

# Vision Screening for Alzheimer's Disease: Prevention from an Ophthalmologist's Perspective (There is More to Vision than Meets the Eye)

By Peter N Rosen, MD

## Abstract

Recent evidence suggests that memory impairment and vision impairment are closely linked in Alzheimer's disease and that special testing for vision impairment can improve early detection and treatment of dementia. Visual images, attention, memory, awareness, and salience are tightly bound together in the cerebral cortex; under normal circumstances, these functions perform seamlessly to produce a visual reality of the external world. Alzheimer's disease—now considered a chronic illness—unravels the fabric of reality woven together over a lifetime of experience: The disease produces disconnected threads of visual perception, memory, and cognition. The earliest neuroanatomic manifestations of this process begin in the limbic system and medial temporal lobe of the brain, areas critical for detailed visual perception and memory management. Thus, by using vision tests to detect impaired image formation and memory, vision care specialists can play a valuable role in secondary and tertiary prevention, as well as in early treatment of eye disease and dementia. In addition to reducing health care utilization, prevention can be expected to improve functioning and health-related quality of life.

*"It is no longer possible to divide the process of seeing from that of understanding ... nor is it possible to separate the acquisition of visual knowledge from consciousness."<sup>1,p 76</sup>*

## Introduction

Interest in early treatment and prevention of Alzheimer's disease (AD) has been fueled by the increased prevalence of AD in our aging population: AD currently affects approximately 10% of the population aged 65 years and older (four million people) and almost 50% of the people aged 85 and older. For persons with AD who receive at-home care, the mean cost of care provided by outside caregivers is about \$12,500 per year; and the mean cost of care is \$42,000 for persons with AD who live in nursing homes. Overall, approximately \$100 billion per year is spent in the United States for care of persons with AD.<sup>2</sup>

The most profound feature of AD is memory impairment, particularly in the early stages of AD.<sup>3-5</sup> Vision is also impaired in early AD,<sup>6-10</sup> although this feature is not widely recognized by most clinicians. Indeed, because cognitive and vision impairments are not widely recognized as closely linked, vision test-

ing and cognitive testing are not conducted at the same visit or by the same provider. This article presents new concepts of how visual perception occurs in the brain; explains the connection between vision impairment and memory impairment; discusses the importance of testing for visual risk factors in pre-symptomatic and early phases of AD; and suggests how such testing may help with secondary and tertiary prevention in AD.

## Links Between Impaired Vision and Impaired Memory in Alzheimer's Disease

Vision, memory, attention, and language are tightly bound together in the first years of life and support the ability to learn, communicate, and plan for the future.<sup>11,12</sup> Dementia in the last decades of life robs us of these essential human qualities and causes their associated processes to unravel. Memory impairment as shown by neurocognitive test results is associated with vision impairment in patients with early AD.<sup>8,10,13</sup> Evidence accumulated during the past decade supports the conclusion that deficits in short-term memory lead to impaired vision and thus result in failure to encode into

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recent memory new experiences of events and objects.<sup>17-19</sup> This evidence also supports the conclusion that the disconnect between visual perception and memory produces faulty cognition—inability to correctly interpret what is seen—and eventually causes difficulty with everyday tasks, including recognizing familiar faces and navigating familiar neighborhoods.<sup>17-19</sup>

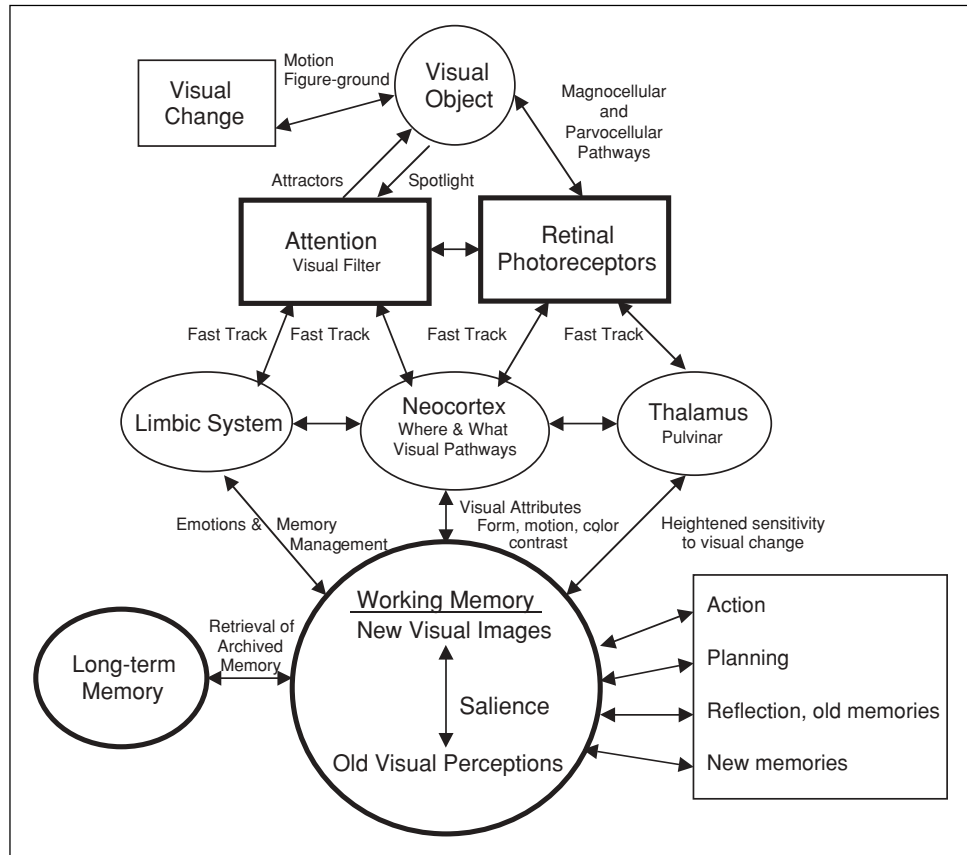
Indeed, memory plays a more central and interactive role in visual awareness than previously thought. “Working memory,” a form of short-term memory, mediates visual awareness by providing a real-time repository for current images received by the visual cortices and memories of similar objects, people, or places retrieved from long-term

memory.<sup>16</sup> Visual synthesis is a widely distributed brain function in which a “division of labor” is used to simultaneously perform different tasks (Figure 1).<sup>1,11,12,14-16</sup> More than 30 specialized areas throughout the association cortices perceive form, motion, contrast, color, depth, shape, spatial location, and other visual attributes. A virtual image is created that unifies and binds together different elements of vision from disparate areas of the brain into what has been called the “blackboard of the mind.”<sup>1,11,12,14-16</sup> Some neuroscientists view working memory as the blackboard which holds visual percepts (mental image) and other sensory inputs in conscious awareness, where these visual percepts remain available for

evaluating novel situations, detecting and evaluating change, and navigating the external world. “Working memory” gives the brain time to compare old and new images to determine the new images’ salience.<sup>1,12</sup> Combining what we see and knowing what we see is a process of cognitive integration largely dependent on memory. Visual consciousness results from seamless merger of synthesizing coherent visual images and understanding their meaning or salience.<sup>12</sup>

That vision and memory are inextricably linked is therefore not surprising. When memory is impaired, vision is suboptimal. Poor visual perception caused by eye disease (eg, cataracts or macular degeneration) contributes to impair-

**Figure 1. Illustration shows the “blackboard of the mind” concept as it relates to patients with Alzheimer’s disease**



ment in vision by distorting newly formed visual images held in working memory.<sup>1,11,12,14-16</sup> In the brain, visual synthesis is distorted by a failure of working memory to bind visual elements into a coherent image. A combination of poor image formation and failure to retrieve archived memories of the same or similar images results in poor vision. Diminished appreciation of salience or the ability to interpret visual percepts (mental images) results in failure to form sufficiently detailed new visual images and consequently memories of current objects and events.<sup>1,11,12,14-16</sup>

### Developmental Processes of Alzheimer's Disease: Paths to Early Detection and Treatment

Interest in early detection of AD has been stimulated by two factors: 1) modest treatment success recently achieved by use of medication and 2) improved understanding of the pathogenesis of AD. However, until the recent introduction of new types of medication, systematic screening for early AD was not recommended. Alzheimer's disease is now considered a chronic illness that begins decades before its earliest clinical manifestation.<sup>20-22</sup> In this regard, the process underlying AD is similar to that of atherosclerotic heart disease, a condition in which chronic imbalance exists between cholesterol production and cholesterol clearance. In patients with AD, a gradual-onset, chronic imbalance in production (versus clearance) of amyloid beta-protein leads to a slow rise in the steady-state levels of this protein in extracellular brain tissue;<sup>22</sup> this result causes a complex biochemical and inflammatory cascade that leads to synaptic failure, loss of synaptic plasticity, and eventual neu-

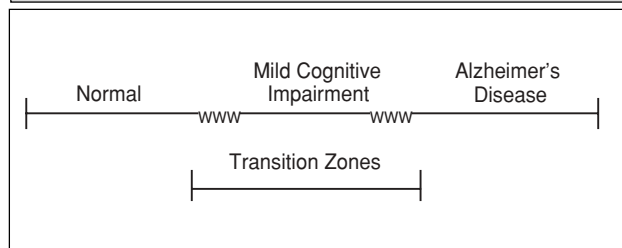
ronal degeneration manifested behaviorally as loss of memory and descent into dementia.<sup>22</sup>

The earliest pathologic changes in patients with AD occur in the entorhinal and perirhinal cortex, hippocampus, and medial temporal (MT) lobe of the brain.<sup>1,11,12,14-16</sup> These areas are considered to be "convergence zones" needed to process and consolidate newly formed visual images into long-term memory. Impairment of the limbic system prevents meaningful consciousness by impeding the brain's ability to determine what is currently salient and to lay down new memories for determining future salience.<sup>16</sup>

The behavioral evolution of AD begins with a slow transition from normal, age-appropriate cognitive functioning to mild cognitive impairment (MCI) characterized by memory deficits that exceed age-related loss.<sup>3-5,23,24</sup> MCI and early AD often remain undetected, because memory impairment may be interpreted by family, friends, and clinicians as age-related. Aggressive efforts at early detection are usually not undertaken, because effective medication for treating AD has only recently become available. As treatment aimed at the earliest genetic and biochemical phases of AD is developed, screening for preclinical AD will become more imperative.<sup>20,22</sup> Despite technologic advances such as genetic testing, imaging studies, and biochemical markers, diagnosis of AD depends largely on clinical assessment and on neurocognitive testing.<sup>25-28</sup> Most cognitive tests have reasonably high sensitivity and specificity and seek to detect memory impairment, particularly short-term "working memory."<sup>26</sup>

Clinical examination and neuropsychologic testing can distinguish patients with MCI (pure

**Figure 2. Transitions: Normal Aging, Mild Cognitive Impairment, Alzheimer's Disease**



*Adapted and reproduced by permission of the publisher and author from: Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001 Dec;58(12):1985-92.<sup>4</sup>*

memory deficit) from patients with probable or early AD,<sup>26,29</sup> but detecting the transition from normal aging to MCI, has proven more difficult (Figure 2)<sup>4</sup> because current tests lack sufficient sensitivity and specificity. For this reason, much effort has been directed toward discovering biomarkers to identify risk of preclinical (asymptomatic) AD.<sup>22</sup> Genetic testing, methods of structural and functional imaging (fMRI, PET, and SPECT scanning), and measurement of A $\beta$ 42 and Tau peptide levels in the cerebrospinal fluid all have shown promise but do not add incremental value to clinical examination results and neuropsychologic profiles.<sup>26,30,31</sup> Testing certain aspects of vision is a new area of early risk detection in AD that might be easily used by a wide variety of clinicians.

### Selecting Appropriate Vision Tests for Early Detection of Alzheimer's Disease

Many vision tests for early detection of AD are inexpensive and can be done quickly and reliably by a wide variety of clinicians other than vision care specialists.<sup>32,33</sup> Therefore, a major benefit of reliable and sensitive vision tests will be to substantially increase the number of clinicians able to screen patients for mild

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cognitive impairment and early AD. Further, these tests may prove to be more sensitive for initial screening, for evaluating disease progression, and for assessing treatment outcomes. Vision tests that are easily understood by patients and families and that are used by insurers, administrators, and regulators will expedite care and may lower costs.

The Benton Visual Retention Test can be used to predict statistically significant risk for AD as long as 15 years before onset.<sup>6</sup> Whether other

vision tests can produce similarly dramatic results is unknown. Vision tests (which detect impairment of vision and memory) are likely both to improve efforts at early detection and to be useful in secondary and tertiary prevention. Vision testing for early detection of AD is likely to be a fruitful area of future research.

However, vision tests done routinely by vision specialists (eg, tests of visual acuity and visual field) are generally not sensitive or specific in patients with early-stage AD. Visual acuity is a limited measure of true visual performance and is a poor predictor of complex, vision-dependent tasks that are likely to be impaired in patients with early-stage AD. For more than a decade, however, visual impairment in patients with AD has been known to include several well-defined deficits: contrast sensitivity; selective and divided visual attention; visual processing speed; and feature recognition of complex objects, particularly faces.<sup>6,8-10,13,19,32,34</sup>

More recently, use of the Benton Visual Retention Test has shown that poor visual memory might represent early expression of AD. Poor performance on this test has been associated with increased risk of AD as long as 15 years before diagnosis.<sup>6</sup>

Vision specialists have not used these tests, because the direct link between vision impairment and AD was not well understood and because more sensitive, potentially valuable tests for AD—tests of contrast sensitivity, visual attention, and facial feature recognition—were not yet available for use in clinical settings. These barriers to effective early detection of AD are being eroded because laser surgery for correcting refractive errors has renewed interest in these tests and because easily administered, computer-based methods are affordable and are widely available.

### Contrast Sensitivity Testing

Contrast sensitivity is the ability to detect different shades of gray. More specifically, contrast sensitivity is the difference in the amount of reflected light between an object and its background. Small differences in contrast result in high sensitivity. Because it allows us to differentiate objects when illumination is low, contrast sensitivity is a critical component of vision. Use of contrast-sensitivity testing has recently gained the interest of vision specialists as a sensitive measure of vision quality after refractive surgery. In a number of medical conditions, including cataracts, macular degeneration, and AD, contrast sensitivity may be substantially impaired even when visual acuity remains relatively good. This deficiency could result in substantial visual impairment under conditions of poor illumination, such as driving at night or in fog.

Contrast is most sensitive for distinguishing large objects and complex surface features (eg, people and faces). In this range of vision, patients with AD have selectively diminished contrast sensitivity, whereas normal aging results in diminished contrast mostly at higher visual acuities. The Pelli-Robson test is commonly used to measure contrast sensitivity in clinical care and research settings (Figure 3).

### Visual Attention Testing

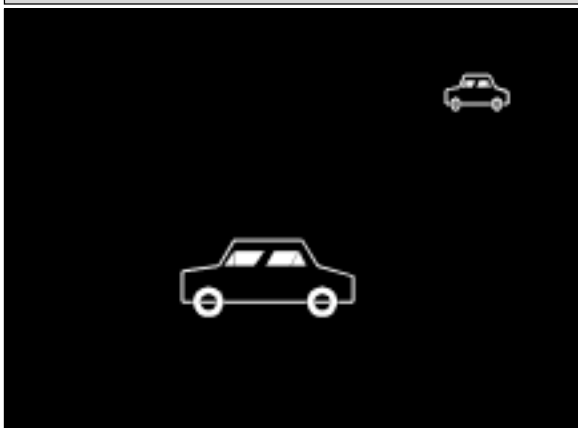
Visual attention is divided into three subsets: speed of processing visual information, divided attention, and selected attention. The speed of processing visual information is defined as the amount of time needed for detecting, localizing, and identifying objects in space. Divided attention is defined as the ability to pay attention to two things at once (eg, driving while keeping an eye

**Figure 3. Photograph shows Pelli-Robson contrast sensitivity chart**



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**Figure 4. Photograph shows tests used for evaluating useful field of vision and divided attention**



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on the road and being aware of people and road signs). Selective attention is defined as the ability to "select" one type of information while ignoring another type of information; for example, being able to assign priority to the most important features of the road while ignoring less consequential features is important for safety because it reduces the likelihood of error and injury. Visual attention declines with normal aging but is more profoundly impaired in patients with AD. Visual attention can be measured using a computer program, the Useful Field of View (UFOV) (Figure 4).

#### Facial Feature Recognition Testing

Recognition of facial features is a complex, poorly understood phenomenon involving vision and cognition. Patients with AD more easily recognize faces with smaller features and high contrast than faces with larger features and low contrast. In addition, patients with AD have selective impairment for recognition of familiar faces, and this impairment supports the theory that "intelligent" vision requires a combination of visual detection and cognition (memory and learning). Computer-generated facial expressions (Figure 5) having progressively diminishing degrees of contrast are therefore used to detect impairment of facial recognition. The test is scored by correctly identifying the correct facial expression at low levels of contrast.

#### Preventive Role of Vision Care Specialists: An Opportunity Whose Time Has Come

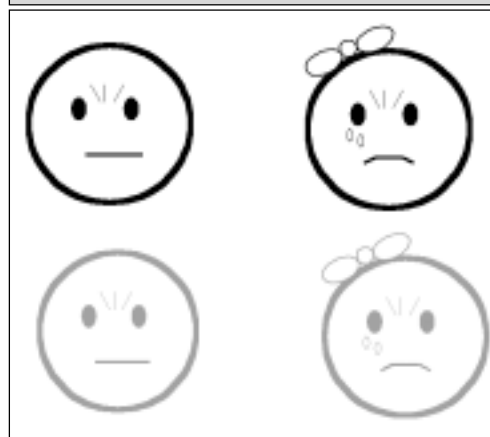
Mounting evidence suggests that vision impairment caused by eye disease in patients with AD is correlated with the severity and fre-

quency of AD symptoms in these patients. Whether patients with MCI or early AD can derive cognitive benefit from early cataract extraction or from more aggressive treatment of glaucoma or macular degeneration is not known with certainty, but recent evidence from the neuroscience literature suggests that this approach may be beneficial.<sup>16,17,35,36</sup> If such benefit is shown, vision specialists would develop greater interest in early detection of AD. If vision impairment caused by intraocular conditions is treated early in patients with MCI or early AD, the sensory loss related to cataracts, glaucoma, macular degeneration, and diabetic retinopathy might be reduced. Improvement in vision quality may lead to enhanced attention and recognition of new objects and thus may improve visual salience and enable consolidation of new memories.<sup>36</sup> Although early treatment of eye disease is unlikely to alter the underlying pathology of AD, such treatment may delay the onset and severity of symptoms in AD. No prospective clinical trials are available to show this benefit, but animal studies suggest that this approach may be beneficial. Currently, medical treatment has a modest impact on the course and symptoms of AD but is more effective when started early than when introduced later in the disease. The possibility of early treatment (made possible by early detection) has stimulated an aggressive search for more effective therapeutic approaches, and future research in this area is needed.

#### Vision Tests for Driver Safety: Independence and Mobility in Patients with Alzheimer's Disease

Department of Motor Vehicles (DMV) personnel traditionally have

**Figure 5. Drawing of high- and low-contrast facial expressions used for visual testing in patients with suspected Alzheimer's disease**



relied both on vision testing and on road testing, but DMV personnel and health care professionals are focusing increasingly on the continuing need for more useful screening tests to evaluate driver safety. Testing high-contrast visual acuity is necessary but is insufficient for evaluating impaired driving ability, particularly in elderly persons. Vision care specialists typically rely on high-contrast visual acuity tests, visual field examination, and physical examination of the eye to detect medical conditions (eg, cataracts, macular degeneration) that impair vision, but these specialists do not routinely test for attention deficit, loss of contrast sensitivity, or cognitive decline.

Combined measurement of visual and cognitive performance during driving simulation is becoming a valuable method of assessing early impairment of driving ability.<sup>13,37-41</sup> Driving simulation has high intuitive validity because many aspects of visual and cognitive performance are widely recognized as a requirement for safe driving and are understood

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by patients, clinicians, and regulatory agencies. Moreover, visual and cognitive performance during simulated driving under varying road and weather conditions is closer to "real-world" activities than are clinical tests of either visual acuity or contrast sensitivity. Impaired visual and cognitive performance is also predictive of injurious and non-injurious car crashes in patients with cataracts.<sup>13,38,40-42</sup>

However, driving simulation tests typically are expensive, lack portability, and are often time-consuming to administer. Further, no published validation studies exist for these tests; and no correlation is available between these tests and known US Department of Transportation Safety Standards, crashes, or clinical measures. For these reasons, driving simulation tests have not been widely deployed in academic, clinical, or DMV settings.<sup>43</sup> New microcomputer-based driving simulation software has been developed recently to overcome many of these barriers (Figure 6). The purpose of this type of platform is to permit automated, minimally supervised measurement of visual performance during driving simulation in clinical settings and in other relatively uncontrolled environments.

Figure 6. Illustration shows driving simulator



Photo courtesy: P. Rosen, MD

## Conclusions

Alzheimer's disease is a big, growing, and costly problem. As more effective medication becomes available for treating this disease, better tests for early detection will be needed. Recent evidence suggests that memory impairment and many attributes of vision are closely linked in patients with AD. Impaired contrast sensitivity, visual attention, and face recognition are known to be present in patients with AD, and testing for these types of impairment may be as sensitive as the traditional neurocognitive tests currently used for clinical diagnosis. Computer-based administration of these vision tests allows them to be done quickly and easily. Performance tests (eg, driving simulation that incorporates vision and cognitive measures) may also contribute to evaluating early AD. Vision specialists examine many elderly patients and can play a vital role by providing secondary and tertiary prevention measures, including early treatment of eye diseases, provision of informed advice regarding driver safety, and early referral to primary care practitioners, neurologists, or psychiatrists. ❖

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