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RESEARCH ARTICLE

Kinematic and Pressure Features of Handwriting and Drawing: Preliminary Results Between Patients with Mild Cognitive Impairment, Alzheimer Disease and Healthy Controls

Josep Garre-Olmo[1,2], Marcos Faúndez-Zanuy[3], Karmele López-de-Ipiña[4,*], Laia Calvó-Perxas[1] and Oriol Turró-Garriga[1]

[1]*Girona Biomedical Research Institute [IDIBGI]-Institut d'Assistència Sanitària, Girona, Catalonia, Spain;* [2]*Deparment of Medical Sciences. University of Girona, Girona, Catalonia, Spain,* [3]*Grup de recerca en tractament del senyal Tecnocampus-Mataró de la Universidad Pompeu Fabra, Barcelona, Catalonia, Spain,* [4]*Deparment of Systems Engineering and Automation. University of the Basque Country, UPV/EHU, Donostia, Gipuzkoa, Spain*

Abstract: ***Background:*** Alzheimer's disease (AD) is the most common neurodegenerative dementia of old age, and the leading chronic disease contributor to disability and dependence among older people worldwide. Clinically, AD is characterized by a progressive cognitive decline that interferes with the ability to perform the activities of daily living. Handwriting and drawing are complex human activities that entail an intricate blend of cognitive, kinesthetic, and perceptual-motor features.

Objective: To compare the kinematic characteristics of handwriting and drawing between patients with AD, patients with mild cognitive impairment (MCI) and healthy controls.

Methods: We used a cross-sectional and observational design to assess the kinematic and pressure features of handwriting and drawing using a computerized system. Participants were asked to copy one sentence, write a dictated sentence and an own sentence, copy two and-three dimensions drawings, and to execute the clock drawing test. By means of discriminant analyses, we explored the value of several kinematic features in order to classify participants depending on their degree of cognitive functioning.

Results: The sample consisted of 52 participants (23 AD, 12 MCI, and 17 healthy controls) with a mean age of 69.7 years (SD=8.11). The degree of correct classification was largely dependent on the nature of the groups to be classified and the specific task, and ranged between 63.5% and 100%. Diagnostic accuracy based on kinematic measures showed higher specificity values for distinguishing between normal and impaired cognition (MCI and AD), and higher sensitivity was obtained when distinguishing between impaired cognition levels (MCI *vs.* AD).

Conclusion: The kinematic features of writing and drawing procedures, rather than the final product, may be a useful and objective complement to the clinical assessment of patients with cognitive impairment.

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1. INTRODUCTION

The concept of dementia refers a clinical syndrome characterized by an acquired cognitive impairment that interferes the adequate performance of the activities of daily living of an individual. Alzheimer's disease (AD) is the most common neurodegenerative dementia of old age, and the leading chronic disease contributor to disability and dependence among older people worldwide [1]. Clinically, AD is characterized by a progressive cognitive decline that interferes with the ability to perform the activities of daily living [2], and during the course of the disease several behavioral and psychological symptoms appear and fluctuate, with remissions and recurrences [3]. According to estimates, 27 million persons have AD worldwide, and as the life expectancy increases, it is expected that by 2050 there will be 115 million persons with AD [1].

However, the early detection of AD is difficult. When patients and their relatives report symptoms of memory loss in the clinical setting usually there is some degree of decline in other cognitive functions. From a clinical point of view, it is fundamental to disentangle the cognitive impairment due to an initial AD from the typical cognitive decline due to the normal ageing process. Mild cognitive impairment (MCI)

*Address correspondence to this author at the Deparment of Systems Engineering and Automation, University of the Basque Country, UPV/EHU, Donostia, Gipuzkoa, Spain; Tel: +34653723757;
E-mail: karmele.ipina@ehu.eus, karmeleipina@gmail.com

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has been defined as an intermediate state between normal cognition and dementia [4]. Clinically, MCI is characterized by a cognitive impairment not enough severe to alter the functional abilities of an individual, and is usually associated to a preclinical stage of AD [4]. Epidemiologic data indicates that between 10-30% of patients with a diagnosis of MCI covert to AD while the conversion rate of normal subjects ranges between 1-2% [5]. Difficulties arise because AD is a slow and progressive disease with no fixed events that define clearly the onset, adding uncertainty to the diagnostic procedure. The current clinical diagnostic criteria for MCI have introduced the possible contribution of biomarkers to the diagnosis but there is still work needed to validate and standardize the biomarker analysis for its use in the community setting [6].

In the clinical setting, the differential diagnosis between MCI and early AD requires an objective assessment of the cognitive and functional capacities. The cognitive examination consists of a neuropsychological assessment of cognitive functions such as attention, memory, language, praxis, and executive functioning by means the administration of standardized tests. There are several single neuropsychological tests available for specific functions such as the Trail Making Test [7] (part A) for attention, the Free and Cued Selective Reminding Test [8] for memory, the Boston Naming Test [9] for language, the Rey-Osterrieth Complex Figure Test [10] for visuospatial construction. Moreover, there also exist integrated neuropsychological batteries such as the Addenbrooke's cognitive examination (ACE) [11] or the Cambridge Cognitive Examination revised (CAMCOG-R) [12] which assess a complete range of cognitive functions. Results of this assessment should be interpreted according to the age and educational level of the patients. The diagnosis of MCI can be difficult, since patients who report having memory problems may have normal scores in global cognitive scales or in brief neuropsychological instruments.

Handwriting and drawing are complex and non-unitary human activities that entail an intricate blend of cognitive, kinesthetic, visuospatial, and motor features [13]. Due to the large number of brain areas related to these tasks, the handwriting and drawing performance may be early indicators of brain dysfunction. In fact, previous studies have attempted to disentangle the association between several neurodegenerative diseases and the handwriting capabilities of the patients. These studies have detected slight motor dysfunctions in AD patients [14-16] and the comparison of kinematic parameters of goal-directed movement between AD patients and MCI subjects has also showed a slowing down of motor performance [17]. One study specifically examined the kinematic parameters of two drawing tasks between healthy controls, MCI subjects and AD or depression patients showing that subjects with MCI and AD patients exhibited a loss of fine motor performance [18]. Movements of patients were less regular than those of healthy controls [19]. Another study analyzed the kinematic parameters of handwriting copying tasks between healthy controls, MCI subjects and AD patients, and results allowed them to classify 69% to 72% of the participants correctly, although the classification for the MCI group was relatively poor [19].

The objective of this study was to perform an exploratory analysis of the value of several the kinematic and pressure features of different handwriting and drawing tasks in order to classify individuals depending on their degree of cognitive functioning.

2. METHODS

2.1. Design and Sample

We used a cross-sectional and observational design with three groups of participants. A sample of individuals with AD, MCI and healthy controls was recruited. Patients with AD and MCI were recruited by a convenience sampling procedure in the outpatient offices of the Hospital Santa Caterina's Memory Clinic located in Girona (Catalonia, Spain). Healthy control subjects were recruited from the group of patients' relatives and were matched by age and gender to the other groups. Patients with AD fulfilled the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Associations for the diagnostic of probable AD [20]. Patients with MCI fulfilled the criteria for MCI of Petersen *et al*. [21]. The diagnostic work-up was based on the usual clinical practice, and included an interview with the patient and the caregiver, a general medical examination, hematology and blood chemistry test, and neuroimaging if required. Cognitive function was assessed using the Cambridge Cognitive Examination—Revised (CAMCOG-R) [12], which assesses several cognitive functions. The score ranges from 0 to 105 points, and the lower scores indicate greater degrees of cognitive impairment. Functional capacities were evaluated using the Disability Assessment in Dementia (DAD) [22]. This scale offers a broad assessment of daily living activities: basic, instrumental and leisure. It comprises forty items and scores range between 0 and 80 points, which are transformed into percentages. We excluded all participants with a history or current clinical evidence of a stroke or any other additional organic condition that could adversely affect cognition or motor function. The study was carried out in compliance with the Helsinki Declaration, and all the study participants were informed on the study objectives and gave a written informed consent.

2.2. Instruments, Procedure and Tasks

Handwriting and drawing movements were recorded using a commercial Intuos WACOM series 4 size L digitizing tablet and a pressure-sensitive Intuos ink pen (https://www.wacom.com). All participants wrote with a wireless electronic stylus on a paper fastened to the digitizing tablet.

Participants were seated on a chair with the digitizing tablet placed on a desk in front of them. All participants were given the possibility to adjust the height of the chair and the position of the digitizing tablet. Researchers asked participants to perform seven tasks: copy a simple spiral, copy a 3D house, copy two crossed pentagons, perform the Clock Drawing Test (CDT), copy a sentence, write a dictated sentence, and write a spontaneous sentence. The CDT is a neuropsychological test extensively used as a screening instrument for detecting cognitive impairment as well as for vis-

ual-spatial, constructional, and executive difficulties [23]. We used the free-drawing version that consists in giving the following instructions to the participants: "*Please, I want you to draw the face of a clock with all the numbers on it, and then set the time to 10 after 11*". The instructions were repeated or rephrased if the participant does not understand, but no other help was given.

2.3. Variables

The digitizing tablet is able to capture several signals with length N. Thus, each of the signals consists of a set of N samples, which can be indexed with n, where 1<=n<=N. These signals include: 1) position of the pen tip in terms of x and y coordinate (x[n]; y[n]); 2) time stamp (t[n]); 3) a binary variable (b[n]), being 0 for pen-up state (in-air movement) and 1 for pen-down state (on-surface movement); 4) Pressure of the pen p[n], which lies in a range from 0 to 2047; 5) altitude/tilt (a[n]) and azimuth (z[n]). See Fig. (**1**).

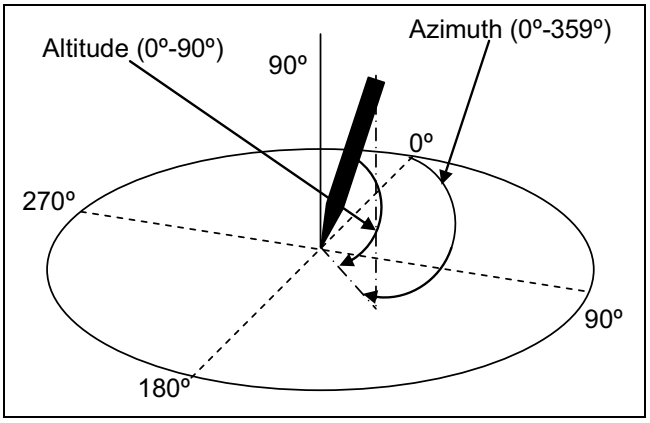

Fig. (1). Azimuth and inclination angles of the pen with respect to the plane of the graphic card

This means that beside the on-surface movement, the tablet is able to track x[n] and y[n] information when the pen is not touching the tablet surface too. It has been already proved that in-air movement brings additional and valuable information to the overall handwriting analysis [24]. Using this set of dynamic data, further information can be inferred, such as acceleration, velocity, instantaneous trajectory angle, instantaneous displacement, tangential acceleration, curvature radius, centripetal acceleration, etc. In order to facilitate the reading of this paper we have established the following variable categories: 1) pressure; 2) time; 3) speed; 4) acceleration; 5) energy; 6) complexity (see annex 1 for a detailed description of these measures).

2.4. Statistical Analysis

A descriptive analysis of the study variables carried out by means of absolute and relative frequencies for qualitative variables and by means of central tendency and dispersion measures for quantitative variables. By means of the Kruskall-Wallis test we compared the kinematic measures of each task between groups.

For each task we performed a discriminant analysis using the kinematic features of handwriting and drawing as variables for subject classification. We defined four groups in order to explore the discriminant capacity of the kinematic measures depending on the kind of groups to be discriminate: healthy controls *vs*. MCI patients *vs.* AD patients; healthy controls *vs*. patients (AD+MCI), healthy controls *vs.* MCI patients, and AD patients *vs.* MCI patients. All discriminant analyses were performed using the stepwise method and the variable selection criteria used was the reduction of the Wilk's lambda parameter in order to define the discriminant function. In order to obtain an approach to the diagnostic accuracy of the kinematic measures, for each dichotomic group comparison (healthy controls *vs*. patients [AD+MCI], healthy controls *vs*. MCI patients, and AD patients *vs.* MCI patients) we estimated the sensitivity and specificity and we computed the 95% confidence interval.

Data processing and analysis were conducted using PASW Statistics version 19 (SPSS; Chicago, IL, USA) for Windows. All the statistical analyses were bilateral, and a *p*-value of less than 0.05 was considered to be statistical significant.

3. RESULTS

The sample consisted of 52 participants and the mean age was 69.7 years (SD=8.11; range=53-85). From the overall sample, 23 (44.2%) participants were patients with AD, 12 (23.1%) were patients with MCI, and 17 (32.7) were healthy controls. The mean age for patients with AD was 72.6 years (SD=7.9), for patients with MCI was 63.5 years (SD=6.5), and for healthy controls was 70.2 years (7.4). We detect statistically significant differences in age between patients with AD and MCI (mean difference=9.1; p<0.005).

Tables **1** and **2** show the results of the discriminant analyses both for drawing and writing tasks respectively. Overall, the discriminant analyses conducted to classify three groups (health controls *vs*. AD patients *vs.* MCI patients) showed moderated percentages of correct classification, that ranged between 63.5% for drawing a 3D house and 80.4% for copy a sentence. Regarding the discriminant variables for three group classifications, the age of the individuals and measures of pressure were the more frequent (Table **3**). Discriminant analyses performed to distinguish between healthy controls and patients (MCI or AD) allowed classifying correctly more than 75% of the cases depending on the task, and up to 92.3% when used the drawing of crossed pentagons. The discriminant factors did not include the subject's age, only pressure and kinematic variables were included into the discriminant functions (Table **3**). The discriminant ability to distinguish between health control subjects and MCI patients ranged between 79.3% and 100%, depending on the specific task. Again, the discriminant variables did not include the subject's age, and only pressure and kinematic variables were included (Table **3**). The distinction between patients with MCI and patients with AD according to the discriminant analyses results showed a similar pattern. Correct classification percentages raged between 77.1% and 100.0%, and age was a variable that was included in the discriminant function (Table **3**).

Table **4** shows the sensitivity and specificity of each discriminant function. The distinction of normal versus pathological cases showed higher specificity than sensitivity for

Table 1. Discriminant analyses results for Drawing tasks.

Function	Wilks' Lambda	Chi-square	df	Sig.	Canonical Correlation	Correct Classification
Crossed pentagons						
3 groups (healthy control *vs.* AD *vs.* MCI)						
1	.594	24.183	4	.000	.517	65.4%
2	.811	9.751	1	.002	.435	
2 groups (healthy control *vs.* AD+MCI)						
1	.329	49.526	7	.000	.819	92.3%
2 groups (healthy control *vs.* MCI)						
1	.608	12.420	2	.002	.626	79.3%
2 groups (AD *vs.* MCI)						
1	.557	17.863	3	.000	.666	77.1%
Spiral						
3 groups (healthy control *vs.* AD *vs.* MCI)						
1	.472	36.078	6	.000	.611	71.2%
2	.753	13.610	2	.001	.497	
2 groups (healthy control *vs.* AD+MCI)						
1	.489	33.996	5	.000	.715	86.5%
2 groups (healthy control *vs.* MCI)						
1	.205	37.191	7	.000	.891	100%
2 groups (AD *vs.* MCI)						
1	.469	23.456	4	.000	.729	88.6%
3D house						
3 groups (healthy control *vs.* AD *vs.* MCI)						
1	.531	29.400	4	.000	.594	63.5%
2	.820	9.201	1	.002	.424	
2 groups (healthy control *vs.* AD+MCI)						
1	.565	26.823	2	.000	.659	84.6%
2 groups (healthy control *vs.* MCI)						
1	.303	28.663	4	.000	.835	89.7%
2 groups (AD *vs.* MCI)						
1	.419	26.068	4	.000	.762	88.6%
Clock Drawing Test						
3 groups (healthy control *vs.* AD *vs.* MCI)						
1	.685	18.370	4	.001	.490	63.5%
2	.901	5.033	1	.025	.314	
2 groups (healthy control *vs.* AD+MCI)						
1	.696	17.579	3	.001	.551	82.7%
2 groups (healthy control *vs.* MCI)						
1	.439	20.607	4	.000	.749	82.8%
2 groups (AD *vs.* MCI)						
1	.154	52.407	10	.000	.920	100%

Table 2. Discriminant analyses results for Handwriting tasks.

Function	Wilks' Lambda	Chi-square	df	Sig.	Canonical Correlation	Correct Classification
Spontaneous sentence						
3 groups (healthy control *vs.* AD *vs.* MCI)						
1	.624	22.379	4	.000	.535	69.2%
2	.875	6.364	1	.012	.354	
2 groups (healthy control *vs.* AD+MCI)						
1	.609	23.328	4	.000	.625	82.7%
2 groups (healthy control *vs.* MCI)						
	.270	31.428	6	.000	.854	96.6%
2 groups (AD *vs.* MCI)						
1	.376	29.361	4	.000	.790	91.4%
Sentence copied						
3 groups (healthy control *vs.* AD *vs.* MCI)						
1	.227	66.824	14	.000	.777	80.4%
2	.572	25.124	6	.000	.654	
2 groups (healthy control *vs.* AD+MCI)						
1	.698	17.236	2	.000	.549	80.4%
2 groups (AD *vs.* MCI)						
1	.255	40.257	5	.000	.863	91.2%
2 groups (healthy control *vs.* MCI)						
1	.237	35.237	5	.000	.873	93.1%
Sentence dictation						
3 groups (healthy control *vs.* AD *vs.* MCI)						
1	.640	21.620	4	.000	.502	71.2%
2	.856	7.557	1	.006	.380	
2 groups (healthy control *vs.* AD+MCI)						
1	.731	15.355	2	.000	.519	75.0%
2 groups (healthy control *vs.* MCI)						
1	.151	45.408	6	.000	.922	100%
2 groups (AD *vs.* MCI)						
1	.500	21.843	3	.000	.707	85.7%

Table 3. Discriminant Kinematic and pressure features.

	3 Groups (Healthy Control *vs.* AD *vs.* MCI)	**2 Groups (Healthy Control *vs.* AD+MCI)**	**2 Groups (Healthy Control *vs.* MCI)**	**2 Groups (AD *vs.* MCI)**
Drawing				
Crossed pentagons	- age - pressure acceleration and speed	- pressure - speed - complexity	- pressure acceleration and speed - complexity	- age - time on-air - complexity
Spiral	- age - pressure acceleration and speed - complexity	- pressure - complexity	- pressure acceleration and speed - complexity	- age - pressure acceleration and speed - complexity
3D house	- age - pressure acceleration and speed	- pressure acceleration and speed - complexity	- pressure - acceleration and speed - complexity	- age - complexity
Clock Drawing Test	- pressure acceleration and speed - complexity	- time on-air - pressure acceleration and speed	- complexity	- age - pressure - pressure acceleration and speed - complexity - time on-air
Handwriting				
Spontaneous	- age - complexity	- speed - complexity	- age - pressure - acceleration - complexity	-age - pressure - complexity
Copied	- age - pressure - complexity	- complexity	- pressure - complexity	- age - pressure acceleration and speed - time on-air
Dictated	- complexity	- pressure acceleration and speed - complexity	- pressure acceleration and speed - complexity	- age - pressure - pressure acceleration and speed

Table 4. Sensitivity and specificity values for discriminant functions.

	Healthy Control *vs.* AD+MCI		**Healthy Control *vs.* MCI**		**AD *vs.* MCI**	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Drawing						
Crossed pentagons	89.7 (78.9-100.0)	100.0 (96.1-100.0)	71.4 (44.1-98.6)	86.6 (66.1-100.0)	85.7 (68.3-100.0)	64.2 (35.6-92.9)
Spiral	85.0 (72.6-97.3)	91.6 (71.8-100.0)	100.0 (95.8-100.0)	100.0 (97.0-100.0)	91.3 (77.6-100.0)	83.3 (58.0-100.0)
3D house	81.4 (68.6-94.1)	100.0 (94.4-100.0)	84.6 (61.1-100.0)	93.7 (78.7-100.0)	88.0 (73.2-100.0)	90.0 (66.4-100.0)
Clock Drawing Test	79.5 (66-4-92.6))	100.0 (93.7-100.0)	81.8 (54.4-100.0)	83.3 (63.3-100.0)	100.0 (97.0-100.0)	100.0 (95.8-100.0)
Handwriting						

(Table 4) contd….

	Healthy Control *vs.* AD+MCI		Healthy Control *vs.* MCI		AD *vs.* MCI	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Spontaneous	84.2 (71.3-97.1)	78.5 (53.5-100.0)	92.3 (73.9-100.0)	100.0 (96.8-100)	91.6 (78.5-100.0)	90.9 (69.3-100.0)
Copied	81.5 (67.9-95.2)	76.9 (50.1-100.0)	91.6 (71.8-100)	94.1 (79.9-100.0)	91.3 (77.6-100.0)	90.9 (69.3-100.0)
Dictated	76.1 (62.1-90.2)	70.0 (36.6-100.0)	100.0 (95.8-100.0)	100.0 (97.0-100.0)	90.9 (76.6-100.0)	76.9 (50.1-100.0)

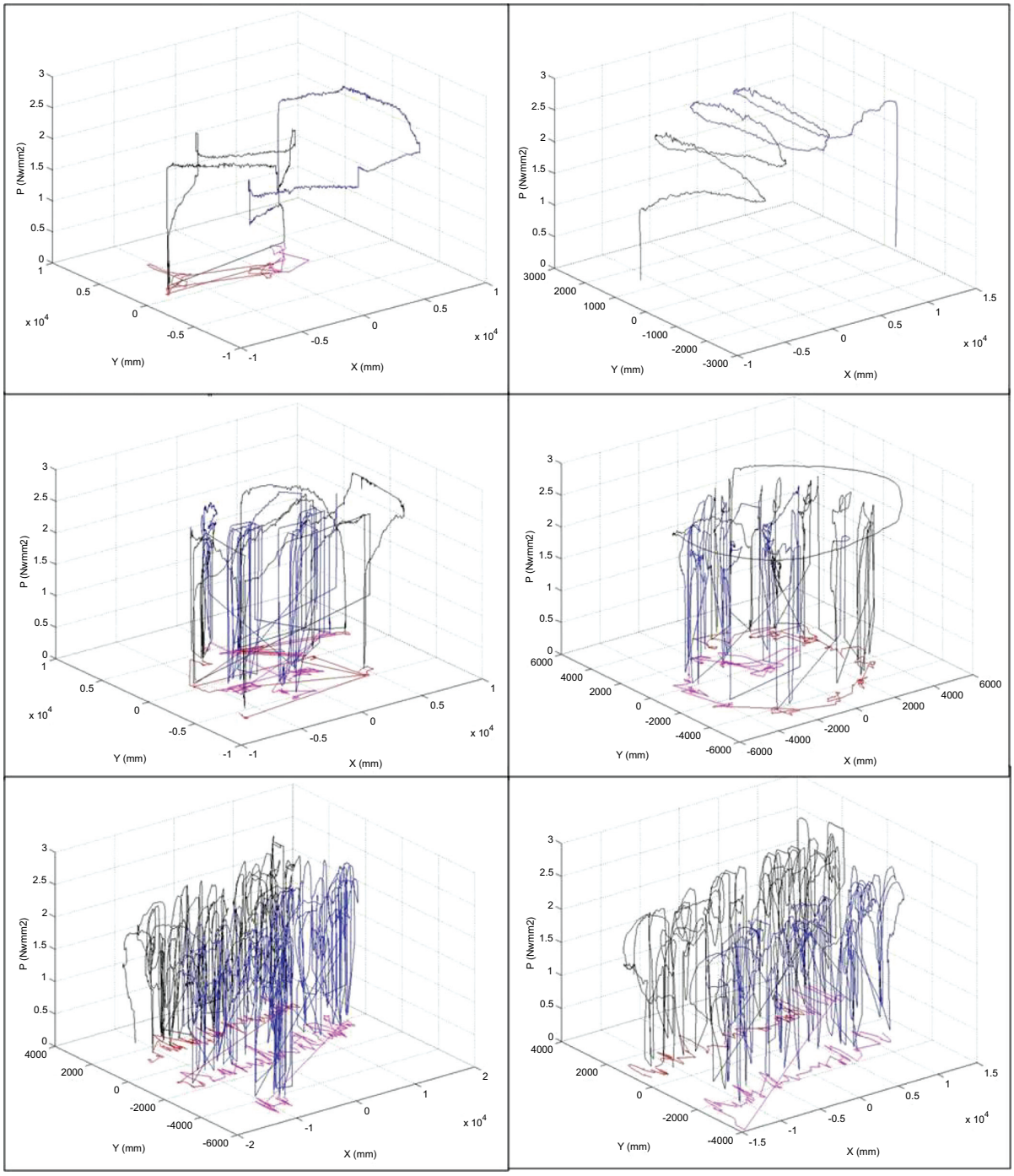

Fig. (2). AD subject, Handwriting and Drawing: Mini-Mental State Examination, the spiral and the 3D house drawings. X-Y-Pressure. On surface pressure (line black: 0-time/2;line blue: time/2-time end). On air pressure, 0 pressure (line red: 0-time/2;line purple: time/2-time end).

the drawing tasks, while handwriting tasks showed lower specificity. The discriminant functions to differentiate health controls versus MCI patients showed also more specificity than sensitivity, both for drawing and writing tasks. However, when comparing AD and MCI patients, the discriminant function showed higher sensitivity than specificity, for both drawing as writing tasks. Fig. (**2**) AD subject, Handwriting and Drawing: Mini-Mental State Examination, the spiral and the 3D house drawings. X-Y-Pressure. On surface pressure (line black: 0-time/2;line blue: time/2-time end). On air pressure, 0 pressure (line red: 0-time/2;line purple: time/2-time end).

4. DISCUSSION

The aim of our study was to assess the discriminant power of several kinematic and pressure handwriting and drawing parameters in order to distinguish between healthy controls and patients with AD and/or MCI. The overall results indicate that these parameters have a large discriminating power, and that the assessment of fine motor function during handwriting and drawing using a digitizing tablet and a pressure-sensitive pen could be a useful resource in the clinical setting. Interestingly, our results shown that for the same task, the discriminant parameters differ depending on the type of group to be discriminated, suggesting that are not the dimensional features of the parameters, but rather the qualitative combination of these parameters that are relevant for group discrimination.

Traditionally, neuropsychologists have used tasks such as those we included in our study in order to assess the cognitive performance of an individual. In fact, the crossed pentagons task is included in the Mini-Mental State Examination [25], the spiral and the 3D house drawings are part of the assessment of visuoconstructional capabilities of the neuropsychological battery of the Cambridge Examination for Mental Disorders of Elder People [26], and the task of drawing a clock showing 10 ten minutes after 11 is the task of the Clock Drawing Test [23]. However, classically the outcomes evaluated are the final performances, that are the drawings, not the entire sequence of the individual behaviours such as each pencil stroke, the pressure on paper, the speed and acceleration, the pauses, or the hand movements in-air or in-paper needed to perform each task. The use of the digitizing pen provides the unique possibility to capture the kinematic and pressure features during the task performance and allows a different framework to study the cognitive functions related to visuoconstructive activities. Previous research using this methodology has illustrated its potential discriminating individuals with neurodegenerative diseases such as Parkinson's disease [27] or Alzheimer's disease [13], and mental health disorders such as depression [28-29].

As a novelty in this research field, we included both drawing and writing tasks, and we used a large set of kinematic and pressure variables that include complexity parameters. We also performed the analyses in a double way, first as screening approach between healthy individuals and patients, and second as a clinical approach in order to distinguish between MCI and AD cases. The differentiation between the three groups of subjects had the lowest classification percentages, both for handwriting and drawing tasks, while de distinction between healthy individuals and pathological cases (MCI and/or AD) showed higher percentages. Specificity was the main feature when distinguishing healthy controls and pathological individuals, while sensitivity was high for distinguishing between MCI and AD cases.

Limitations of this study must be considered when interpreting the results. First, this was a preliminary report, with a reduced sample size and a convenience sampling procedure that limits the generalization of the results. Our results should be viewed as tendencies and as a proof of concept that requires further development. In this sense, future studies using a large sample from a consecutive sampling procedure of individuals attended in the memory clinic consultation offices would help to obtain reliable results generalizable to the daily clinical practice. Second, the limited sample size may have contributed to commit a type II error, failing to identify potential parameters with discriminant capabilities. The strengths of the current study include the use of valid and reliable digital equipment, the standardization of the study tasks and data acquisition, the rigorous clinical diagnostic procedures to classify the study participants, and the exclusion of subjects with conditions that could affect motor function.

CONFLICT OF INTEREST

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

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REFERENCES

[1] Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 11(3): 332-84 (2015).

[2] Galvin JE, Sadowsky CH; NINCDS-ADRDA. Practical guidelines for the recognition and diagnosis of dementia. J Am Board Fam Med 25(3): 367-82 (2012).

[3] Garre-Olmo J, López-Pousa S, Vilalta-Franch J, de Gracia Blanco M, Vilarrasa AB. Grouping and trajectories of neuropsychiatric symptoms in patients with Alzheimer's disease. Part II: two-year patient trajectories. J Alzheimers Dis 22(4): 1169-80 (2010).

[4] Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA 312(23): 2551-61 (2014).

[5] Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: disparity of incidence and prevalence estimates. Alzheimers Dement 8(1): 14-21 (2012).

[6] Fiandaca MS, Mapstone ME, Cheema AK, Federoff HJ. The critical need for defining preclinical biomarkers in Alzheimer's disease. Alzheimers Dement 10 (3): 196-212 (2014).

[7] Reitan, RM. The relation of the trail making test to organic brain damage. J Consul Psychol 19: 393-394 (1955).

[8] Buschke H. Cued Recall in amnesia. J Clin Neuropsychol 6: 433-440 (1984).

[9] Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test 5. Lea and Febiger: Philadelphia, 1983.

[10] Shin MS, Park SY, Park SR, Seol SH, Kwon JS. Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. Nat Protoc 1: 892-9 (2006).

[11] Bak TH, Mioshi E. A cognitive bedside assessment beyond the MMSE: the Addenbrooke's Cognitive Examination. Pract Neurol 7: 245-9 (2007).

[12] Verhey FR, Huppert FA, Korten EC, Houx P, de Vugt M, van Lang N, *et al*. Cross-national comparisons of the Cambridge Cognitive

Examination-revised: the CAMCOG-R: results from the European Harmonization Project for Instruments in Dementia. Age Ageing 32: 534-40 (2003).

[13] van Galen GP. Handwriting: Issues for a psychomotor theory. Human Mov Sci 10(2-3): 165-191 (1991).

[14] Ghilardi MF, Alberoni M, Marelli S, Rossi M, Franceschi M, Ghez C, *et al*. Impaired movement control in Alzheimer's disease. Neurosci Lett 260(1): 45-8 (1999).

[15] Ghilardi MF, Alberoni M, Rossi M, Franceschi M, Mariani C, Fazio F. Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. Brain Res 876(1-2): 112-23 (2000).

[16] Goldman WP, Baty JD, Buckles VD, Sahrmann S, Morris JC. Motor dysfunction in mildly demented AD individuals without extrapyramidal signs. Neurology 53(5): 956-62 (1999).

[17] Camarda R, Camarda C, Monastero R, Grimaldi S, Camarda LK, Pipia C, *et al*. Movements execution in amnestic mild cognitive impairment and Alzheimer's disease. Behav Neurol 18(3): 135-42 (2007).

[18] Schröter A, Mergl R, Bürger K, Hampel H, Möller HJ, Hegerl U. Kinematic analysis of handwriting movements in patients with Alzheimer's disease, mild cognitive impairment, depression and healthy subjects. Dement Geriatr Cogn Disord 15(3): 132-42 (2003).

[19] Werner P, Rosenblum S, Bar-On G, Heinik J, Korczyn A. Handwriting process variables discriminating mild Alzheimer's disease and mild cognitive impairment. J Gerontol B Psychol Sci Soc Sci 61(4): P228-36 (2006).

[20] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34(7): 939-44 (1984).

[21] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56: 303-8 (1999).

[22] Gélinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the Disability Assessment for Dementia. Am J Occup Ther 53: 471–481 (1999).

[23] Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment (4th ed.). New York: Oxfor University Press, 2004.

[24] Sesa-Nogueras E, Faundez-Zanuy M, Mekyska J. An information analysis of in-air and on-surface trajectories in online handwriting. Cogn Comput 4(2): 1-11 (2012).

[25] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189-98 (1975).

[26] Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S, *et al.* CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 149: 698-709 (1986).

[27] Rosenblum S, Samuel M, Zlotnik S, Erikh I, Schlesinger I. Handwriting as an objective tool for Parkinson's disease diagnosis. J Neurol 260: 2357-61 (2013).

[28] Heinik J, Werner P, Dekel T, Gurevitz I, Rosenblum S. Computerized kinematic analysis of the clock drawing task in elderly people with mild major depressive disorder: an exploratory study. Int Psychogeriatr 22: 479-88 (2010).

[29] Rosenblum S, Werner P, Dekel T, Gurevitz I, Heinik J. Handwriting process variables among elderly people with mild Major Depressive Disorder: a preliminary study. Aging Clin Exp Res 22: 141-7 (2010).