Eye Movement Alterations During Reading in Patients With Early Alzheimer Disease

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Purpose. Eye movements follow a reproducible pattern during normal reading. Each eye movement ends up in a fixation point, which allows the brain to process the incoming information and to program the following saccade. Alzheimer disease (AD) produces eye movement abnormalities and disturbances in reading. In this work, we investigated whether eye movement alterations during reading might be already present at very early stages of the disease.

Methods. Twenty female and male adult patients with the diagnosis of probable AD and 20 age-matched individuals with no evidence of cognitive decline participated in the study. Participants were seated in front of a 20-inch LCD monitor and single sentences were presented on it. Eye movements were recorded with an eye tracker, with a sampling rate of 1000 Hz and an eye position resolution of 20 arc seconds.

Results. Analysis of eye movements during reading revealed that patients with early AD decreased the amount of words with only one fixation, increased their total number of first- and second-pass fixations, the amount of saccade regressions and the number of words skipped, compared with healthy individuals (controls). They also reduced the size of outgoing saccades, simultaneously increasing fixation duration.

Conclusions. The present study shows that patients with mild AD evidenced marked alterations in eye movement behavior during reading, even at early stages of the disease. Hence, evaluation of eye movement behavior during reading might provide a useful tool for a more precise early diagnosis of AD and for dynamical monitoring of the pathology.

Keywords: saccadic movements, Alzheimer disease, eye fixation, eye movements

Healthy human subjects move their eyes during reading every quarter of a second on the average, sending new information to the brain each time the eyes remain fixated. In normal subjects, fixation duration is usually between 150 and 250 ms, with values stretching from 100 to over 700 ms. The distance the eyes move in each saccade ranges between 1 and 20 characters, usually moving between 7 to 9 characters, and execution of the saccade takes approximately 20 to 50 ms.[1] Saccade primary function is to bring a new region of text into the foveal vision. Some properties of the not yet fixated incoming words must become available during the ongoing word fixation. Research on the perceptual span established that parafoveal visual information extending approximately 10 characters in reading direction can influence the word processing in progress. In healthy readers, this information is used for selecting the next saccade target and for determining the size of the next saccade. The distance between the last fixation on a word and the next fixation to the right is defined as an outgoing saccade.[2–4] Several authors propose that once a fixation is made, processing of information is critical in programming the next saccadic movement. Hence, brain processing at fixations points appears to be relevant to execute saccades.[5,6] Recent work shows that the number of characters that healthy readers will move their eyes to the right depends, in part, on the difficulty of processing the previously fixated word; in general, the easier the processing, the longer the outgoing saccade.[7–9]

In Alzheimer disease (AD), progressive neuropathological changes within the neocortex[10] make AD patients prone to visual and attentional disturbances.[11] Mendez et al.[11] reported visual field deficits, prolonged visual evoked potentials, abnormal eye movement recordings, and even visual hallucinations, among other disturbances in AD patients. In addition, disturbances and abnormal eye movements during reading have been observed in these patients.[12–15] During the progression of AD, affected individuals evolve from an initial mild cognitive impairment to severe loss of mental function. Patients with early to moderate AD usually show impairment in learning and a deterioration of episodic memory, symptoms that are typically used for diagnosis of the pathology. However, subtle alterations in movement coordination and planning that may also be present while performing fine motor tasks such as writing or reading are harder to detect and go commonly unnoticed.[16,17] Evaluation of eye movements might provide considerable

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insight into the integrity of control circuits in AD. The cognitive control of eye movements is a promising area of research, primarily because of the thorough understanding of the oculomotor system and the ease with which eye movements can be measured.[1] Networks and structures involved in a range of eye movement behaviors are well defined, including those that measure working memory and saccadic execution. The existing knowledge on eye movement control could be extended to improve our understanding of more complex behaviors such as attention, inhibitory control, working memory, and decision-making processes.[18–23]

All the above processes are altered in AD, which leads to early modifications in neurological connectivity that disrupts the processing of incoming information.[24,25] Work from Lueck et al.[13] showed that patients with moderate AD had abnormalities in eye movements during reading of a text and that reading difficulty correlated with dementia severity. Given that the broad spectrum of events involved in reading require processing of information, coordination, and planning, we investigated whether subtle changes in that processing present at early stages of AD might lead to eye movement alterations detectable by the eye tracker. In this work, we evaluated the eye movement behavior in healthy individuals and AD patients at early stages of the disease during reading of sentences, and whether the decision for when and where to execute a saccade (i.e., to refixate a word or saccade to the next word) were influenced by the frequency, predictability, and length of the words used. Our results provide evidence that even at these very early stages of their disease, AD patients showed marked changes in the pattern of eye movements during word processing, compared to control individuals. This suggests that analysis of eye movements might provide new insights into the pathogenesis of AD and contribute an additional, useful tool for an early clinical diagnosis,[26] still a pending problem in AD.

Methods

Ethics Statement

The investigation adhered to the principles of the Declaration of Helsinki, and was approved by the Institutional Bioethics Committee of the Hospital Municipal de Agudos (Bahía Blanca, Buenos Aires, Argentina). All patients and their caregivers, and all control subjects signed an informed consent prior to inclusion into the study.

Participants

Twenty patients (12 females and 8 males; mean age 69 years, SD = 7.2 years) with the diagnosis of probable AD were recruited at the Hospital Municipal of Bahía Blanca (Buenos Aires, Argentina). The clinical criteria to diagnose AD at their early stages remain under debate.[27] In the present work, diagnosis was based on the criteria for dementia outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[28] All AD patients underwent a detailed clinical history, physical/neurological examination, and thyroid function test. Magnetic resonance images were obtained from 12 patients and computerized tomography scans from the other eight patients. Patients also underwent biochemical analysis to discard other common pathologies (hemoglobin, full blood count, erythrocyte sedimentation rate, urea and electrolytes, blood glucose). As a whole, these data contributed to a more precise diagnosis of AD. Patients were excluded if they: suffered any medical conditions that could account for, or interfere with, their cognitive decline; had evidence of vascular lesions in computed tomography or a functional magnetic resonance imaging; or had evidence of an Axis I diagnosis (e.g., major depression or drug abuse) as defined by DSM-IV. To be eligible for the study, patients had to have at least one caregiver providing regular care and support. Patients taking cholinesterase inhibitors (ChE-I) were not included. None of the subjects was taking hypnotics, sedative drugs, or major tranquilizers. The control group consisted of 20 elderly adults (12 females and 8 males; mean age 71 years; SD = 6.1 years), with no known neurological and psychiatric disease according to their medical records, and no evidence of cognitive decline or impairment in activities of daily living. A one-way ANOVA showed no significant differences between the ages of AD and control individuals.

The mean scores of controls and AD patients in the Mini-Mental State Examination (MMSE)[29] were 27.8 (SD = 1.0) and 23.2 (SD = 0.7), respectively, the latter suggesting early dementia. A one-way ANOVA evidenced significant differences between MMSE in AD patients and controls ($P < 0.001$). The mean score of AD patients in the Adenbrook's Cognitive Examination (ACE-R) was 82.4, (SD = 2.1),[30] the cutoff being 84. The mean school education trajectories in AD patients and controls were 15.2 (SD = 1.3) and 15.1 years (SD = 1.0), respectively. A one-way ANOVA showed no significant differences between the education of AD and control individuals.

Sentence Corpus

The sentence corpus was composed of 75 sentences (620 words), and was constructed with the goal of representing a large variety of grammatical structures in Spanish.

Word and Sentence Lengths. Sentences ranged from a minimum of 5 words to a maximum of 14 words. Mean sentence length was 8.3 words (SD = 1.3). Words ranged from 1 to 14 letters. Mean word length was 4.6 letters (SD = 2.5).

Word Frequencies. We used the Spanish Lexical *Léxesp* corpus[31] for assigning a frequency to each word of the sentence corpus. Word frequency ranged from 1 to 264,721 per million. We transformed frequency to $\log_{10}$ (frequency). Mean $\log_{10}$ (frequency) was 3.4 (SD = 1.3).

Word Predictability. Word predictability was determined by performing an independent experiment with 18 researchers of the Electrical Engineering and Computer Science Department, Universidad Nacional del Sur. We used an incremental cloze task procedure in which participants had to guess the next word given only the prior words of the sentence. Participants were between 31 and 62 years old, and did not participate in the reading experiment. Academic background of the reading experiment group and the cloze task group was similar. The average predictability measured from the incremental cloze task was transformed using a logit function. Logits are defined as $0.5 \times \ln(\text{pred}/[1 - \text{pred}])$; predictabilities of zero were replaced with $1/(2 \times 18) = -2.55$ and those among the five perfectly predicted words with $(2 \times 18 - 1)/(2 \times 18) = +2.55$, where 18 represents the number of complete predictability protocols.[32] Mean logit predictability was –0.9 (SD = 0.9).

Apparatus and Eye Movement Data

Single sentences were presented on the center line of a 20-inch liquid-crystal display (LCD) monitor (1024 × 768 pixels resolution; font: regular; New Courier; 12 point, 0.2° in height). Participants were seated in front of the monitor at a distance of 60 cm from the monitor. Head movements were minimized using a chin rest. Correction for the 60-cm viewing distance was performed by using an eye tracker (EyeLink 1000 Desktop Mount; SR Research Ltd., Ontario, Canada), which assessed changes in gaze position by measuring both the reflection of an infrared illuminator on the cornea and the

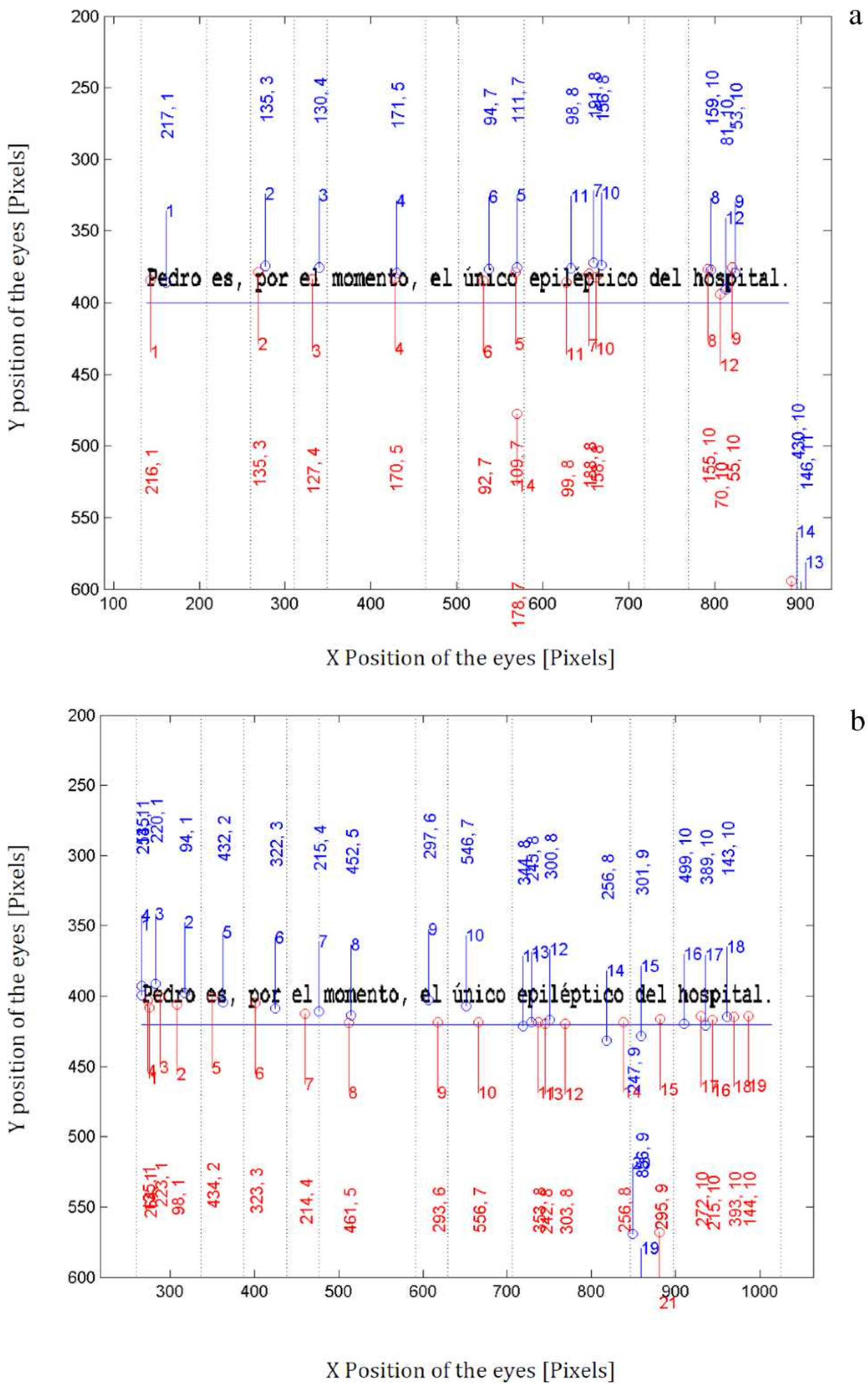

Figure 1. Recording of eye movements during reading of a sentence by a control subject (**a**) and an AD patient (**b**). Fixation points for right (*red*) and left (*blue*) eyes are included in the graphs. The down and right movements signaled the end of reading; numbering linked to points indicates fixation sequences; fixation durations of each eye are listed with their corresponding colors. The number following fixation duration (after the comma), index the word number in the sentence. Note that in AD patients, the number and duration of fixations per word increased compared with controls. In addition, forward saccades were shorted in AD. The Spanish sentence: "Pedro, es por el momento, el único epileptico del hospital," corresponds in English to: "Peter, is at the moment, the only epileptic at the hospital."

pupil size, by means of a video camera sensitive to light in the infrared spectrum.

Eye movements were recorded with an eye tracker (SR Research Ltd.), with a sampling rate of 1000 Hz and an eye position resolution of 20 arc seconds. All recordings and calibration were binocular. Only right eye data was used for the analyses. Eye movement data from 40 participants reading 75 sentences were cleaned from blinks and track losses.

TABLE. Eye Movement Behavior

	Control, *n* (SD)	AD, *n* (SD)	*T* Value
Total fixations	617 (209)	1617 (1098)*	4.79
Total first-pass fixations	284 (110)	434 (224)†	4.34
Total second-pass fixations	112 (94)	745 (746)*	3.98
Regressions	43 (35)	132 (128)‡	3.76
Word skipping	186 (46)	314 (262)†	2.04
Single fixations	164 (37)	114 (36)*	−3.04

The eye movements of AD patients and age-matched individuals (control) while reading 75 sentences were compared. Values between brackets represent SD, calculated using a one-way ANOVA. Linear mixed models were also computed for counterchecking ANOVA's significant effects. Our criterion for referring to an effect as significant was $t = |b/SE| > \pm 2.0$.

* $P \leq 0.001$.

† $P \leq 0.05$.

‡ $P \leq 0.01$.

Fixations shorter than 51 ms and longer than 750 ms and fixations on the first and last word of each sentence were removed for the analysis.

Procedures

Participants' gaze was calibrated with a standard 13-point grid for both eyes. After validation of calibration, a trial began with the appearance of a fixation point on the position where the first letter of the sentence was to be presented. As soon as both eyes were detected within a 1° radius from the fixation spot, the sentence was presented. After reading it, participants looked at a dot in the lower-right corner of the screen; when the gaze was detected on the final spot, the trial ended. Occasionally, external factors such as minor movements and slippages of the head gear could cause small drifts. To avoid them, we performed a drift correction before each spot presentation.

To assess whether subjects comprehended the texts, they were presented with three alternative multiple-choice questions about the sentence in progress on 20% of the sentence trials. Participants answered the questions by moving a mouse and choosing the response with a mouse click. Overall mean accuracy was 95% (SD = 3.2%) in control and 91% (SD = 5.4%) in AD. A one-way ANOVA showed no significant differences between comprehension of the answers in controls and in AD patients. The latter were only marginally less accurate than control subjects, probably because they were in an early stage of the pathology, as indicated by MMSE and ACE-R values. Once the comprehension test ended, the next trial started with the presentation of the fixation spot. The experimenter did an extra calibration after 15 sentences were read or if the eye tracker (SR Research Ltd.) did not detect the eye at the initial fixation point within 2 seconds. An example of the eye movements recorded during reading of a sentence, showing eye fixations of controls and AD, is shown in Figure 1.

First-pass fixations (i.e., the initial reading consisting of all forward fixations on a word) were generally used as the

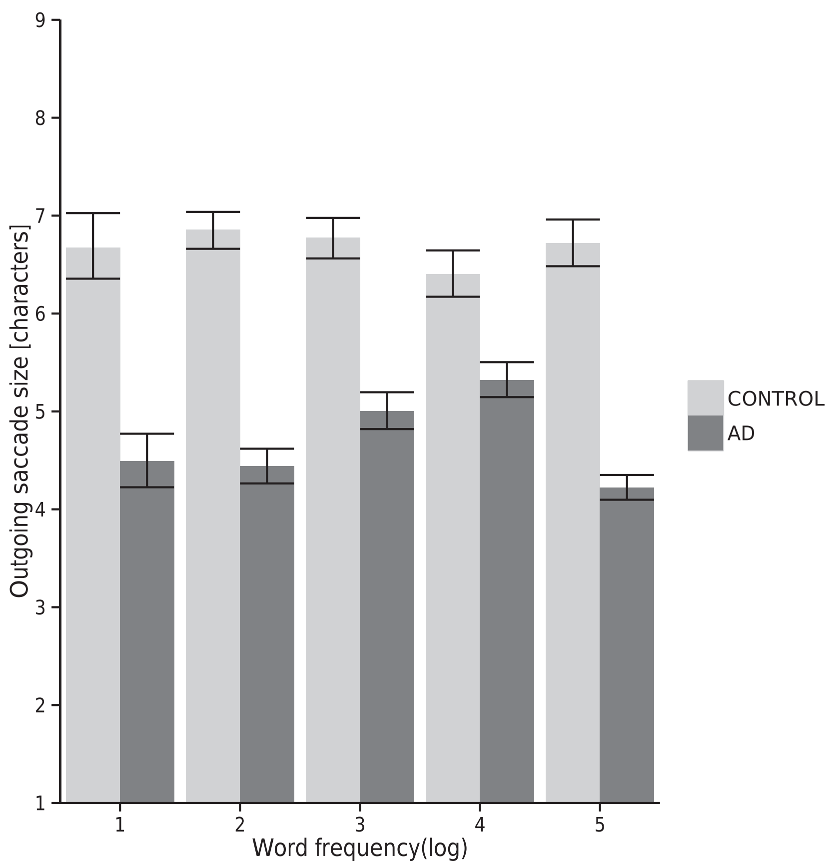

FIGURE 2. Effect of word frequencies on the size of the outgoing saccades in control and in AD patients. The graph represents the size (in characters) of outgoing saccades at different word frequencies as indicated in the Materials and Methods section. Note that the size of outgoing saccades was relatively constant at the different word frequencies analyzed for each group and that the values in AD patients were consistently smaller than in controls: the average decrease in the number of characters of outgoing saccades in AD patients with respect to controls was 30%. $P < 0.001$. *Bars* represent means ± SD, calculated using a one-way ANOVA.

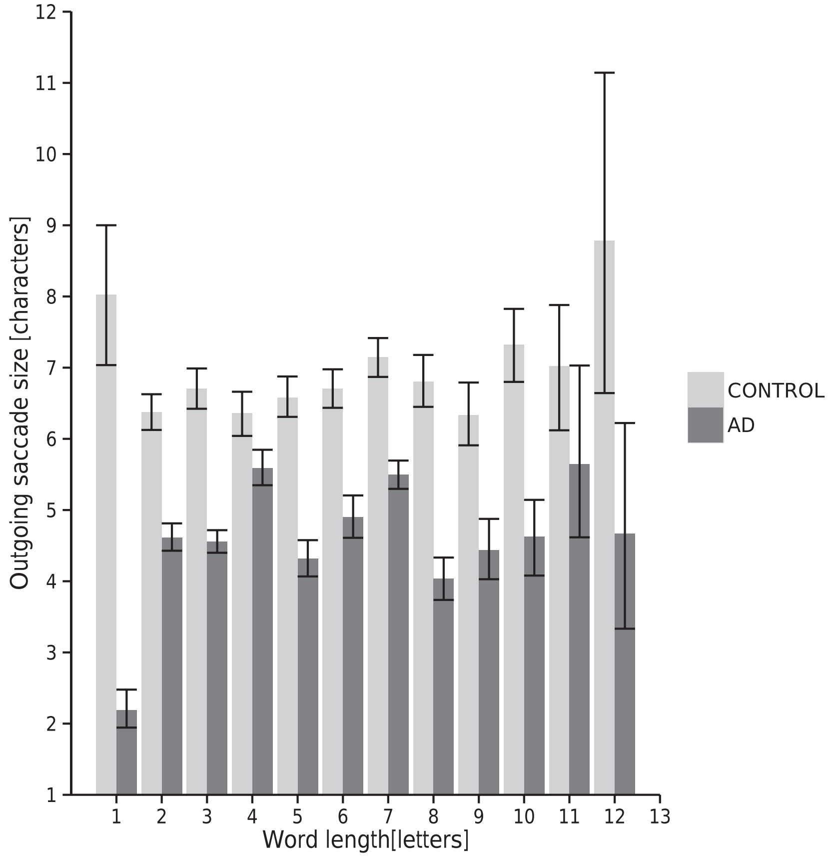

FIGURE 3. Effect of word length on the size of the outgoing saccades. The graph represents the size (in characters) of outgoing saccades at different word length in control and AD patients. Note that in AD patients, the size of outgoing saccades was consistently shorter than in controls; the average decrease in the number of characters of outgoing saccades in AD patients with respect to controls was 36%. $P < 0.001$. *Bars* represent means ± SD, calculated using a one-way ANOVA.

primary measure of interest. Second-pass fixations (i.e., rereading) and single fixations (whenever the eyes fix exactly once, on a given word)[1] were also evaluated.

Statistical Analysis

We performed a one way-ANOVA test for determining whether mean and standard deviations between groups were significant. To further evaluate the source of eye movement behavior during reading, we used the lmer program of the lme4 package (version 0.99975-14) for estimating fixed and random coefficients of the variables analyzed in the Table. The lme4 package is supplied in the R system for statistical computing (version 2.15.2; R Development Core Team, 2008) under the GNU General Public License (Version 2, June 1991). Our criterion for referring to an effect as significant was $t = |b/SE| > \pm 2.0$.

RESULTS

Eye Movement Behavior

Word information is acquired and processed in the brain during fixations. Since patients at early stages of AD already show minor difficulties in processing and interpreting acquired data, we hypothesized that they would increase the number of fixations to compensate for these deficits. We first compared the total number of fixations of AD patients and healthy (control) individuals while reading. As shown in the Table, the mean of the total number of fixations significantly increased from 617 in controls to 1617 in AD patients. The mean number of first-pass fixations doubled between controls and AD patients, significantly increasing from 284 to 434 fixations, respectively (Table). The amount of second-pass fixations increased even more strikingly in AD patients compared with controls (Table), from 112 in the control group, to 745 in AD patients.

Though most saccades carry the eyes forward through the text, a number of eye movements, regressions, are made backward to words that have already been fixated. Noteworthy, the number of regressions increased from 43 in controls to 132 in mild AD patients (Table). We then evaluated the number of single fixations, which would be expected to decrease with a higher level of difficulty in interpreting the acquired data. As predicted, the number of single fixations significantly decreased from 164 in controls to 114 in AD patients (Table). The number of words skipped while reading increased from 186 in controls up to 314 in AD patients (Table). AD progression seemed to markedly affect reading ability; patients with moderate AD not only evidenced greater difficulty to concentrate in reading tasks, but also increased the number of fixations, regressions, and fixations out of the text compared with patients with mild AD (data not shown).

Word-Based Effect on Outgoing Saccade Sizes

We then analyzed the effect on the size (in characters) of the outgoing saccade of word-based effects, such as word frequency, predictability, or length. The size of outgoing saccades ranged from 6.4 to 6.6 characters in controls (Fig.

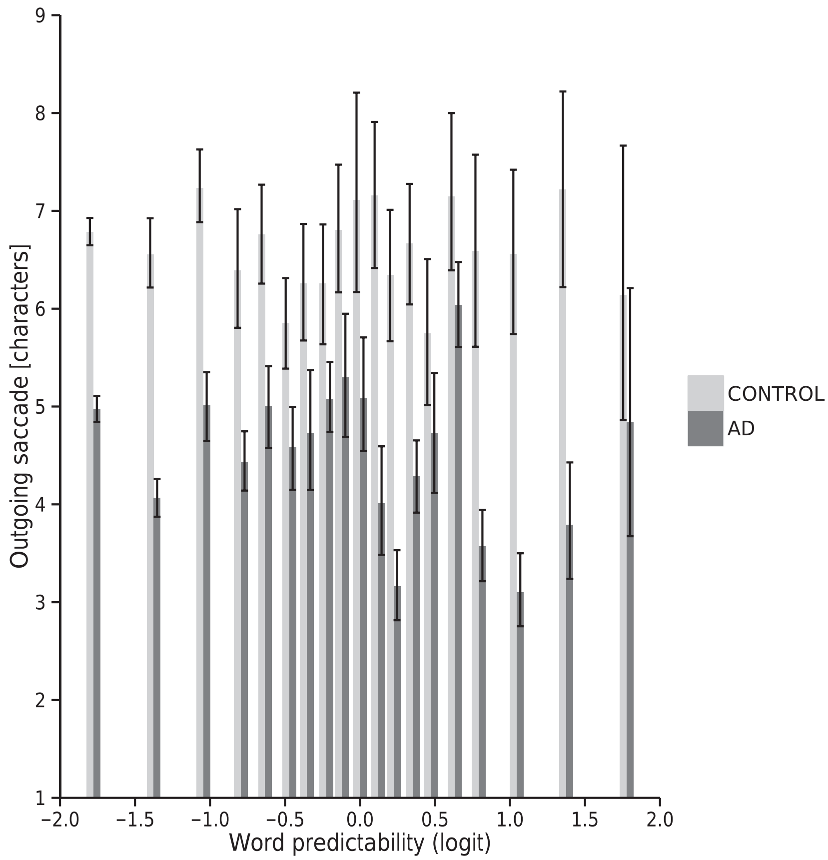

Figure 4. Effect of word predictability on the size of the outgoing saccades. The graph represents the size (in characters) of outgoing saccades at different word predictabilities in control and AD patients. Note that in AD patients the size of outgoing saccades was in every case smaller than in controls; the average decrease in the number of characters of outgoing saccades in AD patients with respect to controls was 32%. $P < 0.001$. *Bars* represent mean ± SD, calculated using a one-way ANOVA.

2) and significantly decreased in AD patients, ranging between 4.2 and 5.3 characters (Fig. 2). The amplitude of the outgoing saccade was independent of the frequency of a given word in both groups.

We then evaluated the effect of word length on the amplitude of outgoing saccades. In controls, outgoing saccades were significantly longer, approximately eight letters, for words having one character, with values of around 6.5 characters for words two or more letters long (Fig. 3). In AD patients, the sizes of outgoing saccades were significantly reduced compared with controls at every word length, ranging between 2.2 and 5.6 characters. The highest reduction was observed for words having one character length (Fig. 3).

We also investigated whether the predictability of a word in a sentence might differentially modify the amplitude of the outgoing saccades. As stated above, the size of outgoing saccades was approximately 6.5 characters in controls, while in AD patients these values were significantly reduced, regardless of the predictability of the word (Fig. 4).

Finally, we analyzed fixation duration as a function of the size of outgoing saccades. In control subjects, fixation durations were 195 and 190 ms for outgoing saccades of one and two characters, respectively. These values significantly increased with the size of the outgoing saccade, up to 215 ms for outgoing saccades of 13 characters. In general, fixation duration in controls increased slightly at longer outgoing saccades. Noteworthy, fixation durations were strikingly longer in AD patients than in controls (Fig. 5) at every saccade size and had a random distribution, evidencing no correlation with the size of outgoing saccades (Fig. 5).

Discussion

The present results reveal that AD patients with mild cognitive impairment already evidenced significant alterations in their eye movements during reading compared with healthy individuals. Patients with mild AD remarkably increased the amount of total fixations and saccade regressions. They also showed longer fixation durations in spite of a reduction in the size of outgoing saccades.

The basic processes involved in eye movements during reading have been thoroughly described in the literature.[1,33] There is now a growing consensus that eye movement behavior could be used to evaluate cognitive processing during reading,[11,34] since several cognitive processes, including working memory, have been shown to influence saccade parameters.[1,35] Changes in eye movements have been linked to neurological conditions such as Parkinson disease and prefrontal cortex damage.[36,37] Mild cognitive impairment and a deficit in working memory are early symptoms of AD, and AD patients have been reported to evidence saccade dysfunctions.[13,38] Our results show that eye movements during reading were affected in AD patients at very early stages of the disease. Patients participating in this study had MMSE and ACE-R score values of 23.2 and 82.4, respectively, which reflect slight cognitive impairment. These patients evidenced a significant increase in their total number of fixations, with both the amount of first- and second-pass fixations being increased, compared with controls. In healthy individuals, as is observed in the Table, second-pass fixations are less frequent than first-pass fixations; noteworthy, the former showed the highest increase in AD

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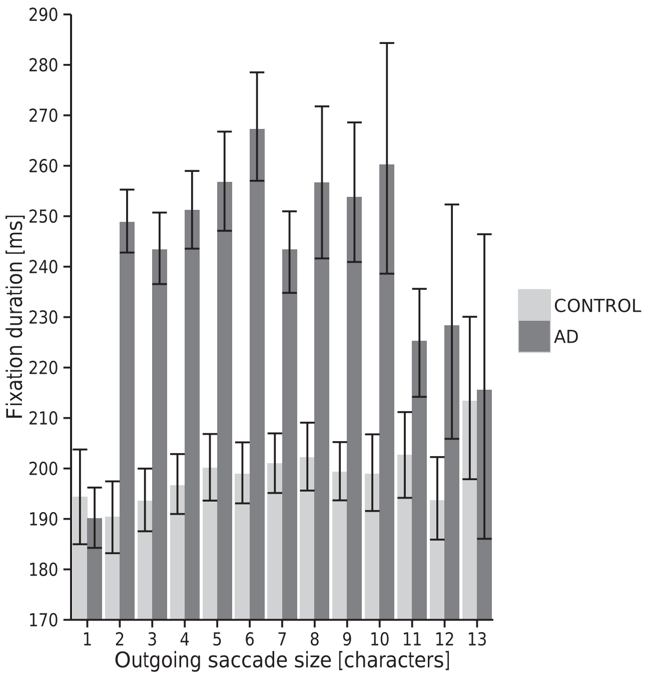

Figure 5. Effect of the size of the outgoing saccade on fixation duration [ms]. The graph represents the fixation duration at different sizes of outgoing saccades in controls and AD patients. Note that fixation durations were longer in AD patients than in controls; the average decrease in the number of characters of outgoing saccades in AD patients with respect to controls was 23%. $P < 0.001$. *Bars* represent mean ± SD, calculated using a one-way ANOVA.

patients, and almost doubled the amount of first-pass fixations observed for this group. Consistently, AD patients exhibited a simultaneous decrease in the amount of single fixations. A number of hypotheses have been proposed to explain the origin of second-pass fixations, including the necessity for comparison with the past image and interpretation of a given word in the context of a sentence.[39] The increase in these parameters might reflect the deficit in processing the current and incoming information in AD patients.

Backward eye movements, saccade regressions, which also occur during reading, are likely aimed to integrate previously acquired data with the new incoming information.[1] The higher number of regressions observed in AD patients compared with controls is consistent with the impairment in perceptual and cognitive processes associated to word processing in these patients and might be an attempt to compensate for this disability. Remarkably, AD patients also skipped a higher number of words than controls, an observation that might be related to mislocated fixations or a consequence of involuntary triggered saccades.[4]

Our work also revealed that fixation duration was significantly longer in AD patients than in controls. Consistent with these data, longer fixation durations have been reported in AD patients during visual search.[40] Information uptake is largely restricted to fixations[1,4]; hence, the longer fixations registered in AD patients might reflect the difficulties in acquiring and processing the visual inputs in these patients. This finding, together with the increase in the amount of fixations, agree with previous observations that readers make more fixations and fixate for longer time when they experience processing difficulty.[41]

In a recent study with subjects reading Chinese,[42] the size of outgoing saccades was proposed to depend on the complexity of the region in which vision is fixated; in general terms: The easier the processing of the fixated region is, the longer the outgoing saccade is. Interestingly, the size of the outgoing saccades was consistently shorter in AD patients than in controls. This reduction might reflect the impairment in memory and interpretation of words in AD patients compared with healthy individuals. Our results also show that the size of the outgoing saccade was more uniform in controls than in AD during processing of word length, word frequency, or word predictability, probably because controls use reading strategies such as word-based strategies or processing-based strategies. These reading strategies seem to be the rule for words of two or more letters. Outgoing saccades were remarkably longer for one-letter words in controls, which might be due to an enhanced parafoveal processing for one-letter words. Alternatively, one-letter words might be processed differently since they are usually connectors and recognized as such by healthy readers. Their use of them for joining previous and incoming words might thus lead to longer saccades. This capacity was absent in AD patients, which showed the shortest outgoing saccades for one-letter words.

The striking modifications observed in the saccadic movements in AD patients at their early stages of development reveal a considerable deterioration of one or more brain structures involved in controlling these behaviors. Visual fixation and saccadic movements are sophisticated responses in which several brain regions participate, including parietal and frontal cortex, basal ganglia, substantia nigra, and subthalamic nuclei, the caudate nuclei and the reticular formation in the brain stem, along with the cerebellum and the superior colliculus in the mesencephalon[43–48]; all of them must act in a coordinate way. The precise identification of which of the areas affected in AD are responsible for each or all of the alterations observed in eye movements requires further study.

The main conclusion of the present work is that AD patients at early stages of their disease, as those participating in this study, evidenced markedly altered eye movements during reading. This suggests that evaluation of these movements might provide an additional and sensitive tool for the much needed early diagnosis of AD disease.

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