinguish between chromatic shadings. It is a visual function that is minimally dependent on cognition, as it does not directly require recognition of colors [4]. Thus, it is a good candidate to determine whether an involvement of peripheral visual structures is present in patients with AD. Deeper knowledge of visual and color discrimination deficits in AD could help diagnosis, interpretation of cognitive performance and potential interventions in patients with the disease. The aims of the current study were to detect differences in color discrimination performance between AD patients and cognitively healthy controls and to assess whether deficits in color discrimination performance are due to cognitive disturbances in AD.

Methods

Subjects

Twenty patients with probable AD and 21 normal control subjects were included in the study.

Individuals with AD were patients at the multidisciplinary dementia unit of the Institute Fondazione Santa Lucia in Rome, Italy. All patients underwent extensive clinical examination including thorough neurological and somatic examination by a specialized neurologist or geriatrician and extensive neuropsychological examination by a trained psychologist. AD was diagnosed according to the NINCDS-ADRDA criteria [12]. We excluded individuals with noncompensated somatic illnesses, a history of a psychiatric disorder, color blindness, severe cranial trauma, focal neurological signs or magnetic resonance imaging examinations

Table 1. Demographic characteristics of the study population and performance on neuropsychological tests

	AD patients (n = 20)	Controls (n = 21)
Demographic characteristics		
Age, years	73.0 ± 5.6	71.8 ± 5.4
Years of education	10.6 ± 4.8	10.5 ± 4.4
Global cognitive performance		
MMSE score	19.4 ± 3.5	27.3 ± 2.0
Verbal memory		
Rey's 15-word recall: immediate	21.2 ± 7.9	39.9 ± 8.2
Rey's 15-word recall: delayed	1.5 ± 2.2	9.0 ± 2.7
Prose Memory recall: immediate	1.8 ± 2.3	6.3 ± 1.4
Prose Memory recall: delayed	1.0 ± 1.7	6.0 ± 1.5
Digit Span Forward	4.7 ± 1.0	5.3 ± 0.8
Spatial memory		
Rey's Figure: immediate recall	4.2 ± 4.9	15.6 ± 5.5
Rey's Figure: delayed recall	1.5 ± 3.2	15.6 ± 5.0
Corsi Span Forward	4.0 ± 0.9	4.6 ± 0.9
Praxis		
Rey's Figure: Copy	21.3 ± 10.5	32.3 ± 5.5
Copy of Drawings with Landmarks	9.3 ± 1.6	48.8 ± 20.7
Copy of Drawings without Landmarks	10.8 ± 1.3	66.2 ± 3.3
Executive functions and attention		
Attentive Matrix	35.2 ± 9.9	48.2 ± 9.4
Wisconsin Card Sorting Test	3.0 ± 4.0	5.1 ± 1.2
Trail Making Test A	157.0 ± 98.2	46.2 ± 27.7
Trail Making Test B	240.2 ± 121.5	92.8 ± 60.4
Phonological Verbal Fluidity	19.1 ± 10.4	31.6 ± 9.9
Digit Span Backward	2.9 ± 1.5	3.9 ± 1.0
Corsi Span Backward	2.7 ± 1.8	4.2 ± 1.2

Results are shown as means ± SD. A significant difference ($p < 0.05$) between AD patients and controls was found on all variables except Digit Span Forward and Corsi Span Forward (analysis of variance considering age and sex as covariates).

suggestive of cerebrovascular disturbances. Ten male and 10 female AD patients were included in this study. Control subjects included healthy volunteers recruited from the general population (8 men and 13 women). The demographic characteristics of the study participants are shown in table 1.

AD patients had mild to moderate disease severity, with a Mini-Mental State Examination (MMSE) [13] mean score of 19.4 ± 3.5 . Control subjects had an MMSE score of 27.3 ± 2.0 . An ophthalmologic evaluation showed that patients and controls had normal visual acuity (6/10 far vision and I/II character near vision; refractive defects were corrected with lenses when necessary); the fundus oculi examination was normal in all subjects.

Color Discrimination Assessment

Color discrimination was evaluated with the Farnsworth-Munsell 100 hue test [14]. This test is performed using 85 color plates of equal saturation; each plate is subdivided into 4 boxes

Cognitive domains	Neuropsychological tests	Anatomical correlates
Verbal memory		
Short-term memory	Digit Span Forward Rey's 15 words and Prose Memory: immediate recall	frontoparietal lobe
Long-term memory	Rey's 15 words and Prose Memory: delayed recall	temporal lobe
Visuospatial memory		
Short-term memory	Rey's Figure and Corsi Span Forward: immediate recall	temporal lobe
Long-term memory	Rey's Figure: delayed recall	frontoparietal lobe
Praxis	Copy of Rey's Figure Copy of Drawings with and without Landmarks	fronto-parieto-occipital lobe
Executive and attentive functions	Wisconsin Card Sorting Test Attentive Matrices Trail Making Test Phonological Fluency Digit Span Backward Corsi Span Backward	frontoparietal lobe

Fig. 1. Neuropsychological tests used to measure deficits of specific cognitive functions in AD, and anatomical localization of the functions.

containing, respectively, plates with shadings of red, green, blue and yellow. The examination is carried out on a surface that is perpendicularly illuminated with a MacBeth Easel Lamp, 1,000 lx, located at a distance of 50 cm. The examiner shows each box of plates separately; the individual plates are distributed randomly on the desk and the subject has to reorganize them according to progressive chromatic tonality. The plates are numbered according to increasing tonality (i.e. from red to green to blue and to yellow). An error score is calculated for each plate as the sum of the absolute value of the difference between the individual plate number and the numbers of the plates that immediately precede and follow it. The total error score is calculated as the sum of the single scores for each of the 85 plates; therefore, subjects who order the plates perfectly obtain a total error score of 170 [15]. We also calculated a partial error score for red-green and blue-yellow colors. The total minimal error score possible in each 2 color spectra is 84 for red-green and 86 for blue-yellow [15].

In this study, the test was administered in the monocular modality. However, a high correlation index (i.e. over 0.95) was found between the right and left eyes in both AD patients and controls, and thus the mean value of the scores obtained for each eye was considered for each patient.

Neuropsychological Assessment

We evaluated the global cognitive performance of our subjects using the MMSE. We also investigated the specific cognitive domains that are often compromised in AD using a battery of neuropsychological tests (fig. 1). Test scores were adjusted for age, sex and education.

Short- and long-term verbal and visuospatial memory were investigated using immediate and delayed recall of Rey's words and figure [16–19], the immediate and delayed recall Prose Memory Test [20] and the Digit Span Forward Test [21].

Praxis-constructive capacities were evaluated with the Copy of Rey's Figure [20] and with the Copy of Drawings with and without Landmarks [19].

Executive functions that represent the capacity of planning, set shifting, reasoning and inhibition were evaluated with the Trail Making Test [22], the Phonological Verbal Fluidity Test [19], the Wisconsin Modified Card Sorting Test [23] and the Digit and Corsi Span Backward tests [21]. Attention, which involves the posterior parietal cortex and the heteromodal prefrontal cortex, was studied with the Attentive Matrices Test [24].

Ethics

The study protocol was approved by the Ethical Committee of the Santa Lucia institute. All the studied subjects and relatives of the patients gave their informed consent to participate in the study.

Data Analysis

Data were analyzed using SPSS, version 15.0. Five steps were taken in the analyses, as described below.

(1) To compare color discrimination performance between normal subjects and AD patients, we carried out a multivariable analysis of covariance, with age and sex as covariates.

(2) To determine whether there was a correlation between MMSE score and color discrimination performance, we calculated a Spearman correlation index for the entire group (AD subjects and controls).

(3) An analysis for repeated measures was carried out to evaluate whether color discrimination differences between patients and controls were specific for 1 of the 2 color spectra of blue-yellow and green-red.

(4) In order to examine whether general cognitive deficits were associated with color discrimination performance, we compared

Fig. 2. Color discrimination differences between AD patients and controls. Comparison of 2 color spectra from the Farnsworth-Munsell 100 hue test (F-100).

Fig. 3. Correlation between color discrimination performance and global cognitive performance in AD patients and controls.

AD patients' and control subjects' scores on the Farnsworth-Munsell 100 hue test, considering MMSE score as a covariate.

(5) Similar analyses of variance were carried out using performance on all specific cognitive domain tests as covariates. We calculated a covariate-adjusted mean difference on Farnsworth-Munsell 100 hue test scores between patients and controls.

Results

The characteristics of the study population are shown in table 1, including mean test performance on all of the neuropsychological tests. As expected, AD patients had significantly poorer performance on most cognitive tests.

Compared to controls, AD patients had significantly higher total error scores on the test for color discrimination (mean $\pm$ SD: 442.4 $\pm$ 84.5 vs. 304.1 $\pm$ 45.9; $p < 0.05$). The differences between AD patients and controls were almost identical for the 2 color spectra (blue-yellow, green-red; fig. 2). For the blue-yellow spectrum, the mean performance for AD patients and controls was 237.6 $\pm$ 51.6 and 167.9 $\pm$ 34.4, respectively. For the green-red spectrum, the mean score was 204.9 $\pm$ 39.7 for AD patients and 137.9 $\pm$ 15.3 for controls. Furthermore, the analysis of variance did not show any significant interaction between color (blue-yellow/green-red) and group (AD patients/controls) ($p = 0.794$). In other words, the difference between the patient and control groups was the same for the 2 color spectra.

Figure 3 shows that the scores on the color discrimination test were inversely correlated with MMSE score ($r = -0.78$); the lower the MMSE score, the higher the number of color discrimination errors. This correlation was evident in AD patients as well as in normal controls. Five AD patients obtained color discrimination scores in the lower range of those obtained by control subjects. A possible explanation is that some controls exhibited a certain degree of mild impairment on the color discrimination test.

The mean crude difference between the color discrimination test scores in normal controls and AD patients was 138.3 (table 2). When adjusted for MMSE score, the difference was almost halved (76.1), but remained significantly higher than 0. As the MMSE measures global cognitive performance, this result suggests that the reduced color discrimination capacity of AD subjects is only partly explained by their global cognitive impairment. We examined this further by comparing the difference in the color discrimination test scores of AD patients and controls with additional adjustment for specific cognitive test performance. These adjusted differences were all lower than the crude differences and higher than those adjusted for MMSE scores (table 2). The crude and adjusted differences were almost identical for tests of verbal memory, whereas differences between crude and adjusted estimates were large for tests exploring executive functions and attention.

The differences in scores estimated by adjusting for impairments in specific cognitive domains all significantly differed from 0; that is, the impairment in color discrimination observed in AD patients was not explained by alterations in the specific cognitive domains. This result suggests that the reduced color discrimination capacity observed in AD patients is not due to their reduced memory, spatial, praxis, executive and attentive capacities.

Discussion

In patients with mild to moderate AD, we found a reduced color discrimination capacity that was only partly explained by the severity and characteristics of their cognitive impairment. Color discrimination impairment in AD is not a purely cognitive problem but seems to be related to damage of the structures responsible for sensation and/or perception of color stimuli.

Previous studies have reported contradictory results; some authors found no differences between AD patients and controls [25], while others found reduced color discrimination capacity in AD patients which was unrelated to the severity of dementia [26, 27]. In the current study, patients with mild to moderate AD were compared with control subjects of the same age. Our findings revealed a more severe visual disturbance in AD patients than that expected in normal aging. MMSE scores correlated inversely with error scores on the color discrimination test, suggesting that color discrimination performance worsens with the severity of cognitive impairment. However, AD patients performed significantly worse than normal controls even after we adjusted for MMSE scores. This suggests that a significant part of the observed impairment in color discrimination in AD is not due to global cognitive decline. The AD patients' color discrimination performances were still worse than those of normal controls even when we took into consideration further adjustment for verbal memory, spatial memory, praxis, attention and executive functions. This finding suggests that the color vision impairment observed in AD patients is at least partly independent of global and domain-specific cognitive decline.

Considering that global and specific cognitive impairment is the expression of damage in the associative cortical areas devoted to cognition, our results are consistent with the idea that AD patients' color discrimination deficits depend on damage to the primary visual cortex and/or the visual subcortical structures (retino-geniculate-

Table 2. Differences between AD patients and controls on the chromatic discrimination test

	Difference in F-100 score (AD patients vs. controls)
Crude	138.3 ± 21.1*
Adjusted for MMSE score	76.1 ± 35.0*
Adjusted for cognitive performance on neuropsychological tests for	
Verbal memory ¹	102.0 ± 46.04*
Spatial memory ²	107.2 ± 42.9*
Praxis ³	86.8 ± 23.5*
Executive functions and attention ⁴	85.3 ± 36.6*

Results are shown as means ± SD. Differences are adjusted for scores on the MMSE and specific neuropsychological tests. F-100 = Farnsworth-Munsell 100 hue test. * $p < 0.05$.

¹ Rey's 15-word recall: immediate and delayed; Digit Span Forward; Prose Memory Test: immediate and delayed recall.

² Rey's Figure: immediate and delayed recall; Corsi Span Forward.

³ Rey's Figure: Copy; Copy of Drawings with and without Landmarks.

⁴ Attentive Matrix; Wisconsin Card Sorting Test; Trail Making Test; Phonological Fluency; Digit Span and Corsi Span Backward.

calcarine pathway). Some evidence from previous studies supports this conclusion. In AD patients, the visual associative areas (pericalcarine and inferotemporal cortex) are frequently affected by the pathological process, and the primary cortex is always involved [9, 10]. Damage of visual pathways in AD might be subcortical, involving the optic nerve, lateral geniculate nucleus and ganglionic cells in the retina [2]. In particular, in AD patients, the loss of ganglionic cells in the central retina is greater than that observed in healthy elderly subjects and is not age dependent [10]. This observation suggests that AD accelerates the normal rate of age-associated cell loss. Instrumental examinations support the existence of a pathological involvement of ganglionic cells, as the electroretinogram pattern is abnormal in AD patients [28] and the contrast-sensitivity thresholds are abnormally elevated [29]. This retinal damage might be specific to AD, as the transmission of signals from bipolar to ganglionic cells is modulated by acetylcholine, and cholinergic systems are primarily affected in AD [30].

Color discrimination is a visual function associated with a particular neural pathway called the P pathway. This pathway, which is part of the ventral visual pathway,

is already individualized at the retinal level as it starts from the parvocellular cells and reaches the inferotemporal cortex through the parvocellular layers of the lateral geniculate nucleus [31]. For this reason, retinal cell damage might cause impairment of color discrimination without involvement of the primary and secondary visual cortical areas.

One of the strengths of the current study was that we used the Farnsworth-Munsell 100 hue test to assess color discrimination. This visual test is particularly sensitive to mild disturbances [32]. In order to use the test, most cognitive capacities must be at least partially preserved. We believe it is crucial to use sensitive instruments to investigate visual function because even a 30–60% loss of ganglionar retinal cells induces minimal disturbances that may be overlooked during routine ophthalmologic examinations [33]. Another major strength of our study was the thorough and comprehensive medical and neuropsychological assessment carried out on all study participants.

However, this led to the inclusion of only a small number of participants. Despite the relatively small sample size, we were able to detect significant associations.

In conclusion, there is a color discrimination deficit characteristic of AD patients that is not related to normal aging and is only partially explained by cognitive impairment. It can likely be attributed to disease-specific damage of the retina or the parvo-retino-calcarine pathways.

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