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Patients with Mild Alzheimer's Disease Fail When Using Their Working Memory: Evidence from the Eye Tracking Technique

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Abstract. Patients with Alzheimer's disease (AD) develop progressive language, visuoperceptual, attentional, and oculomotor changes that can have an impact on their reading comprehension. However, few studies have examined reading behavior in AD, and none have examined the contribution of predictive cueing in reading performance. For this purpose we analyzed the eye movement behavior of 35 healthy readers (Controls) and 35 patients with probable AD during reading of regular and high-predictable sentences. The cloze predictability of words $N-1$, and $N+1$ exerted an influence on the reader's gaze duration. The predictabilities of preceding words in high-predictable sentences served as task-appropriate cues that were used by Control readers. In contrast, these effects were not present in AD patients. In Controls, changes in predictability significantly affected fixation duration along the sentence; noteworthy, these changes did not affect fixation durations in AD patients. Hence, only in healthy readers did predictability of upcoming words influence fixation durations via memory retrieval. Our results suggest that Controls used stored information of familiar texts for enhancing their reading performance and imply that contextual-word predictability, whose processing is proposed to require memory retrieval, only affected reading behavior in healthy subjects. In AD patients, this loss reveals impairments in brain areas such as those corresponding to working memory and memory retrieval. These findings might be relevant for expanding the options for the early detection and monitoring in the early stages of AD. Furthermore, evaluation of eye movements during reading could provide a new tool for measuring drug impact on patients' behavior.

Keywords: Alzheimer's disease, eye movements, memory, reading

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that develops over a period of years. 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 in parts of the frontal cortex and cingulated gyrus [1]. One of its first manifestations is an increase in the loss of connections between

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neurons responsible for memory and learning [2, 3]. Patients with early to moderate AD usually show an impairment of learning and a deterioration of episodic memory and such symptoms are typically used for a diagnosis of the pathology [4]. However, certain movement coordination and planning difficulties that may be present while performing fine motor tasks such as writing or reading are commonly unnoticed [5–7]. AD patients are prone to visual and attentional disturbances [8, 9]. Visual exploration has been characterized during visual search of emotional facial expressions [10–12] and has been employed to measure spatial attention in these patients [13, 14]. Most of these studies reported longer fixation duration and less systematic exploration during visual tasks.

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 healthy subjects, fixation duration is usually between 150 and 250 ms, with values stretching from 100 ms to over 700 ms. The distance the eyes move in each saccade ranges between 1 and 20 characters, usually moving between 7–9 characters, and execution of the saccade takes about 20–50 ms [15]. To make a new fixation, saccades direct the fovea toward a particular element of interest [16]. The sequence of fixations and saccades during visual exploration is crucial for perception and is very effective for sampling information acquisition [17]. Fixation behavior is the end result of a complex interaction of features of the explored picture ("bottom up" processing) and the instruction or question to be solved by the explorer ("top down" processing) [18–24]. Thus, perception involves active predictions of upcoming events to grant smooth sensory analysis [25–27].

A recent study combining eye tracking and fMRI measures [28] pointed out that AD patients exhibited significantly decreased activation of the frontal eye field region in comparison to healthy controls during the anti-saccade task performance. Such a decline in inhibition functioning and the corresponding disruption in frontal lobe activity was suggested as a symptom of early AD [4]. A study [29] reported that AD patients evidence a delayed target detection, exhibiting more fixations and longer fixations times when searching arrays of letters. This delay could be interpreted as an inefficiency in planning a search strategy [4, 30]. On the other hand, memory retrieval is usually associated with activation of the parietal cortex, which is also implicated in the attentional system. A recent work proposes that overt shifts of attention through eye movements are associated with higher accuracy of performance in relational visuospatial memory task [31]. Thus, visuospatial attention and oculomotor planning may reinforce and help to produce stronger visual representations and more accurate memory recognitions. Recognition memory, affected early in the course of AD, is supposed to rely on two distinct processes: recollection (i.e., retrieval of details from the encoding episode) and familiarity (i.e., acontextual sense of prior exposure) [32, 33]. Recollection has repeatedly been shown to be impaired in patients with moderate AD; however, familiarity seems to be preserved [34]. Because our experimental procedure can check recollection, using our well-defined sentences we can assess whether this memory process is impaired or not in mild AD (see below).

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 can also shed light on the inner workings of attention, inhibitory control, working memory, and decision-making processes [18, 35–39]. Networks and structures implicated in a range of eye movement behaviors are well defined, including those that measure working memory and saccadic execution [38–40]. During fluent reading, the duration of a fixation on a word is influenced by the syntactic, semantic, 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 [41]. The cloze predictabilities of the past word (word $N-1$), of the current word (word N), and of the upcoming word (word $N+1$) influence fixation duration [15, 27, 42–44]. Recent work [30, 40, 43, 45] demonstrates that fixation duration on the word N decreases with increasing cloze predictability of word N, but increases with cloze predictability of word $N+1$. 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.

In the present work we investigated whether the positive $N+1$-predictability effect on fixation duration is linked to memory retrieval. To this end, we used the eye tracking technique to evaluate how Control and AD patients read high-predictable sentences (i.e., sentences for which we expected a maximum of average cloze predictability) and regular sentences. Our hypothesis was that the positive $N+1$-predictability effect would increase with overall average cloze predictability. Obviously, high-predictable sentences were expected to contain a substantial number of content words with high cloze predictability. Therefore, with these kinds of sentences we avoid common regular sentence restrictions in which high values of cloze predictability were primarily associated with function words or just with the last word of the sentence [30]. High-predictable sentences of the present study should yield a stronger signal for the pattern of hypothesized positive $N+1$-predictability effects than regular sentences. When reading high-predictable sentences, there is typically a word at which not only the next word but the entire sentence becomes available. To capture this sharp transition in predictability in which a subject matches an entire sentence being read to one held in his/her memory, we determined the word with the maximum change in cloze predictability relative to the previous word in a given sentence. In the context of reading high-predictable sentences we will refer to this word as the “Eureka word” [46]. On the basis of this word we defined the binary variable “maxjump”, assigning the value of 1 for each word after the jump word and a value of 0 to all words prior to, and including, the jump word. We expected that the effect of cloze predictability of individual words on fixation durations would differ for these two regions of the sentences [30].

Patients with moderate AD show abnormalities in eye movements during reading of a text, and reading difficulty correlates with dementia severity [27, 47, 48]. 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 was that AD patients would not enhance their reading performance with an increase in contextual predictability probably due to impairments in the top down processing. To test this hypothesis, we investigated whether working memory and retrieval memory performances affected gaze duration (i.e., the sum of consecutive forward fixations on a word) in Control and AD patients while reading sentences of high predictability. In addition, we hypothesized that increasing cloze predictability during reading high-predictable sentences would not modify the binary maxjump variable in AD patients. If so, gaze durations would be longer in the first region of the sentences only in Controls—when increasing cloze predictability—than in the last one.

METHODS

Ethics statement

The investigation adhered to the principles of the Declaration of Helsinki. All patients and their caregivers, and all control subjects signed an informed consent prior to their inclusion in the study.

Participants

Thirty-five patients (22 females and 13 males; mean age 68 years, SD = 6.4 years) with the diagnosis of probable AD were recruited at the Hospital Municipal and at Clinica Privada Bahiense, both of Bahía Blanca, Buenos Aires, Argentina. The clinical criteria to diagnose AD at its early stages remain under debate [49]. In the present work, diagnosis was based on the criteria for dementia outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [50]. All AD patients underwent a detailed clinical history, physical/neurological examination, and thyroid function test. They all presented an APOE $\varepsilon 3/\varepsilon 4$ genotype. Magnetic resonance images were obtained from 27 patients and computerized tomography scans from the other 8 patients. All the patients underwent biochemical analysis (hemoglobin, full blood count, erythrocyte sedimentation rate, urea and electrolytes, blood glucose), to discard other common pathologies. 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 were not included. None of the subjects was taking hypnotics, sedative drugs, or major tranquillizers. The control group consisted of 35 elderly adults (24 female and 11 male), mean 70 years old (SD = 6.2), 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 diseases 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) [51] were 28.8 (SD = 1.0) and 25.3 (SD = 0.9), 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) [52] was 84.4 (SD = 1.1), the cut-off being of 86. The mean score of INECO Frontal Screening (IFS) [53] was 21.1 (SD = 3.2), the cut-off being of 25. The mean school education trajectories in AD patients and Controls were 15.1 (SD = 1.4) years and 14.1 (SD = 1.2) years, respectively. A one-way ANOVA showed no significant differences between the education of AD and Control individuals.

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, 0.2º 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. We removed for the analysis fixations shorter than 51 ms and longer than 750 ms and fixations on the first and last word of each sentence [44].

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 1º 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 headgear 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 96% (SD = 3.1%) in Control and 90% (SD = 4.4%) 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 at 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 eye tracker did not detect the eye at the initial fixation point within 2 s.

Sentence corpus

The sentence corpus was composed of 75 regular sentences (e.g., "Yesterday I talked to Laura about her daughter") and 45 high-predictable sentences ("Pinocchio's nose grows every time he lies") [48]. Both kinds of sentences comprised a well-balanced number of content and function words, and had similar grammatical structure.

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.

Word frequencies

We used the Spanish Lexical *Léxesp* corpus [54] for assigning a frequency to each word of the sentence corpus. Word frequencies ranged from 1 to 264721 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.

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*ln(pred/(1-pred)); predictabilities of zero were replaced with 1/(2*18) = –2.55 and those among the five perfectly predicted words with (2*18–1)/(2*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).

Maxjump

We determined the word with the largest difference between the cloze predictability of two consecutive words according to the following equation:

$$jump\ word = \max[Logit(pred_{N+1}) - Logit(pred_N)]$$

Jump word separates the sentence in two regions. The variable maxjump was assigned a value of 1 for each word after the jump word and a value of 0 to all words prior to and including the jump word. With this maxjump variable we tested the contextual word predictability effect due to memory retrieval [50]. The expectation is that gaze duration will be more affected before than after jump words. This expectation is based on the assumption that after the jump word, less processing would be required since words have already been recovered from memory.

Linear mixed-effect models (LMMs)

We used the *lmer* program of the lme4 package (version 0.999999-2) [55] 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 [15, 43, 44]. The critical factors of the present work are sentence type (i.e., regular sentences and highly predictable sentences), predictabilities, and group members (i.e., AD versus Controls). Group contrast coding was –1 and 1. Sentence type informs about different aspects of the relevance of retrieval memory and of long-term memory. The main hypothesis is that the effect of predictability, especially the effect of predictability of word $N+1$, depends on the overall level of cloze predictability. Therefore, interactions between sentence type, groups, and predictabilities of word $N-1$, N and word $N+1$ were the initial focus of the *maxjump* LMM. Of course, these interactions may also depend on how quickly in a sentence the jump in predictability occurred. Thus, interactions between *maxjump* and predictability of word $N-1$, N, and word $N+1$ were the main focus of the *maxjump* LMM. Interactions do not inform about the significance of predictability for a given condition. When this information was needed for the interpretation of an interaction, we tested the effect in a *post-hoc* LMM, using the specific level of Group's member as the reference category in an interaction.

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). 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. 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 $t = b/SE > \pm 2.00$.

RESULTS

Maxjump linear mixed model

Word information is acquired and processed in the brain during fixations. Because mild AD patients already show minor difficulties in processing and interpreting word meanings, we hypothesized that they would increase their gaze durations when extracting word information. When considering high-predictable words, gaze durations before and after maxjump differed by 4 ms in Controls (before jump word: 206+-47 SD and after jump word: 202+-43 SD), and by 8 ms in AD patients (before jump word: 255+-67 SD and after jump word: 268+-82 SD). Curiously, gaze durations in AD patients were 8 ms longer after than before maxjump, being their behavior opposite to that reported from Controls. In relation to regular sentences, gaze durations differed by 3 ms in Controls (before jump word: 215 +-57 SD and after jump word: 212+-55 SD); and by 5 ms in AD (before jump word: 266+-69 SD and after jump word: 271+-68 SD).

Evaluation of gaze durations as a function of group and the predictabilities of word $N-1$ up to word $N+1$ (Fig. 1) evidenced they were longer in AD patients than in Controls in every case. The values in Fig. 1 are partial effects. All covariates not related to the variables member group, predictability and random effects were removed from the observed values [56]. As shown in Table 1, log mean gaze duration was significantly higher in AD patients than in Controls both, in regular and in high predictable sentences ($t = 3.95$ and $t = 3.49$, respectively). This increase in gaze duration suggests that AD patients needed more time for processing and integrating words.

*Word $N-1$, word N and word $N+1$ predictability effects * group members * sentence type.* The predictabilities of word $N-1$, word N and word $N+1$ had no significant effects on gaze duration when considering main effects ($t = -0.50$, $t = 0.34$ and $t = 0.58$,

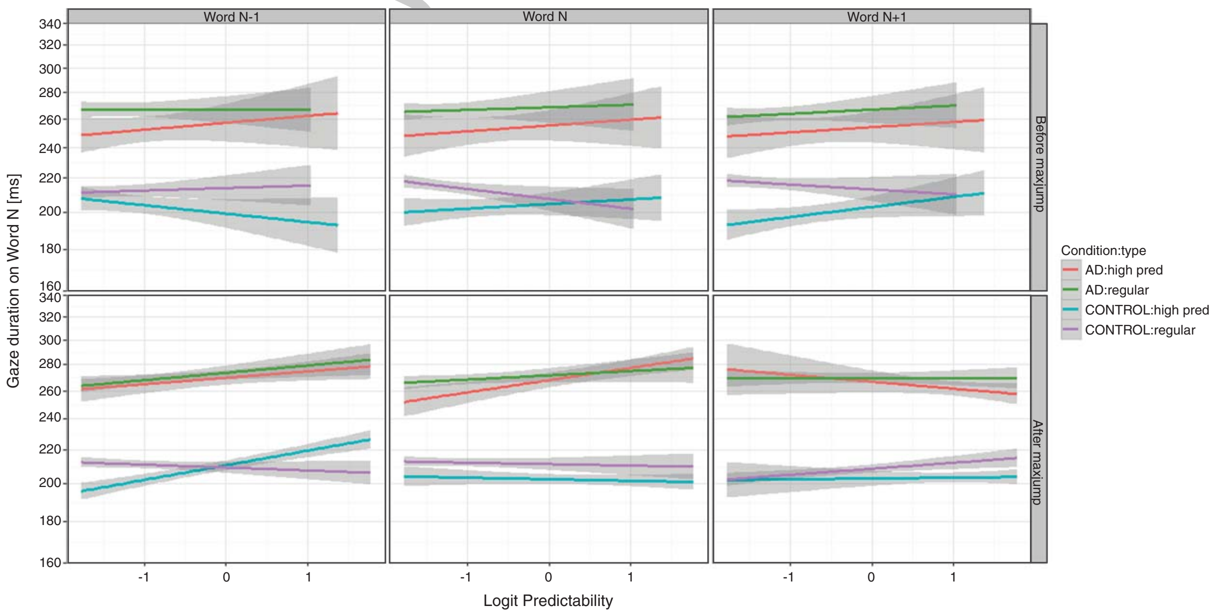

Fig. 1. Predictability effects of words $N-1$, N, and $N+1$ on gaze duration on word N, for Controls and AD readers as a function of word predictability. Panels show partial effects of LMM (i.e., after removal of other fixed effects and variance components). Shaded areas denote 95% confidence intervals.

Table 1
Maxjump Lineal Mixed Model. The model included variance terms (random effects) for the intercept of participants and sentences. The threshold of significance is $t = \pm 2.00$ (numbers in bold represent significant values)

	Gaze duration		
	Maxjump		
Fixed effects	*M*	*SE*	*t-value*
Mean gaze duration (log)	5.484	0.034	**159.73**
Predictabilities(logit)			
Word $N-1$	–0.007	0.016	–0.50
Word N	0.006	0.017	0.34
Word $N+1$	0.012	0.021	0.58
Groups * **Sentence type**			
AD versus CONTROL * Regular	0.239	0.060	**3.95**
AD versus CONTROL * High pred	0.206	0.059	**3.49**
Predictabilities(logit) * **Groups** * **Sentence type**			
Word $N-1$ * High pred versus Regular	–0.103	0.064	–1.59
Word $N-1$ * AD versus CONTROL * Regular	–0.008	0.021	–0.38
Word $N-1$ * AD versus CONTROL * High pred	0.027	0.028	0.95
Word N * High pred versus Regular	0.011	0.070	0.16
Word N * AD versus CONTROL * Regular	0.002	0.029	0.09
Word N * AD versus CONTROL * High pred	0.012	0.027	0.47
Word $N+1$ * High pred versus Regular	–0.030	0.085	–0.36
Word $N+1$ * AD versus CONTROL * Regular	0.033	0.032	1.02
Word $N+1$ * AD versus CONTROL * High pred	–0.029	0.015	**–1.94**
Groups * **Sentence type** * **Maxjump**			
AD versus CONTROL * Regular * Maxjump	0.002	0.035	0.08
AD versus CONTROL * High pred * Maxjump	0.191	0.092	**2.06**
Predictabilities(logit) * **Groups** * **Maxjump**			
Word $N-1$ * High pred versus Regular * Maxjump	0.123	0.082	1.50
Word $N-1$ * AD versus CONTROL * Regular * Maxjump	0.037	0.030	1.23
Word $N-1$ * AD versus CONTROL * High pred * Maxjump	–0.070	0.036	**–1.91**
Word N * High pred versus Regular * Maxjump	0.049	0.084	0.59
Word N * AD versus CONTROL * Regular * Maxjump	0.014	0.034	0.42
Word N * AD versus CONTROL * High pred * Maxjump	0.011	0.036	0.32
Word $N+1$ * High pred versus Regular * Maxjump	–0.057	0.101	–0.57
Word $N+1$ * AD versus CONTROL * Regular * Maxjump	–0.066	0.040	–1.65
Word $N+1$ * AD versus CONTROL * High pred * Maxjump	0.008	0.004	**2.03**
Variance components	*Variance*	*SD*	
Groups			
Subject ($n=70$)	0.048	0.220	
Sentence ($n=120$)	0.001	0.044	
Residual ($n=20119$)	0.182	0.426	

respectively). The interaction between word $N-1$ predictability and group of readers had no significant effect on gaze duration, irrespective of the group and kind of sentences considered ($t = –0.38$ for regular sentences and $t = 0.16$ for high predictable sentences). Regarding word N, there was an effect of predictability on gaze duration between predictability, group members and sentence type ($t = –0.09$ and $t = 0.47$, for regular and highly predictable sentences, respectively). However, as described in previous work [30, 48] Controls reduced their gaze durations in regular sentences with increasing cloze predictability (*post-hoc* LMM: $t = –2.00$), indicating they spent less time processing highly predictable words. Finally, the effect of the predictability of word $N+1$ on gaze duration was only marginal significant ($t = –1.94$); when considering the interaction with group and highly predictable sentences. As we expected, Controls increased their gaze duration when considering word $N+1$ (see Table 1).

Word length and word frequency effects were the canonical and are described in Supplementary Table 1 (See *Supplementary Material*).

*Word N – 1, word N and word N + 1 predictability effects * group members * sentence type * maxjump.*

We then evaluated the effect of increasing cloze predictability on the maxjump variable. We observed marginal and significant interactions of word $N-1$ and $N+1$ ($t = 2.06$, $t = –1.91$ and $t = 2.03$, respectively) involving the maxjump variable, high-predictable sentences and group members. In Controls, maxjump changed the dependency of fixation times when increasing cloze predictability (see Table 1 and Fig. 1).

When considering the effect of $N-1$ predictability on groups, only Controls were significantly affected, showing a negative trend before maxjump and a positive trend after maxjump. As shown in Fig. 1, predictability-related spillover effects were present just before maxjump. Noteworthy, this effect of the predictability of word $N-1$ was absent in AD patients. These results are consistent with the hypothesis that in Controls words were retrieved from memory and hence no further effect of cloze-predictability was expected in the LMM (see Fig. 1 bottom panel). They also suggest that this ability was already lost in AD patients, even at mild stages of their disease. Interestingly, AD patients did not show a significant predictability effect when analyzing word $N+1$ effect on gaze duration. On the contrary, in Controls the distinction between fixations before and after the maximum jump in predictability accounted for positive predictability effects associated with word $N+1$. Finally, when considering regular sentences only Controls showed a positive predictability effect and it was after maxjump.

DISCUSSION

We hypothesized that AD patients would not enhance their reading performance with an increase in contextual predictability and it would be present when considering gaze duration. Additionally, we proposed that only Controls would be able to show a positive $N+1$ cloze predictability effect before maxjump word. By using the eye tracking technique, we clearly evidenced that gaze duration in AD patients was longer than in Controls. Further, only Controls showed a significant decrease on gaze durations when reading high-predictable sentences. Our data also shows that cloze predictability of word $N-1$ and of the upcoming word ($N+1$) affected gaze duration in Controls but not in AD patients (See trends in Fig. 1). Moreover, while in Controls gaze durations were longer (when increasing cloze predictability of word $N+1$) in the first region of the sentences (i.e., before maxjump) than in the last ones (i.e., after maxjump), this did not occur in AD patients. The loss of the maxjump effect in AD patients evidenced that whereas Controls retrieved words from memory up to the point of complete retrieval, AD patients already showed impairments for predicting and retrieving upcoming words even at early stages of the disease. As proposed in the Introduction section, recollection or retrieval of specific context-word information seemed to occur only in Controls. In accordance with previous studies, our results show that recollection is disproportionately impaired in AD patients [32–34].

There is a growing consensus that eye movements might be an indicator of cognitive processing performance [4, 8, 15, 27, 57], since several cognitive processes, including working memory, have been shown to influence saccade parameters [15, 30, 58]. Using high predictability sentences as reading material allowed us to examine if readers used information stored in their memory. Previous work showed that older adults were more likely to switch to a retrieval strategy when the cost of visual scanning or the benefits of retrieval were increased [31, 59–63]. Accordingly, our work showed that when retrieval cues (e.g., reminders, contextual reinstatement) were provided in highly-predictable sentences, Controls improved their reading performance.

The pattern of gaze duration as a function of predictability is complex and depends on the position of the word ($N-1$ up to $N+1$) and on the reader' word processing ability (see Table 1 and Fig. 1). The semantic context of the fixated word, represented by the predictabilities of the preceding word, i.e., word $N-1$, has an impact on the reading behavior. Increasing predictability in highly-predictable sentences increased differences in word processing between groups. While predictability of words $N+1$ increased gaze durations, implying that Controls performed predictions about upcoming words, these effects of words $N+1$ were absent in AD patients, suggesting they showed impairments in their capability for predictions. Extending this finding to the memory domain, recent work [27, 49] demonstrated that in healthy old readers predictive cueing can improve both working and long term memory performances; expectations act as an attentional filter to facilitate the extraction of information, resulting in performance benefits across multiple domains. Thus, highly-predictable sentences were much more familiar and therefore as a whole served as a cue that allowed for more efficient reading in Controls. Interestingly, our data show that high-predictable sentences did not serve as a cue for more efficient reading in mild AD patients. This is consistent with previous evidence that AD patients showed deficits in visual memory recognition [63], and were affected in their processing speed and in their visual short-term memory, even at early stages of the disease [64]. The prevailing view is that the prefrontal cortex mediates this prestimulus activity modulation generating cortical processing in visual areas via top-down signals prior to stimulus presentation [65–67]. A type of top-down modulation that has been shown to involve the prefrontal cortex is expectation, or anticipation, which precedes the presentation of a stimulus that can be predicted [68]. Because cortical regions in the dorsolateral prefrontal cortex are affected in mild AD patients [69–72], their capacity for predicting upcoming words might be impaired.

Using the two types of sentences described, we could explicitly vary the dynamics of memory retrieval during sentence reading. Predictable words in high-predictable sentences are clustered in a sentence instead of being isolated moments of highly regular fragments of a sentence (prepositions, articles). As a consequence, predictability is uncorrelated from other main factors governing fixation duration. Large values of predictability in sentences with a low-average cloze predictability correspond to shorter words, seemingly more related to the grammatical structure of the sentence than to its semantic contents, as connectors, prepositions, and articles. Highly predictable words in sentences with a high-average cloze predictability relate to semantic content and hence might provide a test bed for the investigation of the specific effect of memory retrieval and the subsequent facilitated incoming word-reading process.

Analysis of the effect of word predictability showed that in Controls an increase in the predictability of word $N+1$ increased gaze duration. Previous findings show that in healthy readers, word $N+1$ may have an effect on fixation duration via memory retrieval [27, 30, 37, 39, 40, 41, 64, 66, 73]. The increase in gaze duration in Controls 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 is present in healthy subjects but might be absent or deteriorated in AD patients, even at this early stage (Table 1, Fig. 1). It has recently been suggested [74] that the inferior parietal lobe mediates the automatic allocation of attention to retrieved memory contents, while others [31] proposed that overt shifts of attention through eye movements are associated with higher accuracy of performance in relational visuospatial memory task. These authors argued that the activation of these partial lobe regions may reinforce and help to produce stronger relational spatial representations and, consequently, more accurate memory recognitions. High-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 [27, 43, 44, 62, 75, 76]. 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 [27, 47, 78]. Evaluation of the effect of contextual word predictability could be an important indicator of how working memory and retrieval memory are affected in AD.

Previous reports suggested that AD patients' impairment on semantic memory tasks is the product of deficient memory retrieval in combination with a partially degraded semantic network [79]. The earliest cortical damage present in AD has been proposed to be located in the medial temporal lobe, producing the impairment to anterograde episodic memory [79, 80]. As the cortical damage spreads outward from the medial temporal lobe, numerous cognitive functions can be affected [49]. Specifically, as the damage draws closer to the temporal lobe, the semantic memory system will be disrupted. Retrieval from the semantic system can be damaged during this spread of cortical atrophy as well, perhaps as white matter connections along the temporal lobe are lost. Further research would be required to establish what pathways are involved in the impaired memory retrieval present in AD.

When analyzing the *maxjump* model, we did an operationalization of the word at which readers become aware of the entire sentence they are reading. This word is simply the word having the largest difference in cloze predictability relative to the previous word. Inclusion of the distinction between fixations before and after the maximum predictability jump in the LMM revealed that in Controls the positive $N+1$-predictability effect was solely due to fixations before *maxjump*; there was no evidence for this effect for fixations after *maxjump*. The interpretation is fairly straightforward. First, the positive upcoming predictability effect needs a moderate average level of predictability, as that present in our highly-predictable sentences; in that case, the predictability of the upcoming word affects fixation durations until the complete sentence is retrieved from memory. After this *Eureka* event, predictability loses its relevance as an indicator of cognitive effort in Controls. The lack of the effect of maxjump suggests that for AD patients the *Eureka* event came too late or not at all; their memory impairment did not provide enough cues for the word predictability effect to take effect. The impairment in the ability of AD patients for recollecting, in an integrative way, associative information from memory might be related to early neuroanatomical changes, namely in hippocampus and entorhinal cortex [4, 34].

Overall, the *maxjump* effect allowed us to check whether the contextual incoming word predictability is a consequence of anticipatory retrieval of word meaning from memory up to the point of complete retrieval. Probing online comprehension processes, as operationalized with the identification of a *Eureka* word in highly-predictable sentences, and tracing their effects to fixation durations might give us a tool for the evaluation of cognitive impairments usually linked to deficiencies in semantic, working, and retrieval memory. In addition, these findings might be relevant for expanding the options for the early detection and monitoring in the early stages of AD and for measuring drug impact on patient's behavior.

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SUPPLEMENTARY MATERIAL

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REFERENCES

[1] Wenk G (2003) Neuropathologic changes in Alzheimer's disease. *J Clin Psychiatry* **64**, 7-10.
[2] Hampel H, Bürger T, Teipel S, Bokde A, Zetterberg H, Blennow K (2008) Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimers Dement* **4**, 38-48.
[3] Prull M, Gabrieli J, Bunge S (2000) Age-related changes in memory: A cognitive neuroscience perspective. In The *handbook of aging and cognition*, Craik FIM, Salthouse TA, eds. Lawrence Erlbaum Associates, Mahwah, NJ.
[4] Pereira M, Camargo M, Aprahamian I, Forlenza O (2014) Eye movement analysis and cognitive processing: Detecting indicators of conversion to Alzheimer's disease. *Neuropsychiatr Dis Treat* **10**, 1273-1285.
[5] Förstl H, Kurz A (1999) Clinical features of Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci* **249**, 288-290.
[6] Frank E (1975) Effect of Alzheimer's disease on communication function. *J S C Med Assoc* **90**, 417-423.
[7] Taler V, Phillips N (2008) Language performance in Alzheimer's disease and mild cognitive impairment: A comparative review. *J Clin Exp Neuropsychol* **30**, 501-511.
[8] Mendez MF, Mendez MA, Martin R, Smyth KA, Whitehouse PJ (1990) Complex visual disturbances in Alzheimer's disease. *Neurology* **40**, 439-443.
[9] Fujimori M, Imamura T, Hirono N, Ishii K, Sasaki M, Mori E (2000) Disturbances of spatial vision and object vision correlate differently with regional cerebral glucose metabolism in Alzheimer's disease. *Neuropsychologia* **38**, 1356-1361.
[10] Daffne KR, Mesulam MM, Cohen LG, Scinto LF (1999) Mechanisms underlying diminished novelty-seeking behavior in patients with probable Alzheimer's disease. *Neuropsychiatry Neuropsychol Behav Neurol* **12**, 58-66.
[11] Moser A, Koémpf D, Olschinka J (1995) Eye movement dysfunction in dementia of the Alzheimer type. *Dementia* **6**, 264-268.
[12] Ogrocki PK, Hills AC, Strauss ME (2000) Visual exploration of facial emotion by healthy older adults and patients with Alzheimer's disease. *Neuropsychiatry Neuropsychol Behav Neurol* **13**, 271-278.
[13] Scinto L, Daffner K, Dressler D, Ransil B, Rentz D, Weintraum S, Mesulam M, Potter H (1994) A potential noninvasive neurobiological test for Alzheimer's disease. *Science* **226**, 1051-1054.
[14] Mosimann UP, Felblinger J, Ballinari P, Hess CW, Müri RM (2004) Visual exploration behavior during clock reading in Alzheimer's disease. *Brain* **127**, 431-438.
[15] Rayner K (1998) Eye movements in reading and information processing: 20 years of research. *Psychol Bull* **124**, 372-422.
[16] Martinez-Conde S, Macknik SL, Hubel DH (2004) The role of fixational eye movements in visual perception. *Nat Neurosci* **5**, 229-240.
[17] Rayner K, Pollatsek A (1992) Eye movements and scene perception. *Can J Psychol* **46**, 342-376.
[18] Yarbus A (1967) *Eye movements and vision*. Plenum, New York, NY.
[19] Awh E, Vogel EK, Oh SH (2006) Interactions between attention and working memory. *Neuroscience* **139**, 201-208.
[20] Cowan N, Morey (2006) Visual working memory depends on attentional filtering. *Trends Cog Sci* **10**, 139-141.
[21] Gilbert CD, Sigman M (2007) Brain states: Top down influences in sensory processing. *Neuron* **54**, 677-696.
[22] Khayat PS, Spekreijse H, Roelfsema PR (2006) Attention lights up new object representations before the old ones fade away. *J Neurosci* **26**, 138-142.
[23] Palmer J (1990) Attentional limits on the perception and memory of visual information. *J Exp Psychol Human* **16**, 332-350.
[24] Sigman M, Gilbert CD (2000) Learning to find a shape. *Nat Neurosci* **3**, 264-269.
[25] Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* **3**, 201-215.
[26] Kveraga K, Ghuman AS, Bar M (2007) Top-down predictions in the cognitive brain. *Brain Cogn* **65**, 145-168.
[27] Fernández G, Manes F, Rotstein N, Colombo O, Mandolesi P, Politi L, Agamennoni O (2014) Lack of contextual-word predictability during reading in patients with mild Alzheimer disease. *Neuropsychologia* **62**, 143-151.
[28] Alichniewicz K, Brunner F, Klünemann H, Greenlee M (2013) Neural correlates of saccadic inhibition in healthy elderly and patients with amnestic mild cognitive impairment. *Front Psychol* **4**, 1-12.
[29] Rösler A, Mapstone ME, Hays AK, Mesulam MM, Rademaker A, Gitelman DR (2000) Alterations of visual search strategy in Alzheimer's disease and aging. *Neuropsychology* **14**, 398-408.
[30] Fernández G, Shalom DE, Kliegl R, Sigman M (2013b) Eye movements during reading proverbs and regular sentences: The incoming word predictability effect. *Lang Cognitive Proc* **29**, 260-276.
[31] Olsen R, Chiew M, Buchsbaum B, Ryan J (2014) Delay period eye movements support successful visuospatial memory binding. *J Vis* **14**, 1-11.

[32] Wolk D, Schacter D, Berman A, Holcomb P, Daffner K, Budson A (2005) Patients with mild Alzheimer's disease attribute conceptual fluency to prior experience. *Neuropsychologia* **43**, 1662-1772.
[33] Wolk D, Signoff D, DeKosky S (2008) Recollection and familiarity in amnestic mild cognitive impairment: A global decline in recognition memory. *Neuropsychologia* **46**, 1965-1978.
[34] Besson G, Ceccaldi M, Tramoni E, Felician O, Didic M, Barbeau E (2015) Fast, but not slow, familiarity is preserved in patients with amnestic mild cognitive impairment. *Cortex* **65**, 36-49.
[35] Hayhoe M, Ballard D (2005) Eye movements in natural behavior. *Trends Cogn Sci* **9**, 188-193.
[36] Hoffman J (1998) Visual attention and eye movements. In *Attention*, Pashler H, ed. Psychology Press, Hove, UK
[37] Itoh N, Fukuda T (2002) Comparative study of eye movement in extent of central and peripheral vision and use by young and elderly walkers. *Perceptual Motor Skills* **94**, 1283-1291.
[38] Miela D, Lobel E, Lehericy S, Pierrot-Deseilligny C, Berthoz A (2005) Cortical mechanisms of saccadic generation from execution to decision. *Ann N Y Acad Sci* **1039**, 232-238.
[39] Posner M (1980) Orienting of attention. *Q J Exp Psych* **32**, 3-25.
[40] Fernández G, Laubrock J, Mandolesi P, Colombo O, Agamennoni O (2014) Registering eye movements during reading in Alzheimer disease: Difficulties in predicting upcoming words. *J Clin Exp Neuropsychol* **36**, 302-316.
[41] Kennedy A, Pynte J (2005) Parafoveal-on-foveal effects in normal reading. *Vision Res* **45**, 153-168.
[42] Kennedy A, Pynte J, Murray WS, Paul SA (2012) Frequency and predictability effects in the Dundee corpus. *Q J Exp Psychol* **66**, 601-618.
[43] Kliegl R, Nuthmann A, Engbert R (2006) Tracking the mind during reading: The influence of past, present, and future words on fixation durations. *J Exp Psychol Gen* **135**, 12-35.
[44] Kliegl R (2007) Toward a perceptual-span theory of distributed processing in reading: A reply to Rayner, Pollatsek, Drieghe, Slattery, and Reichle. *J Exp Psychol Gen* **136**, 530-537.
[45] Bäckman L, Jones S, Berger A, Laukka E, Small B (2005) Multiple cognitive deficits during the transition to Alzheimer's disease. *J Inter M* **256**, 195-204.
[46] Landes A, Sperry S, Strauss M, Geldmacher D (2001) Apathy in Alzheimer's disease. *J Am Geriatr Soc* **49**, 1700-1707.
[47] Lueck K, Mendez M, Perryman (2000) Eye movements abnormalities during reading in patients with Alzheimer disease. *Neuropsychiatry Neuropsychol Behav Neurol* **13**, 77-82.
[48] Fernández G, Mandolesi P, Rotstein N, Colombo O, Agamennoni O, Politi L (2013) Eye movement alterations during reading in patients with early Alzheimer disease. *Invest Ophthalmol Vis Sci* **54**, 8345-8352.
[49] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.
[50] American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). American Psychiatric Association, Washington, DC.
[51] Folstein MF, Folstein SE, McHugh PR (1975) 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
[52] Mioshi E, Dawson A, Mitchell J, Arnold R, Hodges JR (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): A brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* **21**, 1078-1085.
[53] Torralva T, Roca M, Gleichgerrcht E, López PL, Manes F (2009) INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia. *J Int Neuropsych Soc* **15**, 777-786.
[54] Sebastián-Gallés N, Martí MA, Cuetos F, Carreiras M (1998) *LEXESP: Léxico informatizado del español*, Ediciones de la Universidad de Barcelona, Barcelona.
[55] Bates DM, Maechler M, Bolker B lme4: Linear mixed-effects models using S4 classes. 2013; R package version 0.999999-0.[Computer software].
[56] Hohenstein S, Kliegl R (2014) Semantic preview benefit during reading. *J Exp Psychol Learn* **40**, 166-190.
[57] Pollatsek A, Lesch M, Morris RK, Rayner K (1992) Phonological codes are used in integrating information across saccades in word identification and reading. *J Exp Psychol Hum Percept Perform* **8**, 148-162.
[58] Boston MF, Hale JT, Vasishth S, Kliegl R (2011) Parallelism and syntactic processes in reading difficulty. *Lang Cogn Proc* **26**, 301-349.
[59] Stine-Morrow E, Miller S, Hertzog C (2006) Aging and self-regulated language processing. *Psychol Bull* **132**, 582-606.
[60] Lindenberger U, Mayr U (2014) Cognitive aging: Is there a dark side to environmental support? *Trends Cogn Sci* **18**, 7-15.
[61] Fernández G, Castro L, Schumacher M, Agamennoni O (2015) Diagnosis of mild Alzheimer disease through the analysis of eye movements during reading. *J Integr Neurosci* **14**, 121-133.
[62] Fernández G, Schumacher M, Orozco D, Castro L, Agamennoni O (2015) Patients with mild Alzheimer's disease produced shorter outgoing saccades when reading sentences. *Psychiatry Res* **229**, 470-478.
[63] Iachini I, Iavarone A, Senese P, Ruotolo F, Ruggiero G (2009) Visuospatial memory in healthy elderly, AD and MCI: A review. *Curr Aging Sci* **2**, 43-59.
[64] Bublak P, Redel P, Sorg C, Kurz A, Foerstl H, Mueller H, Schneider W, Finke K (2011) Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **32**, 1219-1230.
[65] Bressler SL, Tang W, Sylvester CM, Shulman GL, Corbetta M (2008) Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *J Neurosci* **28**, 10056-10061.
[66] Silver MA, Ress D, Heeger DJ (2007) Neural correlates of sustained spatial attention in human early visual cortex. *J Neurophysiol* **97**, 229-237.
[67] Summerfield C, Egner T (2009) Expectation (and attention) in visual cognition. *Trends Cogn Sci* **13**, 403-409.
[68] Puri AM, Wojciulik E, Ranganath C (2009) Category expectation modulates baseline and stimulus-evoked activity in human inferotemporal cortex. *Brain Res* **1301**, 89-99.
[69] Brown DR, Hunter R, Wyper DJ (1996) Longitudinal changes in cognitive function and regional cerebral function in Alzheimer disease: A SPECT blood flow study. *J Psychiatr Res* **30**, 109-117.
[70] Salat D, Kaye J, Janowsky J (2001) Selective preservation and degeneration within the prefrontal cortex in aging and Alzheimer disease. *Arch Neurol* **58**, 1403-1408.
[71] Drzezga A, Lautenschlager N, Siebner H, Riemenschneider M, Willoch F, Minoshima S, Schwaiger M, Kurz A (2003) Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: A PET follow-up study. *Eur J Nucl Med* **30**, 1104-1113.

[72] Pelak V (2010) Ocular motility of aging and dementia. *Curr Neurol Neurosci Rep* **10**, 440-447.
[73] Tsai J-L, Kliegl R, Yan M (2012) Parafoveal semantic information extraction in traditional Chinese reading. *Acta Psychol* **141**, 17-23.
[74] Moscovitch M (2008) The hippocampus as a "stupid," domain-specific module: Implications for theories of recent and remote memory. *Can J Exp Psychol* **62**, 62-69.
[75] Vitu F, Brysbaert M, Lancelin D (2004) A test of parafoveal-on-foveal effects with pairs of orthographically related words. *Eur J Cogn Psychol* **16**, 154-177.
[76] Dambacher M, Rolfs M, Göllner K, Kliegl R, Jacobs AM (2009) Event-related potentials reveal rapid verification of predicted visual input. *PLoS One* **4**, e5047.
[77] Cummings JL, Houlihan JP, Hill MA (1986) The pattern or reading deterioration in dementia of the Alzheimer's type: Observations and implications. *Brain Lang* **29**, 315-323.
[78] Rogers S, Friedman R (2007) The underlying mechanisms of semantic memory loss in Alzheimer's disease and semantic dementia, *Neuropsychologia* **46**, 12-21.
[79] Hodges JR, Patterson K (1995) Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia* **33**, 441-459.
[80] Hodges JR, Salmon DP, Butters N (1992) Semantic memory impairment in Alzheimer's disease: Failure of access or degraded knowledge? *Neuropsychologia* **30**, 301-314.