Dysgraphia in Relation to Cognitive Performance in Patients with Alzheimer's Disease

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Abstract: Dysgraphia has been observed in patients presenting mild to moderate levels of Alzheimer's disease (AD) in several studies. In the present study, 30 AD patients and 30 matched healthy controls, originating from the Lazio region, Rome, Italy, were examined on tests of letter-writing ability and cognitive performance over a series of 10 test days that extended over 19 days (Test days: 1, 3, 5, 7, 9 11, 13, 15, 17, and 19). Consistent deficits by the AD patients over the initial cognition test (PQ1), 2nd cognition test (PQ2) and the difference between them (D∆), expressing deterioration, and writing-time compared the group of healthy control subjects were obtained. Furthermore, the performances of the AD patients on the PQ1, D∆ and writing-time, but not the PQ2, tests deteriorated from the 1st five days of testing (Days 1-9) to the 2nd five days (11-19). Both AD patients' and healthy controls' MMSE scores were markedly and significantly correlated with performance of PQ1, writing-time and PQ2. The extent of dysgraphia and progressive deficits in the AD patients implicate multiple brain regions in the loss of functional integrity.

Keywords: Dysgraphia, cognition, deficit, patients, healthy controls, PQ1, writing-time, PQ2, MMSE, deterioration, Alzheimer's disease.

INTRODUCTION

Writing skill may represent procedural/implicit memory, and dysgraphia errors indicating alterations in long-term memory in dementia of the Alzheimer type (Alzheimer's disease, AD, [1]. Under clinical conditions, dysgraphia presents a deficiency in the ability to write, primarily in terms of handwriting but also in terms of coherence is a transcription disability, implying that it is a writing disorder associated with impaired handwriting [2], In 1907, Alzheimer [3] had observed in these patients abnormal graphic gestures which indicated that hand writing is not constituted by a unitary process, but requires a coordination of the linguistic, visual-spatial and motor domains of the individual [4, 5]. The disruption of these functions reflects brain damage in different associative areas, such as parietal, temporal, occipital and frontal regions and covering different domains, e.g. cognition, language and motor, [6], and subsequently was diagnosed in AD patients [7]. Lambert *et al*. [8] have demonstrated a wide variety of agraphia syndromes, including a far from negligible number of patients with selective damage to one of the central or peripheral components, as well as patients with multiple writing impairments with positive correlation was observed between the severity of the dementia and spelling/writing measures (lexical and allographic). Agraphia or dysgraphia, observed in early AD [9], encompasses a progressive disorganization and degeneration of the various components of handwriting [10]. In the language domain, these disturbances are captured in several ways of expressing speech and writing, such as the complexity of the structure of sentences [11], the diversity, organization and the accuracy of words used and several aspects of language application [1, 5, 12-15]. Fukui and Lee [16] examined the possibility that agraphia/dysgraphia may be an early sign of degenerative dementia, reporting the concurrent or subsequent emergence of non-fluent aphasia, ideomotor apraxia, executive dysfunction and asymmetric akinetic-rigid syndrome that implicated degenerative processes involving the parietal-occipital-temporal regions, basal ganglia and striato-frontal projections. It has been observed that that writing impairment is heterogeneous within the AD population, but nevertheless, there are certain aspects of the writing process that are more vulnerable than others and may present diagnostic signs [17]. Neuro-imaging with MRI, for example, has indicated marked structural defects in patients: Atrophy in the left hemisphere supramarginal gyrus and inferior frontal gyrus (IFG) pars orbitalis correlated with errors in non-word spelling, while thinning in the left temporal pole and fusiform gyrus correlated with errors in exception word spelling [18]. Additionally, in the language domain there is much support for the notion of semantic agraphia in AD [19].

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There is a consensus that dysgraphia arises invariably during the clinical course of dementia [20]. It may be termed "central" if generated at a level that affects spelling or "peripheral" if spelling is correctly generated but the peripheral procedures are not activated properly. The progression of dysgraphia in AD patients seems proportional to the extent of central (linguistic system) and peripheral (allographic or grapho-motor system) as an expression of the disorder staging [21, 22] that increases the dysfunction disproportionately [23, 24]. The syndrome may appear relatively early in the onset of AD [25, 26], as a more sensitive indicator of language deficits than anomia, deficits in the naming of persons/objects [27, 28]. The specific patterns of dysgraphia include lexical or surface dysgraphia [29], phonological dysgraphia [30] and peripheral dysgraphia [31, 32]. AD is associated with visuospatial and language dysfunctions in the disorder pathophysiology with bilateral involvement of the temporoparietal-frontal lobes [33]. In a study of dysgraphia in early-onset AD, linguistic and visuospatial writing errors were observed with severity of dementia and multiple cognitive domains, including language, attention, immediate memory and frontal executive functions correlated markedly with Hangul writing performance [34]. It would appear that the writing disturbances expressed in AD patients are heterogenous encompassing phonological dysgraphia, lexical dysgraphia and mixed dysgraphia [35]. Several brain regions have been linked to dysgraphia, e.g. the left inferior parietal lobule [36], the left posterior temporal area [37] and the left posterior middle frontal gyrus [38].

The purpose of the present study was to examine the extent of dysgraphia and cognitive performance on a specially-adapted test of cognition in a group of 30 AD patients presenting a moderate level stage of the disorder according to MMSE estimations (see below), and in a matched group of 30 healthy controls, and the relationship between dysgraphia, functional assessment (MMSE) and performance (PQ1 and PQ2).

METHODS AND MATERIALS

Participants

There were 30 patients who were selected to participate in the study, 12 male and 18 female AD patients, who met both the inclusion criteria (see Table **1**, below) and the exclusion criteria, i.e. absence of other neuropsychiatric disorders. The age was between 73 to 94 years of age (mean age: 83.06, SD: 6.15). All of the patients were presenting symptoms that indicated a diagnosis of AD from moderate level to relatively severe (see Table **1**). All of these diagnoses were confirmed and verified by resident neurologists at the Department of Neurology at the hospital (Gemelli University Polyclinicl-service neuro psychology, Roma and UVA (Alzheimer Evaluation Unit) ASLRMF and UVA (Alzheimer Evaluation Unit) ASLRMD, 26 patients and 4 patients from the Department of Neurology and Psychiatry, Sapienza Hospital, Rome) in the Lazio (Rome, Italy) region. The diagnosis was based on normal or nonspecific EEG and lateral, occipital brain atrophy on CT brain with documented progression after serial observations, on cognitive test and routine blood tests that aimed at excluding the presence of other medical conditions that can justify dementia. Patients were excluded if they had a history of known or suspected cerebrovascular disease, focal neurological signs or on brain imaging, alcohol misuse, head trauma, significant psychiatric history preceding the current diagnosis or other major physical illness. The clinical characteristics of the participants in the study are presented in Table **1**. They were diagnosed according to the NINCDS-ADRDA criteria [39], and to the DSM-IV diagnostic reference. The mean length of time spent upon education by the 30 patients was 11.06 years (SD ± 3.6 years). A considerable amount of time (regular meetings during 3 months) was invested in each of the patients in order to promote a relationship of trust and understanding, as well as to reduce stress factors [5] that may affect patients' mood and attentiveness, or, more seriously, induce behaviors that suggest hallucinations or auditory illusions, paranoid delirium, difficulty to recognize persons, or loss of cognition of time and places. All the procedures that were adopted according to discussions and meetings with nearest relatives in order to obtain the consent of the patients as well as those relatives (in those cases were the latter were their caregivers/legal representatives) according to the legal practices. The control group of age- and education-matched healthy senior citizens was chosen as individuals that were not in any way influenced by AD and whom presented the following characteristics: mean age 82.73 years (SD ± 5.7 years). The mean amount of time spent upon education by the healthy controls was 12.8 years (SD ± 4.04 years).

AD diagnosis: All the patients evidenced lower performance in the standard tests of neuropsychological assessment that were administered. The cognitive profiles presented by these patients expressed

Table 1: Clinical Characteristics and Neurological Data of each of the AD Patients in the Present Study

Patient No.	Educational (yrs)	Age (yrs)	Sex (M/F)	MMSE[1]	ADL[2]	IADL[3]	Diagnosis	Neurological data (CAT)[4]
1	10	73	F	16(13,7)	4	4	AD	Cerebral atrophy, ventricular enlargement
2	6	93	F	13	4	2	AD	Cerebral atrophy, lateral, occipital
3	10	91	F	12	4	4	AD	Gen. Brain atrophy, gray matter loss affecting hippocampus
4	7	90	F	11	2	2	AD	Atrophy, parietal
5	15	87	F	15(15,3)	4	4	AD	Cortical-subcortical brain atrophy
6	8	77	F	16(15)	5	4	AD	Cerebral atrophy
7	7	78	F	14(12,3)	4	4	AD	Medial temporal lobe atrophy
8	12	79	F	13(11,3)	4	4	AD	Cortical-subcortical brain atrophy
9	14	79	F	15(13,3)	4	4	AD	Cerebral atrophy
10	8	80	F	17(16,7)	5	4	AD	Hippocampus and entorhinal cortex atrophy
11	14	77	F	14(12,3)	4	4	AD	Cerebral atrophy, lateral, occipital
12	13	77	F	17(15,3)	4	4	AD	Hippocampus and entorhinal cortex atrophy
13	12	81	M	15(14,7)	4	4	AD	Cerebral atrophy
14	16	85	M	12(12,3)	4	2	AD	Cerebral atrophy, lateral, occipital
15	15	83	M	11(10,1)	4	2	AD	cortic-subcortical brain atrophy
16	15	83	M	14(13,1)	4	2	AD	Medial temporal lobe atrophy
17	8	80	M	17(16,7)	5	2	AD	Hippocampus and entorhinal cortex atrophy
18	17	80	M	14(13,1)	4	4	AD	Cerebral atrophy, lateral, occipital
19	6	94	M	16	4	4	AD	Ventricular and subarachnoidal space dilation
20	8	93	M	14	4	4	AD	Medial temporal lobe, hippocampus and entorhinal cortex atrophy
21	10	92	F	12	4	4	AD	Atrophy: parietal
22	7	91	F	15	4	4	AD	Cerebral atrophy, ventricular and subarachnoidal space dilation
23	18	80	M	17(16,1)	4	2	AD	Medial temporal lobe atrophy
24	10	78	M	17(16)	5	4	AD	Atrophy: parietal
25	12	77	M	17(16)	4	4	AD	Hippocampus and entorhinal cortex atrophy
26	10	76	F	16(15)	5	4	AD	Cerebral atrophy
27	13	79	F	18(16,3)	5	4	AD	Cerebral atrophy
28	16	83	M	12(11,1)	2	2	AD	Medial temporal lobe atrophy
29	8	85	M	12(12,8)	3	2	AD	Cerebral atrophy, lateral, occipital
30	7	91	F	11	4	2	AD	Atrophy: parietal

[1]MMSE=mini-mental state examination [41] [normal level score=30 points], modified by age and education (numbers in brackets); [2]ADLs=Activities of Daily living [42] [normal level=6/6 for both males and females]; [3]IADLs=Instrumental activities of daily living [43] [normal level=8/8 for both males and females]; AD=Alzheimer's disease; [4]Computerized axial tomography. Gen. = generalized.

cognitive impairments that were widespread and related to a severe dementia syndrome of a progressive nature that was linked to a degenerative dementia of the Alzheimer type. On the basis of the neuropsychological tests and clinical observations this group of patients was classified at the moderate to relatively severe stage of AD [40].

Mini-mental State Examination (MMSE) presents a brief 30-point questionnaire test to screen for cognitive impairment and dementia [41]. It estimates the severity of disorder and follows the course of cognitive changes in an individual over time, thereby allowing effective monitoring of an individual's response to treatment. Table **1** presents the individual

scores of each of the patients. It will be noted that these scores range from 11 to 18 which implies that the patients express a moderate level of AD disorder. Healthy control individuals scored at 30 points.

Activities of Daily Living (ADLs) offers an instrument that measures everyday behaviors necessary for normal functioning on a daily basis [42]. Under normal conditions, individuals must invest a certain amount of time taking care of their personal care and hygiene in order to promote their own health and to a sufficiency of independent initiative and capability.

Instrumental Activities of Daily Living (IADLs) offers an instrument that measures those behaviors that are linked to an independent lifestyle. The instrument has been found to be useful for evaluations of individuals presenting early-stage (or moderate stage) disorders: it has been found applicable for ascertaining both disorder extent and determination of individual capacity for self-care and management [43].

Neurological data for structural neuro-imaging analysis was obtained from computerized axial tomography (CAT) whereas magnetic resonance imaging (MRI) data were not available.

Writing (Graphia) Test and Memory Tests

Each patient was provided with a writing-pad for writing texts or drawing figures, preferably the "vergatina" type (flimsy type, typing paper or tissue type or absorbent) in order to avoid false interpretations of the writings to analyze. A ballpoint pen was used throughout. The patients were invited to sit comfortably at a writing desk. The memory test material consisted of the presentations of a 14-item questionnaire involving questions regarding semantic knowledge as well as spatial and temporal orientation that were modifications of questions that were derived partially from the MMSE and then modified. The questionnaires were handled easily and could be presented to patients by different medical practitioners. Points were assigned on the basis of the complexity of each of the questions.

The total sum from each test session was represented by PQ: the initial session result designated PQ1 and the test session following the letter-writing, graphia, test was designated PQ2. Following the PQ1 memory test, each patient was presented a writing-pad and asked to write a letter to a close relative. On consecutive days of testing patients were invited to write to either the same relative or another one. Using a chronometer to establish length of writing-time (min.), the letter-writing task was interrupted when it seemed that the text produced by the patient was substantially (pathologically) confused (both with regard to spatial disorientation as well as for a sudden lack of readability, disjointedness and incompleteness in meaning). After this, the number of minutes (min) that had been reached for each single patient was registered. The whole procedure involving the letter-writing graphia task was interrupted after 20 minutes. Directly after the letter-writing, the list of 14 questions presented in PQ1 was presented again in a repeated procedure that was designated PQ2. The difference between these two measures (PQ1-PQ2) was designated DΔ. These procedures for testing: 14-item test – graphia test – 14-item test were presented in an identical manner every second over 10 days (Days 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19) at the same hour-of-day on test days in order to hold constant testing procedures over daily curriculum and any clinical interventions that the patients may be subject to.

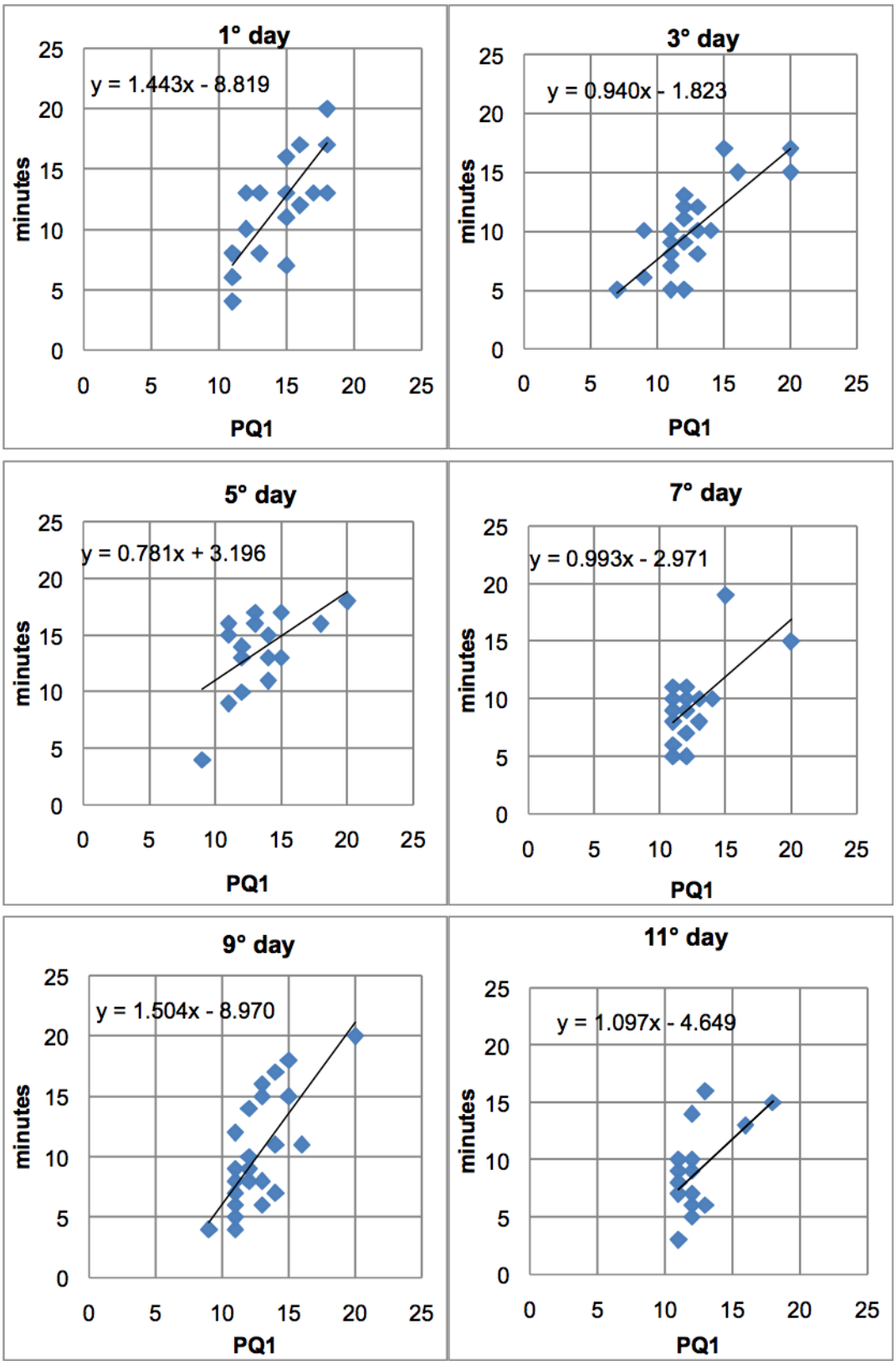
Statistical Analysis

The results consisting of PQ1 and PQ2 scores, min spent writing and DΔ (see above) was calculated as means and standard deviations of the AD patient group and the healthy control group over consecutive days of testing. Pearson's correlation coefficient was used to assess the relationship between writing-time and PQ1 and writing-time over both patients and matched healthy controls for each of the test days. Student's t-tests were used to test for pairwise differences for each of the parameters. Pearson's correlation coefficient was used to assess the relationship between MMSE scores and PQ1, writing-time and PQ2.

RESULTS

Correlational Analyses: Writing-Time and PQ1

Significant and linear correlations were obtained between length of writing-time by patients and their performance on PQ1, the initial test of cognition, on every single day of testing, from Test day 1 to Test day 19, indicating that the extent of dysgraphia, expressed here as an inadequacy to write letters to a close relative, was functionally related to poor performance during PQ1. The one exception to this pattern was Test day 13 wherein a somewhat better cognitive performance (PQ1) was associated with a slightly higher extent of dysgraphia. Figure **1** presents the


1° day
y = 1.443x - 8.819
3° day
y = 0.940x - 1.823
5° day
y = 0.781x + 3.196
7° day
y = 0.993x - 2.971
9° day
y = 1.504x - 8.970
11° day
y = 1.097x - 4.649
minutes
PQ1
0
5
10
15
20
25

(Figure 1). Continued.

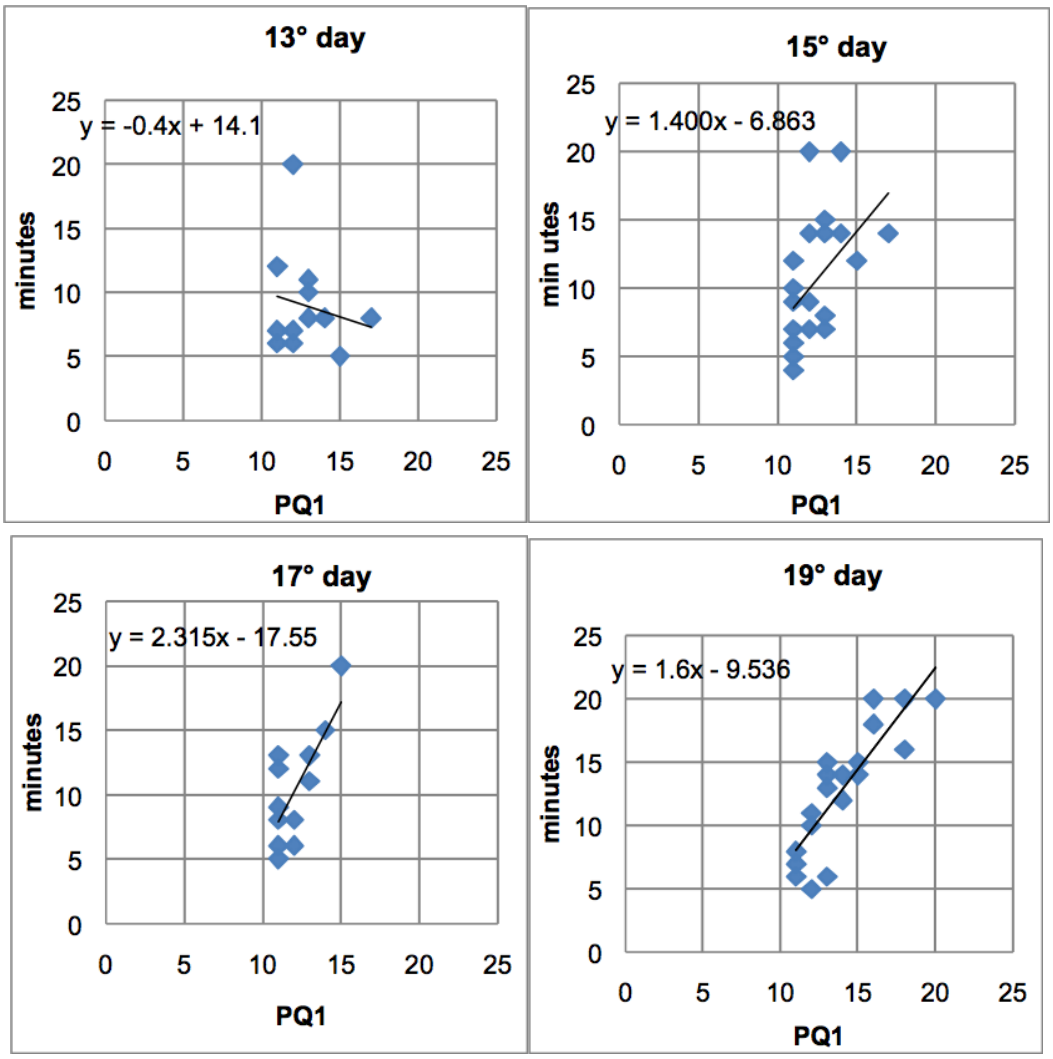


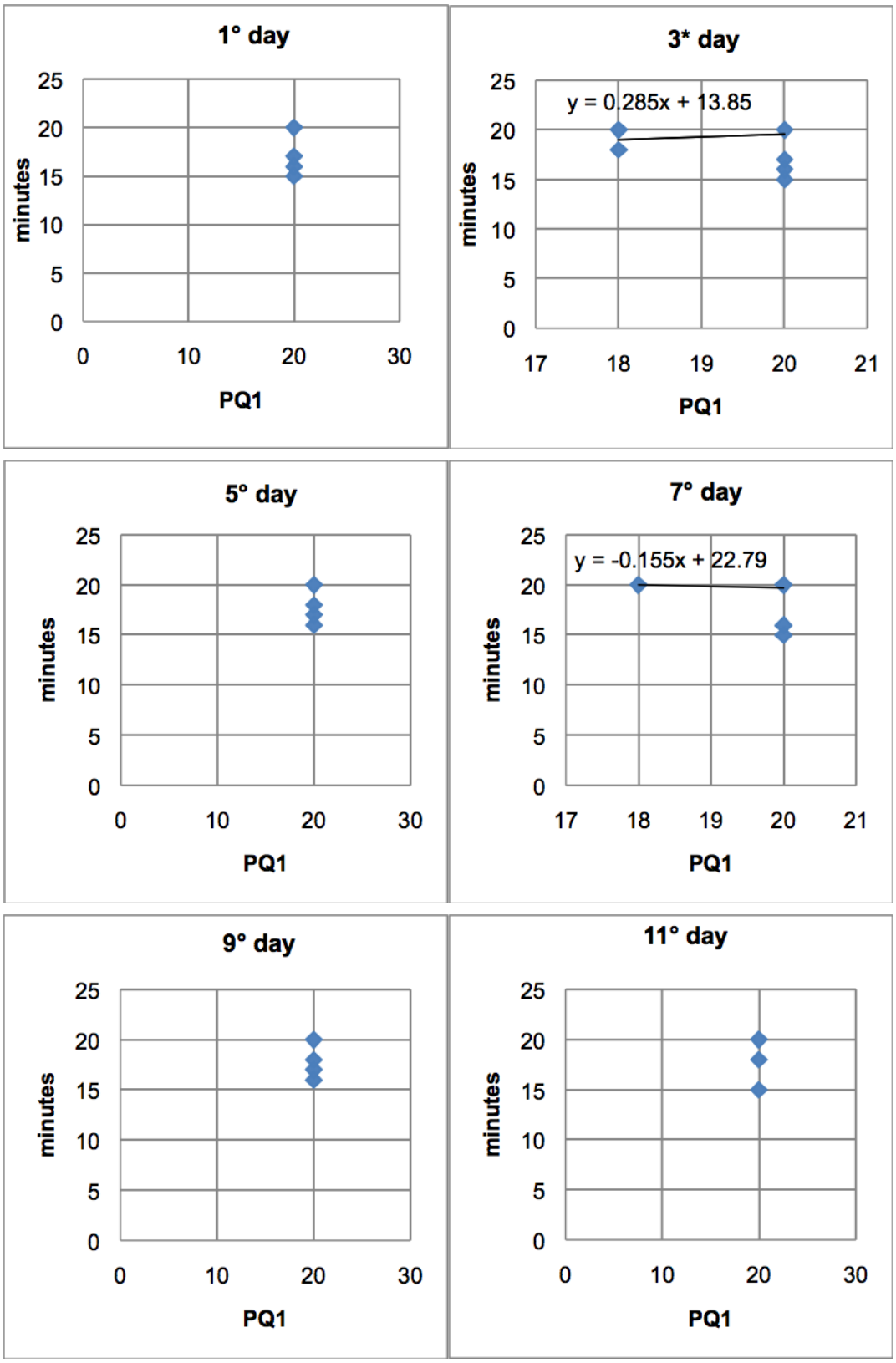
Figure 1: Correlational analysis (Pearson product moment) between PQ1 and writing-time (min) by AD patients from Test day 1 to Test day 19 (10 days of testing). The correlation coefficients were: Day 1: 0.802*; Day 3 0.785*; Day 5 0.603°; Day 7 0.644°; Day 9: 0.732*; Day 11: 0.556▲; Day 13: 0.688*; Day 15: 0.498•; Day 17: 0.767*; Day 19: 0.871*.
* p < 0,0001.•p < 0.005; ▲p < 0.002; °p < 0.001, Pearson Product moment correlations.

Pearson Product moment correlations and slopes on each of the 10 test days for the AD patients.

The correlational analysis of the matched healthy controls differed markedly from that of the AD patients in that only those of Test Days 15, 17 and 19 achieved significance but only a few individuals performed letter-writing and the cognitive test at a level just below maximum scoring. Indeed, maximal performance on both letter-writing and PQ1 defined the output of the healthy controls. The correlations (below) indicate these differences clearly. Figure **2** presents the Pearson Product moment correlations and slopes on each of the 10 test days for the healthy controls.

The performance of the AD patients over all the tests applied, PQ1, PQ2, DΔ, which expresses the deterioration from PQ1 to PQ2, and letter-writing, was significantly impaired compared with the healthy control group (See Tables **2** and **3**). It was observed also that for PQ1, DΔ and writing-time, that performance deteriorated from Test Days 1-9 to 11-19, but improved slightly for PQ2. Table **2** presents the performance of AD patients on the tests of cognition, PQ1 and PQ2, the difference between these tests, DΔ, and in the writing test.

The performance of the healthy control remained relatively constant over the testing parameters, PQ1, PQ2, DΔ, which expresses the deterioration from PQ1 to PQ2, and letter-writing, and the 10 days of testing. Nevertheless, it was observed that for both PQ1 and PQ2 their performance was slightly, significantly worse from Test days 1-9 to 11-19. Table **3** presents the


1° day
minutes
PQ1
3* day
y = 0.285x + 13.85
minutes
PQ1
5° day
minutes
PQ1
7° day
y = -0.155x + 22.79
minutes
PQ1
9° day
minutes
PQ1
11° day
minutes
PQ1

(Figure 2). Continued.

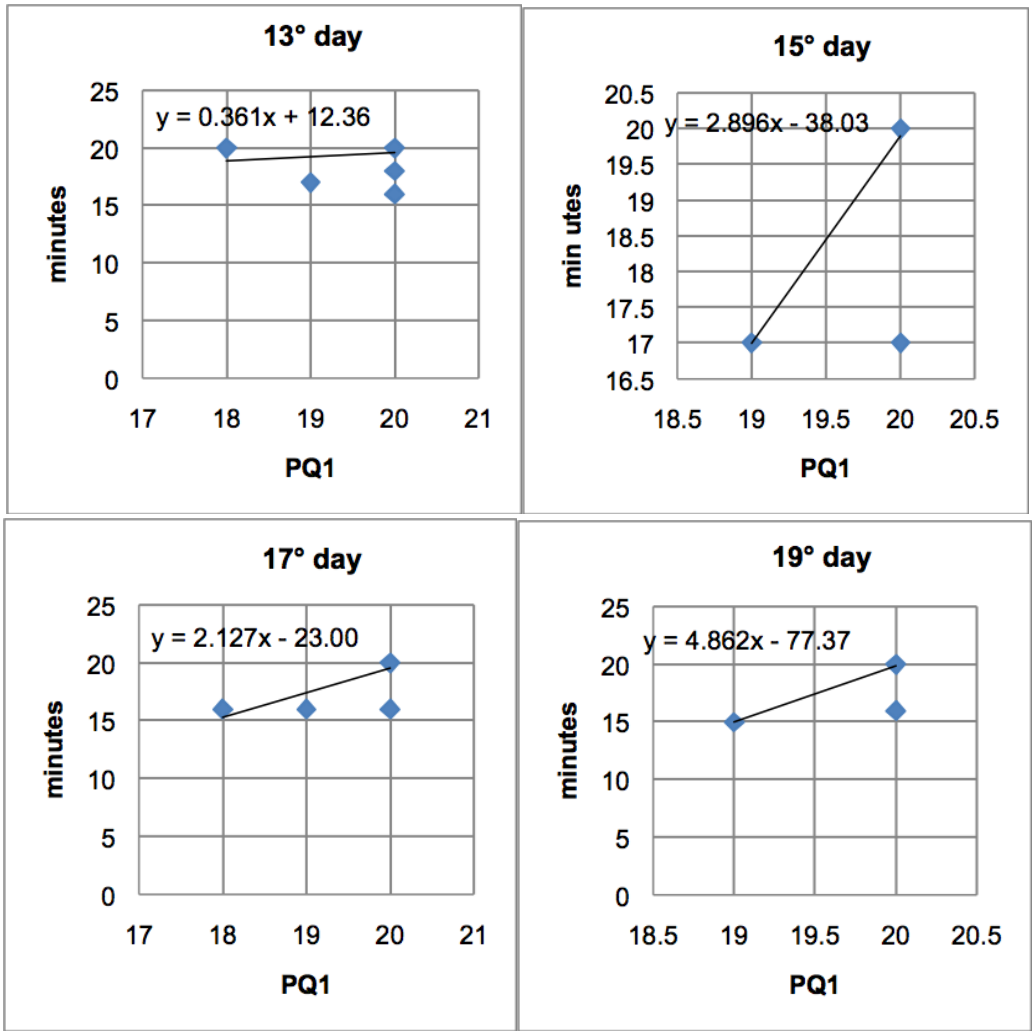


Figure 2: Correlations (Pearson product moment) between PQ1 and writing-time (min) by the healthy matched controls from Test day 1 to Test day 19 (10 days of testing). The correlations were significant only on: Day 15: 0.695•; Day 17: 0.565*; Day 19: 0.772*.

* p < 0,0001.•p < 0.005, Pearson Product moment correlations.

Table 2: The Performance of AD Patients on the Tests of Cognition, PQ1 and PQ2, the Difference between these Tests, DΔ, and in the Writing Test. Comparisons of the Means of Test Days 1-9 with those of 11-19 Using Scheffé's Test (Days 1-9 vs Days 11-19): [1]F (9, 290) = 39.64; [2]F (9, 290) = 7.14; [3]F (9, 290) = 76.98; [4]F (9, 290) = 33.97

Days of Testing	[1]PQ1	[2]PQ2	[3]Δ	[4]Writing-time (min)	No. Pat.
Day 1	11.87±4.8	4.03±1.9	7.83±4.8	8.73±6.4	30
Day 3	10.47±4.2	4.13±1.3	6.31±3.0	8.13±4.9	30
Day 5	9.90±5.1	4.80±2.9	5.10±5.1	8.53±7.1	30
Day 7	9.47±4.6	5.17±2.4	4.30±3.1	5.63±5.3	30
Day 9	11.83±3.1	5.67±2.1	6.21±2.7	8.03±5.9	30
Mean Days 1-9	**10.79±4.3°**	**4.76±2.1***	**5.95±3.7***	**7.81±5.9***	**30**
Day 11	8.90±4.4	5.03±2.7	3.86±2.6	5.33±5.2	30
Day 13	9.27±4.3	5.47±2.7	3.80±3.0	5.56±5.8	30
Day 15	8.90±4.4	5.10±2.9	3.80±2.8	5.36±5.6	30
Day 17	9.47±4.0	5.37±3.0	4.10±2.7	6.43±5.5	30
Day 19	9.43±5.3	4.50±3.4	4.93±2.9	7.4±7.4	30
Mean Days 11-19	**9.19±4.4**	**5.09±2.9**	**4.09±**	**6.01±5.9**	

*p < 0.0001; ° p < 0.01, versus combined mean from Test days 11-19.

Table 3: The Performance of Healthy Control Group on the Tests of Cognition, PQ1 and PQ2, the Difference between these Tests, DΔ, and in the Writing Test. Comparisons of the Means of Test Days 1-9 with those of 11-19 Using Scheffé's Test (Days 1-9 vs Days 11-19): [1]F (9, 290) = 2.98; [2]F (9, 290) = 2.98; [3]F (9, 290) = 1.53; [4]F (9, 290) = 0.09

Days of Testing	[1]PQ1	[2]PQ2	[3]Δ	[4]Writing-time (min)	No. Cont.
Day 1	20±0	19.9±0.5	0.1±0.5	19.6±1.2	30
Day 3	19.86±0.5	19.76±0.6	0.1±0.3	19.53±1.3	30
Day 5	20±0	19.9±0.4	0.1±0.4	19.63±1	30
Day 7	19.93±0.3	19.86±0.5	0.06±0.6	19.7±1.1	30
Day 9	20±0	19.86±0.33	0.13±0.3	19.63±1	30
Mean Days 1-9	**19,96±0.2***	**19.86±0.5***	**0.10±0.4**	**19.62±1.1**	**30**
Day 11	20±0	19.86±0.5	0.13±0.5	19.6±1.3	30
Day 13	19.9±0.4	19.8±0.7	0.1±0.4	19.56±1.2	30
Day 15	19.96±0.1	19.87±0.5	0.1±0.4	19.8±08	30
Day 17	19.9±0.4	18.7±0.8	0.2±0.5	19.33±1.5	30
Day 19	19.96±0.1	19.8±0.5	0.13±0.4	19.7±1.1	30
Mean Days 11-19	**19,94±0.2**	**19.81±0.6**	**0.13±0.4**	**19.60±1.2**	

*p < 0.01, versus combined mean from Test days 11-19.

performance of the healthy controls on the tests of cognition, PQ1 and PQ2, the difference between these tests, DΔ, and in the writing test.

Correlational Analyses: MMSE and PQ1, Writing-Time and PQ2

Marked and significant correlations were obtained between MMSE scores and the performances on PQ1, minutes writing and PQ2 in both AD patients and the control group (see Table **4**).

DISCUSSION

The extent of dysgraphia and deficits in cognitive performance were examined in AD patients and matched healthy controls. It was observed that: (1) The AD patients presented marked and significant linear relationships between the initial cognitive performance (PQ1) and extent of dysgraphia over nine days of testing with the exception of Test day 13 whereas these relationships were not evident in the healthy controls. (2) The AD patients showed marked deficits in all four tests of cognition, PQ1, PQ2, DΔ, which expresses the deterioration from PQ1 to PQ2 testing, and letter-writing, compared with the healthy controls. (3) It was observed also that for the AD patients' PQ1, DΔ and writing-time, that performance deteriorated from Test Days 1-9 to 11-19, but improved slightly for PQ2, whereas for the healthy controls, it was observed that the performance of PQ1 and PQ2 was slightly, significantly worse from Test days 1-9 to 11-19; whether or not this slight deterioration over test days by the control subjects represents anything more than some expression of the monotony of the tasks for these individuals is difficult to assess. Nevertheless, the marked deterioration for PQ1, DΔ and extent dysgraphia by the AD patients suggests some clinical relevance in disease progression. (4) Marked and significant correlation between MMSE scores and PQ1, writing time and PQ2 were obtained.

Dysgraphia appears to be associated with alterations in motor function, as well as language, domains in AD; the consideration of the heterogeneous aspect of this expression of this condition offers novel insights of the cognitive nature of disorder, including linguistic processing, motor programming and motor kinematics. Pauc and Young [44] have observed that the medial walls of the cerebral hemispheres, notably the cingulate gyri, contain species-specific neuron fields that to date are not well known within the

Table 4: Correlations between MMSE Scores and the Performances on PQ1, Minutes Writing and PQ2

	MMSE – PQ1	MMSE – Writing time	MMSE – PQ2
AD patients	0.792***	0.790***	0.788***
Controls	0.711**	0.708**	0.649*

***p < 0.0000003; **p < 0.00001; *p < 0001, two-tailed tests.

scientific community and yet have been implicated as the underlying cause of such varying conditions as dysgraphia and autism in children and obsessive-compulsive disorder and AD in adults. Lambert *et al*. [8] tested mild-to-moderate stage AD patients (n=59) and healthy elderly controls over an extensive assessment of both the central and peripheral components of writing. The healthy elderly controls performed significantly better than the AD patients over a broad spectrum of writing measures. Despite the occurrence of predominantly lexical disorders, there were multiple indications of linked disorders located at different stages in the writing/spelling system (e.g. phonological route, graphemic buffer, allographic store, graphic motor patterns). The authors concluded that there exist heterogeneous profiles of dysgraphia with primary signs of writing impairment in AD originating from changes at different points in the brain networks that subserve writing and spelling performance [8]. It has been shown too that sensory-motor plasticity is impaired in the motor cortex (see below parietal cortex glucose hypometabolism) of AD at an early stage of the disease [45], with evidence for altered parietal-motor connections in AD implicating related motor deficits in dysgraphia [46]. Suh *et al*. [47] performed Hanja (ideogram) and Hangul (phonogram) reading/writing tasks on six Semantic dementia (SD) patients and nine AD patients, in order to distinguish between AD and semantic dementia. SD patients manifested Hanja alexia/agraphia whereas Hangul reading/writing ability was relatively preserved. There were group differences between SD and AD patients in the Hanja tasks but not in the Hangul tasks. In the former, SPM analysis (a directed writing and continuous writing technique) revealed no evidence of hypometabolism in the posterior fusiform gyrus, but only in the middle and the anterior part of the temporal gyrus. Finally, significant differences between AD patients and healthy control individuals have been found for visuomotor task measures demonstrating large effect size deficits by AD patients especially with visuomotor task progression through its varying conditions [48].

During the clinical course of AD, dysgraphia occurs during both the earlier as well as the later stages of disorder progression [49-51]; it is linked to attention and memory deficits that develop during the staging of AD [52]. The regional and functional disturbances in writing disorders have been described quite comprehensively [53] Nevertheless, decline in semantic memory is a key feature of AD, and reading and writing performance deterioration as the extent dysgraphia progresses, reflects this loss [54, 55]. Dysgraphia has been suggested to be a more sensitive indication of language deficits in AD than anomia [9]. In a sample of 75 AD patients and 20 healthy controls, Yoon *et al*. [56] presented Korean participants with Hangul writing tasks. They observed that the writing performance of the AD group was significantly defective with a profusion of different types of errors emerging with disorder progression. Concurrent analysis of PET imaging studies of glucose metabolism indicated that the hypometabolism in the right occipitotemporal lobe and left temperoparietal lobe was linked to Hangul writing impairment, in accordance with lesions studies of dysgraphia [57]. In a sample of 35 patients presenting early onset AD, with a severe degree of hypometabolism in the parietal brain region, exhibited not only linguistic errors but also visuoconstructional manifestations (derived from Hangul scripts) of dysgraphia that were associated with cognitive impairments in multiple domains [34]. Finally, Hayashi *et al*. [58] studied a group of Japanese patients presenting mild AD and 22 healthy controls for performance of Kana writing performance dictation and copying Kanji or dictational Kanji. They found that writing to dictated Kanji words was impaired although Kana writing to dictation and copying Kanji were preserved in these AD patients; impaired writing of dictated Kanji words was associated with dysfunctional cortical activity predominantly in the left frontal, parietal and temporal brain regions [58]. These observations appear to be consistent with those derived from several other Japanese studies pertaining to dysgraphia in AD and applying this type of writing [59-61]. It is relevant in considering the utility of dysgraphia and the cognitive performance tests that marked and significant correlations between MMSE scores and PQ1, writing time and PQ2 were obtained (see Table **4**).

In summary, the present study describes strong relationships between dysgraphia and initial cognitive performance (PQ1) in AD patients, but not matched healthy controls, over all the days of testing were observed. Concurrently, consistent deficits by these patients over PQ1, PQ2, DΔ and writing-time compared the group of healthy control subjects were obtained. Furthermore, the performances of the AD patients on the PQ1, DΔ and writing-time, but not the PQ2, tests deteriorated from the 1st five days of testing (Days 1-9) to the 2nd five days (11-19). Marked relationships were obtained also between MMSE scores and PQ1, writing-time and PQ2 for both AD patients and healthy controls. These observations fit effectively with those observed previous regarding the production of oral and written words in AD patients [62]. Possibly, the manifest benefits arising from a non-invasive, motor system-generated intervention, e.g. physical exercise

programs, may offer a suitable alternative for these patients to maintain a degree of functionality [63].

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CONFLICT OF INTEREST

There is no conflict of interest.

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