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Handwriting analysis to support neurodegenerative diseases diagnosis: A review

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ABSTRACT

Neurodegenerative diseases (NDs) affect millions of people worldwide, with Alzheimer's and Parkinson's being the most common ones, and it is expected that their incidence will dramatically increase in the next few decades. Unfortunately, these diseases cannot be cured, but an early diagnosis can help to better manage their symptoms and their evolution. These aspects explain the importance of developing support systems for the early diagnosis of neurodegenarative diseases.

Handwriting is one of the abilities that is affected by NDs. For this reason, researchers have also investigated the possibility of using the handwriting alterations caused by NDs as diagnostic signs.

This paper presents a review of the literature of handwriting analysis for supporting the diagnosis of Alzheimer's and Parkinson's disease as well as of mild cognitive impairments (MCI), with the goal of providing interested researchers with the state-of-the-art research. Moreover, with the aim of providing some guidelines on the features to use for representing handwriting and the writing tasks patients should perform, we also review some widely used approaches for modeling handwriting. Finally, open issues are also discussed to identify promising areas for future research.

1. Introduction

Neurodegenerative diseases (NDs) represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner [1]. Although treatments may help relieve some of the physical or mental symptoms associated with these diseases, there is currently no cure for them. However, an early diagnosis for these diseases strongly improves the effectiveness of the available treatments, but it is still a challenging task. To date, clinical diagnoses of such diseases are performed by physicians and may be supported by tools such as imaging (e.g. magnetic resonance imaging), blood tests and lumbar puncture (spinal tap).

NDs affect millions of people worldwide, and Alzheimer's disease and Parkinson's disease are the most common types [2], and the risk of being affected by these diseases increases strongly with age [3]. Since health improvements have been lengthening lifespan, in most of the developed and developing countries, it is expected that the incidence of NDs will dramatically increase worldwide in the coming decades. This creates a critical need for the improvement of the approaches currently adopted for the diagnosis of these diseases.

Handwriting results from a complex network made up of cognitive, kinesthetic, and perceptual-motor abilities [4] and it is one of the daily's activities affected by NDs [5]. To date, an example of standard handwriting tests used to support disorder diagnoses is the MHA (Minnesota Handwriting Assessment), which is a clinical test based on handwriting. It is used to identify children (6-8 years) with difficulties related to autism and is a standard in US. It inspects such handwriting characteristics as: legibility, handwriting speed, form, alignment, size and spacing [6].

As for Alzheimer Disease (AD) and Parkinson Disease (PD), it has been observed that they affect handwriting significantly. Handwriting difficulties were already reported for the first patient affected by the Alzheimer's Disease in 1907 [7]. In the last few decades, researchers have found that handwriting of the Alzheimer's patients shows alterations in spatial organization accompanied by poor control of movements [8]. Several studies have also been published to investigate the effectiveness of handwriting

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analysis as a tool for PD diagnosis and monitoring. In this case, the most common anomalies found are micrographia, slower movements and jerk [9].

In the literature, modeling techniques have also been proposed to model handwriting movements [10–12]. They can be subdivided into two main categories: computational and cognitive. The former use mathematics and physics tools and aim to reproduce features of handwriting movements such as velocity profiles and the relations between different aspects of the handwriting dynamics. The latter, instead, focuses on the brain processes generating handwriting and address issues such as learning and brain areas involved in handwriting movements. The knowledge of these models can play an important role in defining effective features for NDs detection and monitoring.

Most of the studies which analyze the effects of NDs on handwriting kinematics published so far have been conducted in the medical and psychology fields, where typically statistical tools are used to investigate the relationship between the disease and each of the variables taken into account to describe patient handwriting. On the contrary, very few studies have been published that use classification systems for detecting people affected by NDs from their handwriting. Moreover, at the moment there is no survey describing the state-of-the-art work on the support to ND diagnosis by the analysis of handwriting.

This paper presents a review of the literature on handwriting analysis used to support the diagnosis of Parkinson's disease and Alzheimer's disease that, as mentioned above, are the most common types of NDs. The goal is to provide interested researchers with the state-of-the-art research. We also want to provide some useful guidelines to researchers. These guidelines regard: (i) The features to take into account for representing handwriting kinematics; (ii) the writing tasks patients should perform. Finally, this paper aims to encourage researchers from the pattern recognition community to work on this research topic. In fact, we think that in the next few decades, the results from this field will have a strong impact on the societies of the developed and developing countries, because of the dramatically increasing incidence of NDs in these countries.

The paper is organized as follows: Section 2 reviews some widely used approaches for modeling handwriting; the knowledge of how handwriting is modeled and described, will allow interested researchers to know which features can be potentially useful to distinguish effectively the handwriting of patients affected by NDs. Sections 3 and 4 describe, respectively, the state of the art for the early detection and monitoring by handwriting analysis of Alzheimer's disease and Parkinson's disease; these sections are both focused on the writing tasks adopted and the analyzed features. Section 5 illustrates the open issues and the challenging researches that still need to be addressed; the purpose of this section is to illustrate to interested researchers which aspects will need to be investigated in order to improve the effectiveness of handwriting analysis as support tool for the diagnoses of disorders such as Alzheimer's, MCI and Parkinson's. Finally, in Section 6, we draw the conclusions and provide some guidelines about the writing tasks and the features to be considered.

2. Modeling Handwriting

Many studies have been conducted, within the handwriting research community, to model the various processes involved in handwriting tasks. Handwriting models can be subdivided into two wide classes, *computational* and *cognitive* [13,14]. The former approach, refers to computational models which try to model or reconstruct the final result of the handwriting movements, in terms of velocity and acceleration profiles or stroke shapes by means of mathematics, physics and computer science. Cognitive models, instead, attempt to model the generative processes of cognitive and/or motor acts. These models typically deal with issues such as learning, movement memory, planning and sequencing, etc.

It is worth noting that most of the studies dealing with the handwriting analysis to support ND diagnosis do not make use of any handwriting model. This section aims to provide a review of the models for handwriting currently available. We think that being aware of these models can help to better understand which are the features that are more effective in distinguishing handwriting anomalies associated with NDs. In the next subsections both approaches for modeling handwriting are introduced.

2.1. Computational models

A very successful method related to velocity is the Kinematic Theory, developed by Plamondon [11,15]. This theory is defined in terms of the agonist and antagonist neuromuscular systems involved in the production of rapid human movements. Plamondon showed that these kinds of system have a log-normal impulse response that results from the limiting behavior of a large number of interdependent neuromuscular networks. The delta log-normal law that follows from this model is very general and can reproduce almost perfectly the complete velocity patterns of an end-effector. [16] tailored Plamondon's kinematic theory to model handwriting changes due to aging.

As for geometry-based models for handwriting, [17] presented a new approach for modeling the mechanisms that govern handwriting movement generation. The proposed model describes cursive handwriting as the superimposition of basic strokes with elliptic form, and each stroke is totally described by a set of parameters that characterizes the movement both in the kinematics and the static domains. Marcelli et al. [18] used Bezine's geometric model to characterize handwriting styles. They showed that these styles can be characterized by using only two parameters and used the *K*-means clustering algorithm for recognizing them.

Oscillatory models, instead, are based on the idea that strokes can be represented by coupled oscillations in orthogonal directions, by using a Fourier-style decomposition. This approach was pioneered by Hollerbach [19], who proposed a handwriting generation model where the hand-pen system was represented by two orthogonal pairs of opposing springs acting on an inertial load. It was pointed out that the oscillatory natural motions of this system resemble real handwriting segments. Several works based on Hollerbach's model have been presented [20,21]. [20] proposed that handwriting can be modeled as a non-linear coupling between the orthogonal oscillators. André et al. [21] presented an improved version of the original Hollerback model named *Parsimonious Oscillatory Model of Handwriting* (POMH). The proposed model, differently from that of Hollerback, was symmetric in the x and y coordinates and allowed an efficient extraction of the parameters for any written trace. Moreover, it is worth noting that also neural networks have been used to implement Hollerbach's oscillatory model [13,22,23].

2.2. Cognitive models

Studies involving neural recordings have provided a large body of knowledge about the neural processes occurring in the brain areas related to motor learning. One of first attempt to model the processes generating handwriting movements was presented in [10]. The proposed model, named *VITEWRITE*, consisted of a motor program that interacted with a trajectory generator to move a hand with a given number of degrees of freedom and implemented a simple control strategy to generate complex handwritten scripts. The work of Bullock had inspired those presented in [24] and [25], which used similar architectures to that of the VITEWRITE model.

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Contreras-Vidal and Stelmach [24] were among the first to integrate previous experimental data on the anatomy of the basal ganglia and on motor impairments in PD. They developed a neural network model of the basal ganglia useful to explain healthy and PD movements. The proposed neural network model was able to reproduce aspects of healthy and PD movements including bradykinesia, akinesia and micrographia. These results were confirmed in the literature [26–28]. In this case basal ganglia nuclei were modeled as lumped units, with activity levels represented by rate codes: basal ganglia dynamic were described in terms of magnitude (faster/slower, larger/smaller, etc. handwriting).

Grossberg and Paine [25], instead, presented a neural model simulating cortico-cerebellar interactions during attentive imitation and predictive learning of sequential handwriting movements. The proposed model suggested how cortical mechanisms interact with predictive cerebellar learning during movement imitation. Their model was tested with a corpus of human handwriting data in the work presented by Paine et al. [29]. Further studies on the brain areas governing handwriting observed that it implies the learning of motor sequences by two distinct neural systems, comprising cortex-basal ganglia and cortex-cerebellum loop circuits [30,31].

More recently, new cognitive approaches for modeling handwriting have been proposed. In [12] a recurrent neural network actor-critic model of the basal ganglia and a feed-forward correlation-based learning model of the cerebellum was proposed, suggesting that basal ganglia and cerebellar learning systems work in parallel and interact with each other. In [32], the authors proposed a new neural scheme with the aim of modeling handwriting motor learning processes; the proposed model was based on the hypothesis that handwriting learning follows two distinct phases: during the early, fast learning stage, humans learn the sequence of points to reach in order to generate the ink trace. Afterwards, the sequence of motor commands is acquired and comes to be executed as a single behavior. The authors found that performing complex motor sequences, such as handwriting, requires the interaction among the cortex, basal ganglia and cerebellum.

Cognitive models have been also used to detail the signature generation process. Marcelli et al. [33] used the approach proposed in [32] for modeling the motor learning mechanisms involved in the signing process. They found that the signature representation stored may not include the entire signature, but only parts of it; these parts are those that have been learned better and therefore are executed more automatically than others; the authors stated that these parts are more distinctive than the remaining ones and also proposed an algorithm for finding them.

Researches on cognitive models have also regarded handwriting styles. Marcelli et al. [34] presented an experimental validation of a model for detailing handwriting styles; the proposed approach was based upon a neurocomputational model of motor learning and execution. The authors hypothesized that handwriting style emerges from the concatenation of highly automated writing movements, called *invariants*, corresponding to the most frequent sequence of characters a writer is familiar with. The experimental results showed that the model was an effective tool for modeling intra-writer and inter-writers variability and provides quantitative estimation of the difference between handwriting styles.

3. Alzheimer's disease and mild cognitive impairments

AD is characterized, at early stages, by short-term memory loss followed by a progressive cognitive and behavioral decline, motor deficits are also common in AD as well as in mild cognitive impairment (MCI) patients. Since handwriting results from a complex network of cognitive skills, Alzheimer's Disease (AD) causes significant changes in writing performance [35].

Handwriting difficulties were already reported by Alois Alzheimer when he was describing the first patient with Alzheimer's Disease (AD) in 1907 [7]. He observed that the patient reduplicated the same syllable and forgot some others. Recently, several studies have analyzed the writing process dynamics to identify and monitor AD, revealing that writing, persevering, substitution, misalignments of strokes, link and spacing errors indicate a deterioration of fine motor skills and of coordination [36–38].

In our literature analysis, we found only three papers reviewing the analysis of handwriting for AD patients [8,39,40]. Croisile [39], reviewed some experimental works, and found that, in AD patients, writing disorders are more severe than language difficulties, as can be seen in written descriptions of complex pictures and in lexical spelling. He also claims that spatial organization of handwriting is rapidly affected and therefore AD patients have mild difficulties in maintaining a straight horizontal writing line and also make some unnecessary gaps between words and letters. He concluded his work by saying that agraphia in AD patients is related to a disruption in the anatomic-functional cerebral network designed for writing processes, mainly in the parietal regions. The same author published a new and more extensive review in 2005 [40]. This review, written in French, aimed to compare the handwriting anomalies due to aging with those due to AD. The author reports that elderly people raise their pens less often and the pressure and width of writing decrease with age. As for people affected by AD, He report that their handwriting gets progressively disorganized during the disease, whereas their spelling is altered by regularization errors which are evidence of lexical agraphia. The author concludes that agraphia of Alzheimer's disease comes from a progressive and hierarchized disorganization of the various components of language and writing, owing to brain lesions in several associative areas (parietal, temporal, occipital and frontal regions).

Neils-Strunjas et al. [8] presented a literature review of the research investigating the nature of writing impairment associated with AD. They reported that in most studies words are usually categorized in regular, irregular, and nonwords. Orthographically regular words have a predictable phoneme-grapheme correspondence (e.g., cat), whereas irregular words have atypical phoneme-grapheme correspondences (e.g., laugh). Nonwords or pseudowords, instead, are non-meaningful pronounceable letter strings that conform to phoneme-grapheme conversion rules, and are often used to assess phonological spelling. From the reviewed papers the authors conclude that writing impairment is heterogeneous in AD patients, affecting words, sentences and discourse levels of written language production.

In the last few decades, several experimental studies have analyzed the dynamics of the handwriting process in order to detect and monitor patients affected by AD. We divided these studies into two groups. In the first group we included the studies investigating the relationship among the handwriting features (variables) and AD or MCI by evaluating whether and how these variables differ across diseases or measuring the correlation between the considered variables and the pathologies taken into account. These studies typically use statistical tests, e.g. ANOVA and MANOVA, or compute correlation coefficients to assess the statistical significance of their results. The second group, instead, comprises the researches that, by means of the handwriting features, use classification algorithms to distinguish patients affected by different dementia diseases. The results of the studies belonging to this second group are expressed in terms of classification performances, such as recognition rate, false acceptance rate and false rejection rate. In the following, we will refer to the studies included in the first group as *statistical studies*, whereas those belonging to the second group will be denoted as *classification studies*. Within these groups, we have ordered them according to the difficulty of the tasks: from

Table 1
Summary of statistical studies of Alzheimer's disease.

#	References	Tasks	Findings
1	[41]; [42]; [43]; [44]; [5].	Straight lines, cursive-connected loops, single circle, continuous circles drawing. "llll" writing.	Slow movements, lower peak velocity, reduced (time) duration.
2	[45]; [46]; [47]; [36]; [48].	Written and oral spelling task; irregular words and non-words; auditive stimuli of concrete and abstract words.	Moderate AD subjects differ from mild subjects and controls for all written and verbal tasks; Grapho-motor impairments come in addition to the lexical and phonological impairments.
3	[37]; [38].	Signature and spontaneous writing.	Repetitions, omissions and substitutions of letters; correlations between spontaneous writing indexes and neuropsychological test results.
4	[49].	Name drawings of objects.	AD patients were more successful in retrieving names of objects presented in the dated compared to contemporary unique conditions.
5	[50]; [51].	Copy of a shopping list and of a letter; copy of a drawing.	Alterations in spatial organization accompanied by poor control of the movement; Time-in-air differs significantly among MCI, AD and HC patients.
6	[52]; [53].	Picture description, word fluency, spelling to dictation and confrontational naming; mnemonic task concerning semantic knowledge and spatial and temporal orientation.	Mild AD patients differ from controls only for verbal and written versions of the word fluency task; performance deterioration along the days.

Table 2
Summary of classification studies of Alzheimer's disease.

References	Tasks	Findings
[55].	Copying task (words, numbers, text with or without cues).	Kinematic measures within to MMSE; pressure and time in-air were the best performing features.
[54].	Signature.	Online signature analysis can be used as a tool for early diagnosis of AD.
[56].	Simple words writing.	Non-smooth movements (irregular velocity profile).
[57].	Copying task (words, drawings, etc.).	Qualitative combination of the parameters is crucial for group discrimination.

those with less cognitive load to those with greater cognitive load. Tables 1 and 2 summarize the main findings for the reviewed papers, based on statistical analyses and on classification algorithms, respectively. The papers in the tables have been organized according to the task difficulty criterion. The reviewed studies are detailed in the following subsections.

3.1. Statistical studies

Starting with the first subgroup (first row of Table 1), we present the studies focused on elementary graphic gestures. In [41] two groups are considered: Dementia of Alzheimer Type (DAT) patients and Healthy Controls (HC). The task to be performed consisted in connecting four targets, placed on a digitizing tablet, by a series of alternating horizontal drawing movements with a non-inking pen, in response to light stimuli. The task was executed in two different conditions: the next target was indicated before (cue condition) or after (no cue condition) the movement initiation. The cue condition allowed the subject to program the next movement, whereas the no cue condition forced the participant to reprogram the movement online. The authors found that DAT patients had programming deficits, taking longer to initiate movements, particularly in the absence of cues.

Slavin et al. [42] asked a group of AD patients to write four consecutive, cursive letter 'l's, on a graphic tablet, with four different visual conditions. These conditions were: A baseline condition with feedback of movement but not of output (no ink), with the presence of external cues (lines), with no visual feedback of the performed movements, and with feedback of output (ink). The authors found that AD patients had writing strokes of significantly less consistent lengths than controls, and were disproportionately impaired by reduced visual feedback. Moreover, AD patients' strokes were of significantly less consistent duration, and had significantly less consistent peak velocity than controls, independently of the feedback conditions.

Schröter et al. [43] analyzed handwriting kinematic to quantify differences in fine hand motor function in patients with probable AD and MCI compared to depressed patients and healthy controls. The protocol consisted of two tasks: Drawing concentric superimposed circles and drawing concentric superimposed circles simultaneously performing an additional distraction task (pressing a counting device as often as possible). The drawn circles were segmented into strokes, corresponding to the vertical up and down movements. The authors, used features such as: arithmetical mean of the velocity peaks of all strokes, the standard deviation of the intraindividual velocity profile, writing frequency, the number of strokes per second, number of changes of direction of velocity and relative velocity. They found that both patients with MCI and patients with probable AD exhibited loss of fine motor performances and that the movements of AD patients were significantly less regular than those of the healthy controls.

In the study presented in [44], instead, the patients performed four types of handwriting movements on a digitizer: The up-down vertical movements that required the finger joint movements; the left-right horizontal movements that primarily required wrist joint movements; the forward-slanted and the backward slanted movements that required the coordination of both finger and wrist movements. Movement time (MT) and smoothness were analyzed between the groups of patients taken into account (probable AD, MCI and HC) and across the movement patterns. Kinematic profiles were also compared among the groups, using MT and jerk as dependent measures. AD and MCI patients exhibited slower, less smooth, less coordinated, and less consistent handwriting movements than their healthy counterparts.

More recently, the goal of the research of [5] was to evaluate fine motor dexterity performance of MCI and AD patients and to investigate its association with different aspects of activities of daily living. The subject must put nine pegs in nine holes organized on a small board and subsequently remove them, as fast as possible. The authors find that patients with AD or multipledomain aMCI had slower motor responses when compared to controls. AD patients were slower than those with single-domain aMCI.

As regards the studies belonging to the second subgroup (second row of Table 1), they analyzed the handwriting of different kind of words. [45] described the evolution of agraphic impairments in DAT patients including lexicosemantic disturbances at the beginning of the disease, with impairments becoming more and more phonological as the dementia becomes more severe. They proposed a writing test from dictation to 22 patients twice, with an interval of 9-12 months between the tests. They found that the agraphic impairment evolved through three phases in patients with AD. The first one is a phase of mild impairment (with a few possible phonologically plausible errors). In the second phase non-phonological spelling errors predominate, phonologically plausible errors are fewer and the errors mostly involve irregular words and non-words. The last phase involves more extreme disorders that affect all types of words. They observed many alterations due to impaired graphic motor capacity and concluded that grapho-motor impairments come in addition to the lexical and phonological impairments.

The study of [46] investigated handwriting performance of participants affected by mild AD, moderate AD, and control participants on a written and oral spelling task. The authors selected thirty-two words from the English language: Twelve regular words, twelve irregular words and eight non-words. The study aims to find logical patterns in spelling deterioration with disease progression. The results suggested that spelling in individuals with AD was impaired relative to HC but the comparison between those with mild AD and moderate AD failed to find evidence of a logical pattern of deterioration.

Luzzatti et al. [47] used a written spelling test made up of regular words, non-words and words with unpredictable orthography. The purpose of the study was to test the cognitive deterioration from mild to moderate DAT. The authors found little correlation between dysgraphia and dementia severity. Thus they found that the hypothesis of a progressive deterioration, initially affecting semantic aspects, then lexical ones, and finally more surface abilities, would not appear to be generally applicable to all patients affected by AD. On the contrary, the data from this study confirmed that DAT is a mosaic of circumscribed cognitive deficits.

In [36] the authors investigated the correlation between writing ability and regional cerebral blood flow (rCBF) in Japanese patients with mild AD compared to control group, using single photon emission computed tomography (SPECT). The task consisted in the writing of fifty words under dictation, equally divided between concrete words and abstract words. Through an error analysis they found that, compared with control subjects, Kana writing to dictation and copying Kanji words were preserved in AD patients, but writing to dictating Kanji words was impaired. The authors concluded that the impaired recall of Kanji words in early AD is related to dysfunctional cortical activity, which appears to be predominant in the left frontal, parietal, and temporal regions.

As for the analysis of the handwriting of simple words, it is worth mentioning the work of Impedovo et al. [48], in which the authors investigated the handwriting kinematics of the word “mamma” (mom in Italian) in AD patients. They motivated the choice of this word stating that it is one of the first learned in speaking and writing. The authors examined the velocity profiles and observed that in healthy person the maximum speed values were almost regular in height, whereas this regularity was strongly reduced at the beginning of the disease and progressively lost as the disease advanced.

Recently, also signatures and spontaneous writing have been investigated for early diagnosis of AD (third row of Table 1). Renier et al. [37], for example, in their study recruited participants with diagnosis of MCI and with the diagnosis of initial dementia. For each subject they collected two samples of signature (an actual and a older one) and an extract of spontaneous writing. Furthermore, they administered a neuropsychological test battery to investigate the cognitive functions involved in decision-making. They found significant correlations between spontaneous writing indexes and neuropsychological test results but the index of signature deterioration did not correlate with the level of cognitive decline.

In [38], instead, the authors compared the signatures of AD patients and healthy controls. The methodology used to examine the samples of the handwritten signatures involved the analysis of two categories of handwriting features: general features (legibility, tremor and line quality, level of connection between letters, velocity, pressure, slant, curvature, overall dimension, spacing between words and shape and direction of the baseline) and constructional features (shape and letter formation, as well as unusual features in the letterâs design). These features were statistically analysed and repetitions, omissions and substitutions were observed as indications of cognitive deterioration.

It is worth noting that also Pirlo et al. [54] investigated how signatures are affected by AD, but their study is reviewed below, with the other classification studies.

Another kind of tasks includes naming drawings of objects (fourth row of Table 1). Small and Sandhu [49] analyzed the handwriting of subjects belonging to three groups: Younger adults, healthy older adults, and older adults with AD. Participants were asked to name drawings of objects in four conditions: dated unique, contemporary unique, dated common, and contemporary common. The results indicated that all participants named the items that were common to both episodic periods more successfully than the items unique to one period. An interaction was observed such that the healthy older and AD groups were more successful in retrieving names of objects presented in the dated compared to contemporary unique conditions, whereas the younger adults showed the reverse pattern.

Also tasks like the copying of a shopping list or of a letter were considered (fifth row of Table 1). Onofri et al. [50] presented a protocol including a copy of a shopping list and a letter. They found that on the third day there were graphic difficulties and alterations in spatial organization accompanied by poor control of the movement. The text appeared inconclusive, with a change between cursive and print and the tract was discontinuous between the letters.

In [51] the authors investigated movement kinematics of patients with early dementia due to AD, patients with amnestic mild cognitive impairment (aMCI), and cognitively healthy control (HC). Participants were asked to copy a three-dimensional house using a digitizing tablet. The results showed that time-in-air differed significantly between patients with aMCI, AD, and HC.

Finally, the researches of Groves-Wright et al. [52] and Onofri et al. [53] investigates more complex writing tasks, requiring a high cognitive load (last row of Table 1). Groves-Wright et al. [52] used parallel measures (picture description, word fluency, spelling to dictation, and confrontational naming) to compare verbal and written language of individuals with mild AD, moderate AD, and HC. The results showed that mild AD subjects differed from healthy controls only for verbal and written versions of the word fluency task. Moderate AD subjects differed from mild subjects and controls for all written and verbal tasks.

Onofri et al. [53] presented a study with mild AD and healthy control group based on a protocol including mnemonic task concerning semantic knowledge and spatial and temporal orientation, which was a variation of Mini Mental State Examination (MMSE) test. The same task was repeated during the course of several days. The statistical analysis showed a marked deterioration in performance during the days.

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3.2. Classification studies

As previously said, in the second group we have collected the studies using classification algorithms to distinguish patients affected by dementia pathologies. Werner et al. [55] performed kinematic measures of the handwriting process of people with MCI compared with those with mild AD and healthy controls. The aim was to assess the importance of measures for the differentiation of the groups and to assess the characteristics of the handwriting process across five different, functional tasks of copying. In order to assess the independent effect of the MMSE score and of the kinematic measures, they examined three separate equations. In the first equation, they entered the MMSE score as the only independent variable to assess its contribution to the correct classification of the diagnostic groups. In the second equation, they performed a stepwise discriminant analysis to assess the relative contribution of the five kinematic measures assessed. Finally, in the third equation, they assessed the contribution of the MMSE score together with the kinematic variables that were found to be statistically significant predictors in the second equation. The classification performances of the three equations considered and of the different tasks were computed in terms of recognition rate. The results showed that the kinematic measures together with the MMSE score were able to distinguish effectively the patients belonging to the different groups considered. As for the feature analysis, pressure and time-in-air obtained the best performances.

Also in [56] (see the reference [48] reviewed above), the authors analyzed the stability of the offline handwritten word “mamma” (mom in Italian) to distinguish AD patients from healthy controls. The stability of the word was computed by splitting its image in elementary parties and measuring the similarity of the adjacent parts. As classification algorithm the authors adopted the Yoshimura approach, based on the comparison of the stability features among the sample to be recognized and those of the training samples.

Pirlo et al. [54] presented a novel approach in which handwritten signatures were analyzed for the early diagnosis of AD. Patients’ signatures were represented by using the Plamondon’s Sigma-Normal model, by means of twelve features. These features comprised, among others, the maximum speed of the signing divided by the time of writing, number of Log-Normal divided by the time and the number of peaks of the speed/time graph. The samples were classified by using three well-known classification algorithms: CART, bagging CART and SVM with linear kernel. The bagging CART outperformed significantly both CART and the SVM classifiers, in terms of False Acceptance Rate (FAR) and False Rejection Rate (FRR).

Finally, the goal of the work reported in [57] was to distinguish participants belonging to three different groups (AD, MCI and HC) by comparing their handwriting kinematics. The authors used discriminant analysis as classification algorithm and adopted a protocol consisting of seven tasks, which included copying and drawing tasks. In the experiments, the authors, for the same task, investigated which were the most discriminating features and the best distinguished groups. They found that: (i) Discriminating features depended on the type of group to be discriminated; (ii) some tasks, e.g. the clock drawing test, allowed some groups, e.g. AD vs. MCI, to be well discriminated (100% of specificity and sensitivity).

4. Parkinson’s disease

Parkinson’s disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system and it arises when dopamine (DA) production decreases consistently. These motor deficits as result of PD include: akinesia (impairment of voluntary activity, [24]), bradykinesia (slowness of movement, [9]), micrographia (reduction in writing size, [65]), and rigidity and tremor which both occur early in the disease [75].

Even if, to date, clinical assessment remains the gold standard in the diagnosis of Parkinson’s disease many studies point out the successful use of handwriting for detecting and monitoring PD, since abnormal handwriting is a well-recognized manifestation of PD, with micrographia being characteristic [76]. Previous researches have shown that handwriting measures have the potential for identifying various stages of PD, effects of varied interventions [64] and the effect of medication [27].

Also in this case we divided the reviewed papers into two groups based on statistical analyses and on classification algorithms. Table 3 summarizes the main findings of the statistical studies on PD patients’ handwriting. As for the classification studies, we found only one paper, that is reviewed at the end of this section. The table has been organized according to the difficulty of the tasks performed by the patients, in increasing order. From the table it can be seen that PD results in impairment of voluntary activity (akinesia, slowness of movements) bradykinesia, reduction in amplitude/dimension of repeated actions and micrographia, tremor and rigidity.

The studies belonging to the first subgroup (first row of Table 3) was focused on simple drawing tasks or sentence writing tasks and found that PD patients had slower movements than their healthy counterparts. For example, in [63] patients were asked to write their name and to copy an address on a paper affixed to a digitizer. Mean pressure and mean velocity was measured for the entire task and the spatial and temporal characteristics were measured for each stroke. The experimental results confirmed that these routine writing tasks can be used to differentiate PD patients from healthy controls since PD patients resulted in smaller (length, width and height) and slower executions.

Reduced dimension of PD patients’ handwriting emerged also from the studies of the second subgroup (second row of Table 3). In particular, Letanneux et al. [66] identified several studies that investigated handwriting in PD, either with conventional pencil-and-paper measures or with graphic tablets, and reported their findings on key spatial-temporal and kinematic variables. They found that kinematic variables (velocity, fluency) differentiate better between control participants and PD patients, and between off and on-treatment PD patients, than the traditional measure of static writing size. Moreover, since handwriting deficit for PD patients is not restricted to micrographia, they propose the term “PD dysgraphia”, which encompasses all deficits characteristic of Parkinsonian handwriting.

As for the tremor and the jerk (third row of Table 3), it has been observed in PD patients when performing tasks such as the drawing of lines in different orientations and circles. In [9], for example, the authors recorded pen tip trajectories during circle, spiral and line drawing and repeated character “elelelel” and sentence writing. The experimental results show that these tasks can provide objective measures for bradykinesia, tremor and micrographia of PD patients.

The researches of Oliveira et al. [69] and Fucetola and Smith [70] (fourth row of Table 3), instead, showed that in figure drawing or “llll” writing tasks the visual feedback can help PD patients to increase stroke dimension. Whereas those of Fucetola and Smith [70] and Van Gemmert et al. [28] (fifth row) indicate that PD patients are less able than Healthy patients to adjust the size of their drawing to a specific target.

As for the studies belonging to the sixth subgroup (sixth row of Table 3), the tasks (circle drawing, “lll” and “eeee” writing) was given before and after medications. The experimental results showed that medications reduces (on a limited timespan) main PD handwriting characteristics.

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Table 3
Summary of statistical studies of Parkinson's disease.

References	Tasks	Findings
[58]; [59]; [28]; [60]; [61]; [62]; [63].	Meanders, circle, star and spiral drawing. Sentence/name writing. Copying task.	Slower movements.
[58]; [64]; [61]; [63]; [65]; [66].	Loops drawing. Sentence/name writing. Copying task.	Reduced dimension.
[58]; [67]; [62]; [9]; [68].	Meanders, horizontal, straight forward and backward slanted lines, circles drawing. Sentence writing	Tremor/jerk.
[69]; [70].	Figure drawing. "llll" writing.	Visual feedback can help PD patients to increase stroke dimension.
[70]; [28].	Figure drawing. Adjust the drawing size based on visual information. "llll" writing under different size and time conditions.	PD patient less able than EC to adjust the size of their drawing to a specific target.
[26]; [27]; [71]; [72]; [73].	Circle drawing before and after medication. "llll" and "eeee" and sentence writing before and after the medication.	Medications reduces (on a limited timespan) main PD handwriting characteristics.
[74].	Writing under visual and auditory feedback.	Training can help PD patients to increase writing dimension.

Finally, Ziliotto et al. [74] (last row of Table 3) found that a writing training with visual and auditory feedback can help PD patients to increase their handwriting size.

As for the classification studies, in [77] the authors presented a novel PD handwriting database consisting of handwriting samples from PD patients and healthy controls. Each sample contained kinematic and pressure data of height handwriting tasks. The tasks included drawing an Archimedean spiral, repetitively writing simple syllables and words, and writing of a sentence. To discriminate between PD patients and healthy subjects, the authors used three classifiers: K-NN, AdaBoost and SVM, which was the best performing one.

5. Open issues and challenging researches

Although some research has already been carried out and some encouraging results have been observed, there are still several open issues that must be addressed. First of all, there is the lack of a well-designed dataset [78]. In fact, even if several standard databases of handwritten patterns have been created so far, none has been specifically designed for research on NDs. Such a database would allow the different approaches proposed to be fairly compared. However, designing a database specifically devoted for NDs involves many different aspects. The first aspect regards the cardinality of the set: in fact, most of reviewed papers make use of datasets made up of very few subjects. More recently some effort has been made in order to get an acceptable dimension (55 individual) [79]. However, this reduced data availability strongly limits the effectiveness of classification algorithms, such as neural networks, SVM and decision trees.

Also the protocol definition is an important aspect for the database development, since it is crucial to understand which handwriting tasks allow subjects affected by NDs to be best discriminated. Finally, in order to better understand the evolution of NDs over time, there is the need for longitudinal studies, in which the same patient is monitored periodically, or when some specific events occur.

Regarding the issue concerning the classification problems, often standard Pattern Recognition techniques are applied with very few cases of specialization to the field. The main problem is that the medical knowledge of the evolution of the disease cannot be ignored: an automatic system able to distinguish an healthy person and a late-stage sick one has a very reduced usefulness in the real word. From this perspective the challenge is to identify patients at different stages, so as to allow the tracking of the disease evolution and the signs of worsening to be understood/identified. It must be underlined that today there is no cure for NDs but they can only be somehow managed, so that an early diagnosis and follow up may have profound implications for the daily life of patients, as well as for carers and doctors. It is worth noting that research on handwriting and NDs is not expected to replace standard techniques, but to support them by allowing an earlier diagnosis. To this aim, Pattern Recognition approaches should be specifically studied and coupled with cognitive and neuromuscular generation models.

As mentioned above, several studies have been performed to investigate the neural processes occurring in the brain areas involved in handwriting learning, however, it is still not clear how these areas interact, which region is involved in a specific movement execution, and at what stage of learning it plays a key role. In order to examine these aspects more deeply, it would be useful to investigate on a novel computational model, comprising basal ganglia, cerebellum and cortex. This model would make it possible to simulate the presence of NDs, such as Alzheimer's and Parkinson's. Moreover, comparing the model results with the data acquired by patients could help to understand the way NDs affects handwriting, and which are the features that better characterize these disorders.

As regards the feature analysis, most of the presented studies investigated the relationship between the disease and each of the considered features, overlooking the complex interactions that may occur among multiple features. In fact, in the pattern recognition field it is well known that a single feature which is weakly correlated to the target class, could significantly improve the classification accuracy if it is used together with some complementary features. In contrast, an individually relevant feature can become redundant when used together with other features. For this reason, to exploit best the information contained in the considered features, feature analyses should be conducted by using typical feature selection approaches, which use effective search techniques to find the optimal feature subset, guided by evaluation functions which evaluate feature subsets as a whole.

Moreover, in previous studies, features based on the Wavelet and Fourier Transform were used for representing both morphological and dynamic properties of groups of strokes [80,81]. Since the shape variations over time may be relevant for people affected by NDs, these features can represent an important source of information for an early diagnosis of NDs, as well as for the monitoring of their evolution. Such features could be also used together with other typical kinematics features proposed in the literature.

6. Conclusions

In this paper we presented a review of the handwriting analysis approaches used to support the early diagnosis, monitoring and tracking of neurodegenerative diseases. In particular we have taken into account Alzheimer and Parkinson diseases as well as MCI. Furthermore, we also discuss the still open issues in the field that need to be addressed.

This review shows that handwriting analysis is an effective tool to support the diagnosis and monitoring of the above-cited diseases. As for Alzheimer's Disease, researchers found that the handwriting of the Alzheimer's patients shows alterations in spatial organization and a poor fine control of the movements. The studies investigating the handwriting of subjects affected by Parkinson's disease, instead, report that the most common anomalies found are micrographia, slower movements and jerking.

Although the studies presented so far have proved the effectiveness of handwriting-based approaches for the support of ND diagnoses, they still face challenges and their potential has not been fully investigated. For example, the protocol definition is an open issue that needs to be further investigated. Related researches should assess many handwriting tasks in order to understand which allow subjects affected by Alzheimer's or Parkinson's disease to be best discriminated. However, the reviewed literature suggests that:

1. Tasks with graphic cues and with free spaces allow the assessment of the spatial organization capabilities;
2. copying tasks and dictation tasks allow the comparison of handwriting variations when different stimuli (visual or sound) are used;
3. tasks involving different numbers of pen up enables the analysis of in air movements, which showed to be altered in Alzheimer's patients;
4. tasks involving different graphic arrangements, e.g. words with ascenders and/or descenders, or complex, variously scaled, graphic forms, permits fine motor control abilities to be tested.

Moreover, to assess patient responses under different fatigue conditions, these tasks should be given by varying their intensity and duration.

Future researches should also investigate the effectiveness of the features used to represent the handwriting movements. In this case, the reviewed studies suggest that: (i) Features such as pressure and time-in-air seems to be particularly effective in discriminating the handwriting of patients affected by Alzheimer's disease, as well as MCI; (ii) Parkinson's patients can be well discriminated by measuring the total-time and jerking of their handwriting movements.

Moreover, even if, to date, many studies have been conducted to model handwriting movements, they have rarely been considered by the researchers of the field. However, in order to devise novel and more effective features these models should be taken into account.

Finally, from the pattern recognition perspective, three main issues arise. First, the reduced size of the datasets currently available limits the effectiveness of typical pattern recognition tools, e.g. neural networks, decision trees and SVM. Second, the feature analysis should be made taking into account the complex interactions that can occur among multiple features. Finally, it would be desirable to define pattern recognition tools specifically devised to support ND diagnosis and monitoring; these tools should include the medical knowledge currently available on these diseases to improve their performance with respect to standard pattern recognition approaches.

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