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Systematic Review

Handwriting Changes in Alzheimer's Disease: A Systematic Review

Carina Pereira Fernandes[a,b,*], Gemma Montalvo[b,c], Michael Caligiuri[d], Michael Pertsinakis[e,f] and Joana Guimarães[g,h,i]
[a]*NCForenses Institute, Porto, Portugal*
[b]*Universidad de Alcalá, Instituto Universitario de Investigación en Ciencias Policiales (IUICP), Alcalá de Henares, Spain*
[c]*Departamento de Química Analítica, Química Física, Universidad de Alcalá, Alcalá d Henares, Spain*
[d]*Department of Psychiatry, University of California San Diego, La Jolla, CA, USA*
[e]*Ingeniería Química, Alcalá de Henares, Spain*
[f]*City Unity College, Athens, Greece*
[g]*Department of Neurology, Centro Hospitalar Universitário de São João, Porto, Portugal*
[h]*Department of Clinical Neurosciences and Mental Health, Faculty of Medicine, University of Porto, Porto, Portugal*
[i]*MedInUP – Center for Drug Discovery and Innovative Medicines, University of Porto, Porto, Portugal*

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Abstract.
Background: Handwriting is a complex process involving fine motor skills, kinesthetic components, and several cognitive domains, often impaired by Alzheimer's disease (AD).
Objective: Provide a systematic review of handwriting changes in AD, highlighting the effects on motor, visuospatial and linguistic features, and to identify new research topics.
Methods: A search was conducted on PubMed, Scopus, and Web of Science to identify studies on AD and handwriting. The review followed PRISMA norms and analyzed 91 articles after screening and final selection.
Results: Handwriting is impaired at all levels of the motor-cognitive hierarchy in AD, particularly in text, with higher preservation of signatures. Visuospatial and linguistic features were more affected. Established findings for motor features included higher variability in AD signatures, higher in-air/on-surface time ratio and longer duration in text, longer start time/reaction time, and lower fluency. There were conflicting findings for pressure and velocity in motor features, as well as size, legibility, and pen lifts in general features. For linguistic features, findings were contradictory for error patterns, as well as the association between agraphia and severity of cognitive deficits.

*Correspondence to: Carina Pereira Fernandes, NCForenses Institute, Rua Pinto Bessa, 522, RC Esq., 4300-428 Porto, Portugal. Tel.: +351 224022684; E-mail: cafernandes@ncforenses.pt.

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Conclusions: Further re-evaluation studies are needed to clarify the divergent results on motor, general, and linguistic features. There is also a lack of research on the influence of AD on signatures and the effect of AD variants on handwriting. Such research would have an impact on clinical management (e.g., for early detection and patient follow-up using handwriting tasks), or forensic examination aimed at signatory identification.

Keywords: Agraphia, Alzheimer's disease, dementia, forensic examination, kinematics, signature

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, affecting approximately 32 million people worldwide [1, 2]. It is an irreversible neurodegenerative disease with an insidious onset that impairs cognitive functions, such as memory, learning, attention, language, visuospatial skills, and decision making [1, 3]. This disease progresses according to three stages (mild, moderate, and severe) [4] and has a multifactorial etiology, with both environmental and genetic causes, although the pathogenesis and underlying mechanisms remain uncertain [5]. The pathological hallmarks are amyloid plaques, which are extracellular deposits of amyloid-β (Aβ) [1, 5] and neurofibrillary tangles, which are intraneuronal structures consisting of hyperphosphorylated tau proteins [1, 5]. Based on the age of onset, AD may be classified as early or late onset. Early onset affects individuals below the age of 65 and is a rarer form that accounts for approximately 5% of all cases, whereas late onset is the most common and affects older individuals [1]. Clinically, AD is characterized by a slowly progressive loss of episodic memory, deficits in working memory, disorientation in space and time, as well as deficits in language and visuospatial skills in more advanced stages. However, particularly in early onset, some patients may show atypical clinical presentations (atypical AD), with deficits centered in executive, visuospatial, language, behavior, or motor features and relatively preserved memory in initial stages [5, 6].

Since handwriting is a complex process that involves fine motor skills, kinesthetic components, and several cognitive domains, such as language, visuospatial skills, memory, and attention, most of which are impaired in AD, it is a possible biomarker for early diagnosis and disease progression [7, 8]. In this context, the aim of the article is to provide a systematic review of handwriting changes in signatures and text, in order to better understand how handwritten language and movement are affected by AD, as well as to identify new lines of research on this topic. In addition, the evidence reported in this review may help professionals (e.g., psychologists, psychiatrists, physical therapists, and forensic handwriting examiners) in their evaluation of handwriting samples executed by AD patients, for both clinical and forensic purposes.

MATERIALS AND METHODS

The current systematic review was performed according to PRISMA guidelines [9, 10]. The search was conducted for all works published before March 31, 2023 on PubMed, Scopus, and Web of Science, using the following Medical Subject Headings (MeSH) Terms: "Handwriting AND Alzheimer disease", "Dementia AND Handwriting", and "Agraphia AND Alzheimer disease". This review was carried out using a peer-review system, in which two researchers independently analyzed and selected the articles based on the following inclusion criteria: only English publications and studies must include participants with a formal diagnosis of AD (typical or atypical AD). In addition, the authors only included studies that featured handwriting or handwriting-type motor tasks, such as writing signatures, sentences or texts, sets of letters (e.g., four cursive l's) or executing circles, since they are key elements involved in the construction of several letters (e.g., letter "a", "o", or "d"). Exclusion criteria were as follows: non-English publications, off-topic articles (e.g., validation of neuropsychological screening instruments), dementia type not specified, literature reviews without inclusion or exclusion criteria for article selection, and articles that did not include handwriting or handwriting-type motor tasks.

RESULTS

Database search revealed a total of 846 articles. Six additional studies were identified using citation searching. After removing duplicate records, the remaining 388 articles were screened on the basis of title and abstract. After the screening process,

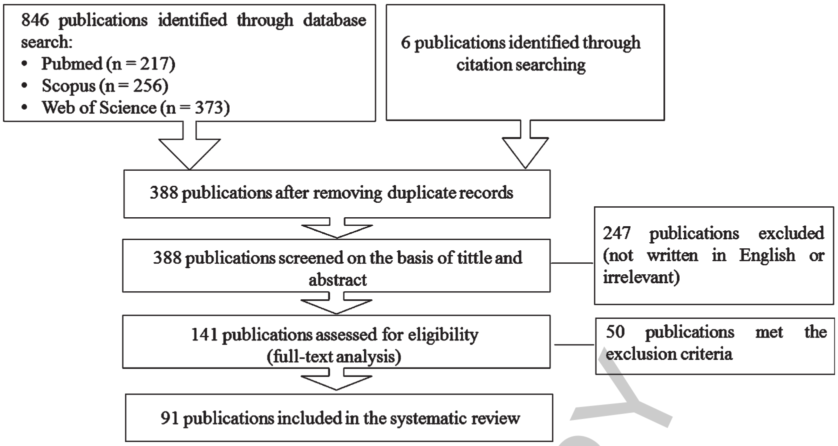

Fig. 1. Article selection flow chart.

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247 records were excluded as they were written in a language other than English or were off-topic. The full-version of the remaining 141 articles were assessed for eligibility, of which 50 met the exclusion criteria: 17 did not include AD subjects or failed to specify dementia type, 20 did not include handwriting tasks, 10 were off-topic (e.g., validation of new screening instruments), and finally 3 consisted of literature reviews without article selection specifications. The remaining 91 studies met the inclusion criteria and were included in the systematic review (Fig. 1).

The studies included in the present review applied different modalities to acquire handwriting samples. Hence, handwriting was collected through different sets of tasks, such as signing, spontaneously writing a text (using picture description or a narrative writing task), executing copy and reverse copy tasks or writing a letter sequence (e.g., writing four cursive l's). These tasks were performed on paper or on digital tablets (digitally captured signatures or handwritten entries). Pen and paper samples provided a more natural setting for handwriting execution, particularly for older subjects, and were examined through direct analysis of the inking trace. Samples executed on digital tablets with specific software allowed the recording and analysis of quantitative data, especially temporal kinematics and pen pressure and were analyzed quantitatively, using machine learning or non-machine learning methods.

A summary of the individual studies included in this review is presented in Supplementary Table 1, detailing AD population characteristics, handwriting tasks, and main results. Findings will be divided into: i) motor features (velocity, fluency, pressure, and temporal features), visuospatial and other general features (spacing, shape of the baseline, size, legibility, pen lifts, and slant) and linguistic features (spelling errors, spelling patterns, syntax, and information content), based on the bottom-up hierarchical organization of these characteristics within the nervous system. Signatures will be discussed separately from the rest of the handwriting, given their higher degree of automatism, personalization and lower cognitive demands [11].

Motor features

Motor features include velocity, fluency, which refers to the smoothness and skill level of writing [12], pressure and temporal features. For the purpose of this review, a stroke is defined as the basic unit that forms the handwriting movement [13].

Research suggests that motor features in signatures are relatively preserved, as first stated by Behrendt in 1984, who highlighted that writing skill may not reflect cognitive decline in AD [14]. These findings were supported by studies that analyzed digitally captured signatures [15, 16] and pen and paper signatures [17], although there was a higher variability in the AD group when compared to the controls [15]. As for fluency, although it appears to be relatively preserved in signature execution in more initial stages of the disease [15], two studies that analyzed pen and paper signatures described lower line quality in more severe cases [17, 18], due to tremor and hesitations. Other handwriting features within the neuromotor realm revealed conflicting results, such as velocity and pen pressure. Some studies that focused on digitally captured and pen and paper signatures [15–17] found velocity and pressure similar between AD and the control groups. On the contrary, studies by Pirlo et al. [19] and Wang et al. [20] that used machine learning methodology to analyze digitally captured signatures revealed intergroup differences in velocity [19] and pressure [20]. Regarding pen pressure, the authors reported lower pressure in the AD group and suggested that these individuals hold the pen in a different way, due to lower muscle tonus [20].

Research on text handwriting suggests that it is more impaired than signatures [21–24]. Results concerning fluency were homogeneous and showed that handwriting movements in AD subjects were more irregular [24–29] and less coordinated [28] when compared to controls. In addition, in AD subjects execution time (duration) was longer and variation was higher [25, 26]. It is also worth noting that some of these findings were irrespective of medication or disease severity [25]. On the other hand, similarly to signatures, results for velocity and pressure were not consensual. For velocity, while some studies did not find significant differences between AD and the control groups [8, 25, 26], other authors found lower velocity in the handwriting movements of AD subjects [27, 28, 30, 31]. With regard to pen pressure, although Delazer et al. [31] did not find significant differences between AD and controls using different tasks (e.g., dictation and 4 cursive l's), additional studies involving copy tasks, picture-naming tasks and spontaneous writing reported lower pressure in the AD group [8, 32–34] or an increase in pressure [35]. Additional studies that applied machine learning methodology have differentiated controls and AD patients with high accuracy using these features [36–42] or lognormal features [43], suggesting that they may be affected by the disease and can be used as a biomarker to track disease progress in AD [44].

The use of digitizers also provided new insights into how time related characteristics and in-air trajectories are affected by AD. In-air trajectories (IATs) are the invisible movements executed when the pen is lifted above the writing surface, and have been considered biomarkers for diagnosis and progress follow-up of other diseases, such as Parkinson's disease [45]. In studies involving copy tasks (numbers, letters, words, or paragraphs), AD patients showed higher temporal measures, with differences in in-air [8, 33, 46] and on-surface time [33, 47]. In the study by Werner et al. [8] and Yu & Chang [46], the ratio of in-air/on-surface time was higher in AD, suggesting less contact time between the stylus and the tablet. Ghita et al. [33] found not only higher in-air time, but also higher on-surface time. Start time or reaction time, which corresponds to the time interval between the stimulus and the beginning of the movement, was also longer for AD subjects [32]. In addition, literature describes a higher duration in AD [48], with an increase in pause time [46, 48–50] and in time intervals between letters [32]. It is worth noting that no studies have addressed in-air trajectories and related temporal features (e.g., time in air and time in contact) in signatures of individuals with AD.

Visuospatial and other general features

Visuospatial features and other general features include spacing, shape of the baseline, size, legibility, pen lifts, and slant [12]. Visuospatial features were impaired in both signatures and text handwriting of AD subjects, although to a higher extent in the latter. Signatures written by AD patients had more irregular spacing between letters or words [17, 18], as well as more irregular shape and direction of the baseline [17, 18]. In text handwriting, Croisile [35] and De Stefano et al. [22] highlighted changes in spatial organization in their literature reviews. These changes consisted of difficulties in maintaining a horizontal baseline, misalignments of letters [29, 34, 51–53], spacing errors between letters and words [22, 35, 53] and, in more severe stages, writing only on one half of the page or dispersed handwriting throughout the page [35, 36, 52]. In addition, Renier et al. found spatial changes in 29.7% of the samples, using a picture description task [54]. The association between AD and the deterioration of visuospatial characteristics was reinforced in writing systems that are more demanding on visuospatial skills, such as Korean writing. Yoon et al. [55], who examined Hangul characters, found visuospatial errors even at early stages of the disease.

Despite the consistent findings for visuospatial features (spacing, alignment and shape and direction of the baseline), results for other general features, such as pen lifts and size, were less consistent. In signatures, Birincioglu et al. [18] reported an increase in pen lifts and size. However, Fernandes & Lopes Lima [17] found no significant differences between AD participants and healthy controls regarding these characteristics, despite reporting cases of micrographia and macrographia in more demented patients. Additional findings in AD signatures included an increase in illegibility [17], incorrect connections between words [14] and deformed letters [18]. Nevertheless, Renier et al. [54], who compared two sets of signatures (a signature executed at the moment of the

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evaluation and an older signature) produced by mild stage AD subjects, found no significant differences between them.

In text handwriting, results included an increase in letter size [53, 54] or greater size variation in a continuous circle drawing task [56], increased illegibility [29, 35], more pen lifts [35], and alterations in slant [53]. Despite these findings, it is worth noting that Yu & Chang [46], in their study involving copy tasks, found no significant intergroup differences regarding size.

Linguistic features and cognition

Research suggests that agraphia is common [35, 57] in signatures, and specially in text handwriting of AD patients [58]. Studies described repetitions [14, 17, 18, 52, 59–68], often as perseverations, as well as omissions of strokes and letters [14, 17, 18, 29, 34, 35, 53, 61–63, 65–69] and substitutions in signatures and text handwriting [17, 34, 35, 53, 61, 68, 70]. For example, Alois Alzheimer had already described omissions and repetitions in the handwriting of his patient August D. [71]. Repetitions and omissions were frequent in letter sequences or letters that involved repetitive movement (e.g., letters "M", "m" or "n") [17, 53] or additional strokes, as studies described missing "i" dots [17, 29, 53], "t" bars [17, 29, 53], and diacritics [69, 72]. In substitutions, letters were replaced by the corresponding uppercase, lowercase, or printed allograph (allographic agraphia) or by a different letter [17, 29, 35, 62, 70, 73]. Moreover, Caligiuri [60] found apraxic agraphia, which is characterized by the occurrence of omissions, additions or substitutions, for signatures (in 26.9%) and for sentences (in 24.2%) of his AD participants. Text handwriting also contained graphomotor errors [35, 52, 53, 59, 63–65, 74], particularly in more advanced stages of the illness. These errors consisted of poorly constructed letters, sometimes rendered illegible or simplified [35, 51, 52, 59, 63, 72, 74], as well as difficulties with stroke placement [53, 64, 66, 70] and inverted loops [35]. Moreover, repetitions, omissions, substitutions and graphomotor errors were not restricted to Latin script and were also found in Chinese [64], Japanese [65, 75], Korean [55, 66], and Arab writings [72].

Although the presence of spelling errors is consensual, results referring to the pattern of spelling errors as disease progresses vary across studies. Such studies considered the following categories of spelling errors: phonologically plausible, non-phonologically plausible and graphomotor errors. Phonologically plausible errors occurred when the phonological structure of the word was preserved (*e.g.*, writing "flud" instead of "flood") [74, 76], whereas in non-phonologically plausible errors the word structure was altered (e.g., writing "toint" instead of "point") [74, 76]. Unlike the previous error types, graphomotor errors reflected impairments in peripheral processes of handwriting, such as allograph selection (e.g., writing "MeMOry" instead of "Memory") or in the graphomotor programs themselves (e.g., poorly constructed or illegible letters) [74, 76, 77]. On this topic, some authors described a hierarchical progression of spelling errors according to three stages [35, 73, 74, 76, 78, 79]: initially, handwriting would contain predominantly phonologically plausible errors, followed by non-phonologically plausible errors and, finally, graphomotor errors in later stages. However, other authors did not find a shift in spelling errors as AD advances [7, 71, 80–86]. Moreover, authors such as Croisile et al. [87] and Carthery et al. [7], found written spelling to be more preserved than oral spelling.

In addition to phonologically plausible, non-plausible and graphomotor spelling errors [88], other linguistic features in AD text included poorly structured narratives [89–91], with shorter sentences [61, 69, 89–95] that were often incomplete or indefinite [29, 34] and contained punctuation errors [29, 69]. These sentences were also less informative [35, 94], as they contained more irrelevant information [35, 52, 90–92] and exhibited lower idea density scores [96], as well as lower complexity due to simplified syntax [35, 69, 92, 95], fewer verbs [69], and reduced vocabulary [35, 51].

Research on the association between agraphia and dementia severity or linguistic, attentional and visuoconstructional deficits in AD, also yielded conflicting results. Some authors found a correlation between writing impairment and disease severity, attention, memory, and other executive functions [49, 51, 52, 54, 58, 71, 72, 74, 79, 82, 83, 93, 97–100], not only in Latin script, but also in Chinese [64], Korean [55], and Arab script [72]. Additionally, Caligiuri [60] found that subjects with apraxic agraphia were more cognitively impaired and had more dysfluent movements. Neils et al. [101] reported an association between attention impairments and the higher number of spelling errors in individuals with mild AD, while Sand Aronsson et al. [90] reported a significant association between syntactic complexity and cognitive impairment. A study by Kavrie and Neils-

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Strunjas [57] also found that linguistic and attention deficits were good predictors of agraphia. Moreover, Onofri et al. [98] and Fontana et al. [102] suggested that a document written by an AD patient may be used to evaluate decisional capacity, given the association between text handwriting, cognitive deficits and neuropsychological evaluation scales. On the other hand, in other studies agraphia was not associated with age at onset [83, 100], family history [83, 100], illness duration [100] or additional measures of language and motor performance [29]. Moreover, some studies found little or no correlation between agraphia type or its presence and dementia severity [76, 78, 80, 86, 103, 104]. As for the association between signatures and cognition, the only study on this subject was by Renier et al. [54], who found no association between the deterioration index and the time interval between the two signature samples, therefore concluding that signature execution may not reflect cognitive status in early stages of AD.

DISCUSSION

Based on the extensive review of the literature, text handwriting in AD is impaired at all levels of the motor-cognitive hierarchy, whereas signature execution is more likely to be preserved. This may be due to the fact that one's natural signature is more automatic and less cognitively demanding than text handwriting [11, 35], allowing it to remain relatively unaffected for longer periods of time, when compared to other forms of handwriting. Despite inconsistent methodological and sampling strategies across the studies included in this review, there are some crucial findings that can be highlighted. Thus, established findings within the neuromotor realm included: i) higher variability of motor features in signatures made by AD subjects, ii) higher ratio of in-air/on-surface time, longer start time/reaction time, longer duration and increased pause time, as well as changes in IATs in text handwriting, and iii) impairment in fluency in text handwriting, as well as in signatures in more advanced stages. Moreover, it should be highlighted that differences in temporal features between AD and healthy subjects have been attributed to visuospatial or perceptual deterioration [48].

Motor features such as velocity and pressure are in need of further research, due to conflicting results in signatures and text. Moreover, there is a very limited amount of research on this topic regarding signatures. Divergent findings between the various studies may be attributed to different factors. Regarding signature velocity and pressure, the differences observed between the studies may reflect the heterogeneity of AD, as well as sample characteristics of the AD population (e.g., age, education, medication, disease severity and sample size). For example, in the study of Pirlo et al. [19] there is no information on population demographics or sample size, whereas in the study by Wang et al. [20] information regarding education and medication is missing. Therefore, the influence of sample characteristics in the results cannot be truly assessed. Another relevant factor that may influence the findings is signature style. For example, in the study of Caligiuri & Mohammed [15], there was a significant association between higher variation in dynamic features and an increase in dementia severity only for stylized and mixed signatures. Since the studies of Caligiuri & Mohammed [15], Fernandes et al. [16], and Fernandes & Lopes Lima [17] include or, in the latter, consist only of text based signatures, whereas the studies of Pirlo et al. [19] and Wang et al. [20] have very few or no text based signatures, results may differ. Experimental design and differences in methodology may also have contributed to the differences in the findings, since Pirlo et al. [19] and Wang et al. [20] apply machine learning methods, whereas other studies apply a different quantitative [15, 16] or qualitative approach [17]. However, it should be highlighted that in the study of Pirlo et al. [19] there is no information regarding the hardware and software solution used to capture the data, which may influence the results [105]. The study by Wang et al. [20] also had limitations, since only two samples were collected from each participant, whereas other studies collected five [15], eight [16], or ten signatures from each subject [17]. Thus, the natural variation of signature writing was not fully assessed, and intergroup differences may have been valued excessively.

In text handwriting and related motor tasks, conflicting results for velocity and pressure may also reflect the heterogeneity of the illness. In addition, they could be due to the complexity of the handwriting task itself and the cognitive load that it requires (e.g., writing to dictation [31] is more cognitively demanding than drawing concentric circles [26]), and therefore may yield more differences between AD subjects and controls. Moreover, sampling effects may affect the results, as demographic features such as age, education, and disease severity, as well as medication, are not always described in the studies. In addition, it is worth noting that no study for signatures or text has taken into account the effect of atypical

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AD variants in handwriting, which may contribute to a higher variability and discordant findings.

Regarding visuospatial features, they were especially affected by AD in both signatures and text with emphasis on: i) the shape and direction of the baseline, ii) spacing, and iii) alignment, which tended to be more irregular compared to controls. There are, however, general characteristics that require additional study, such as size, legibility, and pen lifts in signatures, as well as size in text. Divergent findings regarding size could be connected to medication effect [11] and higher disease severity. The latter could also have influenced different results for pen lifts. For example, the case study described by Birincioglu et al. [18] involved a more severely demented patient than Fernandes & Lopes Lima [17], which could explain the higher number of differences in general features. Experimental design may also have contributed to the lack of differences regarding some studies. For example, Yu & Chang [46], in their study involving copy tasks, used a template that AD patients traced. Therefore, it is natural that no size differences occur between groups.

As for linguistic features, they were also compromised by AD. Established findings of handwriting impairment within the linguistic realm included: i) agraphia in signatures and particularly in text, ii) repetitions, omissions, substitutions and graphomotor errors, especially in text but also in signatures, and iii) poorly structured narratives with shorter sentences, more irrelevant information, simplified syntax, lower word diversity and lower idea density scores. As a result of divergent findings, linguistic features that warrant additional research refer to the pattern of spelling errors in association with disease progression. Furthermore, the connection between agraphia, cognitive deficits and neuropsychological scales for signatures and text also revealed conflicting results.

Differences in error patterns could reflect the individuality of AD [59], as well as the source language used in the study. This is particularly the case of dictation tasks, where the correspondence between the orthographic sequence of the word and the sound may be more complex depending on language.

Regarding the connection between agraphia, cognitive deficits, and neuropsychological scales, it is natural that changes in text handwriting and related motor tasks exhibit a higher association with disease severity and neuropsychological scales than signatures. This may be due to the fact signatures are more automatic and less cognitively demanding than text handwriting [11, 35], hence remaining more preserved. However, it should be highlighted that very few studies address this subject, specifically regarding signatures, and the existing research has limitations. For instance, in the study by Renier et al. [54], only two sets of signatures were compared for each subject: one written at the moment of the evaluation and an older signature. Therefore, even though no differences were found, the study had considerable limitations, due to the restricted number of samples and the fact that disease progression was not considered.

To sum up, the present systematic review has shown that visuospatial, temporal features, and linguistic features in handwriting are particularly affected by AD, especially in text and related motor tasks. The findings reported in this review are relevant, since these features may prove to be more sensitive and more informative in general studies that aim to detect AD in early stages, or to monitor disease progression using handwriting tasks.

The present review has also allowed the authors to identify new lines of research on this topic, based on the established and conflicting findings. In this context, re-evaluation studies are needed to clarify how some motor (e.g., velocity and pressure), general (e.g., size, legibility, and pen lifts), and linguistic features (e.g., spelling error patterns) are affected by AD progression, with emphasis on different handwriting tasks. Such studies would help to design new protocols that incorporate a wider range of features and handwriting tasks, more sensitive to AD, for the purpose of early detection and patient follow-up. In addition, given the effect of AD on temporal features and especially on in-air trajectories, in text handwriting and related graphomotor tasks, this feature should be further explored for signatures, as it could provide valuable information for AD detection and monitorization. Finally, new research should address the impact of AD variants on handwriting, since no studies are available for signatures or text. This could be useful for the development of protocols that help to identify these variants, using handwriting tasks.

Within the forensic field, further research focusing on signatures would be extremely useful. Additional re-evaluation studies that clarify how the motor and general features previously mentioned are affected by AD progression would help forensic document examiners in cases involving signatory authentication. Research of this nature is pertinent, since it would help to distinguish between changes that naturally occur due to disease progression, from differences due to forgery. For forensic purposes, the connec-

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tion between agraphia and cognition in handwritten texts and signatures also warrants further investigation, given its relevance, the contradictory findings and the limited body of research.

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The authors have no conflict of interest to report.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

SUPPLEMENTARY MATERIAL

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