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Eye Movements in Alzheimer's Disease

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Abstract

A growing body of literature has investigated changes in eye movements as a result of Alzheimer's disease (AD). When compared to healthy, age-matched controls, patients display a number of remarkable alterations to oculomotor function and viewing behavior. In this article, we review AD-related changes to fundamental eye movements, such as saccades and smooth pursuit motion, in addition to changes to eye movement patterns during more complex tasks like visual search and scene exploration. We discuss the cognitive mechanisms that underlie these changes and consider the clinical significance of eye movement behavior, with a focus on eye movements in mild cognitive impairment. We conclude with directions for future research.

Keywords

saccade; smooth pursuit; attention; mild cognitive impairment

Understanding the complex behavioral and neuroanatomical changes related to Alzheimer's disease (AD) requires a comprehensive research approach [1]. Here, we review the use of eye-tracking to understand AD in ways that are scientifically and clinically informative. Eye-tracking encompasses the measurement of eye movements, gaze location, and pupil size (for a review of different methods, see [2]). Similar to electrophysiological and hemodynamic measures, which have been used frequently to study AD [3-7], eye-tracking measures do not require additional behavioral responses, such as button presses, to make inferences about psychological changes. However, eye-tracking is relatively less invasive than neuroimaging, making it particularly well-suited for patient studies [8]. The pattern of AD-specific neurodegeneration may affect neural circuitry of the eye movement system in a unique manner that allows the clinical differentiation of AD from other cognitive disorders [9]. Moreover, eye movements manifest top-down, goal directed behavior [10,11] and can be used to measure the distribution of spatial attention [12,13] and behavior in tasks with high ecological validity like visual search within a distracting environment [14]. Eye-tracking can thus provide important information about alterations in visual cognition in patients. We begin our review with an overview of the AD-related changes to oculomotor and pupillary

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function. We then examine changes in complex viewing behavior and clinical applications of eye movement paradigms. Finally, we conclude with suggestions for future research.

Basic Ocular Changes Related to AD

Alzheimer's disease alters fundamental ocular functions. In this section, we review how the disease changes saccades, smooth pursuit, and pupillary responses. *Saccades* are the fast, darting movements of the eyes that shift gaze from one spatial location to another, and can either be directed towards a target (*prosaccade*) or away from a target (*antisaccade*). *Smooth pursuit* occurs when the eyes continuously follow or track a moving target. *Pupillary responses* are the dilations and constrictions of the pupils that are controlled by the autonomic nervous system but are also affected by the central nervous system.

Prosaccades

Measuring prosaccades typically requires a participant to fixate on a central point and then saccade to a peripheral target object as soon as it appears. Prosaccade generation follows a complex pathway through the brain that involves multiple regions in the cortex and brainstem [15]. Activity in the frontal eye field (FEF) and parietal eye field (PEF) triggers intentional and reflexive saccades, respectively [16]. The supplementary eye field (SEF) serves a number of functions, including monitoring saccade errors and conflict in saccadic responses [17,18]. Excitatory activity from these cortical regions, as well as inhibitory signals from the substantia nigra pars reticula [19], converge on the intermediate layers of the superior colliculus (SC) [16, 20]. The saccadic signal from the SC, in addition to signals sent directly from the cortical regions [16], are transmitted to the *saccade burst generator* in the reticular formation [20], which sends the final command to the corresponding ocular motor neurons to move the eyes [21]. Other brain regions that contribute to the prosaccade process include the cerebellum, which is part of a corrective feedback loop in the brainstem that allows for accurate prosaccades [22,23], and the dorsolateral prefrontal cortex (DLPFC), which controls the top-down decisional process determining whether to make a prosaccade by sending signals to the SC [24].

Numerous studies have observed abnormal prosaccadic behavior in AD patients. When compared with healthy controls, patients show increased latency to initiate prosaccades [25-36] and have lower prosaccade velocity [27]. Prosaccades in patients are often *hypometric* and do not reach the target [27,30,33] or are directed in the wrong direction entirely [26,37,38]. In general, prosaccade latency, velocity, and accuracy are more variable in AD patients [35,36]. The neural basis of these changes is unclear, but at least one study has related increased prosaccade latency to decreased bilateral parietal and occipital lobe volumes and right temporal lobe volumes [28].

Prosaccadic impairments in patients may result from known AD-related problems in disengaging and reorienting spatial attention [39,40]. Patients will often make *perseverative* errors, such as leaving hypo/hypermetric prosaccades uncorrected and continually fixating on, or repeatedly making saccades to, target locations from previous trials [37]. Studies using the gap/overlap paradigm provide additional evidence that suggests prosaccadic changes in AD are related to attention. Like other prosaccade tests, participants in the gap/

overlap task are required to prosaccade to a peripheral target. In “overlap” trials, the peripheral target onsets while participants fixate on a central point. In “gap” trials, there is a short delay (~200 ms) between the offset of the central fixation point and the onset of the peripheral target. In healthy populations, saccade latency is reduced in gap trials (“gap effect”) because the offset of the central fixation point facilitates the disengagement of attention, allowing for faster prosaccades to the peripheral target [41]. Similar to healthy older adults, patients with AD exhibit a robust gap effect [34,42-45]. Critically, the gap effect is reportedly larger in patients compared to healthy older adults [35,36]. The enhanced benefit of externally disengaging attention to prosaccade latency in patients strongly suggests that difficulty disengaging visual attention underlies prosaccadic impairment in AD.

However, other research suggests that AD-related prosaccadic changes may reflect inhibitory dysfunction, a widely reported symptom of AD [46]. One study [47] tested AD patients and healthy age-matched controls in a go/no-go prosaccade paradigm that required participants to prosaccade towards targets in one visual hemifield (go) or maintain central fixation during the presentation of targets in the opposite hemifield (no-go). Analysis of the no-go trials revealed that patients were unable to inhibit reflexive prosaccades and frequently made erroneous saccades towards the target. Inhibition errors have also been reported in a task that used predictable target locations, such that patients made anticipatory saccades prior to target onset on approximately half of the trials [30]. Although the degree that problems with disengaging visual attention and inhibitory dysfunction each contribute to AD-related prosaccadic changes is debatable, it is clear that AD-related prosaccadic changes are linked to changes in visual attention. Neuroimaging evidence has shown that declines in prosaccade function are predicted by volumetric decreases in the parietal lobe [28], which is critical for visual attention [48,49] and is affected by AD pathology [50,51].

While the aforementioned studies have reported AD-related changes to prosaccades, prosaccadic impairment may not be ubiquitous in AD. A number of experiments have also found that AD patients can have normal prosaccadic function, exhibiting comparable measures of prosaccade latency [42,45,47], velocity [28,30,31,33-36], and accuracy/amplitude [31,34-37,43,45,47]. Given that prosaccadic impairments are likely indicative of neurological and cognitive decline, one potential explanation for these conflicting findings is the heterogeneity of disease severity across experiments [31]. Consistent with this suggestion, several studies have reported correlations between prosaccadic function and neuropsychological test scores. For example, prosaccade latency and prosaccade velocity have been found to correlate with Mini-Mental State exam (MMSE) scores and measures of IQ [25,27,36], among other measures. This relationship is clinically significant, as it suggests that prosaccadic measurements could be a useful biomarker of AD that would complement frequently used bedside measures like the MMSE.

Antisaccades

The measure of antisaccades requires a participant to saccade in the opposite direction of an onsetting target. The neural process behind antisaccade behavior begins with an inhibitory signal sent from the DLPFC to the SC to suppress the reflexive prosaccade to the target [24].

Then, the direction of the upcoming saccade is inverted from the target to the opposite hemifield by the posterior parietal cortex and FEF [52-54]. Finally, the antisaccade away from the target is initiated by the FEF through the saccadic system [24,55].

Compared to healthy older adults, patients with AD make more incorrect saccades towards the target and fewer corrections after committing an error [28,33,34,38,42-44,47,56]. Patients also show increased latency when executing antisaccades and making corrective saccades following an error [33,43,47,56]. Similar to prosaccade performance, patient performance in antisaccade tasks appears to be correlated with neuropsychological test scores, including the MMSE, Color Form Sorting (CFS), backward digit span, Stroop inhibition, phonemic fluency, verbal fluency, Alzheimer's Disease Assessment Scale (ADAS), Trails A, modified trails, and spatial span [9,42,47,56].

As with AD-related prosaccadic changes, poor performance on antisaccade tasks is consistent with impaired inhibitory control [46]. Because the inhibitory signal in the antisaccade process originates in the DLPFC, Kaufman and colleagues [57] attribute the inability to suppress reflexive prosaccades to degeneration of the DLPFC. Alternatively, successful antisaccade behavior may rely on use of the DLPFC to maintain the task goal in working memory [58]. Consistent with this interpretation, Crawford and colleagues [43] argue that the erroneous saccades made by AD patients in the antisaccade task are due to declines in working memory, a function that is impaired in AD [59] and is known to depend on the DLPFC [60]. In support of this hypothesis, Crawford and colleagues [43] reported a strong correlation between the rate of antisaccade errors and neuropsychological measures of working memory in AD patients. It is currently unclear whether poor antisaccade performance in AD is primarily due to inhibitory dysfunction or impaired working memory. Given that activity related to inhibitory control and working memory overlap in the DLPFC, it is possible that changes to both mechanisms contribute to diminished antisaccade performance in patients as a result of DLPFC degeneration.

Microsaccades & Saccadic Intrusions

In addition to overt saccades, the eyes also make subtle movements while attempting to fixate. *Microsaccades* are minuscule shifts in gaze (<1° visual angle) made during fixation that are thought to enhance visual perception [61]. The neural generation of microsaccades is largely the same as prosaccades, with studies showing that the two functions appear to share a common pathway through the brainstem [62]. These movements are typically oriented horizontally relative to the point of fixation, but microsaccades in AD are notably more *oblique* (non-horizontal) when compared with healthy older adults [63]. During fixation, humans also experience occasional *saccadic intrusions*, which are full saccades away from fixation followed by a corrective saccade back to fixation after a brief pause [64,65]. Importantly, saccadic intrusions are present in healthy populations but occur with greater frequency and/or amplitude in populations with neurological disorders [64,65]. Several researchers have noted the occurrence of saccadic intrusions in AD [27,66,67], which are also more oblique in patients [63] and occur at rates that correlate with MMSE scores [25].

There are two possible causes of AD-related alterations to fixational eye movements. First, the regions within the brainstem that are responsible for overt saccadic movements (e.g. the SC) also control fixational saccadic movements 61,62], so changes in fixational eye movements, in conjunction with changes in prosaccades and antisaccades, may suggest a breakdown in posterior neural regions of the saccadic pathway in AD. However, given that pathology in these regions [68] occurs during the later stages of the disease [50], neurological decline alone may not sufficiently explain these changes. A second and more plausible explanation is that changes in fixational movements stem from cognitive decline. Fixational eye movements are affected by several cognitive processes, including attention and working memory [61]. Thus, altered fixational eye movements in AD may reflect cognitive decline, specifically supporting reports of diminished attentional and working memory function from the prosaccade and antisaccade literature.

Smooth Pursuit

In smooth pursuit tasks, a participant must attempt to continuously follow and hold their gaze on a moving target object. The target may start moving from either a central location or from a peripheral location following an instantaneous translation or step from the center ("step-ramp" motion [69]). Various aspects of target motion can be manipulated to test smooth pursuit, including target velocity, acceleration, and directionality of motion (e.g. linear, curvilinear, sinusoidal). Accurate smooth pursuit performance is defined by the ability to keep gaze on the moving target while minimizing the number of anticipatory saccades in the direction of target motion and compensatory "catch-up" saccades.

Smooth pursuit is implemented by a continuous feedback loop in the brain that undergoes correction throughout the pursuit process [70] and includes neural circuitry that overlaps heavily with the neural pathway for saccade generation [71,72]. Motion information from the moving target is extracted by lateral occipitotemporal cortex, which sends signals to a pursuit-specific portion of the FEF and to the SEF [70,73]. The signal then continues to brainstem regions that subserve saccade generation [74-76] and send the final motor commands to move the eyes. Like with saccades, the cerebellum plays an important role in calibrating smooth pursuit eye movements, while the rostral SC is involved in target selection [71,72].

Patients with AD have smooth pursuit impairments similar to their saccadic dysfunctions. Consistent with the prosaccade literature, patients show increased latency to initiate smooth pursuit following a step displacement of the target [28]. While tracking the target, eye movements have lower initial acceleration, decreased velocity, and decreased gain (the ratio of pursuit velocity to target velocity) [28,34,77,78]. Patients tend to make eye movements that lead the target and often make anticipatory saccades in the direction of target motion [77-79]. Additionally, tracking often trails target motion, causing patients to make significantly more compensatory saccades. These compensatory saccades appear to occur more frequently as cognitive function declines, as the rate of compensatory saccades is negatively correlated with MMSE scores [80]. Despite these changes, at least one experiment has found that patients with mild AD can demonstrate normal smooth pursuit function [31]. Similar to the prosaccade literature, conflicting reports of smooth pursuit

function are suggestive of a relationship between oculomotor function and disease severity in AD.

To the best of our knowledge, no study has implicated specific brain regions in the breakdown of smooth pursuit in AD. Of the studies that have used neuroimaging to investigate smooth pursuit in AD patients, Boxer and colleagues [34] did not find a significant relationship between lobar volume and smooth pursuit performance, while Garbutt and colleagues [28] only analyzed the correlation between lobar volume and saccade performance but not smooth pursuit performance. Because the underlying cause of smooth pursuit function in AD is left to conjecture at this point, more research is needed to elucidate the link between AD pathology and impaired smooth pursuit. Considering that patients have problems with everyday tasks that often require the ability to track moving objects, such as driving [81], understanding why smooth pursuit breaks down is critical to reducing functional impairment in AD.

Pupillary Responses

The size of the pupil fluctuates primarily in response to non-cognitive factors, most notably to changes in physical stimuli such as light. These dilations and constrictions are physiological in nature and are controlled through the autonomic nervous system, but systematic changes in pupil size during cognitive tasks suggest that the central nervous system also affects pupillary responses [82]. The few studies that have examined pupillary responses in AD patients have primarily focused on basic responses to light. These studies have consistently found reduced amplitude of pupillary changes in patients compared to healthy controls [83,84]. While one early study found no difference in response latency to light exposure [84], more recent investigations suggest increased latency in patients [83,85]. Additionally, pupillary response velocity and acceleration are significantly lower in AD patients than in healthy controls [83,84]. In line with previous research that proposed a cholinergic deficit in AD (the cholinergic hypothesis [86-88]), Fotiou and colleagues [83] postulate that abnormal pupillary responses in AD reflect cholinergic deficiency in the visual system. The relationship between cholinergic function and pupillary responses has spurred the development of a diagnostic pupillary test for AD that has had mixed results (see the Clinical Applications section for a brief discussion of this method).

Summary of AD-Related Ocular Changes

In summary, patients with AD experience a number of significant changes to basic eye movements. Frontal, parietal, occipital, and temporal pathology may all contribute to eye movement dysfunction. The overall lack of neuroimaging studies investigating eye movement abnormalities in AD makes it unclear where the oculomotor pathway breaks down in AD and if damage to eye movement circuitry is the primary cause of eye movement dysfunction. A large body of empirical studies, in conjunction with the correlation between neuropsychological test scores and performance on eye movement tasks in patients, indicates that cognitive impairments underlie many of the changes to eye movements. Converging evidence from prosaccade and antisaccade studies demonstrate that changes to eye movements are largely attributable to inhibitory dysfunction. Prosaccades are also marred by impaired attention, while declines in working memory may additionally affect

antisaccades. Changes in pupillary responses more directly implicate alterations to basic neurochemistry, specifically cholinergic function.

Complex Viewing Behavior

Although some eye movements are reflexive and involuntary, viewing behavior is primarily driven by top-down, goal-driven processes [10]. Because there is an intimate link between eye movements and cognition, changes in eye movement patterns can be used to infer AD-related changes in cognitive processing. Only a handful of studies have investigated complex viewing behavior in AD. The following section reviews patient performance and eye movements during visual search and scene exploration.

Visual Search

Generally, visual search is the goal-directed search for a target object among a set of distractors in the environment. Compared to healthy controls, patients are less accurate and have longer response times in visual search tasks [89-92]. Patients' eye movement patterns during search have been characterized as disorganized and stochastic [31,90]. Additionally, the duration of fixations while searching is notably longer in AD [31,90,91]. Declines in visual search behavior in AD patients have been associated with decreased gray matter in bilateral parietal lobes, precuneus, occipital, temporal, and frontal lobes [92].

AD-related changes to eye movements during search are consistent with impaired attention. Longer fixation durations in patients during search may be indicative of a problem disengaging visual attention from the current search target, making it difficult to shift between search items (cf. [39,93]). This account suggests that problems with disengagement could be the overarching factor causing changes observed with prosaccades and visual search. Difficulty disengaging attention may also cause patients to have a smaller useful field of view [94] relative to healthy controls, limiting the amount of visual information that patients can accumulate in a given fixation. With a narrower locus of attention, search may be especially challenging for patients because their ability to select future fixations to guide search is severely reduced [91].

While extended fixation duration during search may be related to difficulties in attentional shifting, increased fixation duration could alternatively be the result of longer target processing times [90]. Spatial attention is necessary for accurate perception of complex objects [95], so impairments in attention could impede stimulus processing. Consistent with this interpretation, patients exhibit greater pupil dilation during difficult searches that are defined by a conjunction of target feature values, suggesting that they expend more attentional resources on searches that place greater demand on visual processing [89]. Notably, patients are able to find search targets at a comparable rate to controls, yet they still have longer response times [92]. The extended response times in patients most likely reflect slower target processing in AD, although longer motor responses may also play a minor role [90].

Scene Exploration

The several studies that have examined eye movements during scene exploration in AD have provided mixed results. In one picture viewing task [26], eye movements were recorded while patients and healthy controls viewed pictures that contained an incongruous element (e.g. a horse with no hind legs). Compared to controls, patients viewed fewer scene areas and allocated fewer fixations that were of shorter duration to the incongruous region. In a similar study [31], no quantitative differences in eye movements between patients and controls were found during scene exploration, but the two groups exhibited qualitatively different eye movement patterns. Specifically, patients often overlooked unusual scene regions or discovered them later during viewing sessions. Together, these two studies [26,31] suggest that patients with AD do not attend to potentially informative scene areas. In line with these findings, Boucart, and colleagues [96] found that patients were less accurate when selecting which of two scenes contained an object of interest (in their experiment, an animal). However, there were no differences in any saccade measures between the controls and AD group in their task.

Although only a few studies have investigated eye movements during scene exploration in AD, hypotheses regarding the cognitive changes underlying patients' behavior have been proposed. One hypothesis suggests that altered scene exploration in AD is due to declines in curiosity and motivation [26,31,97]. Increased apathy is a common characteristic of AD that is manifested by a number of behaviors, including lack of interest [98]. During a passive viewing task, AD patients may be uninterested in exploring the visual environment and fixate fewer areas of interest. Consistent with this speculation, patients with AD have been found to direct attention away from stimuli and allocate more eye movements to non-stimulus areas than controls [26,99].

Based on AD-related changes in visual search, we alternatively propose that altered eye movements during scene exploration may result from changes to attention. Several forms of attentional impairment could cause patients to overlook important scene aspects. Difficulty disengaging and shifting attention from one element in a scene to the next could hinder a patient's ability to fully explore a scene, causing them to miss critical scene areas. A reduced locus of attention could make peripheral areas of interest more difficult to detect in AD, again causing patients to overlook important regions of a scene. Problems with attentional binding of object features [100] could also lead to misperception of anomalous or context-inappropriate objects.

Summary of Changes to Complex Viewing Behavior

Patients with AD have substantially different eye movement patterns than healthy older adults during complex viewing tasks. Altered visual search patterns implicate changes to attention and visual processing in patients. Similar attentional impairments, in addition to increased apathy, may explain changes to scene exploration, but the limited number of studies investigating eye movements during scene exploration necessitates further research.

Clinical Application of Eye Movement Measurements

As previously noted, a number of eye movement measures have been shown to correlate with neuropsychological test scores. This relationship suggests that eye movements may be sensitive to dementia severity and could potentially be a useful biomarker of AD (as well as other neurodegenerative disorders; see [101]). Only a handful of studies have examined the possible clinical application of eye movements in AD, which are discussed below. Additionally, eye movements are considered in patients with mild cognitive impairment, a potential prodromal stage of AD.

Eye Movements in Assessment

In an attempt to develop a clinical oculomotor task that could be used to assess dementia, Currie and colleagues [9] compared the performance of healthy and diseased groups (AD, depressive pseudodementia, Huntington's disease) in a clinical antisaccade task. In the clinical task (later validated by comparable laboratory data), participants fixated on the experimenter's nose and performed an antisaccade in response to the movement of the experimenter's index fingers. Based on percentile error scores from the control group in the clinical task, the majority of the AD patients was classified as having abnormal eye movements and was thus distinguished from the controls. This clinical task also successfully differentiated AD patients from depressive pseudodementia patients, who had comparable levels of cognitive impairment but normal eye movement functioning. Similarly, antisaccade performance has been found to differentiate AD from semantic dementia [28]. While these studies indicate that antisaccade measures are a promising diagnostic tool, antisaccade tasks may be less useful in differentiating patients from controls compared to neuropsychological tests such as the MMSE [102]. In addition to antisaccade performance, saccade latency may also serve as a useful diagnostic measure. For example, Boxer and colleagues [44] demonstrated that increased horizontal saccade latency in autopsy-confirmed AD patients relative to patients with frontotemporal lobar degeneration could distinguish the two groups using receiver operating characteristic (ROC) analyses. Together, these studies highlight the potential diagnostic utility of eye movement measurements in AD patients.

Pupillary responses may also provide useful diagnostic information. Based on a ROC analysis, Fotiou and colleagues [83] reported that maximum pupillary velocity and acceleration could be used to almost perfectly differentiate AD patients from healthy controls. Another body of research has sought to capitalize on the aforementioned AD-related changes in the cholinergic system to establish a pupil-based biomarker. By administering tropicamide, a cholinergic antagonist, to the eyes of patients and controls, researchers have attempted to elicit differential pupillary responses that could be used to identify people with or at-risk of developing AD [103,104]. The efficacy of this method has been hotly debated. While some studies have provided evidence for this method [103,105,106] and have found neuroanatomical correlates of abnormal tropicamide responses in AD [107,108], other studies provide evidence against the use of this test [109-111]. Although the use of pupillary measures as a biomarker for AD is controversial, further investigation could make these tests viable.

Eye Movements in Mild Cognitive Impairment

Of particular interest to the study of eye movements in AD is the investigation of eye movement function in mild cognitive impairment (MCI). MCI is characterized by cognitive decline that exceeds the expected decline from aging, but does not greatly impact independent functioning [112]. Critically, patients with MCI are more likely to develop AD than cognitively normal adults [113-115], with higher conversion rates in amnestic MCI (aMCI) than nonamnestic MCI (naMCI) [113,116; also see 117 for a discussion of conversion rates]. Furthermore, MCI has been viewed as a possible prodromal stage of AD [112-114], so any changes in eye movements that are potentially detectable in MCI, especially aMCI, are greatly important to AD research.

Few studies have investigated eye movements in aMCI. Generally, prosaccades appear to be relatively intact [35,118], but at least one study has found an increase in prosaccade latency in aMCI relative to healthy controls [36]. Antisaccade performance has also been mixed, with reports of intact [56] and impaired [118] performance in aMCI. In both cases, however, antisaccade performance in aMCI has been related to structural and functional changes in frontal regions [56,118]. Microsaccades in aMCI appear to be undifferentiated from AD and are similarly oblique [63]. Taken together, studies of eye movements in aMCI suggest that aMCI patients manifest some of the oculomotor changes that are present in AD. However, the paucity of eye movement studies in aMCI necessitates further research to determine the degree of oculomotor change in aMCI and whether such change is predictive of AD.

There is some evidence that eye movements can be used to detect the early stages of memory impairment that are present in MCI. Previous research has demonstrated that prior exposure to a stimulus reduces subsequent viewing, such that novel stimuli are preferentially viewed over repeated stimuli [26,119]. However, Crutcher and colleagues [120] found that, following a 2-minute delay between initial and repeated presentations, MCI patients did not exhibit a preference for novel stimuli. Instead, MCI patients evenly distributed eye movements between simultaneously presented novel and repeated stimuli, presumably because they had forgotten the original presentation of the repeated stimulus. Based on these findings, Lagun and colleagues [121] attempted to develop a computer algorithm that could be used to distinguish healthy controls from MCI patients using eye-tracking. By incorporating eye movement data from AD patients and controls recorded during a repeated/novel paired viewing task [120], the computer model was able to differentiate healthy controls from MCI patients with 87% accuracy, 97% sensitivity, and 77% specificity. Although these results are the first step in the development of an oculomotor-related biomarker for MCI, it should be noted that the MCI groups in these studies [120,121] were not domain specific, making it difficult to draw definitive conclusions about the diagnosticity of eye movements in aMCI or naMCI. However, these studies provide compelling evidence that suggests eye movements can be used to detect memory impairment and serve as a possible biomarker for MCI and, in turn, AD.

Directions for Future Research

Previous research has created a strong foundation for understanding AD-related changes to eye movements, but there remain many unanswered questions that merit further

investigation. Below, we outline several avenues of research that we believe are pertinent, including additional discussion of some of the ideas already presented in this paper as well as other uninvestigated areas that have not yet been discussed.

Understanding AD-related changes to eye movements could have a profound impact on patients' functions of daily living. Studies have shown that changes in eye movements are connected to some functional impairment in patients, including problems with reading [122,123], discerning facial expressions [99], and telling time [45]. Importantly, some experiments have found that patients can exhibit normal viewing patterns in complex tasks. For example, patients and controls have been found to exhibit similar fixation distributions in a simulated driving task [124], demonstrating that eye movements in patients are to some degree task-dependent. Moreover, emotional stimuli have been reported to elicit similar eye movement patterns in patients and controls [125], demonstrating that eye movements in patients may be stimulus-dependent. Together, these studies [124,125] indicate that certain viewing conditions are conducive to normal cognitive processing in AD. Future studies may provide insight into the conditions that could facilitate a patient's environment, allowing caregivers to better accommodate functional changes in patient viewing behavior.

Beyond clinical and functional applications, our review has demonstrated that eye movement measures can provide insight into the breakdown of cognition in AD. Although the use of eye-tracking has been an asset to investigations of attention and inhibitory function in AD, it is unclear how changes to eye movements affect memory in patients. An emerging literature has shown that eye movements can play a critical role in memory processes. Laboratory studies with healthy populations have found that eye movement patterns are strongly related to multiple aspects of memory, specifically recognition [126,127], memory strength [128,129], and memory accuracy [130]. Importantly, memory-related eye movements are closely related to activity in the hippocampus [131], an area that is a hotbed of AD pathology. By extending this research into AD, we can further the understanding of memory impairments in patients and elucidate how changes to underlying memory-related neural circuitry are expressed through eye movements.

Finally, a common question throughout the prosaccade and antisaccade literature is what degree oculomotor function varies with increasing AD pathology. While it has been suggested that eye movements can index AD-related pathology in certain brain regions, such as the DLPFC [57], it is unclear if this is indeed the case. Because eye movements recruit a large number of brain areas, many regions can be targeted to investigate the link between pathology and eye movement control in patients. In particular, changes to parietal and frontal regions are both implicated by prosaccade and antisaccade studies. Furthermore, in order to investigate how eye movements change throughout the disease course, it is necessary to examine oculomotor function at multiple stages of AD, either through cross-sectional [32] or longitudinal [25] studies. Only by tracking the progression of oculomotor changes along with AD can the relationship between AD pathology and eye movements be fully understood.

Closing Remarks

The culmination of over 30 years of research has demonstrated that eye-tracking can provide a wealth of information for cognitive and clinical studies of Alzheimer's disease. In general, eye movements, including saccades and smooth pursuit, appear to be slower and less accurate as a result of the disease. Even subtle functions, such as microsaccades and pupillary dilations, are transformed by AD. Prosaccades become marred by errors that indicate difficulty disengaging attention and impaired cognitive inhibition, while problems with antisaccade tasks also signify changes to inhibitory function in addition to working memory. The apparently random viewing patterns exhibited by patients during visual search and scene exploration suggest that cognitive changes reflected in eye movements may have a collateral effect on how patients perceive and interact with their environments. With further development, eye movements may be a promising biomarker for AD that could complement other neuropsychological measures and aid diagnoses. The inclusion of aMCI patients in eye-tracking studies is especially critical for AD research, as understanding ocular changes in aMCI may be useful for identifying individuals who will later progress to AD. While the groundwork has been set, the work of future researchers will elucidate the clinical, cognitive, and neurological implications of eye movement changes in Alzheimer's disease.

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