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Current Alzheimer Research, 2020, *17*, 1-12

RESEARCH ARTICLE

Evolution of Writing Impairment in Spanish Patients with Alzheimer's Disease

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ARTICLE HISTORY

Received: ????????????
Revised: ??????????????
Accepted: ??????????????

DOI:
??????????????????????????????

Abstract: ***Background*:** Although some studies suggest that writing difficulties may be one of the early symptoms of Alzheimer's disease (AD), they have been scarcely studied compared to oral language. Particularly noteworthy is the paucity of longitudinal studies that enable the observation of writing impairment as cognitive decline progresses.

***Objective*:** The aim of this study was to examine the characteristics of writing in patients with AD and to monitor the deterioration of their performance over a follow-up period.

***Methods*:** Sixty-four participants (half with AD and half healthy elderly) were compared in a word and pseudo-word dictation task. Patients were evaluated every 6 months over a 2.5 year follow-up period.

***Results*:** The evolution of patient performance and error profile shows a typical pattern of deterioration, with early damage to the lexical pathway, which later extends to the phonological pathway and eventually affects peripheral processes.

***Conclusion*:** These results confirm the presence of writing difficulties from the early stages of AD, supporting the value of this task for early diagnosis. Furthermore, it allows us to explain the contradictory data obtained in previous investigations.

Keywords: ????????????????????????

1. INTRODUCTION

Memory loss is the most characteristic symptom in Alzheimer's disease, although recent research also shows significant language impairment from early stages [1]. Most of the studies have focused on oral language, while writing has gained little attention. Still, some authors, such as Fukui and Lee [2], suggest that dysgraphia may be one of the first clinical manifestations of dementia in certain patients.

Writing is a complex cognitive function in which several processes are involved, some of which entail higher capacities, such as planning and lexical aspects, while others are peripheral, such as the selection of graphemes and allographs and spatial and motor processes. Some authors, such as Croisile [3], point out that these capacities do not deteriorate to the same extent or at the same time in AD. Namely, the first stages of the disease are characterized by a lack of ideas regarding the content of the narrative. As the deterioration progresses, problems appear in the lexical selection and in the spelling of words, eventually compromising the grapho-motor aspects of writing during the final stages of the disease.

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The few studies dealing with the writing of patients with AD mostly focus on lexical aspects in order to determine whether the deterioration of the writing system is diffuse and global or whether there is a differential affectation of one of the two routes proposed by Ellis [4]. The sub-lexical or phonological route enables the writing of pseudo-words and regular words (that is, those with an exact correspondence between phonemes and graphemes). Damage in this route results in phonological dysgraphia, characterized by difficulties in applying the rules of phoneme-grapheme conversion. These patients will make omissions, substitutions or additions of letters, resulting in phonological (or phonologically non-plausible) errors, in which the pronunciation of the stimulus changes. The lexical route enables the writing of known words, for which we have a representation in our lexicon. This is the only pathway that allows us to correctly write irregular words (that is, those whose phoneme-grapheme correspondences are not exact). Damage in this route leads to lexical or surface dysgraphia, characterized by the presence of orthographic (or phonologically plausible) errors, in which the pronunciation of the word does not change despite being misspelled.

The results of the studies carried out with AD patients, however, are contradictory. Some of them [5, 6] do not find writing impairments in patients with mild AD, which leads authors to question the sensitivity of writing tasks for early diagnosis. Other researchers, on the other hand, argue that

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lexical (or surface) dysgraphia is the characteristic pattern of AD, at least in mild and moderate stages. This is the case of the classical work of Rapcsak, Arthur, Bliklen, and Rubens [7], who assessed the spelling abilities of 11 patients with moderate to severe AD and 10 healthy adults. They found no differences between both groups in regular words and pseudo-words, but the patients' performance for irregular words was significantly worse. This, together with the predominance of phonologically plausible errors, indicates selective damage in the lexical route and a loss of orthographic representations, while preserving phonological skills. In addition, the absence of correlation between the scores in the task and in the MMSE [8] would point, according to the authors, to focal damage in certain critical areas. Similar results were obtained by Cuetos, Martínez, Martínez, Izura and Ellis [9] in a study conducted with 20 patients with mild (12) and moderate (8) AD. In a battery of 17 tests, written naming and dictation of the same 40 words were included, as well as writing to the dictation of 30 pseudo-words. The results of the dictation task showed greater difficulties with inconsistent words than with pseudo-words, indicating the use of the phonological route. In addition, in line with the results shown by Rapcsak *et al.* [7], no differences were found according to the severity of the patients, and the correlation between patients' performance and the MMSE score [8] was not significant. Some studies, such as that of Rodríguez-Ferreiro, Martínez, Pérez-Carbajal and Cuetos [10], even indicated that the phonological route may be completely preserved, since they found no differences between controls and patients (with moderate AD in this case) in the writing of regular words and pseudo-words.

In similar research conducted with 23 participants with AD and 20 controls, Luzzatti, Laiacona and Agazzi [11] observed worse patient performance in all types of stimuli, but particularly in words with unpredictable orthography and pseudo-words. One of the possible explanations for these results, according to the authors, is that both routes are partially damaged, but they interact to write words with predictable orthography; however, neither route would be sufficient alone to correctly write words with unpredictable orthography or pseudo-words. Similar results were found by Lambert *et al.* [12] in a study conducted with 12 patients with mild to moderate AD. The pattern of errors (both phonologically plausible and non-plausible) pointed to multiple but focal impairment.

Nevertheless, a few years later, Lambert *et al.* [13] carried out a larger study, increasing the number of patients to 59. In this case, they reported a heterogeneous pattern of dysgraphia in AD, where 25% of patients showed no damage at all, others predominantly showed disorders in the central aspects of writing (mainly in the lexical, but also in the phonological route) and the last group (approximately one-third of patients) that showed damage in the peripheral processes (graphemic buffer, allographs). These heterogeneous patterns can only be explained, according to the authors, by specific damage in different points of the broad anatomical network that supports writing and spelling skills, and not by a general impairment as other researches point out. The study by Silveri, Corda and Nardo [14] agrees that there is no clear pattern of dysgraphia in AD, but thorough analysis of the errors (phonologically plausible and non-plausible in patients with mild impairment, grapho-motor and allographic in patients with greater damage) concludes that milder stages of AD mainly affect the two routes, as well as the graphemic buffer, while other peripheral processes are damaged as the disorder becomes more severe.

Finally, some other investigations [15, 16] have even suggested that spelling difficulties in AD patients, rather than language problems, may be due to more general deficits affecting attention or working memory. For example, Aarsland, Høien, Larsen and Oftedal [17] compared a group of 16 patients with mild and moderate AD with 17 healthy adults, matched in age and educational level, in a dictation task in which regularity, frequency and length were manipulated. They report poorer performance in patients but found no differences depending on the type of stimulus. In addition, a correlation was found between the scores on the task and on the MMSE [8], so they conclude that the results are the product of general impairment rather than specifically linguistic. This is also the case of Pestell, Shanks, Warrington and Veneri [18], who carried out a study comparing the performance of a group of patients with mild and moderate AD in an oral spelling and dictation task of words and pseudo-words. Although their results show that both routes are compromised, the better performance on the spelling task and the length effect suggest, according to the authors, that part of the results could be attributable to damage in the graphemic buffer, since the working memory load would be higher for the dictation than for the oral spelling task. However, Croisile *et al.* [19] also compared these two tasks in a similar study, and found that performance was worse in oral spelling than in dictation. Still, their data and the observed length effect led them to the same conclusion regarding the graphemic buffer deficit. The authors also point out deterioration of the lexical pathway, which would explain the worse performance with irregular words than with regular words or pseudo-words. The contradiction in the results and conclusions of all these studies makes it evident that the characteristics of writing in patients with AD remain unclear.

Furthermore, although cross-sectional studies are useful as a first approach to the study of writing, the progression of deterioration can only be observed through longitudinal studies, in which the patient is followed for as long as possible. Given the difficulty in carrying out these investigations, there are few longitudinal studies on writing in AD. One of them is the research carried out in Italian by Luzzatti *et al.* [11], already mentioned above. The data of the 23 AD patients who participated in the study show a pattern that was initially heterogeneous, with 4 patients showing no writing disorders, 2 with phonological dysgraphia, 5 with surface dysgraphia, 7 with mixed dysgraphia, 3 with undifferentiated writing disorders and 2 with agraphia, which is consistent with previous studies [13, 14]. Nine of these patients participated in the longitudinal study and were evaluated between 6 and 12 months later. In the individual case analysis, the authors highlight that the surface dysgraphics continued to have more difficulty with irregular words; those who did not initially show writing disorders evolved into phonological dysgraphia, and the cases with mixed dysgraphia or undifferentiated writing disorder suffered a further breakdown in one of the two routes (lexical or sub-lexical). However, the authors themselves stress that, given the small number of

patients who participated in this part of the research, it is necessary to be cautious about the conclusions. The other longitudinal study carried out so far, as we are aware, was conducted in French by Platel *et al.* [20] with a group of 22 patients with mild to moderate AD. The dictation task included 30 items: 10 consistent spelling words, 10 inconsistent spelling words and 10 pseudo-words. The patients were tested twice on a 9-12 month interval. In the first session, the observed performance corresponded to lexical dysgraphia, with a worse performance in the inconsistent words than in the other two types of stimuli; in the second session, although the scores in the MMSE had not significantly decreased, phonological impairment was also observed, since the performance worsened slightly in the inconsistent words, and very markedly in the pseudo-words. Finally, the error analysis showed an increment in non-responses (0% to 5.7%) and in grapho-motor errors (16.3% to 33.2%) in the second session, although this difference was not significant. According to the pattern of errors, the authors differentiate 4 groups of patients: A) those who commit few or no phonologically plausible errors; B) those who commit a moderate number of errors, most of them phonologically non-plausible; C) those who commit a large number of errors, predominantly non-responses or incomplete responses; and D) those who commit many errors, mostly of grapho-motor type. Between session 1 and 2, most patients remained in their initial group or moved on to the next one (from group A to B, from B to C, *etc.*). Only one of the patients evaluated shifted two groups (from A to C). All of the changes described, however, went in the same direction, which leads researchers to suggest that these four patterns could show the typical evolution of dysgraphia in AD, with an initial impairment of the lexical pathway, that evolves towards phonological damage to finally affect the grapho-motor processes. These two longitudinal studies provide valuable information about writing impairment in AD. However, in a study by Luzzatti *et al.* [11], the sample was only 9 patients, which greatly limits his conclusions. Furthermore, in both studies, the follow-up period was very short, never exceeding 12 months, implying that many patients would not have deteriorated enough to observe significant changes (*e.g.,* the MMSE score in the study by Platel *et al.*, 1993, was equivalent in both sessions). Further longitudinal and longer-term investigations are therefore needed to clarify this issue.

On the other hand, both the two longitudinal studies and most of the transversal studies discussed above were carried out in languages other than Spanish. This language has a very transparent reading system, since the grapheme-phoneme correspondences are exact, and a much more opaque spelling system that differs substantially from other languages with opaque systems such as English or French. So, in Spanish, each phoneme corresponds to a single grapheme, except for some sounds that can be written in two ways (*e.g.* /b/ can be written with "b" "v"; /ʎ/ can be written with "ll" or "y"; /xe/ and /xi/ can be written with "j" or "g"). In addition, many of these ambiguous phoneme correspondences are regulated by spelling rules taught during the school years. As far as we know, only two studies in Spanish [9, 10] have addressed the lexical aspects of writing in AD, both concluding that in the early stages of the disease, the damage mainly affects the lexical route, while the phonological processes remain relatively preserved. However, as mentioned previously, no longitudinal studies have been carried out in our language.

The aim of this research, therefore, was to evaluate the writing skills of a group of AD patients by comparing their performance on a word and pseudo-word dictation task with the outcomes obtained by a control group with the same characteristics. The assessment will be repeated regularly over 2.5 years in order to observe the evolution of the patients as the degree of deterioration increases.

2. METHODS

2.1. Participants

A total of 64 participants took part in this study. Half of them were healthy adults and the other half were patients with probable AD, according to the diagnostic criteria NINCDS-ADRDA [21], developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. The diagnostic methodology was similar in all cases, and always applied by the same professional. For each patient, a neuropsychological evaluation and the complementary tests recommended by the Neurological Behavioral Neurology and Dementia Group of the SEN were performed, including a basic analytical determination, a standard 12-lead electrocardiogram and neuroimaging. This could be a CT, performed following a standard protocol with a GE team, including sequential axial slices, without intravenous contrast administration, or a cranial MRI test, carried out in a 1.5T machine (Signa EchoSpeed, GE Medical Systems), including images of cuts in the sagittal, coronal and axial planes (with T1 and T2 sequences) [22].

The severity of dementia was categorized by the Global Deterioration Scale (GDS) [23], a popular classification of the phases of Alzheimer's, consisting of 7 stages according to the degree of cognitive impairment and functional dependence of the patient, 1 being the total absence of cognitive impairment and 7 the presence of very severe cognitive impairment, in which the person will need help to perform even the most elementary daily functions. According to this grading, 19 of our patients were classified in stage 4, 11 in stage 5 and the remaining 2 in stage 6.

The 32 participants of the AD group were 20 females and 12 males aged between 64 and 85 years, with a mean of 75.22 years (standard deviation: 5.48). Formal schooling years ranged from 3 to 17, with an average of 7.59 years (standard deviation: 2.83). The most frequent occupation was housewife among females, and skilled worker among males. The majority of the Alzheimer's patients lived in the family home and none of them had sensory defects that rendered it impossible to do the tasks.

The control group consisted of 32 healthy subjects, 20 women and 12 men, selected from an elderly social center and among the relatives of patients participating in this research (26 and 6, respectively). The mean age was 75.44 years (standard deviation: 5.12), with a range between 65 and 84 years. Formal schooling years ranged from 5 to 18, with an average of 7.97 years (standard deviation: 2.57).

The two groups (AD and control) were matched for gender, age ($t_{(1,62)}$=0.213, p=.832) and educational level ($t_{(1,62)}$=0.555, p=.581). The Mini Mental State Examination (MMSE) [8] was administered to all participants. The total scores obtained by patients were between 13 and 24 points, with an average value of 18.56 points (standard deviation: 3.18). Although the subjects in the control group were fully autonomous and independent for activities of daily living, they were administered MMSE to rule out the existence of possible cognitive impairment. All of them obtained a total score between 27 and 30 points, with an average of 29.03 (standard deviation: 0.90).

All participants in the study were native Spanish speakers and had no history of alcohol abuse or psychiatric or neurological disorders, other than AD. They (and their relatives in the case of Alzheimer's patients) agreed to take part in the study and signed a consent form after being informed about the project.

2.2. Materials

A total of 80 stimuli (60 words and 20 pseudowords) from 4 to 8 letters were selected for this study. Twenty of them were regular words, in which phoneme-grapheme correspondences are exact and thus, there is only one possible way to write them correctly (*e.g.,* arco – bow). Another 20 were ruled words, whose phoneme-grapheme inconsistencies obey some orthographic guideline (*e.g.,* tornillo – screw: "tornillo" and "torniyo" sound the same, but a Spanish orthographic rule says that all words ending in "-illo", "-illa" must be written with "ll"), so it is necessary to know this rule to write them correctly. The last 20 words were arbitrary, in which the phoneme-grapheme correspondences are inconsistent, but they do not follow any orthographic rules (*e.g.,* banco – bench: "banco" and "vanco" would sound the same and there are no rules about this), so the person must know the word to be able to spell it correctly. The other stimuli were 20 pseudowords, specifically created for this work by changing one or two graphemes of real words not included in the task. To write them, one needs to correctly apply the phoneme-grapheme conversion rules, since we do not have orthographic representations for these stimuli. Twenty of the words corresponded to living beings and 40 to inanimate objects.

The four groups of stimuli (pseudo-words and regular, ruled and arbitrary words) were matched in length (measured in letters). In the case of words, there were no differences among the groups either in terms of lexical frequency [24] or the number of orthographic neighbours [25] (Table **1**).

2.3. Procedure

The evaluations were carried out in a room isolated from noise and without any other distracting elements. In the case of AD patients, the same test battery was administered every 6 months for a total of 2.5 years, in two different sessions, separated by a maximum time interval of seven days. The control group members completed the same set of tasks in similar order and in a single session. Tasks were administered to each person individually by an experienced researcher, who provided each participant with the time needed to complete each task.

Dictation of words, in random order, was performed first, followed by the dictation of pseudo-words. The stimuli were distributed to the AD patients between the two sessions to avoid fatigue, so that they wrote the first 30 words and the first 10 pseudo-words in the first session and the remaining stimuli in the second.

No specific instructions were given about the type of allograph to use or the orientation of the words on the sheet of paper (whether they were on the same line or one was below the other). Some letters (*e.g.,* F, f, h) could be "practiced" when the subject showed some difficulty in writing. There was no answer to any questions about spelling, and the participants were encouraged to decide according to their best judgment. In the case of pseudo-words, to confirm that the examinee had heard it correctly, they were asked to repeat it before beginning to write. If it was observed that the response did not correspond to the stimulus given, it was told again. If the participant showed fatigue, a short break was allowed during the task.

3. RESULTS

Only the first response was considered for the analysis of the task, subsequent attempts and corrections were not taken into account. The correct answers were rated 1 and the errors were classified among one of the following modalities: phonological (equivalent to phonologically non-plausible), neologism, non-response, unreadable, incomplete or perseveration. In the case of word dictation, errors could also be orthographic (equivalent to phonologically plausible), semantic or unrelated. As for pseudo-words, some errors were also classified as lexicalizations. When the number of errors of a given subtype was very small, several modalities were grouped under the heading "other". The errors were classified by the three authors independently and there was practically unanimity throughout the rating.

Table 1. Summary of the main psycholinguistic characteristics of the stimuli.

	Lexical frequency	Orthographic neighbors	Length (in letters)
Regular words	10.67	3.60	5.40
Ruled words	10.52	2.55	6.10
Arbitrary words	10.06	3.65	5.45
Pseudo-words	-	-	5.35

Separate analyses were carried out for cross-sectional and longitudinal data, using the statistical software SPSS, version 19.

3.1. Cross-sectional Study

AD patients correctly wrote an average of 55.25 items (S_x=12.78), which, in terms of percentages, represents 69.6% of the total. Depending on the type of stimulus, they succeeded in writing 16.78 regular words (S_x=2.64), 12.63 ruled words (S_x=4.59), 10.28 arbitrary words (S_x=4.36) and 15.56 pseudo-words (S_x=3.42). The controls, on the other hand, correctly wrote 70.78 items on average (S_x=7.22), which corresponds to 88.48% of the total. Depending on the type of stimulus, they were successful in writing 18.81 regular words (S_x=1.45), 17.63 ruled words (S_x=2.38), 15.41 arbitrary words (S_x=4.26) and 18.94 pseudo-words (S_x=1.13).

An item-by-item analysis was carried out using a univariate ANOVA. The group (control vs. Alzheimer) and the type of stimulus (regular, ruled, arbitrary and pseudo-words) were included as fixed factors (Table **2**).

Differences were found in the variable group ($F_{(1,248)}$=89.848, p=.000), as Alzheimer's patients scored lower than controls. The type of stimulus was also significant ($F_{(3,248)}$=30.347, p=.000); Tukey's post-hoc test showed that regular words were written significantly better than ruled (p=.000) and arbitrary (p=.000), but no differences were found between regular words and pseudo-words (p=.781); ruled words, on the other hand, were written significantly better than arbitrary (p=.001), but worse than pseudo-words (p=.002); finally, arbitrary words were significantly worse than pseudo-words (p=.000).

A significant interaction between the group and the type of stimuli was also observed ($F_{(3,248)}$=3.217, p=.023), as the differences between controls and AD patients were greater in ruled and arbitrary words than in regular ones and pseudo-words (Fig. **1**).

Analyses were carried out taking into account the degree of deterioration of the patients and the type of stimulus. To do so, participants with AD were divided into two subgroups, according to the severity of their cognitive impairment measured with the GDS scale. Thus, the 19 subjects in GDS stage 4 were classified as mild AD and the remaining 13, in stages 5 and 6, as moderate. Given the different number of subjects in each group and the small size of the samples, a non-parametric statistic, the Kruskal-Wallis test, was used. According to the deterioration degree, the average range was highest for the control group (164.17), followed by the mild AD group (113.11), and the lowest value corresponded to the moderate AD group (63.18). The chi-square value for 2 degrees of freedom was 74.54, and the asymptotic significance, p=.000, indicating that the differences between the three groups were significant. Regarding the type of stimulus, the average range was greater for regular words (161.41), followed by pseudo-words (152.83). Ruled words and arbitrary spelling words had the lowest ranges (114.58 and 85.19, respectively). The chi-square value, in this case, was 44.355 for 3 degrees of freedom, and the asymptotic significance was p=.000, indicating that the differences between the different types of stimuli are significant (Fig. **2**).

Correlation analyses were conducted to determine which variables of the patients (age, educational level, MMSE score, and GDS score) are related to their performance in the task. Only the MMSE score (.697, p<.01) and the GDS score (-.556, p<.01) significantly correlated with the total hits. In the case of controls, the educational level correlated highest with achievement in the task (.544, p<.01), followed by the age of the participants (-.401, p<.05).

The two tasks were analyzed separately with respect to error, since the error categories are different. In word dictation, the most frequent errors in both groups were orthographic (19.6% in patients and 10.7% in controls) and phonological (13% in patients and 2.9% in the control group). However, Student's T-test carried out confirms that there are significant differences between the two groups in the number of orthographic ($t_{(1,62)}$=-4.11, p=.000) and phonological errors ($t_{(1,39)}$=-4.86, p=.000). The other types (neologisms, incomplete, non-responses, semantics and perseverations) were very rare in patients (3.7%) and nonexistent in controls.

In pseudo-word dictation, phonological errors were the most frequent type of error in both groups (16.7% in patients and 4.7% in controls), although, again, significant differences between healthy adults and participants with AD were found ($t_{(1.42)}$=-5.27, p=000). Lexicalizations were the next

Table 2. Results of the univariate ANOVA of the cross-sectional study.

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Eta Squared	Non central Parameter	Observed Power[b]
Intercept	63535.504	1	63535.504	5916.313	.000	.960	5916.313	1.000
Subject	964.879	1	964.879	89.848	.000	.266	89.848	1.000
Type of stimulus	977.699	3	325.900	30.347	.000	.269	91.042	1.000
Subj.* Type of stimulus	103.637	3	34.546	3.217	.023	.037	9.650	.737
Error	2663.281	248	10.739					

b. Computed using alpha = .05

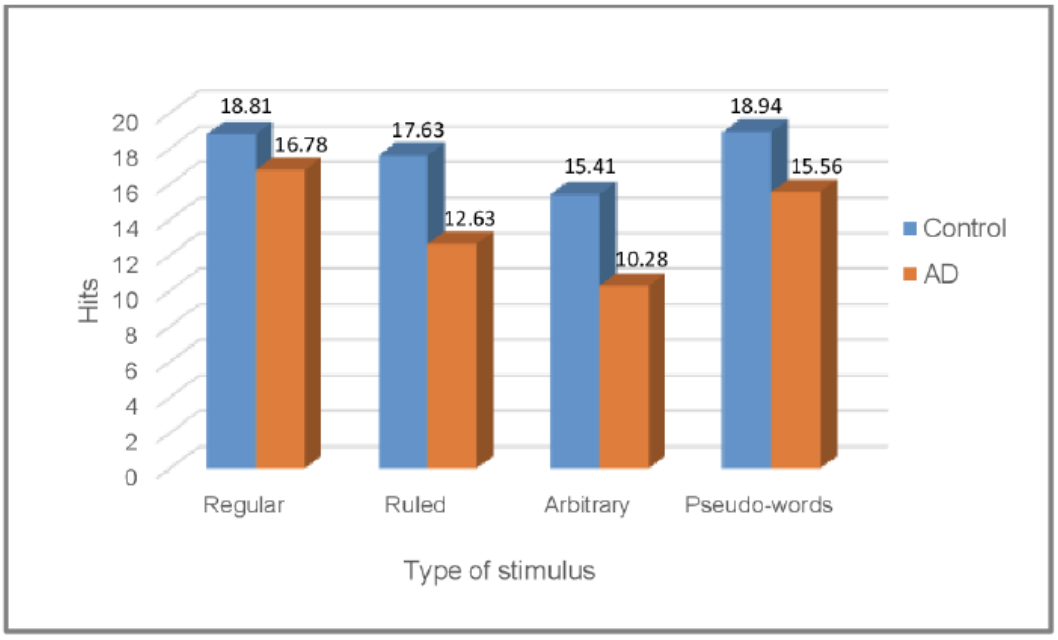

Fig. (1). Average of both groups according to the type of stimulus. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

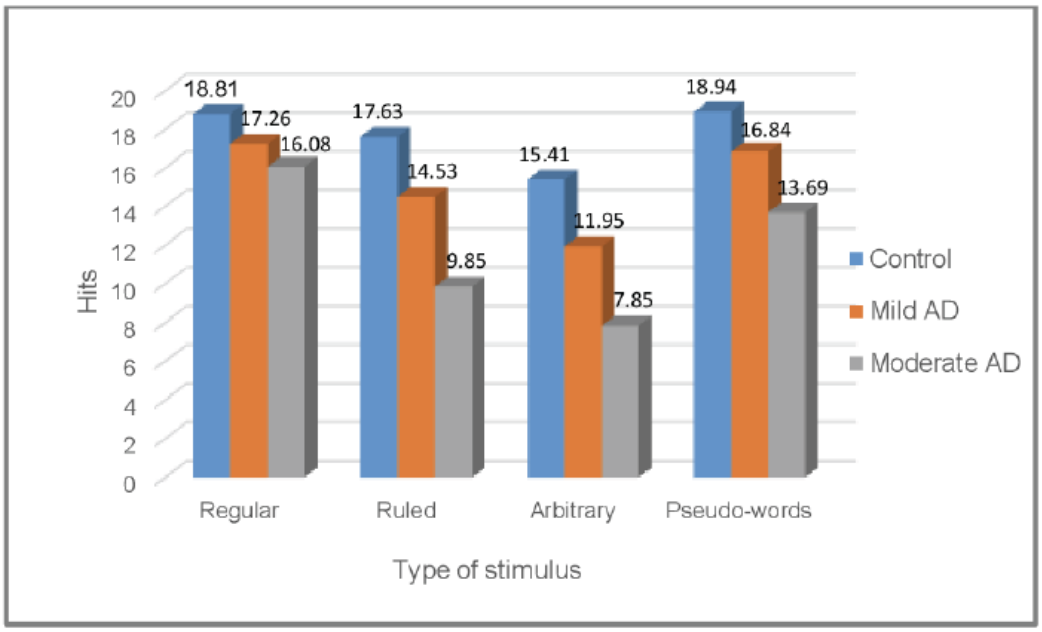

Fig. (2). Average of groups according to the degree of deterioration of patients and the type of stimulus. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

most frequent error in the patients' group (3.4%), but they were rarely found in controls (0.3%), showing significant differences between both groups ($t_{(1,36)}$=-4.13, p=.000). In this task, contrary to expectations, participants made some orthographical errors (*e.g.,* rraco: "rr" must never be written at the beginning of a word; graqe: in Spanish the letter "q" must always be followed by a "u"), although both groups made very few. The remaining error types (non-response and incomplete) were rare in the patients and non-existent in the control group.

3.2. Longitudinal Study

As explained in the procedure section, patients were evaluated using the same test battery every 6 months for a total of 2.5 years in order to test the evolution of performance as cognitive impairment progresses. A total of 21 subjects, which represented 65.62% of the initial sample, concluded the study and completed the 6 scheduled evaluations. The most frequent reason for dropping out was the severe progression of cognitive decline, which made it impossible

to complete tasks. The mean MMSE score of the 21 patients who completed the study went from 19.76 (S_x=3.05; range: 20-24) in the first assessment to 15.95 (S_x=4.88; range 6-25) in the sixth assessment. The time needed to complete the evaluation increased over time. Thus, while the interview lasted, on average, 45.05 minutes during the first evaluation (S_x=9.98; range: 30-60), it lasted 48.95 minutes during the last evaluation (S_x=12.16; range: 32-77). The severity of cognitive impairment in all 21 patients showed a striking change during the observation period. In the first assessment, 15 subjects were in a GDS-4 stage and the remaining 6 in a GDS-5, but at the end of the 30-month follow-up, the sample was distributed as follows: 5 patients remained in a GDS-4 stage, 9 were in a GDS-5 stage and 7 progressed to a GDS-6 stage. The progressive decrease in MMSE scores and the distribution of subjects according to GDS stage over time indicated a progressive cognitive decline in patients.

Concerning their performance on the task, of the 10,080 total responses (80 stimuli x 6 sessions x 21 patients), the patients correctly wrote 7,034 (69.78%).

An ANOVA of repeated measures was carried out to check if there were differences in the patients' performance of this task in the successive evaluations (Table **3**). In the within-subject effects test, no assumed sphericity was found, so the Greenhouse-Geisser correction was taken. The results show significant differences in the mean scores of each session ($F_{(2.842,56.841)}$=5.789, p=.002). As expected, and as can be seen in (Fig. **3**), the number of hits in each type of stimulus declined over time.

A univariate ANOVA was also carried out, taking the evaluation session (1st vs. 6th) and the regularity as independent variables, with the objective of finding out which type of stimulus was most affected by the deterioration (Table **3**). The results showed major effects of both the session ($F_{(1,152)}$=12.414, p=.001) and the type of stimulus ($F_{(3,152)}$=26.179, p=.000), but the interaction between the two was not significant, indicating that the deterioration was uniform in all three types of words. Tukey's post-hoc test showed that there were significant differences between regular and the other types of words: ruled (p=.000) and arbitrary (p=.000); it also showed differences between ruled and the other types of stimuli: arbitrary words (p=.019) and pseudo-words (p=.001) and, finally, it showed differences between arbitrary words and pseudo-words (p=.000). There were no differences between regular words and pseudo-words.

Correlation analyses were performed in order to know what characteristics of Alzheimer's patients (age, educational level, MMSE initial and final scores) are related to progressive deterioration (ratings in the GDS were not included because they highly correlate with those obtained in the MMSE). The dependent variable was the decline of performance in the task, obtained by subtracting the scores of the patients in the 6th session from those obtained in the 1st session. The only variable that significantly correlated with poorer patient performance was the final score on the MMSE (-.715, p<.001).

With regard to the analysis of errors in the word dictation task, orthographic errors were the most numerous during the follow-up period, although they showed a tendency to decrease. Phonological errors, on the other hand, were less numerous at the beginning, but increased over time, eventually equalling the number of orthographic errors (Fig. **4**). The rest of the errors observed (neologism, non-response, incomplete word, and unrelated), collected under the heading of "other", were scarce in all sessions.

Qualitative analysis of the errors showed that patients changed the type of response from one session to the next, even for the same items. Of the 6300 responses in word dic-

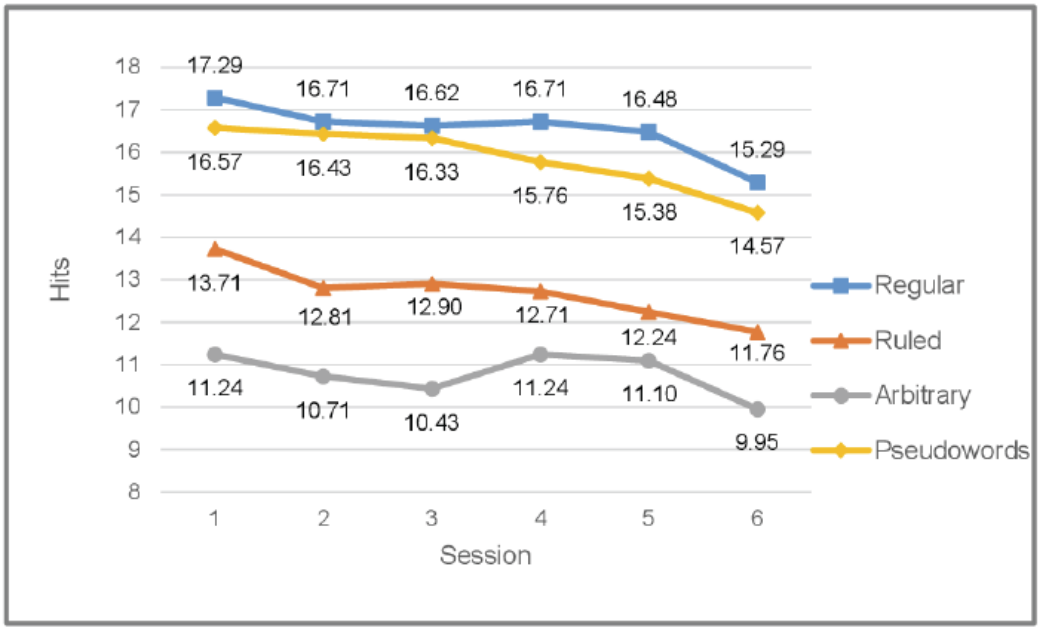

Fig. (3). Average scores for each type of stimulus. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 3. Results of the repeated measures and the univariate ANOVA of the longitudinal study.

Repeated measures Anova

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Eta Squared	Non central Parameter	Observed Power[a]
Session	Greenhouse-Geisser	602.444	2.842	211.975	5.789	.002	.224	16.454	.928
Error	Greenhouse-Geisser	2081.222	56.841	36.615					

a. Computed using alpha = .05

Univariate Anova session 6th-1st

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Eta Squared	Non central Parameter	Observed Power[b]
Intercept	33582.025	1	33582.025	2887.142	.000	.950	2887.142	1.000
Type of stimulus	913.525	3	304.508	26.179	.000	.341	78.538	1.000
Session	144.400	1	144.400	12.414	.001	.076	12.414	.938
Type of stimulus*Session	4.050	3	1.350	.116	.951	.002	.348	.071
Error	1768.000	152	11.632					

b. Computed using alpha = .05

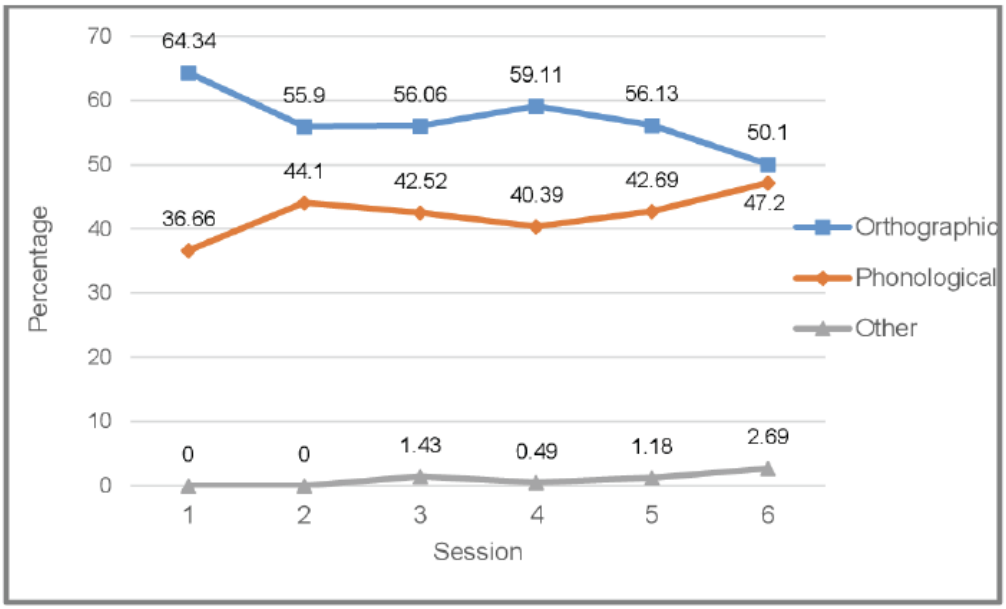

Fig. (4). Percentage of errors in the word dictation task in each session. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

tation (60 stimuli x 5 possible changes between 6 assessments x 21 subjects), 1587 involved a change in response type (25.19% of total responses). Even though patients' performance tended to worsen performance during follow-up, they sometimes succeeded with stimuli that they had failed in the previous session. The most frequent changes of errors were as follows: correct - phonological error (CP), which accounted for 23.1% of the total response changes; correct - orthographic error (CO), which amounted to 20.2%; phonological error - correct (PC), whose percentage reached 18.6%; orthographic error - correct (OC), with a percentage of 18.5%; orthographic error - phonological error (OP), which accounted for 9.6%, and phonological error – orthographic error (PO), with 7.9% of the total response changes.

As for the dictation of pseudo-words, the most abundant errors were phonological, followed by lexicalizations and orthographic. The remaining errors (2 non-responses and 1 incomplete pseudo-word), grouped under the label "other", reached 0.6% of the total number collected during the 30 months of follow-up (Fig. **5**).

As in the previous task, patients were not fully consistent in their responses from one session to the next. Thus, specifically, out of 2100 responses (20 stimuli x 5 possible

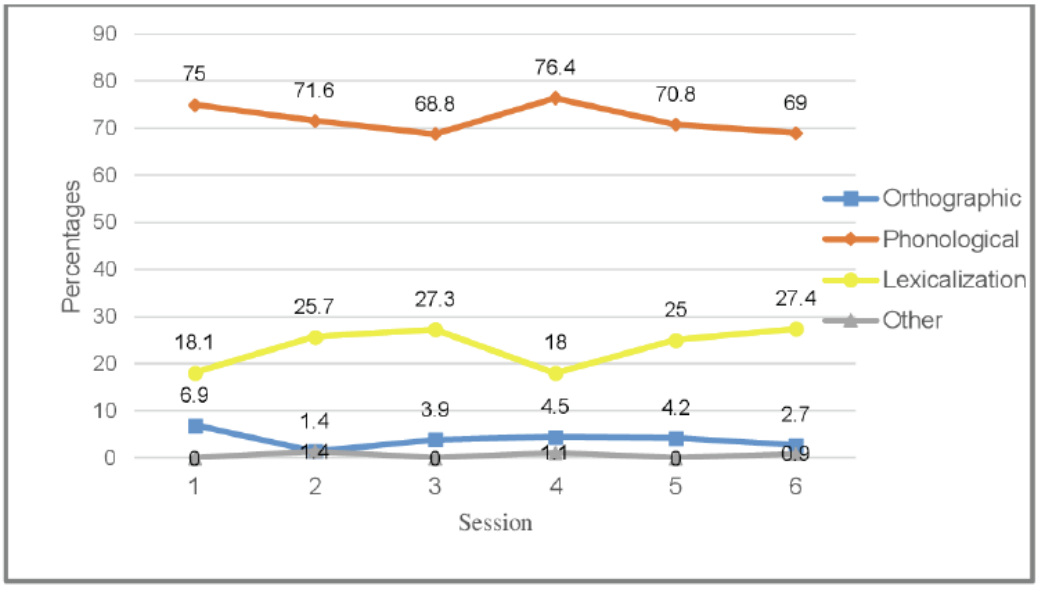

Fig. (5). Percentage of errors in the pseudo-word dictation task in each session. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

changes between 6 assessments x 21 subjects), 482 were a change in the error type, equivalent to 22.95% of the total. The most frequent response changes were the following: correct - phonological error (CP), which accounted for 35.9% of the total response changes; phonological error - correct (PC), with a percentage of 31.7%; correct - lexicalization (CL), which amounted to 12.7%, and lexicalization - correct (LC), with 8.1% of the total response changes.

Given the heterogeneity of the patients and the variability of the types of errors throughout the sessions, individual analysis of each participant was carried out to compare the evolution of their profile. Based on the study by Platel *et al.* [20], 4 impairment profiles were established depending on the amount and type of error: 1) Patients with few errors (less than 20% of total stimuli) and mostly orthographic; 2) Patients with a moderate number of errors (between 20 and 40% of the stimuli) of both orthographic and phonological type; 3) Patients with many errors (more than 40%) mostly orthographic and phonological; 4) Patients with many errors (over 40%), many of them grapho-motor (a mixture of allographs, letter distortions, duplications or omissions, perseveration of letter features or unintelligible writing). Profile 1 corresponds to those patients who begin to show lexical dysgraphia; the phonological route is still preserved, so they can write both words and pseudo-words, although with orthographic errors. Considering that many controls also show this same pattern, it could also correspond to patients with a low educational level who therefore do not have correct representations of the words. Profile 2 would be those patients who begin to show certain alterations in the sub-lexical pathway as well, which results in an increase in phonological errors. In profile 3, both lexical and phonological pathways are clearly damaged, and this results in a large amount of both lexical and phonological errors. However, the peripheral processes would still be preserved, allowing the patient to choose the correct allographs and appropriately shape the letters. Finally, profile 4 is that of those patients whose deterioration also reaches the peripheral processes. The evolution of the patients was observed in sessions 1, 3 and 6 (Table **4**).

In the first session, 6 patients fit in profile 1; 7 in profile 2; 5 in profile 3 and only 1 patient in profile 4. There were also two patients with a doubtful profile, since by the number of errors (very low), they fit in profile 1, but by the type (similar number of orthographic and phonological errors) could also fit in profile 2.

In the third session, one year later, 7 of the patients had evolved to the next profile (1 to 2, 2 to 3, *etc.*). As for the two dubious patients, they clearly fit profile 2. Curiously, the patient (P5) who appeared in profile 4 in the first session, fit more into profile 2 in the third, due to the decrease in the large number of grapho-motor errors that had been made a year earlier. A closer look at the data showed that most of these errors were due to letter omissions.

In the last session, 9 patients evolved to the next level, resulting in 8 patients in profile 4. One of the patients (P9), who was initially doubtful between profile 1 and 2, showed a similar performance to the first session, with a relatively small number of errors but with both orthographic and phonological. Finally, the patient (P5), who had improved in the third session, remained in profile 2, which could indicate that his poor performance in the first session was merely incidental. The total count in this sixth session was 2 patients in profile 1; 8 in profile 2; 2 in profile 3 and 8 in profile 4. The last patient (P9) is borderline between profile 1 and 2.

4. DISCUSSION

The aim of this study was to evaluate the writing skills of a group of AD patients through a word and pseudo-word dictation task, as well as to observe the deterioration of the patients' performance, and the variables related to it, over a period of 2.5 years.

The results seem to confirm the presence of a writing deficiency in patients with AD, which results in a worse overall performance than the control group. The analyses by the degree of deterioration of the patients, on the other hand, indicate that this deficit is present from the first stages of the disease, contradicting the results of previous studies, in which no alterations in writing were found in patients with mild AD [5, 6, 15].

With regard to the type of stimuli, the deterioration seems to affect mainly the words that contain some ambiguous grapheme, i. e., that could be written in two different ways without the pronunciation being affected. As mentioned above, there are some words in Spanish that contain ambiguous graphemes but follow orthographic rules that establish their correct spelling. However, we have not found better performance with these words than with arbitrary ones that do not follow any spelling rules. It is true that in the case of the control group, although the performance was generally better, no differences were observed between the ruled and arbitrary words, which is probably due to the participants' lack of knowledge of these norms. Most of these orthographic rules are learned during the years of schooling, so this pattern of performance may be due to the low educational level of both groups.

Our data, however, also show that the differences between patients and the control group were greater in the case of ruled and arbitrary words. This indicates the presence of damage to the lexical route, which is consistent with what was found in most studies [7, 9, 10, 26] indicating that the first manifestation of dysgraphia in AD patients is lexical or surface dysgraphia. The sub-lexical pathway, on the other hand, would be relatively preserved in these early stages, allowing patients to perform better with regular words and pseudo-words. This is consistent with the findings of the research on the neurological basis of writing: previous studies [27, 28, 29] have pointed out that the left temporo-occipital area is involved in the processing of the orthographic form of words, i.e., access to the orthographic lexicon, one of the key processes in the lexical route. In a study carried out by our research group [10], it was found that spelling difficulties were related to volume loss in that area, as well as in the fusiform gyrus and the posterior middle and anterior superior areas of the left temporal lobe. As far as the sub-lexical pathway is concerned, no significant correlation with volume loss in any particular area was found in the mentioned study, which could indicate that this pathway was still reasonably well preserved in patients.

Analysis according to the degree of deterioration, however, shows that as the disease progresses, this route also becomes damaged and begins to affect the spelling of pseudo-words as well. The spelling of regular words is preserved longer, probably because, as Luzzatti *et al.* [11] pointed out, both partially damaged routes cooperate to write this type of stimuli.

Regarding the correlation analyses carried out, the variable most related to patient performance in both the cross-sectional and longitudinal study was the degree of deterioration, as measured by the MMSE [8] and the GDS scale [23]. This contradicts the results found in some previous studies [7, 9] and is consistent with the findings of Aarsland *et al.* [17], although, unlike these authors, we cannot claim that the damage on both routes is similar. It is possible that our results are due to the fact that milder patients show surface dysgraphia, so their performance with regular words and pseudo-words is still good, while patients with moderate impairment already show damage in the sub-lexical route and therefore made errors in other types of stimuli as well. These differences in the results and conclusions could be due to the size of the sample, which is larger in our case (32 patients) than in the mentioned studies (16 in Aarsland *et al.*, 1996; 20 in Cuetos *et al.*, 2003 and 11 in Rapcsak *et al.*, 1989). This allows us to observe the effects that are not possible to find with smaller sample size.

The results of the longitudinal study are even more clarifying. The homogeneous decrease of performance in all types of stimuli indicates a uniform but uneven deterioration of both routes, since regular words and pseudo-words maintained a much better performance than words containing ambiguous graphemes throughout the follow-up. Such a pattern could be due to the fact that the sub-lexical route is preserved to some extent at all stages of deterioration. This would allow patients to spell correctly by applying phoneme to grapheme conversion rules, although the decrease in performance over time indicates that patients begin to forget some of these correspondences. This interpretation is also supported by the fact that no differences were found between regular words and pseudo-words in any of the evaluation sessions. If regular word spelling was supported by both routes, performance in the latter sessions should be better for this type of stimuli than for pseudo-words, as found by Luzzatti *et al.* [11]. In their study, patients wrote words with unpredictable spelling better than pseudo-words, so they concluded that both routes were equally affected and cooperated in writing the regular words. In our case, however, the pattern is very different and seems to suggest better conservation of the sub-lexical route during disease progression.

The pattern of errors seems to confirm this statement, as patients made twice as many orthographic errors as phonological errors during the first session (which indicates either partial damage in the lexical route or a lack of orthographic representations due to a low educational level) and an equal amount of orthographic and phonological errors in the last session (which indicates partial damage also in the phonological route). However, the presence of phonological errors from the first session indicates that the damage in the sub-lexical route could start already in the early stages of the disease. In the same way, the presence of lexicalizations, and their increase in the last sessions, could show that the lexical route does not deteriorate completely and that patients make use of it even when the cognitive decline is already advanced. This pattern of errors, nevertheless, may have another explanation that has already been pointed out by Croisile *et al.* [26] and Silveri *et al.* [14]. They claim that the damage in one or both routes could be compounded by the damage to the graphemic buffer in the later stages, which would increase phonological errors, both in words and in pseudo-words. This can be verified by analyzing the amount and type of grapho-motor errors. Thus, omissions, duplications or substitutions of letters would indicate damage at this level. The individual analysis of the patients, however, does not support this statement, as these errors are rare (33 in the

first session, an average of 1.5 per patient; 73 in the third, an average of 3.5, and 61 in the sixth, an average of 3). Most grapho-motor errors are omissions of letter features (the dot on the i or the line on the t), suggesting more of an attention problem than difficulties in the graphemic buffer. In addition, we did not find that the length of the word was a determining variable in the errors, which rules out damage in this process.

The individual analysis of the patients, on the other hand, provides interesting information about the pattern of writing impairment in AD and its evolution. Following Platel *et al.* [20], we classified patients into 4 possible profiles according to their performance. As explained above, profile 1 is characterized by a low amount of errors, predominantly orthographic, which would indicate the absence of correct orthographic representations either because of the low level of education or the presence of surface dysgraphia. Profile 2 is characterized by a moderate amount of both orthographic and phonological errors, which is a symptom of the incipient deterioration of the sub-lexical route. Profile 3 is characterized by a large amount of both orthographic and phonological errors, indicative of damage to both routes. Finally, profile 4 includes grapho-motor and allograph selection errors, which would indicate an emerging decline of the peripheral writing processes. Thus, as Platel *et al.* [20] stated, the profile of the patients was heterogeneous at the beginning, possibly due to the stage of deterioration they were in at the time, and most (15) evolved towards one of the following profiles during the follow-up. This evolution was usually progressive (from profile 1 to 2, from 2 to 3, *etc.*), although a few patients (P1 and P16 in Table **2**) showed a sudden decline and went directly from profile 2 to 4 without going through profile 3. It is possible that these patients passed through the intermediate profile, rapidly worsening and advancing to the next one. This finding is consistent with that found by Platel *et al.* [20], as their patients also showed an evolution of deterioration towards the following profile.

Among the 3 patients with the highest educational level, one, with a university degree, remained stable in profile 1 during the entire time of the study. Another, with intermediate studies, remained in profile 1 until the 6th session, when he moved to profile 2. Finally, a patient who had completed high school remained in profiles 1 and 2 until he suffered a sudden deterioration, and in the 6th session moved directly to profile 4. Although this might suggest that educational level is a protecting variable with respect to the deterioration of cognitive functions in general and to spelling in particular, the small number of participants with higher education hampers us from checking this statement. The rest of the patients who remained stable did so in profiles 1 and 2 (except P14, who remained for all sessions in profile 3).

In sum, our study confirms the presence of writing disorders from the early stages of Alzheimer's disease. This deterioration, far from being heterogeneous, follows a similar pattern in most patients and is characterized by an early impairment of the lexical route, followed by a later deterioration of the phonological pathway. The rate of progression of this decline varies from patient to patient, as it does in other cognitive functions. These findings make the dictation task an interesting addition to the Alzheimer's detection batteries. The spelling of arbitrary and ruled words has been shown to be quite sensitive to the degree of impairment, so analysis of overall performance and error pattern can be very informative. With regard to peripheral processes, the data seem to indicate that they also deteriorate in the later stages of the disease, although the peculiarities of this decline remain to be determined.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

The patients signed a consent form after being informed about the project.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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