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

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A R T I C L E   I N F O

A B S T R A C T

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.

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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

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