Neuropsychologia 65 (2014) 12–17

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Neural correlates of spelling difficulties in Alzheimer's disease

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ARTICLE INFO

Article history:
Received 11 December 2013
Received in revised form
2 September 2014
Accepted 2 October 2014
Available online 14 October 2014

Keywords:
Alzheimer's disease
Spelling
Writing
Dysgraphia
Voxel-based morphometry

ABSTRACT

Alzheimer's disease (AD) is associated with a general cognitive decline that affects the memory and language domains. Thus, an oral production deficit with a lexical-semantic origin has been widely observed in these patients. Their written production capacities, however, have been much less studied. We assessed the spelling abilities of 22 AD patients and a group of matched healthy controls with a test battery including written picture naming and word and pseudoword dictation tests, as well as text dictation and spontaneous writing tasks. The results of the AD patients in the discriminative tasks were then entered into voxel-based morphometry analyses along with their grey matter volumes. The patient group presented a selective impairment for word dictation, which contrasted with a spared capacity to spell pseudowords, and showed more difficulties for words with arbitrary and rule-based orthography. Moreover, they also produced less complete syntactic units in the spontaneous writing task. These results point out the lexical-semantic, as opposed to sublexical, nature of the spelling deficit associated to AD. In addition, we recognized a mainly left-lateralized cortical network, including areas in the posterior inferior temporal lobe and the superior region of the parietal cortex, which might be responsible for this impairment. Other regions, such as the putamen, were also associated to the deficit. The results of this study, hence, improve our understanding of the neuropsychological and neuroanatomical mechanisms that underlie the cognitive symptoms associated to AD.

1. Introduction

The cognitive profile of Alzheimer's disease (AD) patients is mainly characterized by an episodic memory impairment that complicates the acquisition of new information (Fox et al., 1998). However, a linguistic deficit is also present in many of the cases. The verbal output of AD patients, even in the early stages of the disease, lacks lexical diversity and presents semantic errors and circumlocutions (Cuetos et al., 2009, 2012; González Nosti et al., 2008; Rodríguez-Ferreiro et al., 2009). This linguistic pattern has been extensively documented in the oral domain, but there is much less evidence regarding writing abilities of these patients (for a review see Neils-Strunjas et al., 2006).

Writing difficulties associated to the disease were observed by Alzheimer (1907) himself in the patient Auguste D. Since then, a variety of deficits, with origins ranging from central to peripheral, have been described in the AD population. This line of research has gained certain popularity in the last years with the case-studies of the renowned writers Iris Murdoch (Garrard et al., 2005; Pakhomov et al., 2011) and Agatha Christie (Lancashire, 2010).

The most common pattern of deficiency includes lexical dysgraphia (Croisile et al., 1996; Forbes et al., 2004; Hughes et al., 1997; Rapcsak et al., 1989) which may be concurrent with a phonological or sublexical deficit (Aarsland et al., 1996; Luzzatti et al., 2003; Neils and Roeltgen, 1994; Pestell et al., 2000; Platel et al., 1993) in later stages of the disease. In some cases, peripheral impairments are also present (Forbes et al., 2004; Horner et al., 1988; Neils-Strunjas et al., 1998; Venneri et al., 2002).

Following the influential model by Ellis (1982), lexical dysgraphia is characterized by errors in real word, as opposed to pseudoword, writing, and, more specifically, a diminished capacity to correctly spell irregular words with arbitrary orthography due to damage in the orthographic lexicon. On the other hand, phonological dysgraphia is present when the patient is incapable of writing pseudowords or rare unfamiliar words, and is caused by damage to the route that allows conversion of phonemes into their corresponding graphemes. Finally, peripheral dysgraphias involve a deficit in the mechanics of written output, including

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http://dx.doi.org/10.1016/j.neuropsychologia.2014.10.006
0028-3932/

inappropriate allograph selection, inaccurate graphomotor patterns, awkward letter construction, poor letter spacing or spatial misalignment, among others.

Hence, the profile of spelling impairment present in AD patients is congruent with the deficit described in the oral domain and could be caused by degradation of specific linguistic subcomponents (Croisile et al., 1996; Forbes et al., 2004; Rapcsak et al., 1989). Nonetheless, some authors ascribe it to the general cognitive decline associated to dementia (Aarsland et al., 1996; Glosser and Kaplan, 1989; Silveri et al., 2007), especially in the cases of peripheral disorders (Neils-Strunjas et al., 1998).

The cognitive deficit associated to AD is grounded in the degradation of neural structures responsible of the different capacities affected. Histopathological studies have shown that neuronal changes associated to AD initiate in the hippocampus and the trans-enthorrinal region and, later on, spread to the neocortex (Braak et al., 1999; Braak and Braak, 1995). More recently, automatic analyses of structural MRI scans through voxel-based morphometry (VBM) have confirmed that brain atrophy in AD patients starts in medial temporal structures and gradually extends to more lateral temporal regions as well as to the parieto-occipital area and the frontal lobe (Derflinger et al., 2011). In contrast, regions like the occipital pole, the sensoriomotor cortices and the cerebellum appear to be spared (Karas et al., 2003). In the last years, several studies have used VBM to examine the relationship between cortical changes and different symptoms of AD such as depression (Hyun Son et al., 2013), delusions (Bruen et al., 2008) or semantic deficits (Rodríguez-Ferreiro et al., 2012). However, the link between the spelling impairment of AD patients and their pattern of brain atrophy remains unstudied.

Historically, peripheral writing mechanisms have been situated in the Exner's area, just above Broca's area in the left frontal lobe (Exner, 1881), while central components have been associated to the angular gyrus in the parietal lobe (Dejerine, 1891). Thus, the extrasylvian temporo-parietal cortex has been linked with the processing of orthographic representations (Patterson and Kay, 1982; Rapcsak et al., 1990) and lesions in the posterior temporal area appear to be linked to lexical agraphia (Croisile et al., 1989) as well as to tasks involving the retrieval of orthographic word forms (Beeson et al., 2003). Moreover, activity in the angular gyrus has been specifically associated with lexical subprocesses of writing in AD participants (Penniello et al., 1995).

In this study we aimed to obtain a broad profile of the spelling capacities of our participants and investigate its relation with brain atrophy. Given its preeminence in the AD population, we decided to focus in the more common deterioration of central, rather than peripheral, components of written language processing. Thus, we measured the amount of correctly spelled words in each subtest while ignoring errors related to peripheral subcomponents of written language, such as case misuse or misalignment. We assessed the capacity of a group of AD patients to write in different tasks, including spontaneous narrative, dictation and written naming, with both sentence and single word stimuli. In order to differentiate between lexical and sublexical contributions to spelling, we also included a pseudoword dictation task, and we distinguished between different types of real word stimuli depending on their degree of spelling ambiguity in the word writing task. Due to the high amount of one-to-one correspondences between sounds and letters in the Spanish orthographic system, most of the words can be spelled correctly following the basic, sublexical, phoneme-to-grapheme correspondences. On the other hand, the correct spelling of words containing non-univocal correspondences (i.e. /b/ to “b” or “v”; /y/ to “y” or “ll”) depends entirely on lexical knowledge, although orthographic rules based on letter groupings might be applied to assist accurate spelling in some cases (i.e. all words ending in /*–iyo*/ are spelled with “ll”, and not “y”; all words starting with /*ue*/ are spelled with an initial mute “h”).

The results of the AD patients in those tasks sensitive enough to differentiate between healthy and impaired seniors were then introduced into VBM analyses along with their brain volumes in order to investigate the relationship between cognitive capacity and the degradation of neural structures.

2. Materials and methods

2.1. Participants

Twenty-two outpatients with probable AD and the same number of healthy seniors took part in the study. They all were native Spanish speakers and came from similar socio-economic backgrounds. None of them had a history of alcohol abuse, or neurological or psychiatric disorders other than AD. Other possible sources of cognitive impairment such as focal lesions or microbleeds were ruled out by neuroimaging tests. Participants with sensory impairments were also ruled out from the sample. All the patients had been diagnosed a priori by the neurology group of the Cabueñes Hospital (Gijón, Spain) according to the NINCDS-ADRDA criteria (McKhann et al., 1984; Tierney et al., 1988). The severity of dementia was assessed according to the Global Deterioration Scale (GDS, Reisberg et al., 1982). Eighteen of the patients were in stage four, three were in stage five and only one was in stage six. A group of 22 healthy seniors selected amongst the participants' relatives participated in the experiment as a control group. The two groups of participants were matched on age and years of education. Nevertheless, differences in cognitive capacity between the AD and control group were evidenced by their scores in the MiniMental State Evaluation test (MMSE, Folstein et al., 1975). A summary of the demographic characteristics of the participants is presented in Table 1. Informed consent was obtained from all participants or their caregivers where appropriate. Ethical approval was obtained from the hospital board where data collection was undertaken.

2.2. Tasks

We present the results obtained by the participants in six tasks that were administered in the context of a wider assessment protocol. Five of the tasks were designed to study the participants' writing abilities: written picture naming; text writing to dictation; word writing to dictation, pseudoword writing to dictation; and narrative writing. In order to confirm the presence of the lexical-semantic deficit reported in previous studies an oral picture naming task was also included in the battery as a control test for the oral production domain. The different tasks were distributed in two sessions separated seven days apart. Longer tasks were split into two and each half was presented in one of the sessions. For those tasks with overlapping stimuli sets, we avoided repetition of stimuli in the same session.

2.2.1. Oral picture naming

A list of 50 pictures were selected from the coloured version (Rossion and Pourtois, 2004) of the Snodgrass and Vanderwart (1980) picture set. They all had high name agreement values (>85%) and corresponded to familiar objects (M=5.77, SD=0.77). Picture names ranged from three to ten phonemes (M=5.76, SD=1.44) and their lexical frequency values (LEXESP, Sebastián-Gallés et al., 2000) were between 0.36 and 107.86 (M=13.15, SD=18.65).

2.2.2. Written picture naming

The participant was presented with 15 object pictures, natural kinds (i.e. “oveja” *sheep*; “cebolla” *onion*…) and six artefacts (“campana” *bell*; “cepillo” *brush*…), from the list used in the oral naming task. The average length of the picture names was 6.4 letters (SD=1.8, range 4–11). Their frequency values were between 0.89 and 34.46 (M=8.6, SD=9.25). Each picture was presented in print in a separate paper sheet. The participant was asked to write down the name of the object. No time limit was imposed so the trial ended when the patient had finished writing or when she said “I don't know”. No semantic or phonological cues were given at any time. The participant was free to write the answers in lower or upper

Table 1
Summary of participants' characteristics.

	n (females)	Age *M* (SD)	Years of schooling *M* (SD)	MMSE out of. 30 *M* (SD)
AD	22(12)	75.4(4.3)	8.6(2.9)	20.1(3.8)
Control	22(12)	75.4(4)	8(2.7)	29.3(0.7)