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Journal of Clinical and Experimental Neuropsychology
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ncen20

Registering eye movements during reading in Alzheimer's disease: Difficulties in predicting upcoming words

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Published online: 28 Feb 2014.

To cite this article: Gerardo Fernández, Jochen Laubrock, Pablo Mandolesi, Oscar Colombo & Osvaldo Agamennoni (2014) Registering eye movements during reading in Alzheimer's disease: Difficulties in predicting upcoming words, Journal of Clinical and Experimental Neuropsychology, 36:3, 302-316, DOI: 10.1080/13803395.2014.892060

To link to this article: http://dx.doi.org/10.1080/13803395.2014.892060

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Journal of Clinical and Experimental Neuropsychology, 2014
Vol. 36, No. 3, 302–316, http://dx.doi.org/10.1080/13803395.2014.892060

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(*Received 4 April 2013; accepted 3 February 2014*)

Reading requires the fine integration of attention, ocular movements, word identification, and language comprehension, among other cognitive parameters. Several of the associated cognitive processes such as working memory and semantic memory are known to be impaired by Alzheimer's disease (AD). This study analyzes eye movement behavior of 18 patients with probable AD and 40 age-matched controls during Spanish sentence reading. Controls focused mainly on word properties and considered syntactic and semantic structures. At the same time, controls' knowledge and prediction about sentence meaning and grammatical structure are quite evident when we consider some aspects of visual exploration, such as word skipping, and forward saccades. By contrast, in the AD group, the predictability effect of the upcoming word was absent, visual exploration was less focused, fixations were much longer, and outgoing saccade amplitudes were smaller than those in controls. The altered visual exploration and the absence of a contextual predictability effect might be related to impairments in working memory and long-term memory retrieval functions. These eye movement measures demonstrate considerable sensitivity with respect to evaluating cognitive processes in Alzheimer's disease. They could provide a user-friendly marker of early disease symptoms and of its posterior progression.

Keywords: Reading; Eye movements; Word predictability; Fixation duration; Alzheimer's disease.

Alzheimer's disease (AD) is a nonreversible brain disorder that develops over a period of years. Initially, people experience memory loss and confusion, which may be mistaken for the kinds of memory changes that are sometimes associated with normal aging (Waldemar, 2007). AD is characterized by a loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe and parts of the frontal cortex and cingulated gyrus (Wenk, 2003). Studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have documented reductions in the size of specific brain regions in people with AD as they progress from mild cognitive impairment to Alzheimer's disease, and in comparison with healthy older adults (Moan, 2009). There are three major

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Funding: This work was supported by the Agencia Nacional de Promoción Científica y Tecnológica from Argentina [grant number PICT 2010 1421]; the Universidad Nacional del Sur [grant number PGI 2010 24/K038]; Deutsche Akademische Austausch Dienst [grant number A/11/77105].

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hallmarks in the brain that are associated with the disease progression of AD: increases in (a) amyloid plaques (Hardy & Allsop, 1991; Mudher & Lovestone, 2002; Priller et al., 2006; Tiraboschi, Hansen, Thal, & Corey-Bloom, 2004; Van Broeck, Van Broeckhoven, & Kumar-Singh, 2007), (b) neurofibrillary tangles (Braskie et al., 2010; Lee et al., 2005), and (c) loss of connections between neurons responsible for memory and learning (Hampel et al., 2008; Prull, Gabrieli, & Bunge, 2000).

Patients with early to moderate AD usually show an impairment of learning and a deterioration of episodic memory; such symptoms are typically used for a diagnosis of the pathology. However, while performing fine motor tasks such as writing or reading, certain movement coordination and planning difficulties that may be present are commonly unnoticed (Förstl & Kurz, 1999; Frank, 1994; Taler & Phillips, 2008). Eye movements could thus provide considerable insight about the integrity of control circuits in AD. The cognitive control of eye movements is a thriving area of research, primarily because of the thorough understanding of the oculomotor system and the ease with which eye movements can be measured. Understanding eye movement control could also shed light on the inner workings of complex behaviors such as attention, inhibitory control, working memory, and decision-making processes (Hayhoe & Ballard, 2005; Hoffman, 1998; Itoh & Fukuda, 2002; Miela, Lobel, Lehericy, Pierrot-Deseilligny, & Berthoz, 2005; Posner, 1980; Yarbus, 1967). Neurological connectivity changes early on in the course of the disease, disrupting controlled information processing (Arnáiz & Almkvist, 2003; Bäckman, Jones, Berger, Laukka, & Small, 2005; Förstl & Kurz, 1999; Landes, Sperry, Strauss, & Geldmacher, 2001). Networks and structures implicated in a range of eye movement behaviors are well defined, including those that measure working memory and saccadic execution (Itoh & Fukuda, 2002; Miela et al., 2005; Posner, 1980).

Reading is an ideal field for exploring the relationships between eye movements and memory processes.

When reading, healthy readers move their eyes on average every quarter of a second. During the time that the eyes are fixated, new information is brought into the processing system. The average fixation duration is 150–250 ms; the range is from 100 ms to over 700 ms (Rayner, 1998). The distance the eyes move in each saccade (or short rapid eye movement) is between 1 and 20 characters with the average being 7–9 characters. A saccade's primary function is to bring a new region of text into the foveal vision. Saccade execution takes about 20–50 ms. Information uptake for processing is largely restricted to fixations. Reading studies have relied on different measures of fixation durations (Kliegl, Nuthmann, & Engbert, 2006; Rayner, 1998, 2009). Based on these, we use in this paper: (a) gaze durations, which result from accumulating all the fixation times for a given word during first-pass reading, also including single-fixation cases; (b) single fixations, which result from words fixated exactly once.

Reading requires the efficient integration of several cognitive systems including attention, control of eye movements, word identification, and language comprehension. During fluent reading, the duration of a fixation on a word is influenced by cognitive factors such as syntactic, semantic and morphologic properties of the words in addition to low-level perceptual and oculomotor factors such as word length, spacing, and saccade landing position. Indeed, some of this information is necessary for programming saccades (Boston, Hale, Vasishth, & Kliegl, 2011; Just & Carpenter, 1980; Kliegl et al., 2006; Rayner, 1998, 2009). At the same time, printed frequency and cloze predictability of the fixated word (word *N*) as well as of its right neighbor (word *N*+1) exert their influence on fixation duration (Rayner, 1998, 2009; Vitu, Brysbaert, & Lancelin, 2004). Cloze predictability is the probability that the next word in a sentence is guessed, given only the prior words of the sentence (i.e., incremental cloze task procedure; Taylor, 1953; see Method section for an incremental cloze task procedure description).

Recent works (Fernández, Shalom, Kliegl, & Sigman, 2013; Kennedy & Pynte, 2005; Kennedy, Pynte, Murray, & Paul, 2012; Kliegl et al., 2006) demonstrated that fixation duration on word *N* decreases with increasing cloze predictability of word *N* (as expected), but increase with cloze predictability of word *N*+1. As the investigators showed, it is not the effect of the parafoveal visual presence of the word *N*+1 per se that increases the duration of the fixation on word *N*. Instead, it is its likelihood of appearance determined by the regularities of the sentence that evokes memory retrieval mechanisms prior to the initiation of the saccade. With enough contextual long-term memory support for an upcoming word, readers may start to process this word before their eyes move to it. Thus, the upcoming word predictability effect may have little to do with *visual* parafoveal processing; quite the contrary, it reflects an important contribution of long-term memory that facilitates comprehension during reading.

In the present work we analyze the effects of current and incoming word predictability on fixation duration. When a sentence is read by healthy readers, expectations about the next incoming word are incrementally generated and confirmed. We hypothesize that this is not the case for AD patients. Readers' incoming word predictions provide an ideal measure of this particular activity that is potentially distorted during the first stage of the illness. We also hypothesized that predictions of upcoming words are processed differently in healthy readers and AD patients. In this context, identifying cognitive operations that are specifically impaired in patients with AD might represent a significant improvement, which could help physicians to get an early diagnosis of AD. Since AD patients show evidence of impairments in memory, thinking skills, and word finding along with other aspects of cognition, it is reasonable to hypothesize that outgoing saccades (i.e., the distance between the last fixation on a word and the next fixation to the right) during reading might be shorter in these patients (Frank, 1994; Taler & Phillips, 2008).

In the first part of the paper we compare basic eye movement measures such as regression rates and the number of fixated, multifixated, and skipped words between the AD and control groups. In the second part we test the more specifically memory retrieval-related hypothesis about a group difference in positive *N*+1 predictability effects on fixation durations. We use linear mixed model analyzes to test word predictability and other fixed effects (i.e., length and frequency of word *N* and word *N*+1, word number, and the launch site effect).

These analyzes give us new insights and a measure of how AD patients process complex information in the early stage of the disease. Most importantly, these analyzes could help to distinguish whether the impairment is related with normal aging or whether it is specific to AD.

METHOD

Participants

A total of 18 patients (11 female and 7 male; mean age 69 years, *SD* = 7.2 years) with the diagnosis of probable AD were recruited in the Municipal Hospital of Bahía Blanca, Argentina. Diagnosis was based on the criteria for dementia outlined in the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (*DSM–IV*; American Psychiatric Association, 1994). In accordance with these criteria patients were excluded if: (a) they suffered any medical conditions that could account for, or interfere with, their cognitive decline; (b) had evidence of vascular lesions in computed tomography or fMRI; (c) had evidence for 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 tranquillizers. The control group consisted of 40 elderly adults (29 female and 11 male; mean age 71 years; *SD* = 6.1 years). By history, they had no known neurological and psychiatric disease and no evidence of cognitive decline or impairment in activities of daily living. A one-way analysis of variance (ANOVA) showed no significant differences between ADs' & controls' age, *F*(1, 56) < 1.

ADs' & controls' mean scores in the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) were 23.2 (*SD* = 0.7) and 27.8 (*SD* = 1.0), respectively. A one-way ANOVA showed significant differences between ADs' and controls' MMSE, *F*(1, 56) = 259.5, *p* < .00001. The ADs' & controls' mean high-school education trajectories were 15.2 (*SD* = 1.3) years and 15.1 (*SD* = 1.0) years, respectively. A one-way ANOVA showed no significant differences between ADs' & controls' education, *F*(1, 56) < 1. The ethics committee of the Hospital Municipal de Bahía Blanca approved the study. All patients and their caregivers and all control subjects gave written informed consent prior to inclusion into the study.

Apparatus and eye movement data

Single sentences were presented on the center line of a 20″ LCD monitor (1024 × 768 pixels resolution; font: regular; New Courier; 12 point, 0.5º in height). Participants were seated in front of the monitor with the head positioned on a chin rest at a distance of 60 cm from the monitor. Eye movements were recorded with an EyeLink 2K Desktop Mount (SR Research) eyetracker, with a sampling rate of 1000 Hz and an eye position accuracy of better than 0.5 deg. All recordings and calibration were binocular.

Eye movement data were cleaned for loss of measurement and blinks. Data of sentences without problems were reduced to a fixation format. This first level of screening led to a pool of 57,946 defined fixations (30,808 fixations in AD and 27,138 fixations in control, respectively). For this pool, we only considered for our analyzes first-pass reading fixations. There were 16,277 first-pass fixations in AD and 19,482 first-pass fixations in controls. In a second level of data screening, we excluded fixations on first (2320 fixations in AD and 4553 fixations in controls) and last words (5303 fixations in AD and 3974 fixations in controls) of sentences, and fixations shorter than 51 ms (204 fixations in AD and 16 fixations in controls) or longer than 1000 ms (64 fixations in AD and 350 fixations in controls). This second level of screening left us 8113 and 9970 first-pass reading fixations (in AD and in controls, respectively). Our first-pass constraint excluded fixations prior to and after regressions to previous words irrespective of whether these words had been skipped or fixated before.

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° distance from the fixation spot, the sentence was presented. At the same time, a small dot was shown in the lower right corner of the screen. Participants were instructed to indicate the end of reading by looking at this dot. When the gaze was detected there, the trial ended, and the next trial began with the presentation of the fixation spot. On 20% of the trials, a three-alternative multiple-choice question about the current sentence was presented. Participants answered the question moving a mouse and choosing the response with a mouse click. Then, the next trial started with the presentation of the fixation spot. The experimenter did an extra calibration after reading 15 sentences or if the eyetracker did not detect the eye at the initial fixation point within 2 s (see Figure 1 with example sentences including fixations of both eyes).

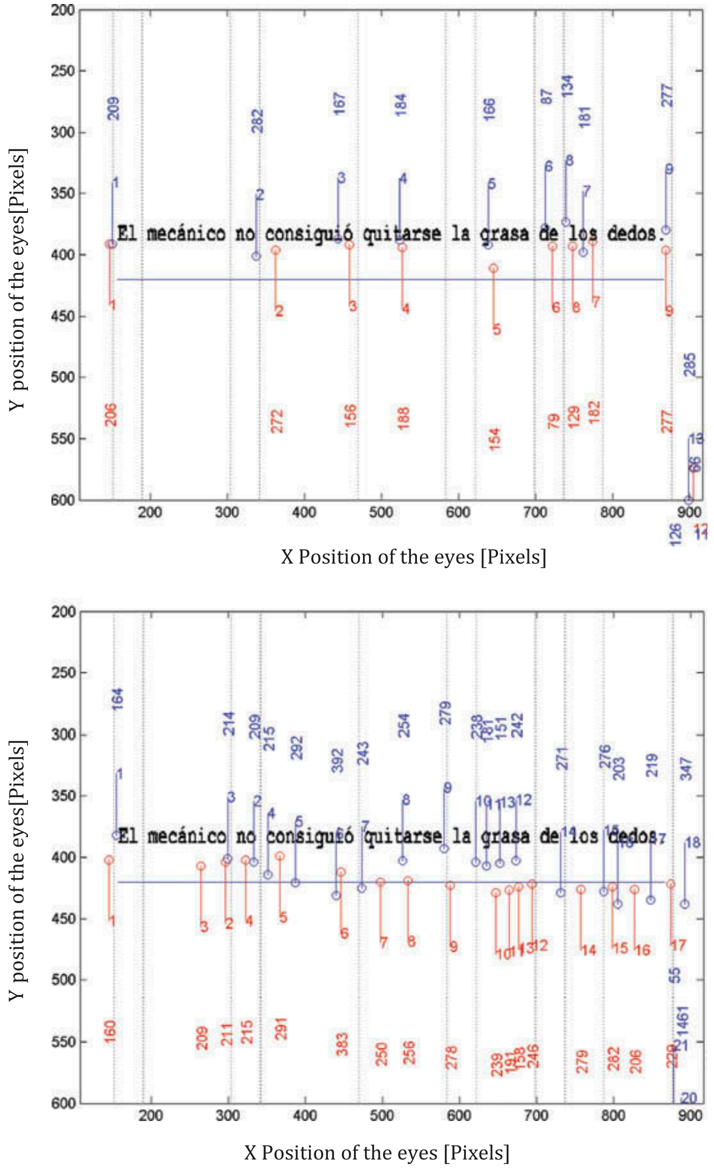

Figure 1. Example sentences of (a) control and (b) Alzheimer's disease (AD) with fixation point for right (red or points linked to bottom numbers) and left (blue or points linked to top numbers) eye. The down and right movements signaled the end of reading; numbering linked to points indicates fixation sequences; fixation durations of each eye are listed with their corresponding color. To view a color version of this figure, please see the online issue of the Journal.

Sentence corpus

The sentence corpus was composed of 75 sentences (620 words). They were constructed with the goal to represent a large variety of grammatical structures.

Word and sentence lengths

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

Word frequencies

We used the Spanish lexical *Léxesp* corpus (Sebastián-Gallés, Martí, Cuetos, & Carreiras, 1998) 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 $\log_{10}$ base. Mean $\log_{10}$ (frequency) was 3.4 (*SD* = 1.3).

Word predictabilities

Word predictability was measured in an independent experiment with 18 researchers of the electrical engineering and computer science department of 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 guessed the first word of the unknown sentence and entered it via the keyboard. In return, the computer presented the first word of the original sentence on the screen. Responding to this, participants entered their guess for the second word and so on, until a period indicated the end of the sentence. Correct words stayed on the screen. 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. Word predictabilities ranged from 0 to 1 with a mean of 0.38 (*SD* = 0.36). The average predictability measured from the cloze task was transformed using a logit function. Logits are defined as .5 × ln(pred)/(1 – pred); predictabilities of zero were replaced with 1/(2 × 18) = –2.55 and those of the five perfectly predicted words with [2 × (18–1)]/(2 × 18) = +2.55, where 18 represents the number of complete predictability protocols (Cohen & Cohen, 1975). Mean logit predictability was –1.03 (*SD* = 0.9).

Linear mixed-effect models

We used the lmer program of the lme4 package (Version 0.999999-2; Bates & Maechler, 2013) for estimating fixed and random coefficients. This package is supplied in the R system for statistical computing (Version 3.0.1; R Development Core Team, 2013) under the GNU General Public License (Version 2, June 1991).

The dependent variable was log of gaze duration in one model and log single-fixation duration in the other one. Fixed effects in linear mixed model (LMM) terminology correspond to regression coefficients in standard linear regression models. They can also estimate slopes or differences between conditions. A number of fixed effects were entered into the model: predictabilities of word *N* and of word *N*+1, lengths and frequencies of word *N* and of word *N*+1, launch site, and the interaction of frequency and length of word *N*.

A traditional variable in coding predictability in event-related brain potentials (ERPs) research has been the ordinal position of a word in the sentence (e.g., Dambacher, Kliegl, Hofmann, & Jakobs, 2006; Van Petten & Kutas, 1990). Kuperman, Dambacher, Nuthmann, and Kliegl (2010) reported that the absolute word number is a significant predictor in addition to predictability. Given the focus on predictability, it was important to control for this effect as well. In our work, the correlation between the absolute word number and predictability was r = .40. In addition, we estimated how strongly mean log gaze duration and log single-fixation duration varied with participants, words, and sentences by fitting crossed random intercepts for participants, sentences, and words. Instead of estimating a slope or a difference between conditions, random effects estimate the variance that is associated with the levels of a certain factor.

For the LMMs we report regression coefficients (*b*s) standard errors (*SE*s) and *t*-values ($t = b/SE$). There is no clear definition of "degree of freedom" for LMMs, and therefore precise *p*-values cannot be reported. In general, however, given the large number of observations, subjects, and items entering our analysis and the comparatively small number of fixed and random effects estimated, the *t*-distribution is equivalent to the normal distribution for all practical purposes (i.e., the contribution of the degrees of freedom to the test statistic is negligible). Our criterion for referring to an effect as significant is $t = b/SE > 2.0$.

RESULTS

The presentation of results is organized into two main sections. In the first section, we present statistics on the number of fixations, multiple fixations, regressions, and word skipping for each group during reading of our sentence corpus. In the second section, we present the results of LMM statistical analyzes.

As in other languages, we find strong correlations in Spanish between word length, word frequency, and word predictability. Long words are of low frequency (r = –.80), frequent words are highly predictable (r = .47), and highly predictable words tend to be short words (r = –.47).

Eye movement behavior

Eye movement registers of 18 AD patients and 40 controls reading 75 sentences generated a total number of 30,808 and 27,138 defined fixations, respectively. Thus, AD patients significantly increased the number of fixations as compared with controls. During the first-pass reading, the AD group produced 8113 (26%) fixations and the control group 9970 (36%) fixations. Interestingly, AD group did a large number of second-pass reading fixations, which represented 14,531 (47%) of all defined fixations. In the control group, second-pass reading fixations only represented 7656 (28%) of all defined fixations. Regressions to previous words were larger in the AD group than in the control group: 4313 (14%) versus 1944 (7%). The pattern of regressions between groups shows that the AD group returned to previous words more times than controls did. At the same time, there were 5545 (18%) intraword regressions in the AD group versus 2193 (8%) in the control group. It seems that AD group needed to do more fixations to previous and on current words, probably for integrating and recovering word information. In the analysis of skipping rates between both groups we observed that the AD group patients skipped only 5660 (18%) words, whereas the control group participants skipped 8415 (31%) words. As expected, the word skipping probability is higher in the control group than in the AD group, probably indicating difficulties in the AD group for predicting upcoming words during reading.

Additionally, the AD group performed only 2050 (6%) first-pass single fixations, compared to 6024 (22%) in the controls. Finally, the AD group generated 4926 (16%) gaze fixations versus 8429 (31%) in the control group.

Gaze duration linear mixed model

Main effect of groups

Mean gaze duration was clearly longer in the AD group than in the control group (t = –11.32; see Figures 2a, 2b, and 2c and Table 1), due to the much higher multiple fixation rate. We address explanations about the gaze duration differences between groups in the Discussion section.

Word N and word N+1 predictability effects

LMMs are summarized in Table 1. As expected, the word N predictability effect was only negative and significant for the control group (t = –2.07), indicating that the controls spent less time processing highly predictable words. On the other hand, the effect of word N predictability for AD was null (t = 0.12); the interaction with group was not significant (t = –1.41). With respect to the incoming word predictability, and as we predicted, only in the control group did gaze durations increase significantly with the predictability of word N+1 (t = 2.19) interpreted as evidence for memory retrieval of predictable words (Fernández et al., 2013; Kennedy et al., 2012; Kliegl et al., 2006). Moreover, in agreement with expectations, there was no upcoming word predictability effect in the AD group (t = –0.91). The interaction between groups was significant (t = 2.05). Our main prediction was that once healthy readers (i.e., control group) could predict syntactic and semantic contextual structures during reading, they could also infer what word might come up next (less processing might be required since common word structures have already been recovered from memory), whereas the AD group due to deficits in memory cannot use memory to predict the upcoming word effectively. Indeed, the AD group did not generate an incoming word predictability effect (see Figure 2a).

Effects of other covariates

With respect to word frequency, the effect of word N was significant for both the AD group (t = –13.39), and the control group (t = –10.42), in agreement with previous works (Fernández et al., 2013; Kliegl et al., 2006). The word frequency effect was more pronounced in the AD group, as indicated by a significant interaction with group (t = 4.45). In the main effects analysis, we identified a suppressor constellation relating to length and frequency of the fixated word N. This suppressor constellation disappeared when we included a multiplicative interaction term of frequency and length. The interaction was highly significant in AD and in the control group (t = 9.32 and t = 8.42, respectively), and the interaction between groups was significant too (t = –2.54). A 2 × 2 breakdown of word length (fewer than five words vs. five words and

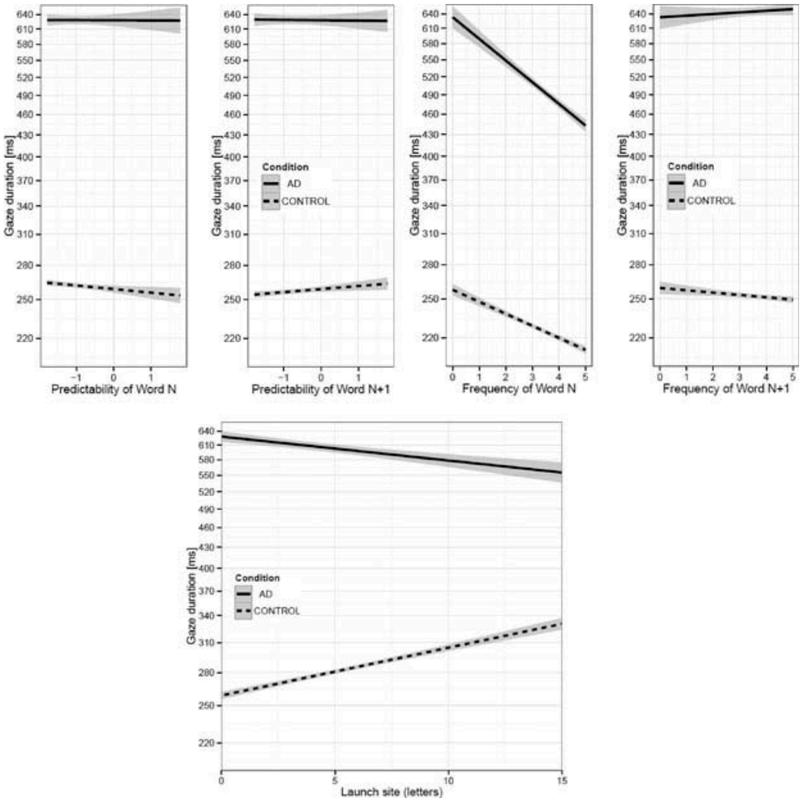

Figure 2. (a) Predictability effects of word *N* (left) and word *N*+1 (right) on gaze durations on word *N*, for control (dotted line) and for patients with probable Alzheimer's disease (AD). (b) Frequency effects of word *N* (left) and word *N*+1 (right) on gaze durations on word *N*, for control (dotted line) and for patients with probable Alzheimer's disease. (c) Launch site effects on gaze durations, for control (dotted line) and for patients with probable Alzheimer's disease. Panels show partial effects of linear mixed model (LMM; i.e., after removal of other fixed effects and variance components for mean fixation durations of subjects, sentences, and words). Shaded areas are 95% confidence intervals; fixation duration is plotted on a log scale for correspondence with the LMM. To view a color version of this figure, please see the online issue of the Journal.

more) and frequency (median split) revealed a well-differentiated word frequency effect for short words and for long words in AD (b = –6.143, SE = 1.708, t = –3.59 vs. b = –2.281, SE = 0.295, t = –7.73, respectively) and in the control group (b = –3.340, SE = 1.128, t = –2.96 vs. b = –0.759, SE = 0.209, t = –3.63, respectively).With this relative-frequency effect in the regression equation, effects of reciprocal word length and word frequency were in the expected direction (i.e., long fixation durations for long and low-frequency words). The effect of word *N* +1 frequency was not significant for the AD group (t = 1.36) but, as in previous works (Fernández et al., 2013; Kliegl et al., 2006), it was for the control group (t = –2.30). The interaction between groups was significant (t = –2.46; see Table 1 and Figure 2b).

When we considered word length, the effect of word *N* was significant for both the AD (t = –12.09) and the control group (t = –9.55). Both groups showed a significant inverse *N*-length effect, and the group interaction was significant (t = 4.20).The length of word *N*+1 had no significant effect in either group (t = 0.11 in AD and t = 0.71 in the control group).

Gaze durations increased significantly with word number only in the control group (t = 2.13). The word number effect was not significant in AD (t = 1.35), and the interaction between groups was not significant (t = –1.48). Finally, the largest effect in both groups was associated with launch site: The larger the distance between the last fixation location and the beginning of the fixated word, the shorter the current word gaze duration in the AD group (t = –7.12), but the longer the current word gaze duration in the control group (t = 9.49). The effect thus switched sign between groups, as indicated by the significant interaction between groups (t = 11.63; see Table 1). This is suggestive of between-group differences in parafoveal preprocessing of the upcoming word (see Figure 2c and Discussion section).

TABLE 1
LMM for gaze duration

			AD			*Control*			*Interaction AD vs. control*		
Fixed effects	*Variance*	SD	M	SE	t	M	SE	t	M	SE	t
Mean gaze duration (log)			6.804	0.097	**69.95**	5.729	0.082	**69.70**	–1.074	0.094	**–11.32**
Lengths											
Word *N*			–2.833	0.234	**–12.09**	–1.607	0.168	**–9.55**	1.226	0.286	**4.27**
Word *N*+1			0.004	0.046	0.11	0.022	0.031	0.71	0.017	0.055	0.31
Frequencies (log)											
Word *N*			–0.140	0.010	**–13.39**	–0.082	0.007	**–10.42**	0.058	0.013	**4.45**
Word *N*+1			0.009	0.007	1.36	–0.011	0.005	**–2.30**	–0.021	0.008	**–2.46**
Predictabilities (logit)											
Word *N*			0.000	0.007	0.12	–0.012	0.006	**–2.07**	–0.013	0.009	**–1.41**
Word *N*+1			–0.006	0.007	–0.91	0.011	0.005	**2.19**	0.018	0.008	**2.05**
Launch site			–0.010	0.001	**–7.12**	0.011	0.001	**9.49**	0.021	0.001	**11.63**
Word number			0.012	0.009	1.35	0.019	0.009	**2.13**	–0.006	0.004	–1.48
Interaction (freq *N*)/(length *N*)			0.432	0.046	**9.32**	0.287	0.034	**8.42**	–0.145	0.057	**–2.54**
Variance components											
Word	0.005	0.072									
Sentence	0.002	0.046									
Subject	0.032	0.180									
Residual (n = 13,355)	0.162	0.403									
N readers			18			40			58		
N of first-pass fixations			4926			8429			13,355		

Notes. Parameter estimates for fixed effects of linear mixed models. Threshold of significance is set at $t = \pm 2$. AD = Alzheimer's disease; LMM = linear mixed model. Numbers in bold represent significant values.

First-pass single-fixation duration linear mixed model

As we mentioned in the introduction, studies of reading rely on different measures of fixation durations. Many analyses reported in healthy readers were based on single-fixation durations. Here, we investigated the robustness of this effect by repeating the LMM analysis with single-fixation durations. Results (Table 2) were similar to those obtained on gaze durations (Table 1). There were coincidences for 8 out of 9 effects in AD and for 8 out of 9 effects in controls. The incoming word predictability effect for the control group remained significant and positive in both models. Interestingly, when considering the effect of single-fixation durations, while the trends were similar, data showed lower patterns of significance. This is evident when comparing the left columns of Table 1 (gaze duration) and Table 2 (single-fixation duration), with most of the interactions reaching significance in the analysis of gaze duration. In other words, the results were more marked when analyzing gaze durations than when analyzing single-fixation durations.

Outgoing saccade amplitude

We built a model with outgoing saccade amplitude as the dependent variable using the same predictors as those in the other two LMM analyzes (i.e., gaze and single-fixation analyzes). Mean outgoing saccade amplitude (in characters) was markedly smaller in the AD group than in the control group ($t = 4.87$ vs. $t = 16.17$, respectively), and the interaction between groups was significant ($t = 6.15$). In the AD group, the significant effects were related to the length of word N (length N; $t = 2.97$), the frequency of word N (freq N; $t = 5.91$), and the (freq N)/(length N) interaction ($t = –4.83$; see Table 3). In the control group, the length of word N ($t = –2.62$), the predictability of word N+1 ($t = 2.53$), and launch site ($t = –10.42$) exerted a significant influence on the outgoing saccade amplitude. Interestingly, the word length effect was significant in both groups, albeit with opposite slopes. In addition, the predictability of word N+1 only produced a significant and positive effect in controls. The other significant effect in controls was related to launch site, where, as usual, long saccades were followed by short saccades (Rayner, 1998; see Table 3). Therefore, outgoing saccade amplitudes were smaller in the AD group than in the control group.

Using eye movements to predict AD

Thus, there is evidence for large group differences on the microlevel of individual fixations. Can we also use aggregate subject-based summaries of eye movement measures to predict group membership? A logistic regression analysis was conducted to determine whether average log gaze duration, launch site, frequency of fixated words, and predictability of upcoming words were able to differentiate patients from controls. Interestingly, on a per-subject level only mean log gaze duration ($b = 8.7$, $z = 2.51$, $p = .012$) and, marginally, mean word frequency ($b = 11.7$, $z = 1.96$, $p = .0505$), were significant predictors of AD; nevertheless, mean upcoming predictability ($b = 15.3$, $z = 1.56$, $p = .118$) was kept in the model because it helped improve classification accuracy. Eye movement measures, although only used exploratively in this study, already proved quite diagnostic: Overall, group membership of 91% of participants was correctly predicted; sensitivity (hit rate) of the classification was 78%, and specificity (1 – false-alarm rate) was 98% (see Table 4). Of course, there is room for improvement by further research as far as the sensitivity is concerned, but given the fact that this was the result of just an explorative use, measurement of eye movements should be regarded as a potentially powerful addition to the diagnosticians' tool set.

DISCUSSION

In the present work we found that all patients with probable AD could recognize letters and words and could understand written material. Although AD patients were able to overtly read written material, they showed slow eye movements during reading. Compared with controls, the patients with AD had significantly longer fixation durations, fewer first-pass fixations, more intraword and second-pass reading fixations, and less word skipping.

Previous experiments (Hogson, Bajwa, Owen, & Kennard, 2000; Hogson, Tiesman, Owen, & Kennard, 2002; Land, Mennie, & Rusted, 1999) showed the importance of a selective strategy for successful performance in neuropsychological tasks, where subjects who made errors spent more time looking at irrelevant items. This also seems to be very descriptive of AD eye movement behavior, where first-pass fixations represented only 26% of all valid fixations. Simultaneously, the high percentage of ADs' second-pass fixations (47% of all valid fixations) probably reflected problems for extracting word information with just one or two fixations per word. These kinds of patterns suggest that controls are significantly better than ADs at recognizing words and shifting attention (controls' second-pass fixations represented only 28% of all valid fixations).

TABLE 2
LMM for single-fixation duration

			AD			*Control*			*Interaction AD vs. control*		
Fixed effects	*Variance*	SD	M	SE	t	M	SE	t	M	SE	t
Mean single-fixation duration (log)			5.778	0.134	**43.08**	5.083	0.085	**59.27**	–0.694	0.140	**–4.94**
Lengths											
Word *N*			–1.798	0.378	**–4.75**	–0.571	0.217	**–2.63**	1.227	0.434	**2.82**
Word *N*+1			–0.090	0.068	–1.32	0.052	0.005	1.48	0.142	0.077	1.86
Frequencies (log)											
Word *N*			–0.101	0.020	**–5.03**	–0.027	0.010	**–2.55**	0.073	0.022	**3.25**
Word *N*+1			0.023	0.016	1.36	–0.009	0.009	–1.00	–0.032	0.019	–1.68
Predictabilities (logit)											
Word *N*			–0.006	0.009	–0.70	–0.016	0.006	**–2.55**	–0.009	0.011	–0.80
Word *N*+1			0.000	0.008	0.10	0.014	0.005	**2.85**	0.014	0.010	1.38
Launch site			0.008	0.002	**3.19**	0.020	0.001	**13.92**	0.011	0.002	**4.03**
Word number			0.010	0.009	1.09	0.020	0.008	**2.42**	0.010	0.005	1.82
Interaction (freq *N*)/(length *N*)			0.008	0.002	**3.19**	0.020	0.041	**2.39**	–0.246	0.083	**–2.97**
Variance components											
Word	0.004	0.064									
Sentence	0.003	0.055									
Subject	0.033	0.183									
Residual (n = 8074)	0.110	0.331									
N readers			18			40			58		
N of first pass fixations			2050			6024			8074		

Notes. Parameter estimates for fixed effects of linear mixed models. Threshold of significance is set at $t = \pm 2$. AD = Alzheimer's disease; LMM = linear mixed model. Numbers in bold represent significant values.

TABLE 3
LMM for outgoing saccade amplitude

			AD			*Control*			*Interaction AD vs. control*		
Fixed effects	*Variance*	SD	M	SE	t	M	SE	t	M	SE	t
Mean saccade amplitude (characters)			3.326	0.679	**4.87**	8.082	0.499	**16.17**	4.756	0.772	**6.15**
Lengths											
Word *N*			6.436	2.160	**2.97**	–4.088	1.557	**–2.62**	–10.525	2.570	**–4.09**
Word *N*+1			0.538	0.068	–1.32	–0.564	0.403	–1.39	–0.102	0.664	–1.65
Frequencies (log)											
Word *N*			0.539	0.091	**5.91**	0.033	0.071	0.46	–0.505	0.109	**–4.61**
Word *N*+1			–0.002	0.063	–0.03	–0.021	0.047	–0.45	–0.002	0.063	–0.25
Predictabilities (logit)											
Word *N*			0.065	0.076	0.85	0.013	0.066	0.20	0.065	0.076	0.85
Word *N*+1			–0.072	0.149	–0.48	0.290	0.114	**2.53**	0.362	0.180	**2.00**
Launch site			0.006	0.011	0.58	–0.103	0.009	**–10.42**	–0.011	0.015	**–7.33**
Word number			–0.072	0.039	–1.82	0.048	0.034	1.42	0.012	0.037	**3.23**
Interaction (freq *N*)/(length *N*)			–1.905	0.394	**–4.83**	0.393	0.297	1.32	–1.905	0.394	**–4.83**
Variance components											
Word	0.024	0.157									
Sentence	0.289	0.537									
Subject	2.136	1.461									
Residual (n = 13,355)	10.624	3.259									
N readers			18			40			58		
N of first-pass fixations			4926			8429			13,355		

Notes. Parameter estimates for fixed effects of linear mixed models. Threshold of significance is set at $t = \pm 2$. AD = Alzheimer's disease; LMM = linear mixed model. Numbers in bold represent significant values.

TABLE 4
Logistic regression

	Actual group	
Predicted group	*AD*	*Control*
"AD"	14	1
"Control"	4	39

Notes. Classification result of a subject-based logistic regression of group status (AD vs. control) on predictor variables of mean log gaze duration, mean fixated word frequency, and mean upcoming word predictability. AD = Alzheimer's disease.

Additionally AD patients only skipped 18% of upcoming words versus 31% of skipped words in the control group. The expectation was that once readers could predict syntactic and semantic contextual structures during reading, they could also infer what words should come next, thereby skipping more upcoming words. This low rate of skipped word suggests problems for AD patients in integrating and using word stored information, presumably due to impairments in the working memory and in retrieval memory. Furthermore, prior research on AD indicates that reading comprehension declines progressively with increased dementia severity as the result of a decline in semantic processing for meaning or in lexical access (Cummings, Houlihan, & Hill, 1986; Lueck, Mendez, & Perryman, 2000).

Memory is guiding eye movements during reading

Incoming word predictability effect

Previous findings showed that the word $N+1$ may have an effect on fixation duration via memory retrieval in healthy readers (Fernández et al., 2013; Kennedy & Pynte, 2005; Kennedy et al., 2012; Kliegl et al., 2006). The likelihood of appearance is determined by the regularities of the sentence, which evoke memory retrieval mechanisms prior to the initiation of the saccade. Our results suggest that the retrieval mechanism may be impaired in AD. Namely, there were no significant effects related to the predictability of upcoming words. In normal readers, distributed processing effects tied to properties of upcoming words exert an influence on fixation duration not only with respect to visual processing in the perceptual span, but also by indicating whether an accurate representation of the sentence has already been achieved by relying on memory retrieval for predicting incoming words. Probing online comprehension processes and tracing their effects to fixation durations might facilitate a very early measure of ADs' text comprehension and eye-movement patterns during reading.

Word predictability effect modulates the incoming word frequency effect

There were other empirical effects related to the incoming word: The positive $N+1$ predictability and the negative $N+1$ frequency slope were only present in the control group. A negative $N+1$ frequency effect and a positive $N+1$ predictability effect are remarkable because frequency and predictability are positively correlated with each other. Thus, their opposite relation with fixation duration may offer a probe about higher order memory and lower order visual processes (Ungerleider & Haxby, 1994). This pattern was not present in the AD group, which suggests that in AD the predictability effect did not exert an influence on higher order memory processes during reading.

Launch site effect

Launch site distance had a large effect on fixation duration, and the size and direction of this effect clearly differed between groups: For control subjects, as usual, the further away from the fixated word's beginning the saccade was launched, the longer the word had to be fixated. This effect seems to indicate either a preprocessing of the upcoming word in the parafovea or an influence of the predictability of the incoming word (Rayner, Warren, Juhasz, & Liversedge, 2004; Rayner & Well, 1996). For the AD group, the further away from the fixated word's beginning the saccade was launched, the shorter the word was fixated in first pass. There are studies (Daffne, Scinto, Weintraub, Guinessey, & Mesulam, 1992; Mosimann, Felblinger, Ballinari, Hess, & Müri, 2004) about occipito-temporal and occipito-parietal networks for addressing a potential explanation about ADs' launch site behavior during reading. As the studies have shown, the occipito-temporal network is important for central vision and for generating small saccades, and the occipito-parietal network for spatial global vision and for generating long saccades. Thus, an imbalance between the two networks with a more pronounced occipito-parietal function may lead to predominantly shorter saccade amplitudes and longer fixations during exploration. This explanation was supported by a fMRI study, which found a reduced parietal activation and increased temporal activation during visuospatial processing in the AD group (Moser, Köompf, & Olshinka, 1995). Thus, longer fixations are in agreement with impaired parietal function due to impaired disengagement of fixations, as reported in previous studies (Ball , Beard, Roenker, Miller, & Griggs, 1998; Cummings et al., 1986; Rizzo, Anderson, Dawson, & Nawrot, 2000; Rösler et al., 2000).

Outgoing saccades amplitudes and top-down processes

Smaller outgoing saccades may also be the consequence of a reduced visual area from which information can be acquired within one fixation (Filoteo et al., 1992; Parasuraman, Greenwood, & Alexander, 2000), or of impaired shifting between foveal and parafoveal vision (Rizzo, Anderson, Dawson, Myers, & Ball, 2000; Slavin, Mattingley, Brandshaw, & Storey, 2002). Visually guided saccades are mainly driven "bottom-up" by the visual stimuli, whereas the exploration of words during reading needs a more "top-down" control for target selection (i.e., word selection) and fixation disengagement (Rizzo, Anderson, Dawson, & Nawrot, 2000). The "top-down" control might also be tied to a working memory deficiency in the AD group, since to make effective use of preview, the upcoming word needs to be stored in a temporary buffer. When we analyzed the influences of upcoming words on outgoing saccades in old healthy subjects (i.e., controls), only word predictability was significant. Other works (Drieghe, Brysbaert, & Desmet, 2005; Kennedy, 1998; Rayner, White, Kambe, Miller, & Liversedge, 2003) reported, additionally, an increase of saccade amplitudes due to word *N*+1 length. Curiously, in our work this last effect was not significant. Obviously, more research will be needed for explaining the absence of an effect related to word *N*+1 length.

In summary, we propose that analysis of eye movements during reading provides a valuable measure to assess important components of the disease. Our study supports the hypothesis that memory-guided eye movements and abnormalities sensitively reflect deficits in attention, working memory, and semantic memory processes in AD. We suggest that a more comprehensive evaluation of eye movements during reading, incorporating both an in-depth analysis of eye movements and assessment of cognitive processes (i.e., incoming word predictions), may well provide a user-friendly marker of early disease symptoms and of its posterior progression.

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