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Lack of contextual-word predictability during reading in patients with mild Alzheimer disease

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ABSTRACT

In the present work we analyzed the effect of contextual word predictability on the eye movement behavior of patients with mild Alzheimer disease (AD) compared to age-matched controls, by using the eyetracking technique and lineal mixed models. Twenty AD patients and 40 age-matched controls participated in the study. We first evaluated gaze duration during reading low and highly predictable sentences. AD patients showed an increase in gaze duration, compared to controls, both in sentences of low or high predictability. In controls, highly predictable sentences led to shorter gaze durations; by contrary, AD patients showed similar gaze durations in both types of sentences. Similarly, gaze duration in controls was affected by the cloze predictability of word N and $N+1$, whereas it was the same in AD patients. In contrast, the effects of word frequency and word length were similar in controls and AD patients. Our results imply that contextual-word predictability, whose processing is proposed to require memory retrieval, facilitated reading behavior in healthy subjects, but this facilitation was lost in early AD patients. This loss might reveal impairments in brain areas such as those corresponding to working memory, memory retrieval, and semantic memory functions that are already present at early stages of AD. In contrast, word frequency and length processing might require less complex mechanisms, which were still retained by AD patients. To the best of our knowledge, this is the first study measuring how patients with early AD process well-defined words embedded in sentences of high and low predictability. Evaluation of the resulting changes in eye movement behavior might provide a useful tool for a more precise early diagnosis of AD.

1. Introduction

In Alzheimer's disease (AD), progressive neuropathological changes affect certain laminae and cell types within the neocortex, which may lead to cortico-cortical disconnections (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001; Mosimann, Felblinger, Ballinari, Hess, & Müri, 2004). This pathology preferentially involves temporo-parietal association areas (Levine, Lee, & Fisher, 1993; Hendrie, 1998; Wong, 2008). This makes patients with AD prone to visual and attentional disturbances (Fujimori, et al., 2000; Mendez, Mendez, Martin, Smyth, & Whitehouse, 1990). Further, neurological connectivity changes early in the course of the disease, disrupting controlled processing of information (Arnáiz & Almkvist, 2003; Bäckman, Jones, Berger, Laukka, & Small, 2005; Förstl et al., 1999; Landes, Sperry, Strauss, & Geldmacher, 2001). In AD, visual exploration has been employed to measure spatial attention (Scinto et al., 1994; Mosimann et al., 2000), and has been characterized during visual search of emotional facial expressions (Daffne, Mesulam, Cohen, & Scinto, 1999; Moser, Koempf, & Olschinka 1995; Ogrocki, Hills, & Strauss, 2000). Most of these studies reported longer fixation duration and less systematic exploration during visual tasks.

The sequence of fixations and saccades during visual exploration is crucial for perception and is very effective for sampling information acquisition (Rayner & Pollatsek, 1992). In healthy subjects, visual information is processed during fixation. To make a new fixation, saccades direct the fovea towards a particular element of interest (Martinez-Conde, Macknik, & Hubel, 2004). Fixation behavior is the end result of a complex interaction of features of the explored picture ("bottom up" processing) and the

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instruction or question to be solved by the explorer ("top down" processing) (Awh, Vogel, & Oh, 2006; Cowan & Morey, 2006; Gilbert & Sigman, 2007; Khayat, Spekreijse, & Roelfsema, 2006; Palmer, 1990; Sigman & Gilbert, 2000; Yarbus, 1967). Thus, perception involves active predictions of upcoming events to grant smooth sensory analysis (Corbetta & Shulman, 2002; Kveraga, Ghuman, & Bar, 2007).

Early diagnosis of AD is still difficult. People 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, the subtle alterations in movement coordination and planning that may also be present while performing fine motor tasks such as writing or reading at the very beginning of the disease, are harder to detect and go commonly unnoticed (Frank, 1975; Taler & Phillips, 2008). Therefore, it is difficult to get an early diagnosis of this disease. Evaluation of eye movements might provide considerable insight into the integrity of control circuits in AD (Crawford et al. 2012; Daffner et al., 1999; Fernández et al. 2013a; Mosimann et al., 2004; Moser, KoÈmpf, and Olschinka 1995; Ogrocki et al., 2000; Rösler et al. 2000; Leigh and Zee, 2006).

Reading, a well-overlearned activity for many, is ideally suited to investigate the interplay of input and expectancy driven processes, because it involves highly optimized object-recognition. During fluent reading, the duration of a fixation on a word is influenced by the syntactic, semantical and morphological properties of the words. One of these properties is called cloze predictability, defined as the probability that the next word in a sentence be guessed, given only the prior words of the sentence (Taylor, 1953). Both, the printed frequency of a word and the cloze predictability of the past word ($N-1$), of the current word (word N) and of the upcoming word (word $N+1$) influence fixation duration (Kennedy & Pynte, 2005; Kennedy, Pynte, Murray, & Paul, 2012; Kliegl, Nuthmann, & Engbert, 2006; Rayner, 1998). Recent work (Fernández, Shalom, Kliegl, & Sigman, 2013b; Fernández, Laubrock, Mandolesi, Colombo, & Agamennoni, 2014; Kliegl, 2007; Kennedy et al., 2012) demonstrated that fixation duration on the word N decreases with increasing cloze predictability of word N, but increases with cloze predictability of word $N+1$. As the mentioned 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.

Eye movements in healthy old readers showed significant effects on fixation duration when considering printed word frequency and an increase in reading speed when considering word predictability (Kliegl, Grabner, Rolfs, & Engbert, 2004; Rayner, Reichle, Stroud, Williams, & Pollastek, 2006). In parallel, Laubrock, Kliegl, & Engbert (2006) proposed that healthy old readers perform better when using the semantic context of the sentence. Other studies propose that skilled old readers might know (or guess) the location and the length of words and can move their eyes to a particular location (McConkie, Kerr, Reddix, & Zola, 1988; Rayner, Fischer, & Pollastek, 1998; Fernández et al., 2013b). Though healthy older readers apparently have a slightly smaller (and less asymetric) perceptual span, and a decrease in the preview benefit obtained from the word to the right of fixation (Rayner, Castelhano, & Yang, 2010). Laubrock et al., (2006) proposed that their use of the semantic context of the sentence compensate an asymmetry in their perceptual span. Using a different measuring technique, the electroencephalogram (EEG), Federmeier & Kutas (2005) suggested that reductions in working memory capacity might be one source of older adult's difficulty in rapidly using sentence-level information. Further, Federmeier, Kutas, & Schul (2010) reported that older adults as a group are less likely to manifest prediction-related benefits during sentence processing. Recently, Lindenberger & Mayr (2014) proposed that healthy older adults´ performance increases when the environment provides task-appropriate cues. At the same time, predictive category cueing has been shown to enhance the speed and accuracy with which stimuli are detected and discriminated (Esterman & Yantis, 2009; Gazzaley, 2013).

Healthy readers, with a normal long-term memory support for an upcoming word, may start to process this word before their eyes move to it. In principle, the effect may have very little to do with visual parafoveal processing, but instead reflect a contribution of long-term memory that facilitates reading comprehension. Previous work (Fernández et al., 2013a; Lueck, Mendez, & Perryman, 2000) has shown that patients with moderate AD show abnormalities in eye movements during reading of a text and that reading difficulty correlates with dementia severity. Furthermore, patients with AD develop progressive language, visuoperceptual, attentional, and oculomotor changes that can have an impact on their reading comprehension (Arslan, Larsen, & Hoein, 1993; Cummings, Houlihan, & Hill, 1986). In healthy readers, the ability of predicting the incoming word when reading a sentence increases while progressing in a sentence. Measuring the ability to perform upcoming word predictions provides a tool for identifying cognitive operations related with semantic, working and retrieval memory that are potentially distorted in patients with incipient AD.

Our hypothesis is that in AD patients, an increase in average cloze predictability of the incoming word would not facilitate reading probably for impairments in the top down processing. To test this hypothesis, we evaluated the eye movements in control and AD patients during reading sentences with either high or low average word predictability and investigated whether an increase in the average predictability of the upcoming word affected gaze duration (i.e., the sum of consecutive forward fixations on a word) in both groups. Our results showed that while high predictable sentence and word predictability exerted its influence on gaze duration in healthy subjects, such predictability did not modify word processing during reading in mild AD patients. This suggests that a loss in reading facilitation was already present at the early stages of AD.

2. Methods

2.1. 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 their inclusion in the study.

2.2. Participants

Twenty patients (12 Females and 8 Males; mean age 69 years, SD=7.3 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 its early stages remains under debate (McKhann et al., 1984). In the present work, diagnosis was based on the criteria for dementia outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). All AD underwent a detailed clinical history, physical/neurological examination and thyroid function test. They all presented an APO E3E4 Genotype. Magnetic resonance images were obtained from 12 patients and computerized tomography scans from the other eight patients. All the patients underwent biochemical analysis to discard other common pathologies (hemoglobin, full blood count, erythrocyte sedimentation rate, urea and electrolytes, blood glucose), as a whole all these data provided a more precise diagnosis of AD. Patients were excluded if: (1) they suffered from any medical conditions that could account for, or interfere with, their cognitive decline; (2) had evidence of vascular lesions in computed tomography or FMRI; (3) had evidence for an Axis I diagnosis (e.g. major depression or drug abuse) as defined by the 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 71 years old (SD=6.1), with no known neurological and psychiatric disease according to their medical records, and no evidence of cognitive decline or impairment in daily activities. A one-way ANOVA showed no significant differences between the ages of AD and Control individuals. Those participants diagnosed of suffering from Ophthalmologic disease such as glaucoma, visually significant cataract or macular degeneration as well as visual acuity less than 20/20 were excluded from the study.

The mean scores of Controls and AD patients in the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) were 27.8 (SD=1.0) and 24.2 (SD=0.8), respectively, the latter suggesting early mental impairment. 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 – Revised (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) was 84.4, (SD=1.1), the cut-off being of 86 (see Table 1). The mean school education trajectories in AD patients and Controls were 15.2 (SD=1.3) years and 15.1 (SD=1.0) years, respectively. A one-way ANOVA showed no significant differences between education of AD and Control individuals.

2.3. Apparatus and eye movement data

Single sentences were presented on the center line of a 20-inch LCD Monitor (1024 × 768 pixels resolution; font: regular; New Courier; 12 point, 0.2° in height). Participants sat 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 the Eyelink 1000 corneal reflection system, which assessed changes in gaze position by measuring both the reflection of an infrared illuminator on the cornea and the pupil size, by means of a video camera sensitive to light in the infrared spectrum.

Eye movements were recorded with an EyeLink 1000 Desktop Mount (SR Research) eyetracker, with a sampling rate of 1000 Hz and an eye position resolution of 20-s arc. All recordings and calibration were binocular. Only right eye data were used for the analyses. Eye movement data from 60 participants reading 120 sentences resulted in 54,901 number of total fixations for the controls and 67,315 for the people with AD. These data were cleaned from blinks and track losses. For controls, these procedures resulted loss of 1852 (12%) of data in highly predictable sentences and 7273 (18%) in low predictable sentences. For the AD group, these procedures resulted in loss of 4676 (19%) of data in highly predictable sentences and 6618 (15%) in low predictable sentences. Before removing for the analysis fixations shorter than 51 ms and longer than 750 ms and fixations on the first and last word of each sentence (see Kliegl et al., 2006, for a description of the analytic procedure), we calculated times from when sentences were first presented to when participants looked at final spot: mean reading time in high-predictable sentences was 3495 ms vs. 5635 ms (controls and AD) and in low predictable-sentences was 4828 ms vs. 6881 ms (controls and AD).

2.4. Procedures

Participant's 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 presentation of each spot.

To assess whether subjects comprehended the texts, they were presented with a three alternative multiple-choice question about the sentence in progress in 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 the MMSE and ACE-R values. Once the comprehension test ended, the next trial started with the presentation of the fixation spot. An extra calibration was done after 15 sentences or if the eyetracker did not detect the eye at the initial fixation point within 2 s. An example of the eye movements recorded during reading of two sentences, showing eye fixations of both controls and AD is shown in Fig. 1

2.5. Sentence corpus

The sentence corpus was composed of 75 low predictable sentences and 45 high-predictable sentences (Fernández et al., 2013a). Both kinds of sentences comprise a well-balanced number of content and function words, and had similar grammatical structure.

2.5.1. Word and sentence lengths

Sentences ranged from a minimum of 5 words to a maximum of 14 words. Mean sentence length was 8.1 (SD=1.4) words for low predictability sentences and 7.6 words (SD=1.5) for high predictability sentences. Words ranged from 1 to 14 letters. Mean word length was 4.6 and 4.1 (SD=2.5 and SD=2.3), respectively.

2.5.2. Word frequencies

We used the Spanish Lexical *Léxesp* corpus (Sebastian-Gallés, Martí, Cuetos, & Carreiras, 1998) for assigning a frequency to each word of the sentence corpus. Word frequencies ranged from 1 to 264,721 per million, so we transformed it to $\log_{10}$(frequency). Mean $\log_{10}$(frequency) was 3.4 (SD=1.3) for low predictability sentences and 3.4 (SD=1.5) for high predictability sentences.

2.5.3. Word predictability

It 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 $0.5 \times \ln(\text{pred}/(1\text{-pred})$; 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. Mean logit predictability was -0.9 (SD=0.9) for low predictability sentences and 0.0 (SD=1.29) for high predictability sentences.

As in other languages, we find strong correlations in Spanish between word length, word frequency, and word predictability. Long words are of low frequency ($r=-0.80$ and $r=-0.75$ in low and in high pred. sentences, respectively). Frequent words are highly predictable (r=0.47 and r=0.37 in low and in high pred. sentences, respectively), and highly predictable words tend to be short words ($r=-0.47$ and $r=-0.38$ in low and in high pred. sentences, respectively).

2.6. Linear mixed-effect models (LMMs)

We used the *lmer* program of the *lme4* package (version 0.999999-2) (Bates, Maechler, & Bolker, 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).

We chose log gaze duration as the dependent variable because this measure includes refixations on a word, and refixations usually reflect a lexical-processing difficulty for word *N* (Rayner, 1998; Kliegl et al., 2006; Kennedy et al., 2012). Fixed effects in 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: logit predictabilities, log frequencies and 1/length of word $N-1$, word N and of word N+1. Using the reciprocal of word length (i.e., 1/length), renders the multiplicative interaction of frequency and length or predictability and length as a ratio or relative frequency and predictability measure (i.e., normalized on word length). A traditional variable in coding predictability in event-related brain potentials (ERPs) research has been

Table1
Addenbrooks's Cognitive Examination-Revised (ACE-R).

AD	Attention/Orientation	Memory	Fluency	Language	Visuospatial	SCORE
MEAN(SD)	17.3(0.7)/18	22.5(1.4)/26	11.4(0.8)/14	18.9(1.5)/26	14.1(0.7)/16	84.4(1.1)/100

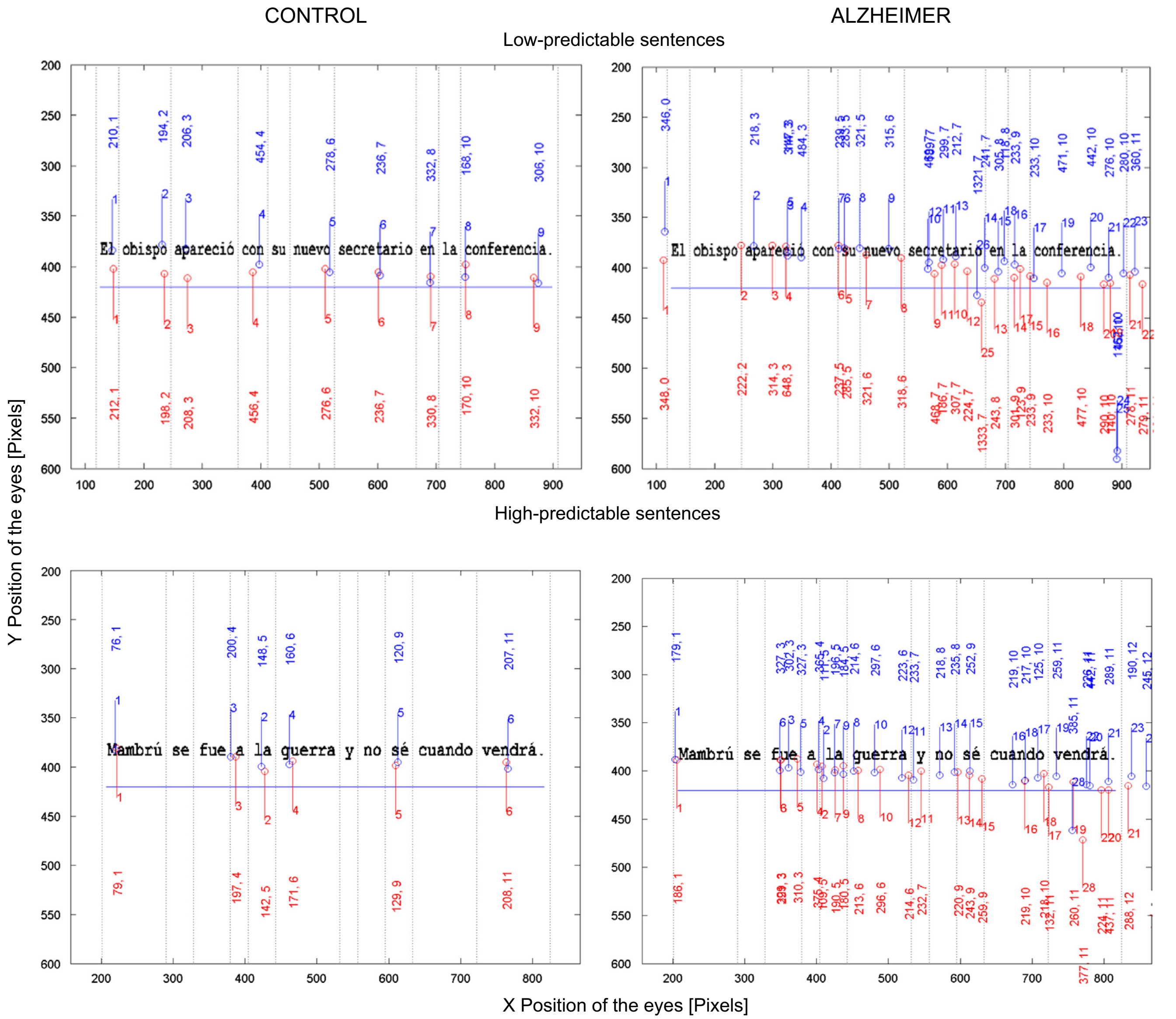

Fig. 1. Recording of eye movements during reading low and highly predictable sentences by a control subject (left) and an AD patient (right). Fixation points for right (red) and left (blue) eyes are included in the graphs. The down and right movements signaled the end of reading; numbering linked to 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. The English translation of the Spanish sentences "el Obispo apareció con su nuevo secretario en la conferencia", and " Mambrú se fue a la guerra y no sé cuando vendrá" are: "the bishop appeared with his new secretary in the conference" and "Mambrú went to war and I do not know when he will come back", respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the ordinal position of a word in the sentence (e.g., Dambacher, Kliegl, Hofmann, & Jakobs, 2006; Van Petten & Kutas, 1990). Kuperman, Dambacher, Nuthmann, & 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 $r=0.50$ in high predictable sentences and $r=0.40$ in low predictable sentences.

In addition, we estimated how strongly the mean log gaze duration varied with participants and sentences by fitting crossed random intercepts for participants and sentences. Instead of estimating a slope or the difference between conditions, random effects estimate the variance that is associated with the levels of a certain factor. Regression coefficients (*bs*) standard errors (*SEs*) and *t*-values ($t=b/SE$) are reported for the LMMs. Since there is no clear definition of "degree of freedom" for LMMs, 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 statistics is negligible). Our criterion for referring to an effect as significant is $t=b/SE > \pm 1.95$.

3. Results

3.1. Sentence context and word based effect on gaze duration

In Table 2 we report, (a) effects related to the mean values when averaging over all predictors i.e., collapsing sentence type (High-pred. vs. Low-pred. sentences) and Group members (AD vs. Control); (b) those interactions of predictors x sentence type x Group members.

We first evaluated the effect of reading low and high-predictable sentences on mean gaze duration in the control group. As shown in Table 2, gaze duration significantly increased in controls when reading low-predictable sentences ($t=2.73$), compared to its value in high-predictable sentences. We then evaluated whether gaze duration was affected in AD patients at the early stages of their disease. As shown in Table 2 and in Fig. 2, the log mean gaze duration was significantly longer in AD patients than in controls, both for sentences of low or high predictability. Noteworthy, no significant decrease in gaze duration was observed for AD patients when reading highly predictable sentences ($t = -1.40$). This implies that, while controls, i.e., healthy subjects, were able to use the context sentences for predicting words, significantly reducing gaze duration, patients with mild AD had already lost this ability. Additionally, word number was not significant when considering averaging over all predictors, but it was when we analyzed group interaction ($t = 2.28$) and Control's sentence type interaction ($t = -2.27$). Thus, only controls showed a reduction on gaze duration while increasing word number.

We then analyzed the effect of the predictability of word $N-1$, N and $N+1$ on log gaze duration on word N during reading low and high-predictable sentences in controls and in AD patients. LMM results are summarized in Table 2. The predictability of word $N-1$ had no significant effect when analyzing averaging over all predictors ($t = 0.27$). Additionally, the effect of word $N-1$ on gaze duration was not significant neither in controls nor in AD patients when reading low and high-predictability sentences ($t = 0.23$ and $t = -0.61$, respectively), being the interaction between groups not significant too ($t = 0.27$). An increase in the cloze predictability of word N not decreased significantly gaze duration when considering averaging over all predictors ($t = -1.78$), but was significant when analyzing group interaction ($t = 2.12$) and Control's sentence type interaction ($t = -2.14$). In contrast, gaze duration in AD patients was not affected by word N predictability ($t = -1.08$) (Table 2 and Fig. 2, central panel).

Analysis of the effect of cloze predictability of word $N+1$ on gaze duration was not significant when considering averaging over all predictors ($t = -0.42$), although group interaction evidenced that controls significantly increased their gaze duration with the increase in the cloze predictability of word $N+1$ ($t = 3.12$), being the sentence type interaction significant too ($t = -1.95$). On the contrary, gaze duration in AD patients was unaffected by word $N+1$ predictability irrespectively of what kind of sentences we were considering ($t = -0.40$). (See Table 2 and Fig. 2, right panel).

Next, we evaluated the effect on log gaze duration of the frequency of word $N-1$, N and $N+1$. Gaze duration decreased significantly with an increase in the frequency of word $N-1$ when considering averaging over all predictors ($t = -5.87$), probably due to a partial processing of the word N in the previous fixation (i.e., spillover). Additionally, there were no significant interactions neither by group ($t = 0.66$) nor by sentence type irrespective of whether we were considering controls or AD patients ($t = 0.65$ and $t = 0.00$, respectively). Similarly, gaze duration significantly decreased with an increased frequency of word N when considering averaging over all predictors ($t = -5.87$), although in these case group interaction was significant ($t = 2.28$) given the strongest word frequency effect in AD patients (See Fig. 3). This suggests that more frequent words require less processing thus leading to shorter gaze durations and that the ability to recognize these words is unaffected in AD patients, at least at this early stage of their disease. The increased frequency of word $N+1$ was not significant when considering averaging over all predictors ($t = -0.11$), although the interaction between groups indeed it was ($t = 1.96$). Curiously, neither controls nor AD patients showed significant effects when considering sentence type interaction ($t = -0.43$ and $t = -1.45$, respectively) (See Table 2).

We also investigated the effect on log gaze duration of 1/length of word $N-1$, N and $N+1$. The 1/length of word $N-1$ significantly increased gaze when considering averaging over all predictors ($t = 2.94$), reflecting probably a partial processing of the word N in the previous fixation; the interaction between groups was not significant ($t = 0.81$). Increasing 1/length of word N significantly reduced gaze durations when considering averaging over all predictors ($t = -9.17$).; although again the interaction between groups was not significant ($t = 0.94$). Finally, the length of word $N+1$ had no significant effect on gaze duration in none case (See Table 2).

4. Discussion

We have investigated how well-defined word properties embedded in low predictable and highly-predictable sentences influenced gaze duration in controls and in AD patients. Our results evidence that gaze duration in AD patients was longer than in controls and was not reduced by sentence predictability, as occurred with controls. Our data also shows that cloze predictability of word N and of the upcoming word ($N+1$) noticeably affected gaze duration in controls, but not in AD patients, probably reflecting impairment in working memory, in memory retrieval and in top down processing.

Controls showed shorter gaze duration than AD patients both in low and in highly-predictable sentences. In addition, the mean-time duration in controls was shorter in high than in low-predictable sentences, implying that in healthy readers brain processing can rapidly reconstruct the sentence, thus facilitating ongoing reading (Fernández et al., 2013b; Rayner, 1998; Katz & Ferreti, 2001; Kliegl et al., 2006;). By contrast, the longer gaze duration in AD patients strongly suggests an increased difficulty in processing the meaning of sentences. Interestingly, gaze duration in AD patients was similar when reading low and highly-predictable sentences (Table 2, Group x Sentence interaction), suggesting that the predicting process did not facilitate reading to AD patients, even at these early stages of the disease.

Predictive cueing (e.g., upcoming words prediction in our high-predictable sentences) has been shown to enhance the speed and accuracy with which stimuli are detected and discriminated (Esterman & Yantis, 2009; Puri & Wojciulik, 2008; Fernández et al., 2013a). Extending this finding to the memory domain, Gazzaley (2013) demonstrated that predictive cueing can also improve both working and long term memory performance in healthy old readers. They suggest that expectations act as an attentional filter to facilitate the extraction of information, resulting in performance benefits across multiple domains. The prevailing view is that the prefrontal cortex (PFC) mediates this prestimulus activity modulation. Extensive evidence suggests that the PFC generates cortical processing in visual areas via top-down signals prior to stimulus presentation (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Esterman & Yantis, 2009; Silver, Ress, & Heeger, 2007; Summerfield & Egner, 2009). A type of top-down modulation that has been shown to involve the PFC is expectation, or anticipation, that precedes the presentation of a stimulus that can be predicted (Esterman & Yantis, 2009, Puri, Wojciulik, & Ranganath, 2009). Because cortical regions in the dorsolateral prefrontal cortex are affected in mild AD (Brown et al., 1996; Drzezga et al. 2003; Pelak, 2010; Salat, Kaye, & Janowsky, 2001), their capacity for predicting upcoming words could be impaired. However, at present there is not evidence to support the involvement of LTM impairments in the changes in the use of predictability.Further research is needed to distinguish whether these changes are due to long term memories impairments per se or on executive impairments needed to use top down processing.

Analysis of the effect of word predictability on gaze duration showed that in controls the cloze predictability of word N reduced mean gaze duration both in low and highly-predictable sentences, implying that an increase in cloze predictability facilitated reading. In contrast, in AD patients this parameter had no effect at all in gaze duration in either type of sentence, suggesting that in these

Table 2
Effect of word 1/Length, log(Frequency) and (logit)predictability on Mean Gaze duration in Controls and AD patients.

	Gaze duration		
	M	SE	*t*-value
Fixed effects			
Mean Gaze duration (log)	5.552	0.031	**178.43**
Absolute word number	0.481	0.330	1.46
1/Length			
Word $N-1$	0.015	0.051	**2.94**
Word N	−1.788	0.195	−**9.17**
Word $N+1$	−0.113	0.158	−0.72
Frequencies(log)			
Word $N-1$	−0.029	0.005	−**5.87**
Word N	−0.092	0.015	−**6.07**
Word $N+1$	−0.001	0.016	−0.11
Predictabilities(logit)			
Word $N-1$	0.024	0.009	−0.63
Word N	−0.047	0.026	−1.78
Word $N+1$	−0.002	0.005	−0.42
Group x Sentence			
High-pred vs Low-pred x AD vs Control	−0.879	0.121	−**7.25**
High-pred vs Low-pred x Control	0.024	0.022	**2.73**
High-pred vs Low-pred x AD	−0.026	0.019	−1.40
Word x Group x Sentence			
Word number x AD vs Control	0.028	0.012	**2.28**
Word number x High-pred vs Low-pred x Control	−0.024	0.010	−**2.27**
Word number x High-pred vs Low-pred x AD	0.005	0.008	0.61
1/Length			
Word $N-1$ x AD vs Control	0.147	0.182	0.81
Word $N-1$ x High-pred vs Low-pred x Control	−0.204	0.472	−0.43
Word $N-1$ x High-pred vs Low-pred x AD	−0.011	0.016	−0.65
Word N x AD vs Control	0.666	0.709	0.94
Word N x High-pred vs Low-pred x Control	0.120	0.119	1.01
Word N x High-pred vs Low-pred x AD	−0.120	0.467	−0.26
Word $N+1$ x AD vs Control	0.638	0.560	1.14
Word $N+1$ x High-pred vs Low-pred x Control	−0.204	0.472	−0.43
Word $N+1$ x High-pred vs Low-pred x AD	0.050	0.367	0.14
Frequencies(log)			
Word $N-1$ x AD vs Control	0.111	0.016	0.66
Word $N-1$ x High-pred vs Low-pred x Control	0.009	0.014	0.65
Word $N-1$ x High-pred vs Low-pred x AD	0.000	0.011	0.00
Word N x AD vs Control	0.121	0.053	**2.28**
Word N x High-pred vs Low-pred x Control	0.055	0.045	1.22
Word N x High-pred vs Low-pred x AD	−0.014	0.035	−0.41
Word $N+1$ x AD vs Control	0.031	0.015	**1.96**
Word $N+1$ x High-pred vs Low-pred x Control	0.020	0.046	0.43
Word $N+1$ x High-pred vs Low-pred x AD	−0.053	0.036	−1.45
Predictabilities(logit)			
Word $N-1$ x AD vs Control	0.001	0.018	0.27
Word $N-1$ x High-pred vs Low-pred x Control	0.003	0.015	0.23
Word $N-1$ x High-pred vs Low-pred x AD	−0.007	0.012	−0.61
Word N x AD vs Control	0.034	0.016	**2.12**
Word N x High-pred vs Low-pred x Control	−0.058	0.027	−**2.14**
Word N x High-pred vs Low-pred x AD	−0.024	0.023	−1.08
Word $N+1$ x AD vs Control	0.055	0.017	**3.12**
Word $N+1$ x High-pred vs Low-pred x Control	−0.027	0.014	−**1.95**
Word $N+1$ x High-pred vs Low-pred x AD	−0.004	0.012	−0.40
Variance components		Variance	SD
Sentence ($n=120$)		0.003	0.058
Subject ($n=60$)		0.047	0.217
Residual ($n=17368$)		0.182	0.427

Parameter estimates for fixed effects of Linear Mixed Models. Fixed effects are logit predictability of word $N-1$, word N and word $N+1$; 1/length of word $N-1$, word N and word $N+1$; log frequency of word $N-1$, word N and word $N+1$ and absolute word number. Random intercepts are participants and sentences. Threshold of significance is set at $t=\pm 1.95$. Numbers in bold represent significant values.

patients the capacity for processing a prediction, at least while reading a sentence, might be seriously compromised.

Noteworthy, an increase in the predictability of word $N+1$ significantly increased gaze duration in controls, both in low and highly-predictable sentences. In contrast, in AD patients an increase in cloze predictability of word $N+1$ had no effect on gaze duration, neither with low nor with highly predictable sentences. Previous findings show that in healthy readers word $N+1$ may have an effect on fixation duration via memory retrieval (Fernández et al., 2013b, 2014; Tsai, Kliegl, & Yan, 2012; Kennedy & Pynte, 2005; Kliegl et al., 2006; Kennedy et al., 2012). Thus, the increase gaze duration might reflect the time required for the brain to retrieve the possible incoming word in a sentence. Our data suggest that this rather complicated analysis present in

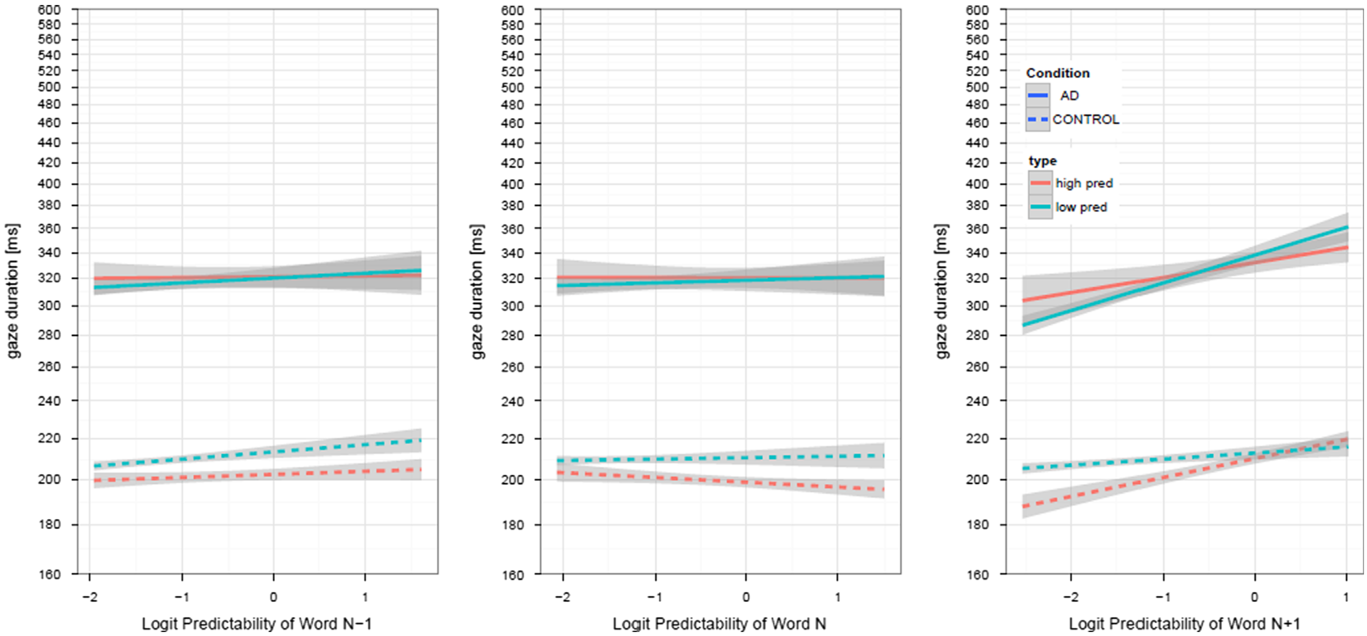

Fig. 2. Effect of the predictability of word $N-1$ (left), word N (center) and word $N+1$ (right) on gaze durations on word N, broken down by low-predictable sentences and high-predictable sentences, for controls and for AD. Panels reflect regression of gaze durations on word N on respective logits of predictability. Shaded areas are 95% confidence intervals.

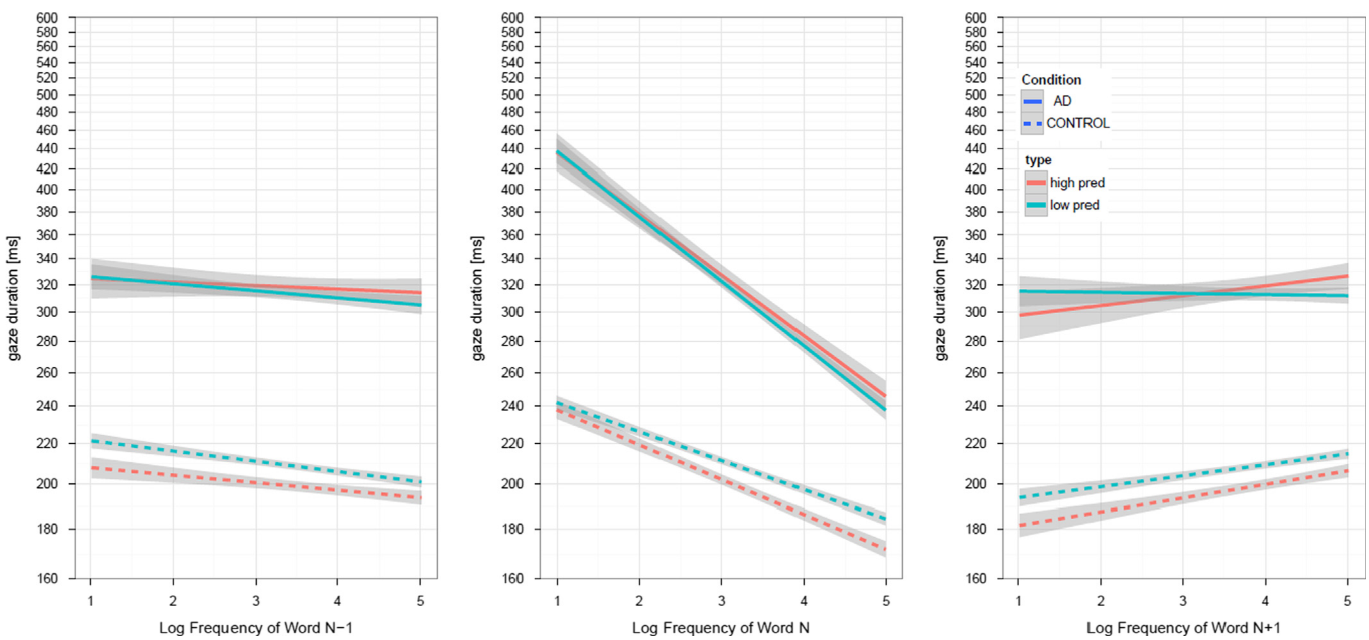

Fig. 3. Effect of the frequency of word $N-1$ (left), word N (center) and word $N+1$ (right) on gaze durations on word N, broken down by low-predictable sentences and high-predictable sentences, for controls and for AD. Panels reflect regression of gaze durations on word N on respective log of frequency. Shaded areas are 95% confidence intervals.

normal subjects might be absent or deteriorated in AD patients, even at this early stage (Table 2). Highly-predictable sentences with a high average cloze predictability related to semantic content might provide a test bed for the investigation of the specific effect of memory retrieval on ongoing word processing during reading (Boston, Hale, Vasishth, & Kliegl, 2011; Dambacher, Rolfs, Göllner, Kliegl, & Jacobs, 2009; Kliegl et al., 2006; Kennedy et al., 2012; Vitu, Brysbaert, & Lancelin, 2004). In addition, evaluation of the effect of contextual word predictability could be an important indicator of how working memory and retrieval memory are affected in AD. This observation is in agreement with neuropathological (Lewis, Campbell, Terry, & Morrison, 1987; Morrison et al. 1986) and neuroimaging studies that reported pronounced parietal dysfunction in AD (Bartenstein et al. 1997; Jagust, Eberling, Reed, Mathis, & Budinger, 1997; Meltzer et al., 1996; Pietrini, Alexander, Furey, Hampel, & Guazzelli, 2000), making AD patients prone to impaired internal representation and reduced 'top down' control of the exploration strategy (Fujimori et al., 2000; Tetewsky & Duffy, 1999). Prior research in 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 et al., 1986; Fernández et al., 2013a; Lueck et al., 2000). The loss of the effect of cloze predictability on gaze duration in AD patients might be a sign of the onset of this progressive decline.

In controls, an increase in the frequency of a given word led to a reduction in gaze duration; i.e., the higher the frequency of a word, the shorter the fixation time on word *N*. In other words, the occurrence of a familiar, frequent word, led the brain to rapidly indicate the eyes to move forward to the next incoming word. Similar effects have been reported in healthy subjects when analyzing word frequency effects (Fernández et al., 2013b; Kliegl et al., 2006; Kuperman et al., 2010). Our results show that AD patients presented a reduction in gaze duration with word frequency both for $N-1$ and *N* words similar to that observed in controls, implying that this apparently simple mechanism of facilitation might still be present in AD patients.

Finally, analysis of the effect of 1/word length on gaze duration showed that control subjects significantly reduced gaze duration in both low and highly-predictable sentences, with the reduction in the length of word *N*, but not of words $N-1$ or $N+1$. Interestingly, AD patients showed a similar reduction both for highly-predictable and low-predictable sentences. This implies that another simple mechanism of reading facilitation, i.e., the one derived from a shorter word, was retained by patients with mild AD.

In conclusion, our data suggest that though reading seems preserved in AD patients at early stages of the disease, top down processing might be distorted. To our knowledge, this is the first study using word-based properties and contextual predictability for identifying cognitive abnormalities. Our results support that this evaluation provides a test bed for the investigation of cognitive impairments usually linked to deficiencies in semantic, working and retrieval memory. We suggest that memory-guided eye movements reflect deficits in how AD patients process complex information. In addition, these findings might be relevant for expanding the options for the early detection and monitoring of in the early stages of AD.

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