

Central and peripheral agraphia in Alzheimers disease: from the case of Auguste D. to a cognitive neuropsychology approach

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Abstract

Since the observation of Auguste D. by Alois Alzheimer, it is an acknowledged fact that writing is one of the cognitive functions that are weakened early in Alzheimer's disease (AD). This study aimed to examine the cognitive nature of this disorder and question the hypothesis of a standard progression (Platel et al., 1993) from lexical to other central and more peripheral processes. A large group of mild to moderate AD patients (n = 59) and a group of healthy elderly controls were submitted to an extensive assessment of both the central and peripheral components of writing. A comparison of groups indicated that AD patients performed more poorly than controls on a wide range of writing measures. It revealed a predominantly lexical disorder, but also found evidence of associated disorders located at different stages in the spelling system (phonological route, graphemic buffer, allographic store, graphic motor patterns). A multiple single-case analysis, using a specific methodology, allowed us to delimit individual profiles of agraphia. It revealed a wide variety of agraphia syndromes, including a far from negligible number of patients with selective damage to one of the central or peripheral components, as well as patients with multiple writing impairments. A positive correlation was observed between the severity of the dementia and spelling/writing measures (lexical and allographic). This study does not support the hypothesis of a uniform progression. Rather, it points to heterogeneous profiles of agraphia and suggests that the first signs of writing impairment in AD stem from changes at different points in the broad anatomical network subserving spelling and writing abilities.

MESH Keywords Aged ; Aged, 80 and over ; Agraphia ; classification ; complications ; diagnosis ; Alzheimer Disease ; complications ; Case-Control Studies ; Female ; Humans ; Language Disorders ; complications ; diagnosis ; Male ; Middle Aged ; Motor Skills ; physiology ; Reference Values ; Vocabulary ; Writing

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Introduction

Writing about Auguste D., in his first and most famous observation, Alois Alzheimer reported disorders in written language: "in writing, she repeats separate syllables many times, omits others, and quickly breaks down completely" (Stelzmann et al., 1995 – Alzheimer, 1907). "For example, when asked to write her name ("Frau Auguste D."), she stopped after the word "Frau". Only when she was told to write each word individually, one after the other, could she note them down correctly (a symptom termed "amnesic writing disorder" by Alzheimer)" (Dahm, 2006, p. 40). For many years, however, these deficits were largely ignored by researchers. The first reason is that writing is a communication mode of secondary importance compared with oral language (later acquisition, more limited use). A second reason is that, from a theoretical point of view, the writing system was long represented as the simple transposition of oral language (Geschwind, 1969). A third one concerns the lack of methodological tools and a suitable theoretical framework for the neuropsychological study of AD. Until the '70s and '80s, studies were very wide-ranging and based on the analysis of a small corpus of dictated sentences or written descriptions of stories in picture form. These laid stress on the early appearance of the deficits, on their severity compared with the deterioration of oral language, and on their relationship with the severity of dementia (Appell et al., 1982 ; Cummings et al., 1985 ; Faber-Langendoen et al., 1988 ; Horner et al., 1988). The late '80's proved more prolific and coincided with an upsurge in multidisciplinary research and the contribution of cognitive psychology. Indeed, it was in the field of written language that cognitive neuropsychology first came to the fore. Rapcsak et al. (1989) were thus the first to apply the theoretical frameworks and experimental paradigms used in research into agraphia by focal lesion to the study of central writing disorders in AD. That said, since their paper, there have been relatively few publications, compared with other cognitive areas such as memory or attention.

Although agraphia is nowadays regarded as a common feature of AD, the multicomponential cognitive aspects of this disturbance have still to be elucidated. Most reports have underlined the disturbance of central spelling processes and few studies have focused on peripheral damage to writing.

Cognitive models of spelling and writing (Ellis, 1982, 1988 ; Caramazza et al., 1987 ; Margolin and Goodman-Schulman, 1992) usually distinguish between the central processes (phonological and lexical routes, graphemic buffer) involved in the generation of spelling, whatever the modality of output (handwriting, oral spelling, writing with block-letters, typing, etc.), and peripheral processes which are specific to one particular output modality. Three levels are described for handwriting. In the first stage, referred to as the

allographic system (Ellis, 1982) or physical letter code (Margolin, 1984), specific letter shapes are generated in terms of the visuospatial features relative to the case (lower or upper) and style (cursive or print) of the letters. In the second stage, the graphic motor pattern specifies the direction, relative size, position and order of strokes. The final stage - the graphic code - corresponds to the execution and control of neuromuscular commands.

Regarding central processes, studies of AD patients have often highlighted a pattern of lexical agraphia, characterized by a regularity effect and the production of phonologically plausible errors. In other words, compared with controls, patients make more errors on irregular words or orthographically ambiguous words than on regular words or nonwords. This deficit of lexical orthographic processing, first described by Rapcsak et al. (1989) , has since been reported in several papers (Platel et al., 1993 ; Hillis et al., 1996 ; Lambert et al., 1994 , 1996 ; Hughes et al., 1997 ; Glosser et al., 1999 ; Pestell et al., 2000 ; Luzzati et al., 2003 ; Forbes et al., 2004). This lexico-semantic impairment can be observed in association with other central disturbances in the form of damage to the phonological route or graphemic buffer (Neils et al., 1995 ; Croisile et al., 1996 ; Glosser et al., 1999 ; Pestell et al., 2000 ; Forbes et al., 2004).

The prevalence of phonological disorders or an impairment of the graphemic buffer has also been detected as the first sign of agraphia by Aarsland et al. (1996) and in multiple single-case analyses (Penniello et al, 1995 ; Luzzati et al., 2003). The predominance of surface agraphia in the early stages of the disease emerges from most transversal studies. However, longitudinal studies have had conflicting results, for while this profile is confirmed by Platel et al. (1993) , Luzzati et al. (2003) have observed a high degree of variability, albeit in a small number of patients (9).

Peripheral aspects of writing have been investigated less thoroughly, even though they are mentioned in early reports. Several studies have noted that the spatial aspect of handwriting starts to deteriorate at an advanced stage of dementia (Horner et al., 1988 ; Croisile et al., 1995 ; Ross et al., 1996). Research is often restricted to the observation of one particular component of apraxic agraphia, characterized by stroke errors in the formation of letters. In their first cognitive assessment, Rapcsak et al. (1989) concluded that agraphia observed in AD arises from a central lexico-semantic impairment. The authors used a writing-to-dictation task for 6 of their 11 patients, but had to assess the spelling abilities of the remaining 5 through oral spelling, as they claimed that the latter "suffered from apraxic agraphia". It is therefore rather surprising that although the authors encountered methodological problems due to peripheral deterioration, they did not take this into account in their characterization of agraphia. Peripheral errors have also been reported by Henderson et al. (1992) , LaBarge et al. (1992) and Forbes et al. (2004) , using a spontaneous or narrative writing task. Forbes et al. (2004) showed that it concerned not only letter formation and stroke placement skills but also the production of case-mixing errors and a tendency to shift from lower-case cursive to upper-or lower-case print. Luzzati et al. (2003) only observed case-mixing errors in one member of a 23-patient group. Only two studies (Hughes et al., 1997 ; Venneri et al., 2002) have explored the peripheral processes of writing within a cognitive neuropsychological framework. To this end, they included tasks such as cross-case transcription and copying specially designed to distinguish between impairments at the level of allographic processing and at the level of the graphic motor pattern. Hughes et al. (1997) found that patients were more severely impaired when it came to transcribing across cases, suggesting a deficit at the level of allographic processing. They also found that performances were better for upper-case letters than for lower-case ones. The opposite profile has only been reported by Venneri et al. (2002) . These authors described two mild AD patients (AF and EZ) who showed a double dissociation between cursive and print styles: AF was impaired when asked to write in cursive, whereas EZ had difficulties with print style. The relative preservation of copying but the difficulty of performing a form judgment task, restricted to the affected style, implied that allographic representations were either inaccessible or lost.

A multiple single-case analysis (Hughes et al., 1997) revealed several profiles: no spelling or writing disturbance, selective evidence for a pattern of central agraphia, selective evidence for a pattern of peripheral agraphia and impairment in both central and peripheral processes. Although deficits in letter formation have been observed in the early stages of the disease (Lambert et al., 1994 ; Ross et al., 1996 ; Hughes et al., 1997 ; Neils-Strunjas et al., 1998 ; Eustache et al., 2004), comparisons between AD patient subgroups according to the severity of their dementia (Hughes et al., 1997 ; Forbes et al., 2004) have established that peripheral disorders become more pronounced as the illness progresses, as previously demonstrated by Platel et al. (1993) in a longitudinal study.

One must therefore bear in mind that (1) although lexical impairment is the most frequent pattern, it is not the sole deficit, either during the course of the disease or at its onset, (2) the hypothetical profile of agraphia in AD, evolving from lexical impairment towards other central and peripheral deficits (Platel et al., 1993) , remains plausible but the number of cases with a different pattern of deterioration in spelling and writing skills is far from negligible and it has been suggested (Luzzati et al, 2003) that the two spelling routes may undergo an independent decline. This variability across subjects needs to be explored further, in studies including a large number of patients and investigating both central and peripheral writing abilities.

The main purpose of the present study was to examine the assumption of a general profile of agraphia in AD which affects central lexical components first, followed by other central processes, then peripheral ones (Platel et al, 1993). We addressed this issue by analyzing deficits in the spelling and writing abilities of a large cohort of AD patients (n = 59) by means of an extensive assessment (Eustache et al, 2004) of both central and peripheral writing processes (writing to dictation and oral spelling of words and nonwords for

central processes, and tasks involving single letters with writing to dictation, copying, cross-case transcription and mental imagery of lower- and upper-case letters for peripheral ones). Our analyses were guided by the general admitted hypotheses (Ellis, 1982, 1988; Caramazza et al, 1987; Margolin and Goodman-Schulman, 1992; Rapsack, 1997) that for central processes: 1- a deficit of the graphemic buffer is evidenced by lower performance on long items than on short ones, 2- a deficit of the lexical processing by lower performance on irregular words than on regular words, 3- a phonological deficit by lower performance on nonwords than on regular words. For peripheral components: 1- a deficit at the level of the graphic motor patterns will affect tasks involving the written production of a letter (dictation, cross-case transcription and at a lower rate copying but not mental imagery), 2- a deficit at the level of allographic representation will affect tasks requiring access to the mental form of the letter (mental imagery, dictation but not copying).

Our first step was to identify differences between the AD group and the control group through quantitative and qualitative measures (scores and types of errors) for central and then peripheral components. This group study would reveal the predominant pattern of disturbance that can be expected in a cohort of mild to moderate AD patients, i.e. central lexical impairment in most patients. Our second step was to highlight the variability across subjects and gather data on the dispersion of the individual patterns of disturbance at the level of both central and peripheral processes. To this end, we used a specific methodology (adapted from Penniello et al, 1995) to gauge the functionality of each central and peripheral component, in order to delineate a specific profile of disturbance for each patient. Lastly, we tested whether agraphia in general, as well as distinct spelling and writing skills, is related to other cognitive measures, at either a general level of efficiency (severity of the disease) or a more specific one (i.e. gestural praxis, visuoconstructional abilities, semantic processing).

Materials and Methods

Participants

Fifty-nine mild to moderate AD patients and 20 normal control subjects were included in this study. All were French speakers and right-handed. None had a history of alcoholism or other neurological or psychiatric illness. All subjects had a minimum level of education equivalent to the "certificat d'études primaires" – a diploma generally obtained at around 14 years of age, after 8 years of schooling.

Patients (18 males and 41 females) were diagnosed as probable AD patients on the basis of the NINCDS-ADRDA criteria (McKhann et al, 1984). None were institutionalized.

The control subjects (7 males and 13 females) were healthy volunteers matched with the AD patients on the basis of age and level of education.

The demographic data for the two groups, severity of dementia according to the Mini-Mental State Examination (MMSE, Folstein et al, 1975) and the Dementia Rating Scale (DRS, Mattis, 1976) and scores in the "auditory sentence to picture-matching" language comprehension subtest of the MT86 (Nespoulous et al, 1986) are summarized in Table 1.

Tasks and Procedure

Assessment of central processes

In order to assess the central processes, i.e. the lexical route, phonological route and graphemic buffer, subjects were asked to write to dictation and spell aloud the following words and nonwords (see Eustache et al, 2004, for the list of the items):

- - 24 regular words with one-to-one sound-letter correspondences (with reference to Catach's criteria, 1980): douche /δuʃ/ (shower), pipe /pip/ (pipe);
- - 24 words with unpredictable transcription: 22 irregular words and 2 words with a low degree of orthographic predictability: femme /fɑm/ (woman), oignon /No/ (onion);
- - 24 nonwords with a phonological and graphemic structure characteristic of French regular words: dari /δɑʁi/, gondy /gɔdy/.

All words were matched for lexical frequency (Brulex, Content et al, 1990) with two classes (low frequency: regular words $m = 1.415$; irregular words $m = 1.298$; high frequency: regular words $m = 13.294$, irregular words $m = 14.319$). All items (words and nonwords) were matched for length (number of letters) and comprised, in equal number, items of 4, 5, 6, 7, 8 and 9 letters (within each group of low- and high-frequency words). Thus, the following psycholinguistic variables of this material were: type of item (regular words, irregular words, nonwords), frequency (low/high) and length (short: 4, 5, 6 letters; long: 7, 8, 9 letters).

Each target word was included at the end of a sentence. Subjects had to listen to the sentence, repeat the last word, then write or spell it aloud. For nonwords, repetition was also required prior to writing or oral spelling. Several attempts sometimes had to be made to obtain a correct repetition. Writing to dictation was always performed before oral spelling and in the following order: regular words, irregular words and nonwords. Subjects were asked to write in lower cursive letters, which corresponded to the usual French practice.

Scoring/24: each item (word or nonword) was scored in a binary manner as either correct (1 point) or false (0).

Assessment of Peripheral Processes

The peripheral process (allographic system and graphic motor pattern) assessments were based on single letters. Twenty-three of the 26 letters of the alphabet were used in lower-case cursive style and upper-case print style. Three letters (c, u, o) were excluded because they had a high degree of physical similarity (visual and/or stroke similarities) in the lower and upper cases. Four tasks were proposed: writing to dictation, copying, cross-case transcription and mental imagery of letters:

- - Writing to dictation: subjects were asked to repeat the letter pronounced by the experimenter and then to write it;
- - Copying: subjects were required to copy a letter written on a sheet of paper;
- - Cross-case transcription: subjects were requested to transpose from the presented single letter to an alternative form: first, from lower-case cursive to upper-case print (m → M) and second from upper-case print to lower-case cursive (M → m);
- - Mental imagery of letters: this task was used to assess knowledge of the general shape of a target letter (at the allographic level). It did not require either the written production of the letter or the verbal description. The general principle of the task involved pointing to visual characteristics in a multiple-choice questionnaire (one question by letter). For lower-case cursive letters, questions involved the relative size and position of a letter on a baseline, represented by frames (Appendix, Figure a) corresponding to the different types of cursive letters: corpus-sized letters (m, e, a, etc.), letters with an upward stroke (l, t, d, etc.), a downward stroke (j, p, g, etc.) and upward and downward strokes (f). The instruction was "Point to the frame in which you could write the letter "m" in lower-case cursive style." For upper-case print letters, questions concerned the direction of the strokes of a target letter. The multiple choices comprised 4 strokes with different forms (straight, curves) and orientations (Appendix, Figure b). The instruction was "Point to the stroke which is present in the letter "M" in upper-case print style".

The order in which the subjects performed the tasks was as follows: writing to dictation, mental imagery, cross-case transcription and copying.

Scoring/23: in each peripheral task, a response was judged in a binary manner as either correct (1 point) or false (0).

For each task, the 23 lower-case cursive letters were assessed before the 23 upper-case print letters. The order of letters was randomized in each set. Cross-case transcription and copying were performed on individual sheets for each letter. Before beginning a task, a sample of the target case and style was provided to subjects: one word written in lower-case cursive style or in upper-case print style. In order to familiarize subjects with mental imagery, a short object imagery task was administered before the letter imagery. Subjects were required to mentally represent a pair of current objects and say which one was the largest (trousers or cap?). Four pairs of objects were proposed.

Assessment of other cognitive functions (semantic, praxic, visuoconstructional)

In order to link the patients' writing deficits to other cognitive measures, semantic knowledge, gestural praxis, and visuoconstructional abilities were assessed.

- - Semantic knowledge assessment (Giffard et al, 2001): drawn from a protocol developed by Martin (1987) and Desgranges et al. (1996 , 1998) , the semantic knowledge task tested naming, categorical knowledge and attribute knowledge of concepts. The 30 concepts assessed in this task belonged to four semantic categories (animals, plants, body parts and objects). First, we asked the subjects to name 30 drawings. If they failed, a recognition task was administered, in which the correct noun and three other ones from the same semantic category were presented to the subjects one after the other. Next, the subjects were asked to answer a series of questions for each of the 30 items. The first question concerned the knowledge of the superordinate category ("Does it occur naturally or is it man-made?"). The second question concerned category membership ("Is it an animal, a plant, an object, or a body part?"). The third question referred to the subcategory ("Is it a domestic or a wild animal?"). Finally, there were three questions concerning specific attributes: either functional ("Is it edible?"), or perceptive ("Does it have a mane?").

Scoring/236: The correct naming of each drawing was scored 2 points, and the correct recognition (proposed in the case of a wrong naming) was scored 1 point. Concerning the six other questions, each response was scored as correct (1) or false (0).

- - Gestural praxis: gestural praxis was assessed through the imitation of 5 meaningless unilateral gestures (e.g., stretching the arm forward, fist closed and then bending the elbow) and 4 bilateral gestures (e.g., placing the index fingers on the opposite cheeks).

Scoring/18: each gesture was scored a possible 2 points: success (2), partial success (1): in the case of an error corrected spontaneously, or failure (0).

Visuoconstructional abilities: in our adapted version, subjects had to copy 18 simple geometric figures (Appendix, Figure c) taken from the Goldstein-Scheerer Stick Test (Goldstein and Scheerer, 1973).

Scoring/18: each item was scored in a binary manner as either correct (1 point) or false (0).

Data analysis and results

Group study

Data analysis

Quantitative and qualitative scores of the subjects' groups were analysed. In the analysis of quantitative scores, the number of correct responses on writing to dictation and oral spelling of words and nonwords was taken into account for central processes, and the number of correct responses on single-letter tasks (writing to dictation, copying, cross-case transcription, and mental imagery) for peripheral processes.

Qualitative analyses regarding the types of error were also carried out. All the errors made by patients and controls on words and nonwords were classified according to the following 3 categories:

- - Phonologically plausible errors (PPE), which respected the phonology of the target word (femme / φ A μ / -woman- → fame / φ A μ /);
- - Non-phonologically plausible errors (NPPE), which resulted from letter errors such as the substitution, omission, addition or transposition of one or several letters in the word or nonword (carabine / $\kappa\alpha\{\alpha\beta\iota\nu\}$ / -carbine- → cadabine / $\kappa\alpha\delta\alpha\beta\iota\nu\}$ /);
- - Non-responses (NR), which included absent or incomplete responses. For single letters, 4 categories of errors were found:
- - Graphomotor errors (GE): ill-formed or illegible letters with stroke errors;
- - Case errors (CE): substitution of a letter of a different case or style (M → m; j → J) for the target letter;
- - Substitution errors (SE): substitution of another legible letter in the same case and style for the target letter. In this category, we distinguished between substitutions which had a phonological link with the target (q → k; j → g may have a similar phonemic representation: /k/ and /Z/ respectively) and ones which did not (n → m; k → z);
- -No response (NR): absence of production.

Statistical methodology

As normality could not be assumed because of control ceiling effects, non-parametric procedures were employed. Nonparametric Mann-Whitney rank sum tests were used to compare performances between the controls and the AD group. Friedman tests and Wilcoxon tests for paired samples were carried out in order to compare in each subjects' group subtests of the writing tasks. For all analyses an alpha level of .05 was adopted.

Central process assessment: word and nonword tasks (written and oral spelling)

Quantitative results (Figure 1)

On the whole, as shown by Mann-Whitney tests, the AD group performed significantly worse compared to the controls, whatever the output modality (written spelling, $z = -4.26$, $p < .0001$; oral spelling, $z = -3.99$, $p < .0001$), the type of item (regular words, $z = -3.88$, $p = .0001$; irregular words, $z = -3.58$, $p = .0003$; nonwords, $z = -3.26$, $p = .001$), the length of item (short, $z = -3.16$, $p = .002$; long, $z = -4.54$, $p < .0001$), and the frequency of words (low, $z = -4.09$, $p < .0001$; high, $z = -3.29$, $p = .001$).

Wilcoxon test for paired samples revealed in the AD group no significant effect of output modality (written spelling vs . oral spelling, $z = -0.74$, $p = .46$), suggesting a central spelling deficit. Because of this lack of difference between oral and written spelling further results are restricted to the analysis of written performance, the most common modality of spelling output.

We first analyzed the quantitative data, namely the scores obtained on writing-to-dictation of regular, irregular words and nonwords and focused on the results of non parametric analyses which were tied to our hypotheses. We searched which components of the central processes were disturbed (graphemic buffer, lexical route, phonological route) based on the general admitted hypotheses that: 1- a deficit of the graphemic buffer is evidenced by lower performance on long items than on short ones, 2- a deficit of the lexical processing by lower performance on irregular words than on regular words, 3- a phonological deficit by lower performance on nonwords than on regular words.

For both groups, Friedman tests revealed a significant effect of type of item (AD patients, $\chi^2 = 55.74$, $p < .0001$; controls, $\chi^2 = 19.86$, $p < .0001$). More precisely, Wilcoxon tests for paired samples showed for both groups significantly better scores for regular words

than for nonwords (AD patients, $z = -1.97$, $p = .049$, vs. controls, $z = -2.24$, $p = .025$). In the AD group, the irregular words were proportionally much less performed than the regular words ($z = -6.05$, $p < .0001$) and than the nonwords ($z = -5.43$, $p < .0001$) compared to the pattern of the controls (irregular vs. regular, $z = -3.11$, $p = .002$; irregular vs. nonwords, $z = -3.01$, $p = .003$). This pattern of results in the control group demonstrated that the accuracy of writing performance was linked to predictable orthography (one-phoneme-to-one-letter grapheme correspondence) and to lexicality.

Deficit of the graphemic buffer?

We observed significant effects of length for both groups which indicated lower performance for long items than for short ones, but the difference short vs. long items was much more significant for the AD patients than for the controls ($z = -5.90$, $p < .0001$; $z = -2.02$, $p = .005$, respectively). The effect of length was significant in AD patients whatever the type of item (regular words, $z = -4.8$, $p < .0001$; irregular words, $z = -6.133$, $p < .0001$; nonwords, $z = -4.86$, $p < .0001$) but for controls this effect of length was not significant for regular words and less significant than in AD patients for irregular words ($z = -2.32$, $p = .02$) and nonwords ($z = 2.27$, $p = .02$). Moreover, concerning the regular words, the difference between controls and patients did not reach significance for short words ($z = -1.84$, $p = .066$), whereas the difference was very significant for long words ($z = -2.86$, $p = .004$). These results suggested a deficit of the graphemic buffer in AD.

Lexical deficit?

Previous analyses revealed that the difference between regular and irregular words was more significant in the AD group ($p < .0001$) than in the control group ($p = .002$), suggesting a lexical deficit. Moreover, this lexical deficit in AD was corroborated by a frequency effect ($z = 2.53$, $p = .011$) that was not observed in the control group ($z = 1.13$, $p = .26$).

Because of the hypothesis of a deficit at the level of the graphemic buffer in AD patients, we took the variable of length into account in further analyses. We observed that AD patients had significant worse performance than controls for long irregular words ($z = -3.70$, $p = .0002$) and also for short irregular words ($z = -2.88$, $p = .004$) confirming the lexical deficit. Furthermore, in the AD group, the scores for regular words were very significantly better than for irregular words both for short ($z = -4.65$, $p < .0001$) and long items ($z = -5.90$, $p < .0001$). The scores for irregular words were significantly better than for nonwords both for short ($z = -4.48$, $p < .0001$) and long items ($z = -5.24$, $p < .0001$). In the control group, the differences were less significant (regular vs irregular, short: $z = -2.12$, $p = .03$; long: $z = -3.14$, $p < .01$; nonwords vs irregular, short: $z = -2.12$, $p = .03$, long: $z = -2.67$, $p < .01$).

Phonological deficit?

We saw above that AD patients performed worse than the control group on regular and nonwords and that a significant difference between regular words and non words was observed in both groups ($p < .05$). The difference was not more pronounced for AD patients. Further analyses showed that AD patients had significant lower scores than controls for short nonwords ($z = -2.57$, $p = .01$) whereas no significant difference was observed between AD patients and controls for short regular words ($z = -1.84$, $p = .06$). This increased difficulty for nonwords was in agreement with the hypothesis of a phonological deficit in AD. No significant difference was noted between AD patients and controls for long nonwords.

Qualitative results (Figure 2)

The analysis of the type of errors was conducted in order to confirm or not the quantitative results. A lexical deficit would be confirmed by a greater number of PPE in AD patients compared to controls and a higher rate of PPE on irregular words than on regular words. This indicates that patients had difficulties retrieving the orthographic representation of words which cannot be written following rules of phoneme-to-grapheme correspondence. A phonological deficit would be evidenced by a higher rate of NPPE on nonwords than on regular words.

NPPE, PPE and NR were noted. As there were very few NR either for the controls or for the AD patients, these were not included in the statistical analyses. Mann-Whitney tests comparing controls and AD group revealed significant differences concerning the type of error (PPE, $z = -3.34$, $p = .0008$; NPPE, $z = -4.13$, $p < .0001$). In the AD group, the numbers of PPE and NPPE were equivalent ($z = -0.31$, $p = .76$) (but see below), whereas in the control group, there were significantly more PPE than NPPE ($z = -2.91$, $p = .004$).

In the AD group, the lexical deficit was confirmed by the number of PPE which was significantly greater than in the control group ($z = -3.34$, $p = .0008$). Moreover, AD patients, as controls, produced a significant higher rate of PPE on the irregular words than on the regular ones but the difference was more significant (AD patients, $z = -6.25$, $p < .0001$; controls, $z = -3.07$, $p = .002$). AD patients, as controls, produced also significantly more PPE than NPPE on the irregular words but with a more significant difference (AD group, $z = -5.45$, $p < .0001$; controls, $z = -3.08$, $p = .002$). AD patients committed significantly more NPPE than PPE on the regular words ($z = -2.64$, $p = .008$) whereas no difference was noted in controls.

In the AD group, the phonological deficit was confirmed by the number of NPPE on nonwords significantly more frequent than on regular words ($z = -3.74$, $p = .0002$).

Peripheral process assessment: letter tasks (writing to dictation, mental imagery, cross-case transcription, letter copying)

Quantitative results (Figure 3)

In the following section, we looked whether the AD group performed worse than the control group and whether the performance varied according to the task with the hypotheses that: 1- a deficit at the level of the graphic motor patterns will affect tasks involving the written production of a letter (dictation, cross-case transcription and at a lower rate copying but not mental imagery), 2- a deficit at the level of allographic representation will affect tasks requiring access to the mental form of the letter (mental imagery, dictation but not copying).

For lower-case letters, the AD group performed significantly worse than controls in writing-to-dictation ($z = -2.22$, $p = .026$), cross case transcription ($z = -2.54$, $p = .01$), and copying ($z = -2.27$, $p = .02$), but the difference was not significant in mental imagery ($z = -1.5$, $p = .12$). For upper-case letters, the difference between AD patients and controls was significant in writing-to-dictation ($z = -2.63$, $p < .01$), cross case transcription ($z = -4.13$, $p < .0001$), and mental imagery ($z = -2.38$, $p = .017$). Ceiling effects were observed in copying for both groups.

Friedman tests revealed in both groups a significant effect of the task for lower-case letters (AD patients, $\chi^2 = 64.56$, $p < .0001$; controls, $\chi^2 = 36.79$, $p < .0001$) and for upper-case letters (AD patients, $\chi^2 = 65.20$, $p < .0001$; controls, $\chi^2 = 23.04$, $p < .0001$). Detailed analyses are shown in Table 2. Wilcoxon tests for paired samples revealed in the AD group a significant effect of the case to the detriment of lower-case, in the task of imagery (lower-case vs. upper-case, $z = -2.87$, $p = .004$) and of copying (lower-case vs. upper-case, $z = -2.87$, $p = .004$) whereas no effect was observed in the control group. These data were compatible with the hypothesis of difficulties for AD patients both in accessing the mental representation (allographic representation) and in activating the graphic motor pattern of a letter.

Qualitative results (Figure 4)

The hypothesis of a deficit at the level of the graphic motor patterns will be confirmed if AD patients commit graphomotor errors in each written task but at a lower rate in copying. The hypothesis of an allographic perturbation will be retained if a high rate of case errors is observed.

The control group committed very few errors (two types of errors: 18 substitutions and 6 case errors) only in the dictation and transcription tasks. AD patients produced a larger panel of errors within the following decreasing rate: case errors, graphomotor errors, substitution errors and "no response".

Wilcoxon tests for paired samples revealed in the AD group that case errors, graphomotor errors and "no response" were significantly more frequent in cross-case transcription than in dictation (respectively, $z = -2.00$, $p = .04$; $z = -2.61$, $p < .01$; $z = -2.99$, $p < .01$) or than in copying (respectively, $z = -4.675$, $p < .001$; $z = -3.23$, $p = .001$; $z = -3.75$, $p < .001$). The rates of substitution errors were not significantly different between cross-case-transcription whereas the difference was significant comparing cross-case-transcription or dictation and copying (respectively, $z = -3.97$, $p < .001$; $z = -2.80$, $p < .01$).

Summary of the group analysis

The main findings concerning central processes can be summarized as follows. First, the scores in the oral and written spelling of regular, irregular words and nonwords indicated that the AD patients as a group had significantly lower scores than the controls and that there was no significant difference between the two output modalities (written and oral). This profile of performance confirms the central nature of the spelling damage in AD.

The second set of results in written spelling helped to identify which components of the central processes had been damaged. For both groups (controls and AD patients), we noted an effect of length but it was more significant for the AD patients. In AD patients this effect was observed for each type of item. The hypothesis of a deficit of the graphemic buffer was also supported by results that revealed that if patients did not differ from controls when writing short regular words, they had significant worse performance for long regular ones.

We observed a significant effect of type of item, with more difficulty in correctly writing irregular words than nonwords or regular words. The difference between regular and irregular words was more significant in AD patients, for both short and long items suggesting a lexical deficit. It was corroborated by significant worse performance of the AD group compared to the controls both for short and long irregular words. In line with this assumption, the analysis revealed a significant effect of frequency in the AD group but not in the controls.

Both groups showed a significant difference between regular words and nonwords. However analysis indicated that the difference between AD patients and controls was significant when writing short nonwords but not when writing short regular words. These results support the hypothesis of a phonological deficit.

The analysis of errors revealed that AD patients produced more PPE and NPPE than the controls. Contrary to the control group, the difference in AD between PPE and NPPE was not significant. In AD, PPE were produced at a significant higher rate in irregular words whereas NPPE were significantly more frequent in regular words.

The third set of results concerned peripheral components of writing. AD patients performed significantly more poorly than controls on all the tasks except in mental imagery (lower-case letters) and in copying (upper-case letters). The analyses revealed that for lower-case letters, AD patients exhibited a profile similar to the controls but with lower rates of performance within the following gradient of difficulty (copying, dictation, cross-case transcription, mental imagery). For upper-case letters, the profile was slightly different with more pronounced difficulties in the task of cross-case transcription.

An effect of case to the detriment of lower-case was noted only in AD patients in the tasks of mental imagery and copying. Controls produced only case and substitutions errors whereas AD patients produced a larger panel of errors including graphomotor errors and substitutions. The results suggest that AD patients are impaired both in accessing the mental representation of a letter and in activating the corresponding graphic motor pattern.

Multiple single-case analysis

Data analysis

An original method (adapted from Penniello et al, 1995) was designed in order to make a precise assessment of the efficiency of the central and peripheral processes of writing for each patient, according to the current conception put forward by Ellis (1988) , Margolin and Goodman-Schulman (1992) , and Caramazza et al. (1987) . In current analyses, the deficit of a component is estimated on the basis of the total score for a list of words (for example, orthographically irregular/unpredictable words for the lexical component). As it takes errors into account which may occur because of associated deficits, this calculation tends to exaggerate the dysfunction of each component. Indeed, in the example of a lexical deficit, the quantitative score for irregular words might include EPP (errors indicating that patients do not retrieve the orthographic representation of a target and lie on sub-lexical processing) but also other errors which can originate from embedded perturbations of other components of the spelling/writing system or some which can have several interpretations. For example, a NPPE can arise from different sources of disturbance: phonological route, lexical route (partial access to orthographic representations, Ellis, 1982), graphemic buffer (Caramazza et al, 1987), as well as impaired access to graphic motor patterns (Black et al, 1989). Our methodology paid attention to the impact of several associated deficits on a task. To this end, residual scores were calculated, taking into account both the types of error and the rate of correct responses. To quantify the capacity to correctly use lexical processing, we analyzed performance on irregular words, retained correctly written words and words with errors that typically arise from a selective writing disorder (EPP for lexical deficit), but we discarded words containing errors which can have several (or ambiguous) interpretations. These scores were then converted into Z-scores, calculated on the basis of the results of the control group. Our analysis, as far as the hypotheses driven from classic theoretical models are reliable, tends to play down the magnitude of the deficit. Furthermore, although a certain number of items are removed during the analysis for the 3 lists (words and nonwords), our method does not mask possible related deficits, as their effect is taken into account during the analysis of the other residual performance scores.

We calculated 4 residual performance scores: 2 for central processes (lexical and phonological) and 2 for peripheral ones (allographic and graphic motor patterns). Furthermore, we searched for an effect of length in order to test the integrity of the graphemic buffer.

Residual lexical performance score

A deficit of the lexical route corresponds to difficulty in recovering orthographic information about the words. It results merely in PPE on irregular words or orthographically unpredictable words, demonstrating reliance on the preserved phonological route, i.e. phoneme-grapheme conversion rules (Beauvois and Derouesné, 1981). The residual lexical performance score was based on the 24 irregular words requiring activation of orthographic representations. We removed errors that were not typical of a lexical deficit and those that were open to several interpretations (NPPE, NR and GE). We obtained a subtotal X (≤ 24) composed of correctly written words and words with PPE.

Residual lexical performance score = Number of correct responses on irregular words / Su

Residual phonological performance score

A deficit of the phonological route is defined as difficulty in applying procedures involving word subunits, such as phoneme-grapheme conversion rules. It mainly affects nonwords, with the production of NPPE or NR (Shallice, 1981). The residual phonological performance score was based on the 24 nonwords requiring the involvement of the phonological route. We removed items with errors that

were not typical of a phonological deficit (GE) and obtained a subtotal X (≤ 24) composed of correctly written nonwords and words with NPPE.

al phonological performance score = Number of correct responses on nonwords / Subtotal X *Residual allographic performance score*

An allographic disorder corresponds to difficulty in controlling case (De Bastiani and Barry, 1989) or in accessing, the general shape of a letter (Patterson and Wing, 1989) and results solely in case errors and NR. The residual allographic performance score was based on the task of cross-case transcription (23 letters) from uppercase print letters to lower-case cursive letters, which requires the activation of allographic representations in a specific case and style. We removed items with errors that were not typical of a deficit of the allographic system (GE and SE). We obtained a subtotal X (≤ 23) composed of correctly written letters and letters with case errors (CE) and/or NR.

ic performance score = Number of correct responses on cross – case transcription of cursive letters *Residual graphic motor patterns performance score*

An impairment at the level of GMP (impaired access or impaired representation) results in stroke errors leading to illegible letters and possibly substitution errors (Margolin 1984, Baxter and Warrington, 1986). The residual GMP performance score was based on the task of writing the 23 lower-case cursive letters to dictation. We removed items with errors that were not typical of a graphic motor pattern deficit (CE and SE when target and production may have a similar phonological representation and NR) and obtained a subtotal X (≤ 23) composed of correct letters and letters with GE and/or substitution errors.

or patterns performance score = Number of correct responses in writing to dictation of cursive letters *Deficit of the graphemic buffer*

A deficit of the graphemic buffer is usually viewed as difficulty in temporarily storing the graphemic information conveyed by the lexical or nonlexical route. It results in NPPE, with more errors being made on longer words and nonwords than on shorter ones (Caramazza et al., 1987). In our study, disturbance of the graphemic buffer was identified by a length effect calculated for each subject on words and nonwords (short: 4, 5, 6 letters and long: 7, 8, 9 letters).

Results

Calculating residual performance scores and z-scores for phonological, lexical, allographic and graphic motor pattern systems and looking for a length effect to gauge the functionality of the graphemic buffer led us to delineate precise individual writing abilities for both central and peripheral processes (Table 3). For each patient, components or systems were considered as deficient when the z-score was less than -1.96 . We found that 15 (25.4%) patients had no disturbance, 23 (39%) suffered from deficits confined to central processes, 18 (30.5%) presented with central and peripheral disturbances, and 3 (5.1%) had selective damage to peripheral processes.

Regarding central processes, damage to the lexical route was more often noted than to the phonological one or the graphemic buffer. For peripheral components, the allographic system appeared to be more often affected than the graphic motor patterns.

Comments

This multiple single-case analysis was based on an original method whose aim was to assess the state of every central and peripheral component for each subject. We therefore calculated residual performance scores - guided by a cognitive hypothesis - for lexical, phonological and allographic processes, and graphic motor patterns. We also calculated Z-scores in order to estimate the degree of disturbance in comparison with the control group. Impairment of the graphemic buffer was assessed (present or not) on the basis of length effects. Our data showed that signs of agraphia were present in 74.6 % of the AD patients. As expected, central impairments were observed in the majority of patients (69.5%) but peripheral disorders were also obvious in 35.6 % of them. Central deficits involved the lexical component (46%) more frequently than the phonological one (32%) or the graphemic buffer (27%). For peripheral processes, an allographic deficit was more frequent (25.5%) than damage to graphic motor patterns (15%). Moreover, our analysis produced three individual agraphic profiles in terms of central and peripheral distinctions: (1) central impairment (restricted to one or several central components) - the most frequent profile (23 patients); (2) peripheral impairment (restricted to one or several peripheral components) - rare (3 patients); (3) mixed impairment (both central and peripheral impairments) - moderately observed (18 patients). Furthermore, by taking into account each spelling component, our method provided evidence of the heterogeneity of the deficits (Table 3), in that alongside the well-known purely cognitive syndrome of agraphia, we also observed agraphia resulting from associated spelling and/or writing disorders.

Agraphia and other cognitive measures

To assess the relationship between agraphia and other cognitive deficits (see Table 4), we carried out regression analyses between residual performance scores and scores reflecting the severity of the disease (MMSE), gestural praxis and visuoconstructional abilities (stick test), and semantic processing (semantic knowledge task). The simple regression analyses (Table 5) indicated significant

relationship between severity of the disease and both lexical ($p = .04$) and allographic abilities ($p = .007$). Multiple regression analyses showed, independently of the severity of dementia, significant relationship between visuoconstructional performance (stick test) and phonological processing ($p = .02$), or graphic motor patterns ($p = .002$).

Comments

Although inconsistent data are reported in the literature, as expected, the regression analyses revealed a significant and positive relationship between MMSE scores and spelling and writing performances. These data demonstrated that as the disease progresses, lexical and allographic abilities are increasingly impaired. It is worth noting that very little variability was found in graphic motor patterns. We expected that lexical-orthographic knowledge would be linked to semantic knowledge, as semantic deficits may have negative effects on orthographic knowledge. However, we failed to confirm this relationship, and the independence of semantic and orthographic knowledge has indeed already been reported (Lambert et al., 1996). The analysis indicated a significant correlation between graphic motor pattern scores and the stick test. This relationship is consistent with neuropsychological data showing that apractic agraphia is often associated with visuoconstructional deficits. It has also been observed that impairment of global cognitive performance was correlated with drawing disabilities (Förstl et al., 1993). Our results must be carefully considered because of the brief assessment of the gestural and visuoconstructional components (see Förstl et al., 1993; Derouesné et al., 2000; Blondel et al., 2001 for more extensive testing at both levels of production and conceptual systems).

General Discussion

Grounded on current cognitive models, this study conducted an extensive assessment of the spelling and writing abilities of a large cohort of AD patients with a good level of premorbid orthographic abilities. The first innovative element was the use of a wide range of tests to assess every central and peripheral component. No other study has carried out such a full examination of agraphia to date. A second methodological strong point was the multiple single-case analysis which, thanks to in-depth analyses, allowed us to define individual agraphic profiles and relate these profiles to other cognitive deficits.

The oral and written spelling of regular, irregular words and nonwords was used to assess the central processes. As in most previous studies (Platel et al., 1993; Croisile et al., 1996; Hughes et al., 1997; Pestell et al., 2000; Groves-Wright et al., 2004) with the exception of Croisile et al. (1996), who recorded better performances on written than on oral spelling, and Pestell et al. (2000) who observed the opposite tendency, our analysis revealed that the performances of the AD patients were impaired in both oral and written spelling, compared with those of the control group, and that this deficit was similar regardless of the output modality. Focusing on written performance, we observed that patients scored at a significant lower rate than controls both in words (regular, irregular) and nonwords. The analyses indicated more difficulties on irregular words than on other types of items with a greater number of PPE than other errors and worse performance for nonwords than for regular words. These first results suggested that AD patients were impaired both in the generation of long-term stored orthographic representations (because of the significant difference between regular and irregular words) and in the ability to use phoneme-to-grapheme correspondence rules (because of significant difference between regular words and nonwords). The analyses also revealed an effect of length regardless of the type of item which supports the hypothesis of damage of the graphemic buffer. It is commonly assumed that the graphemic buffer is based on a working memory process which maintains the abstract graphemic representation, i.e. the string of abstract letter identities computed lexically and/or sublexically which will later be converted sequentially into letter shapes or names. Damage to this process is thought to entail an abnormally rapid decay rate of the graphemic representation and to result in more errors when longer sequences are stored. The impact of length of item has not always been taken into account in group studies using the same assessment protocol as ours (Rapcsak et al. 1989, Platel et al., 1993, Niels et al., 1995; Hughes et al., 1997; Glosser et al., 1999; Luzzati et al., 2003) and when it has been, the method used to calculate this effect of length has sometimes been very different (Aarsland et al., 1996; Croisile et al., 1996). Lastly, findings do not always entirely reveal the pattern expected to result from damage to the graphemic buffer. For instance, Aarsland et al. (1996) found a length effect for nonwords but not for words. In the present study, given the rigorous matching of the items' key characteristics (length, frequency and orthographic regularity), we are surely right to dwell on this observed effect of length. Because of this deleterious effect on long items we searched whether the hypothetical lexical and phonological impairments will be retained when taking into account this variable of length.

Confirming the lexical deficit, we found significant difference both between short regular and irregular words and long ones. This assumption is also corroborated by the effect of frequency which is known to be associated to this syndrome and the high number of phonologically plausible errors which indicates that patients rely on phoneme-to-grapheme rules. Confirming the phonological impairment, analysis indicated that patients committed also more errors on short nonwords than on short regular words. These results suggest that damage is predominantly sustained by the lexical route, as is classically reported (Rapcsak et al., 1989; Platel et al., 1993; Penniello et al., 1995; Croisile et al., 1996; Hillis et al., 1996; Lambert et al., 1996; Hughes et al., 1997; Pestell et al., 2000; Luzzati et al., 2003). However our data also indicate that, in AD, the central spelling processing deficit is not confined to lexical orthographic impairment and

we found arguments in favour of damage to sublexical processing and of impaired graphemic buffer. Thus, our results concur with other studies which have also pointed to the disturbance of non-lexical central components (Platel et al., 1993 ; Neils et al., 1995 ; Penniello et al., 1995 ; Aarsland et al., 1996 ; Croisile et al., 1996 ; Glosser et al., 1999 ; Pestell et al., 2000 , Luzzati et al., 2003 ; Forbes et al., 2004).

Impairment of the peripheral processes of writing has previously been mentioned in studies showing abnormalities in letter formation, the production of case errors and shifting from lower-case to upper-case letters (Rapcsak et al., 1989 ; Henderson et al., 1992 ; LaBarge et al., 1992 ; Platel et al., 1993 ; Eustache and Lambert, 1994 ; Lambert et al., 1994 ; Penniello et al., 1995 ; Luzzati et al., 2003 ; Forbes et al., 2004). However, these studies have rarely featured tasks specifically designed to assess peripheral components (Hughes et al., 1997 , and Venneri et al., 2002 , in a case study). Hughes et al. (1997) only used two tasks (letter copying and cross-case transcription). Because of poorer performances on transcription than on copying tasks, they concluded that their patients' peripheral impairments mainly concerned the allographic store. Damage to the graphic motor patterns was also evoked, because of slight impairment on copying. An effect of case showed that upper-case letters were always better produced than lower-case.

Our study included four single-letter tasks in order to tap the different peripheral components of writing: writing to dictation, cross-case transcription, letter imagery and the copying of upper-case print letters and lower-case cursive letters. Our results revealed that AD patients as a group suffered from a mild impairment of peripheral processes. They had lower scores than controls but with a similar pattern, in that they preferentially made case errors, although they differed from controls as they made graphomotor errors. Graphomotor errors suggest a deficit at the level of graphic motor patterns. This hypothesis is also supported by the quality of copying, which was better than dictation. Models of written production (Margolin and Goodman-Schulman, 1992 ; Rapcsak, 1997) propose that copying may be performed by an alternative route to the one which requires the activation of graphic motor patterns: writing through a pictorial strategy requiring intact visuoconstructional abilities. We ourselves observed that AD patients obtained near normal scores in a task of visuoconstruction. Therefore they would be able to use a pictorial strategy to perform copying. However shifting from one system to another is not automatically processed and more recent studies (Adi-Japha and Freeman, 2000) pointed to the difficulty of modelling the activation of alternative expert systems such as writing and drawing ones.

With reference to current models which postulate two distinct levels - allographic and the graphic motor pattern (but see Rapp and Caramazza, 1997 , for the lack of sufficient theoretical grounds) -, we hypothesized that a deficit at the level of the graphic motor patterns would impair tasks which require the written production of a letter (dictation, cross-case transcription and copying, but only if the alternative pictorial route is inefficient) but not the imagery of a letter, and that, by the same token, a deficit in allographic representations (activation of the general abstract form of the letter) would affect tasks in which the letter shape is not provided (imagery of letters, dictation and cross-case transcriptions) but not copying. With regard to this theory, several of our results also suggest that AD patients suffered from an allographic processing disorder. Thus, we found that patients were impaired in all three tasks - dictation, cross-case transcription and imagery of letters - and that the majority of errors were case-errors. As in agraphia resulting from focal vascular lesions, case and style may be dissociated in AD. Venneri et al. (2002) reported a double dissociation in two mild AD patients: one was impaired when asked to write in cursive, whereas the other was impaired when asked to write in print. Predominant difficulties for lower-case letters have previously been reported (LaBarge et al., 1992 ; Hughes et al., 1997 ; Forbes et al., 2004), but our study, which featured more tasks and generated more data, did not entirely confirm these results. AD patients only performed worse on lower-case letters in the mental imagery task and copying but not in writing to dictation.

Luzzati et al. (2003) suggested that the pattern of agraphia observed in AD patients is "simply an amplification of the general difficulty effect observed in control subjects". Rather, we hypothesize that agraphia in AD patients stems from specific deficits in several components of the spelling system: the lexical route, phonological route and graphemic buffer. The non parametric analysis used in the group analysis does not represent an adapted method to question this point but multiple single-case analyses provide an opportunity to test this kind of hypothesis and identify different profiles of disturbance. In our study, this analysis was based on an original method allowing a fine-grained assessment of each spelling and writing component. In order to calculate scores of residual performance, we deliberately excluded words with ambiguous errors, which could lead to several interpretations, such as non-phonologically plausible errors in regular and irregular words. By this means, we obtained distinct profiles, showing the deficit of one process or mixed deficits. The results of these individual analyses revealed that 25.5 % of the AD patients did not exhibit agraphia. In the paper by Hughes et al. (1997) , this proportion was 30 % (10/31), but in the study of Luzzati et al. (2003) , it was lower, at just 13 % (3/23). We found that central impairments largely predominated over peripheral ones. Unfortunately we cannot compare all our findings with previous studies because Hughes et al. (1997) did not assess sublexical components (no nonwords included) and Luzzati et al. (2003) did not explore the peripheral aspects of writing. Our results found evidence that lexical deficits were present in a greater number of patients than damage to the sublexical route and the graphemic buffer, as in Penniello et al. (1995) and Luzzati et al.'s (2003) studies. We also observed that allographic impairment was more frequent than disturbance in graphic motor patterns. Another important result of our analysis was that more than a third of patients displayed a "pure type" of agraphia, i.e. resulting from the disturbance of a single spelling or writing component, lexical, phonological, graphemic buffer, allographic system and graphic motor patterns. These data call into question the hypothesis of a unitary pattern of agraphia in AD and consequently cannot be used as evidence of a unitary profile of evolution. Then again, nor do they support the

conclusions reached by Glosser et al. (1999) , who argued that specific impairment of central spelling components does not account for the agraphia presented by the overwhelming majority of patients and that instead, impaired spelling performance arises from various non-linguistic factors, including semantic impairment and disturbance of attention, executive control and praxis. Rather, in line with other research (Penniello et al., 1995 ; Hughes et al. 1997 ; Pestell et al., 2000 ; Luzzatti et al., 2003) , our study suggests that agraphia in AD patients results from damage to various but specific spelling or writing components which can occur even in the early stages of the illness. These findings may reflect the hypothesis of a mosaic of circumscribed pathogenic lesions distributed over different cerebral areas. The anatomical substrate subserving spelling and writing is indeed represented as a wide network extending from parieto-temporal to frontal regions.

We observed here that the severity of agraphia generally worsened as the disease progressed; nevertheless researchers have found inconsistencies in the relationship between AD severity and the rate of impairment of spelling and writing processes. Pestell et al. (2000) failed to demonstrate that phonological impairment is more prevalent in moderate AD patients than in mild AD ones. Neither Glosser et al. (1999) nor Luzzatti et al. (2003) found a relationship between the severity of agraphia and the lexical or phonological route. For their part, Hughes et al. (1997) pointed to the heterogeneity of agraphic profiles and underlined the presence of peripheral agraphia even in minimally affected cases. Our data indicate that as the disease progresses, the lexical and allographic abilities are more and more disturbed, but the analyses do not reveal any relationship with other spelling or writing components.

Conclusion

Based on a longitudinal study, Platel et al. (1993) suggested that the progression of the disease would follow the following steps: (1) lexical impairment; (2) extension to other central components; (3) occurrence of peripheral damage. Our study has supplied arguments for qualifying this conclusion. Although, as in other group studies, lexical impairment was found to be the most frequent spelling impairment, a multiple single-case analysis revealed heterogeneous profiles of agraphia and an almost significant number of patients with only one affected component, either central or peripheral. Every agraphic syndrome was represented in the AD group. Consequently, there cannot be a single profile of evolution. These assumptions need to be confirmed by longitudinal studies featuring multiple single-case analyses.

APPENDIX

Fig. a

Mental imagery of letters: lower-case cursives letters

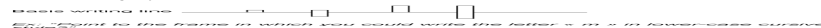


Fig. b

Mental imagery of letters: upper-case print letters

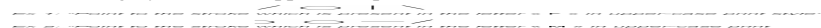
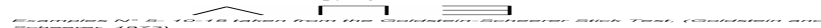


Fig c

Visuoconstructional abilities: Copying from models



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Fig 1

Number of correct responses by controls and AD patients in the spelling tasks.

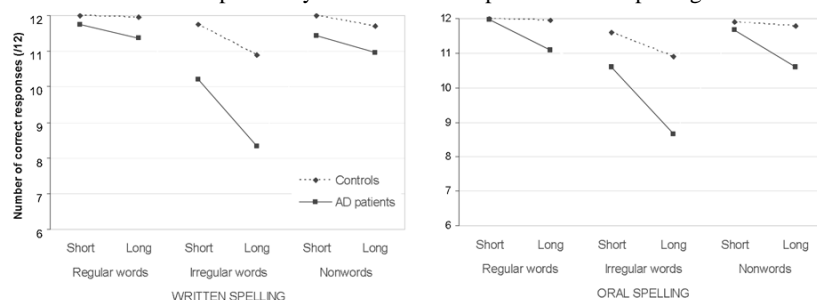
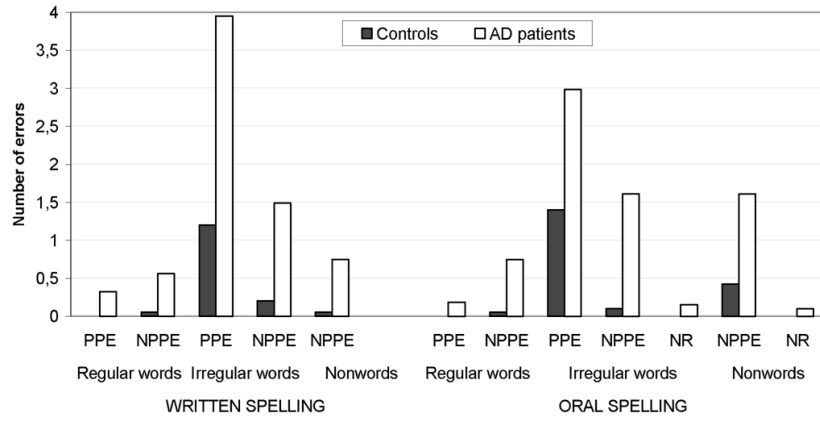


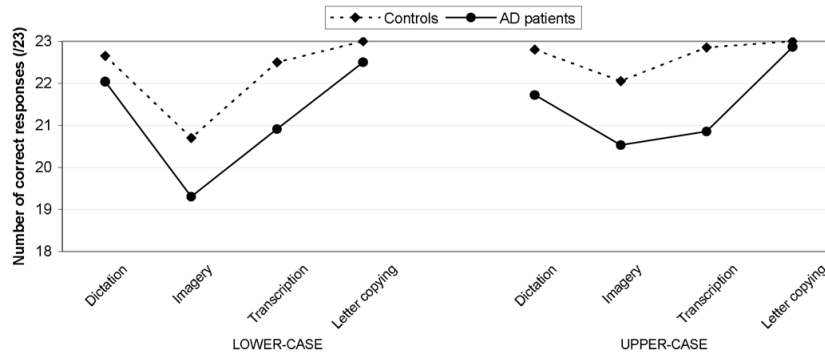
Fig 2

Nature of errors in control and AD groups for each type of item and each modality of output

PPE: phonologically plausible errors; NPPE: non-phonologically plausible errors; NR: non-response

**Fig 3**

Number of correct responses (/23) by control and AD groups for the two types of case and peripheral tasks.

**Fig 4**

Nature of errors in the three peripheral tasks and in each case

GE: graphomotor errors; SE: substitution errors; CE: case errors; NR: non-response.

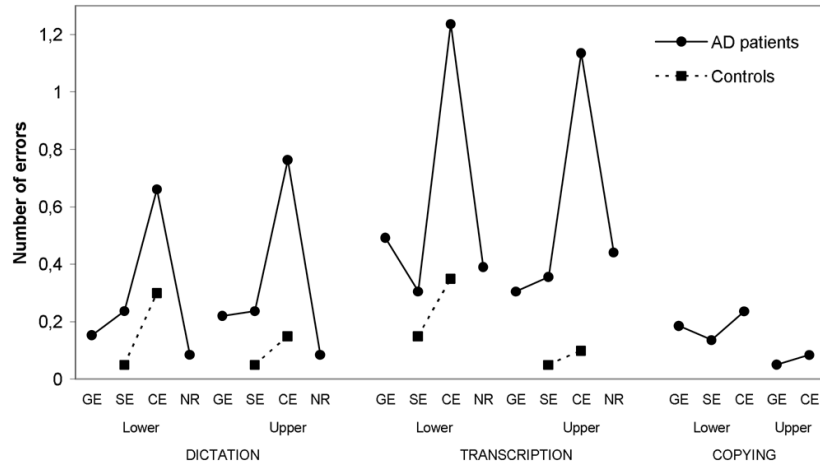


Table 1

Demographic and psychometric data in controls and AD patients

	Controls (n = 20)		AD patients (n = 59)		ANOVA	
	M (sd)	Range	M (sd)	Range	F [1,77]	p
age	72.9 (5.8)	60–83	73.15 (6.7)	47–85	0.022	.88
education (in years)	9.1 (1.3)		9.1 (1.4)		0.004	.95
MMSE (out of 30)	29.1 (±1)	27–30	21.8 (±3.3)	14–27	93.6	< .001
DRS (out of 144)	138.1 (±3.9)	132–144	118.8 (±8)	101–136	109.6	< .001
MT 86 (out of 24)	23.8 (0.6)	22–24	22.8 (1.3)	19–24	11.05	.0014

Table 2

Comparison between each letter task in lower- and upper-case letters for the AD and control groups (p values from Wilcoxon tests).

	Lower-case		Upper-case	
	AD group	Control group	AD group	Control group
Copying vs. Writing-to-dictation	.004	copying: ceiling effects	copying: ceiling effects	
Writing-to-dictation vs. Transcription	< .0001	ns	.001	ns
Transcription vs. Mental imagery	.0003	.0008	ns	.008
Writing-to-dictation vs. Mental imagery	<.0001	.0008	.0004	.01

Table 3

Individual writing abilities divided into 4 patterns: 1- Isolated central deficits; 2- Isolated peripheral deficits; 3- Central and peripheral deficits; 4- No deficits

	CENTRAL PROCESSES	PERIPHERAL PROCESSES	Number of patients (N=59)	
1-	Lexical		5	}
	Phonological		2	
	GB		3	
	Lexical + Phonological		5	
	Lexical + GB		5	
	Phonological + GB		2	
	Lexical + Phonological + GB		1	

2-		Allographic	2	}	5.1%
		MGP	1		
3-	Lexical	Allographic	5	}	30.5%
	Lexical	MGP	1		
	Phonological	MGP	2		
	Phonological	Allographic	1		
	Phonological	Allographic + MGP	1		
	GB	Allographic	1		
	GB	MGP	1		
	Lexical + Phonological	Allographic	2		
	Lexical + Phonological	Allographic + MGP	1		
	Lexical + GB	MGP	1		
	Phonological + GB	Allographic	1		
	Lexical + Phonological + GB	Allographic + MGP	1		
4-	No deficits		15		

GB: Graphemic buffer; MGP: Motor Graphic Pattern

Table 4

Performances of controls and AD patients on cognitive tasks

	Controls (n = 20)	AD patients (n = 59)	Mann-Whitney test	
			z	p
Semantic knowledge/236	233.75 (\pm 1.37)	227.89 (\pm 4.58)	-6.05	< .0001
Gestural praxis/18	17.8 (\pm 0.4)	16.6 (\pm 2.1)	-2.70	= .007
Visuoconstruction/18	18 (0)	17.1 (\pm 2.1)	-2.57	= .01

Table 5

Regression analyses between residual performance scores and severity of the disease (MMSE), semantic processing, gestural praxis and visuoconstructional (Stick Test) abilities.

	MMSE	Semantic knowledge	Gestural praxis	Stick test
Phonological	r = 0.15; p = .27	r = 0.19; p = .49	r = 0.14; p = .98	r = 0.33; p = .02
Lexical	r = 0.27; p = .04	r = 0.33; p = .65	r = 0.29; p = .47	r = 0.28; p = .96
Allographic	r = 0.35; p = .007	r = 0.31; p = .74	r = 0.38; p = .16	r = 0.39; p = .13
GMP	r = 0.14; p = .28	r = 0.17; p = .87	r = 0.19; p = .33	r = 0.41; p = .002

The significant regressions are in bold type. Regressions between residual performance scores and MMSE were simple regression analyses. Regressions between residual performance scores and semantic knowledge, gestural praxis and stick test were multiple regression analyses i.e. independent of the severity of dementia (MMSE).

GMP: Graphic Motor Pattern