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Full Length Article

Characterization of the fine motor problems in patients with cognitive dysfunction – A computerized handwriting analysis

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ABSTRACT

This study proposed a new technology to assess the accuracy of Chinese handwriting by comparing every stroke movement between a template model and a handwritten script. It tested the feasibility of a computerized evaluation in the parameterization of the handwriting deterioration caused by impaired cognitive function. This study recruited 22 participants with Alzheimer's disease (AD) and 14 with amnestic mild cognitive impairment (aMCI); 18 age- and gender-matched healthy elderly individuals made up the health control. The graphomotor tasks included drawing four straight lines (vertical, horizontal, and two diagonal) as well as writing Chinese words with simple vertical, horizontal and diagonal strokes. The temporal and spatial data were calculated to measure the motor coordination.

The results in geographic drawing tests reveal significant differences among the three groups in task accuracy and movement fluency, especially in nonequivalent and wrist movements. The accuracy control of the graphic drawing in the AD and aMCI groups was significantly lower than that for the subjects in the normal group. These two groups also showed longer pauses in stroke movement with the handwriting tasks. The handwriting accuracy in the AD and aMCI groups was found to be significantly different from that of the subjects in the normal group. The results of this study can be used as an indicative reference for early detection of AD or aMCI, an objective evaluation for the effectiveness of interventions, and an assessment of disease progression.

1. Introduction

Alzheimer's disease (AD) has a long preclinical phase, during which its characteristic pathology accumulates and patient function declines, but symptoms are insufficient to warrant a clinical diagnosis of dementia. There have been increasing reports of non-cognitive symptoms, including loss of motor function, apparently associated with AD (Buchman & Bennett, 2011).

During the past decade, the scientific community has started to focus attention on individuals who have symptoms of forgetfulness that exceed those associated with normal aging, but who are not severely enough affected to meet criteria for AD or other forms of dementia. These individuals, who are often diagnosed with mild cognitive impairment (MCI), may be in the very earliest or pre-clinical phase of AD.

Theoretically, initiating treatment in those individuals with MCI at the earliest possible stages may help delay and/or reduce the risk of conversion to AD or other forms of dementia (Petersen, 2004; Petersen et al., 1999). If changes in motor function and control occur in MCI, these findings may help clinicians to differentiate these impaired individuals from their healthy peers, and to identify those individuals with memory problems who are at increased risk for conversion to AD. In addition, quantifying the specific

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characteristics of motor performance in MCI patients may help further our understanding of the possible mechanisms underlying the motor and cognitive deficits of AD.

In subjects with AD or MCI, the source of motor dysfunction may result from cognitive dysfunction (Yan, Rountree, Massman, Doody, & Li, 2008). Cognitive deficits or "noise" in the sensory-motor system may contribute to reduced levels of motor performance associated with aging or AD (Petersen et al., 2000; Walker, Philbin, & Fisk, 1997). Changes in the brain from neurodegenerative dementia (e.g., brain atrophy, neuronal loss, cellular or synaptic dysfunction) cause both cognitive and motor dysfunction or impair the performance of previously learned motor skills (Dick, Nielson, Beth, Shankle, & Cotman, 1995; Pennanen et al., 2004). This suggests that there may be a motor phenotype of decline in cognitive performance, which could be used to improve the prediction of dementia.

Handwriting is a typical skill that requires integrated sensorimotor functions. Related neuropsychological tests have been proposed for studying the clinical course and transition of diseases (Fukui & Lee, 2008; Hughes, Graham, Patterson, & Hodges, 1997; Werner, Rosenblum, Bar-On, Heinik, & Korczyn, 2006; Yoon et al., 2011). For early detection of disease, peripheral-type progressive agraphia has received attention as an early symptom of degenerative dementia (Hughes et al., 1997). Peripheral or nonlinguistic agraphia describes mechanical distortions of writing in which the output processes specific to writing "rather than spelling" are disrupted. It was assessed by copying and cross-case transcription (transpose single letters from upper-case print to lower-case cursive and vice versa). They found that the patients with mild AD had difficulty producing appropriate single letters even in letter copying but especially in cross-case transcription.

In a recent study, Yoon et al. (2011) explored the diverse error patterns manifested in writing single syllables in Korean patients with early onset AD. They used the "visuoconstructional script" characteristics of the Korean writing system, Hangul, to measure the neuropsychological variables as well as the severity of dementia. Visuoconstruction is an organizing activity in which the spatial relations among the component parts must be accurately perceived if these parts are to be synthesized into the desired unity. The primary goal of visuoconstruction research was to understand the relationship between local brain lesion site and neuropsychological test performance. Hangul writings were used as visuoconstructional tasks since they are syllables typically made up of an initial consonant-grapheme, followed by a vowel-grapheme, and then another consonant-grapheme. These graphemes are arranged in a square pattern and a combination of these syllables form a word. They found the performances of early onset AD patients were significantly worse than those of the healthy controls. Early onset AD patients demonstrated not only linguistic errors but also visuoconstructional errors even in the early stages of the disease. They revealed that agraphia for Hangul writing was associated with cognitive impairments in multiple domains such as attention, language, immediate memory, and frontal executive function.

In addition to conventional neuropsychological tests, the computerized or tablet handwriting process has also been used to study the impacts of mild cognitive dysfunction. In a study that kinematically examined the handwriting process of persons with MCI, Werner et al. (2006) compared those with mild AD and the healthy controls. They found participants with MCI and with mild AD spent a significantly longer time with the pen in the air (i.e., in-air time) than did healthy participants, with the MCI group assuming a position between the other groups. With the exception of velocity, all kinematic measures (in-air time, on-paper time, on-paper length, and pressure) consistently differentiated between healthy and mild AD participants. Information gathered about kinematic measures, together with cognitive functioning, allowed them to classify 69%–72% of the participants correctly; however, the classification for the MCI group was relatively poor.

Our previous study also revealed that the AD and MCI participants had more difficulty drawing perfect circles than did the healthy controls, but this was not the case in the tasks involving straight lines and cursive-connected loops. There were no significant deteriorations in aMCI and AD subjects in such graphomotor tasks without an accuracy constraint. By measuring the mean velocity in the aiming-related tasks, the AD and MCI participants were revealed to perform the task more slowly than did the healthy controls. When accuracy was specified, the AD and MCI participants were also revealed to perform the graphomotor tasks requiring wrist and finger coordination more slowly than did the healthy controls. Similar to other kinematic studies, the degree of motor impairment, particularly in aiming movements with accuracy constraints, was related to the level of cognitive dysfunction (Yu & Chang, 2016).

In a similar study, Kawa, Bednorz, Stępień, Derejczyk, and Bugdol (2017) found that subjects with confirmed MCI needed more time to complete tasks because their writing was significantly slower. They found a longer time was needed to complete a single stroke of written text. In addition, they found a substantially longer pause between strokes. In the MCI group, a less fluent writing was found from an increased number of separable strokes in the whole task whereas the number of full pen strokes per time unit was reduced. They also noted the written characters were noticeably larger in the MCI group.

MCI is an early and transitional stage between normal brain aging and dementia, affects an array of cognitive or motor functions (Yan & Dick, 2006). However, relatively little is known about changes in motor function and control in patients with MCI. Most researchers agree that motor coordination problems evident in MCI are, in part, the result of perceptual and cognitive processes, but the limited research available remains inconclusive. In view of the lack of classification in neurological signs or physical impairment, it is important to understand the nature of motor coordination problems observed in patients with MCI.

The present study evaluated motor control in handwriting across AD, MCI, and the healthy controls. Chinese handwriting tasks were used for their visuoconstructional script characteristics. In Chinese handwriting, the primary requirement for legibility and accuracy is the correct placement of strokes in an appropriate position with the required length and slope. Most strokes in Chinese characters are horizontal or vertical, and they occasionally include diagonal lines. By matching every handwritten stroke to the corresponding template, we have proposed a computerized method to identify the accuracy of written Chinese characters. The legibility and accuracy of handwritten text can be scored by calculating the distance and the difference in length and orientation between the template and the corresponding handwritten strokes. The purpose was to explore whether the declines in fine motor control and coordination characterize sensory-motor deficiencies of cognitively impaired populations such as AD and MCI patients.

Through the above reviews and deliberations from previous studies, three questions have been raised: What major differences exist in handwriting characteristics between subjects with or without cognitive impairment? What are the important factors in using computerized handwriting in a clinical setting for screening or monitoring the degenerative process? Finally, are these parameters and their variances different between subjects with or without insidious cognitive degeneration? The aim of this study was to compare the handwriting process in subjects with different levels of cognitive dysfunction.

The objective of this study aimed at the characterization of handwriting deficits sourced from motor dysfunction. Taking into account previous reports of motor impairment in MCI and AD, we hypothesized that motor complications would be detectable in simple fine motor tasks and that motor and cognitive performance might be differently associated with handwriting-related skills. The objective of this study was to evaluate group differences among healthy controls, subjects with MCI, and subjects with AD, using a series of simple handwriting tasks, and in addition to investigate potential associations with cognitive function.

2. Methods

2.1. Subject recruitment and confirmed diagnosis

A total of 54 individuals participated in the present study. Twenty-two individuals with AD (mean age 74.6 ± 4.9 years), 14 individuals with amnestic mild cognitive impairment (aMCI) (mean age 74.9 ± 5.2 years), and 18 older adults (mean age 75.8 ± 5.8 years) as healthy controls (HC) with no history of neurological or current physical disease were recruited for the study. We recruited from among persons with aMCI and from those diagnosed with AD from the Veterans Home and EDA Hospital in southern Taiwan. The participants in HC group were recruited from the Veterans Home and three day-care centers in the same area. They were free of significant underlying medical, neurological, or psychiatric illness.

All the participants underwent a complete physical and neurological evaluation by a neurologist and completed a standardized dementia workup. To be included in the study, participants needed to be at least 65 years of age, be free of significant underlying medical illness, have a Clinical Dementia Rating (CDR) (C. P. Hughes, Berg, Danziger, Coben, & Martin, 1982) of normal (CDR = 0), aMCI (CDR = 0.5), or AD (CDR ≥ 1]), and be willing to participate in the study procedures. A detailed history and interview with the patient and informant, as well as neurological and physical examinations, were performed as part of the initial visit. The diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). These criteria required a history of cognitive decline and impairment in at least two cognitive domains, one of which had to be memory, for a diagnosis of AD. Possible AD cases with atypical onset or progression or other systemic brain diseases capable of producing dementia were excluded from this study.

We recruited aMCI patients, since this disorder is known to be a high-risk factor for developing dementia. Participants were classified as having aMCI if they met the following conditions: (a) memory complaint usually corroborated by an informant, (b) objective memory impairment for age, (c) essentially preserved general cognitive function, (d) largely intact functional activities, and (e) no presence of dementia (Petersen, 2004). The healthy controls (HC) were confirmed as non-demented based upon the standardized dementia workup. Within the cohort of the longitudinal investigation, the HCs were selected to match the AD and aMCI patients as much as possible with respect to age, education, and gender. All participants were right-handed and had normal or corrected-to-normal vision. Each participant or their legal representative signed an informed consent form approved by the Institutional Review Board prior to the experiment.

2.2. Instruments and apparatus

Participants were seated on a chair in front of a table on which a digitizer tablet (487 × 318 × 12 mm, Wacom Intuos 5, Japan) was positioned so that the tablet's lower edge lined up with the edge of the table at which the participant was seated. On the digitizer tablet, an A4-sized piece of paper was positioned with the vertical and horizontal edges parallel to the horizontal and vertical edges of the digitizer. The participant's forearm was positioned at an angle of about 30 deg with the horizontal edge of the digitizer tablet. A standard sized wireless electronic inking pen with a force-sensitive tip (2048 levels) was used to collect the movement data on the digitizer tablet. The axial pen force and X (horizontal) and Y (vertical) positions of the pen tip were sampled at a frequency of 200 Hz with a spatial resolution of 0.005 mm.

2.3. Graphomotor tasks

The experiment included two graphic and two handwriting tasks to assess fine motor function. These were (1) three 50-mm squares (i.e., two horizontal and two vertical lines forming a closed square) (Fig. 1A), (2) three diagonal crosses in a 50-mm square (Fig. 1B), (3) Chinese character "井," pronounced "Jing," in a row (5 copies) and a column (5 copies), (4) Chinese character "正," pronounced "Zheng," in a row (5 copies) and a column (5 copies). The first two tasks were related to basic biomechanics and sensorimotor control of handwriting. They were used to investigate movement accuracy, which is necessary in Chinese character formation. The first task required the participants to make equivalent movements (i.e., they were required to flex the fingers and the wrist together and vice versa to extend both together) to draw vertical lines. When drawing horizontal lines, the participants needed to make nonequivalent movements (i.e., they were required to flex the wrist but extend the fingers or to extend the wrist but flex the fingers simultaneously). In the diagonal cross task, the left-top to right-bottom line required mostly finger movements; the right-top to left-bottom line required mostly wrist movements. This task separately tested the coordination of fingers and wrist movements.

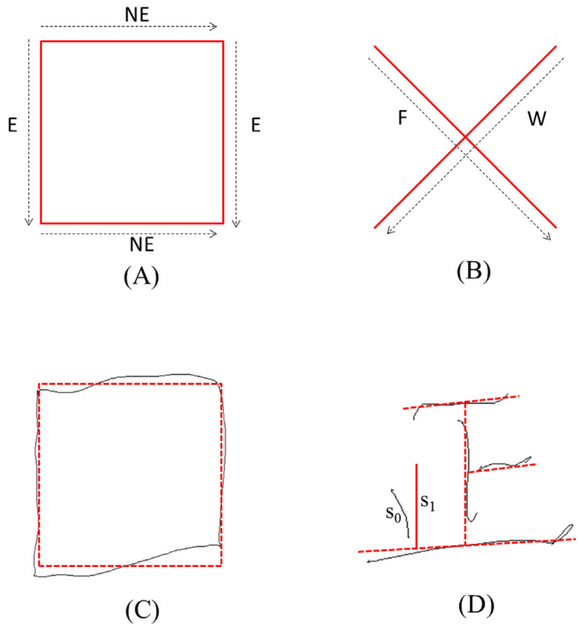

Fig. 1. (A) The model for requiring equivalent (EQ) and nonequivalent (NE) movements. (B) The model for requiring wrist (W) and finger (F) movements. (C) An example of mean squared errors in the four straight line drawings. (D) An example for scoring the placement of the stroke (s_0) by comparing with the corresponding stroke (s_1) in the character "正" (Red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the two handwriting tasks, we used a typically Chinese character task to test the participants' ability to precisely control the wrist and fingers. The characters were chosen to measure the control of stroke placement with either short or long length and with either vertical or horizontal orientations.

Before every test, the examiner showed and instructed participants how to copy the template. The participants were requested to perform three practice trials prior to the measurements. They were instructed to perform the task as quickly and as accurately as possible. During the trial, a template with the exact dimensions required was presented on the table just above the digitizer tablet. The participants were instructed to copy exactly the provided templates; size accuracy and correct alignment were emphasized in these conditions. They were instructed to perform the task as accurately and as consistently as possible. The order of task presentation was randomized across the participants.

All the subjects understood the instruction to perform the handwriting tasks. To avoid the effect of different education levels, simple tasks were chosen to reduce interference from the education-level-related cognitive factors. With a minimum education level of elementary school, every subject was confirmed as knowing how to copy the two characters.

Since Chinese handwriting runs from the top down for vertical writing and from left to right for horizontal writing, the subjects were instructed to copy the testing task character by character on the test sheet from the top or left. The examiners gave instructions and monitored the practice process. After confirmation that the subjects knew how to proceed, the measurement started. The whole process was recorded, and the data were saved to a computer hard disk for further offline analysis.

2.4. Data processing and analyses

To estimate spatial accuracy, the mean squared error (MSE) of the deviation between the drawing trajectory and the target line was computed. Fig. 1C shows an example of a square drawn by a participant (solid line) and the reference square (dotted line). The reference square has the same center location and size as those of the drawn figure.

After surveying the results of related research (Rosenblum & Livneh-Zirinski, 2008; Werner et al., 2006) and the results and experiences of our previous studies (Chang & Yu, 2013; Chang, Yu, & Shie, 2009), a number of spatial and kinematic parameters were chosen for the evaluation of the handwriting process. They examined the movement fluency by observing the pauses of pen tip and the ratio of in-air to on-paper motion. To examine the handwriting accuracy, they measured the ability of the arrangement of characters or individual strokes. The parameters were obtained directly from the registered coordinate or derived from the temporal or spatial data of the pen-tip movement. The following are the operative definitions of the parameters processed from the registered coordinates.

2.4.1. Movement fluency in handwriting tasks (Chang & Yu, 2013; Rosenblum & Livneh-Zirinski, 2008)

1. **Pause time per stroke (PTS):** This measures the dysfluency of movement from the temporal data. If two consecutive sampling

points had the same registered coordinate, the period was cumulated and referred as pause time. This parameter is derived by dividing the cumulative pause time by the total stroke number.
2. **Ratio of In Air to On Paper time (RAPT):** This parameter measures the proportion of pen-tip halting time in the air. It is derived by dividing the total In Air time spent on the task by the total On Paper time.
3. **Ratio of In Air to On Paper trajectory length (RAPL):** This parameter measures the proportion of wandering length in the air. It is derived by dividing the total In Air trajectory length by the total On Paper trajectory length.

2.4.2. Handwriting accuracy

1. Size and alignment of characters (Chang et al., 2009)
   (1) **Character size variation (CSV)**: This is a rating procedure that rescales the handwritten character to the same size of the template character. Since the template is a squared layout, however the handwritten character may be different between vertical and horizontal scales. As such, the handwritten character was first placed into a square grid with the side length equal to the larger one of the original vertical or horizontal scale. The handwritten character may be enlarged or shrunk to fit the size of the template. The variation of the character size indicates the degree of ability in character-size control. The value of 0 indicates perfect control.
   (2) **Character alignment control (CAC)**: This includes vertical and horizontal alignment control. The vertical or horizontal midline was computed as to minimize the total distances from registered geometrical centers to the midline. The deviant distances of all character centers in relation to the central vertical or horizontal line are summed up. The value of 0 indicates perfect control.
2. Position, length and orientation of individual strokes
   (1) **Stroke position control (SPC):** This is the summed distance between the centers of the corresponding strokes of the template and the handwritten texts. The value of 0 indicates perfect control.
   (2) **Stroke length control (SLC):** The length difference between the template and the handwritten strokes is divided by the length of the template stroke to get a ratio that indicates the deviant from the template length.
   (3) **Stroke orientation control (SOC):** The slopes of the two strokes are calculated to measure the angle between the corresponding strokes. By taking the arctangent of the slopes, the program can determine the angle between the stroke line and the horizontal line. The difference in angles between the corresponding strokes indicates the deviation in stroke orientation.

2.5. Demographic data and statistical analyses

For the statistical comparison of the participants' demographic and handwriting characteristics among the groups, one-way analysis of variance (ANOVA) for continuous measures was used to compare the three groups of subjects. The relevant pairwise comparisons were made between adjacent groups (e.g., HC vs. aMCI and aMCI vs. AD) using the Bonferroni test with a level of significance set at the 0.05 level. Repeated-measures ANOVA was used to test the significance of difference across the groups and graphic tasks and the interaction effect of the group and task. Post hoc tests with Bonferroni correction were utilized to determine the locus of significant effects of the group (i.e., HC, aMCI, and AD). All statistical analyses were conducted using PASW Statistics (Version 18, SPSS Inc., Hong Kong, 2009).

Table 1
Demographics and psychometrics of the participants (N = 54).

	HC CDR 0	MCI CDR 0.5	AD CDR 1–2
N	18	14	22
Age (years), mean (SD)	75.8 (5.8)[a]	74.9 (5.2)[a]	74.6 (4.9)[a]
Gender, Male/Female	13/5[a]	10/4[a]	15/7[a]
Education (years), mean (SD)	8.9 (3.6)[a]	9.1 (2.9)[a]	9.6 (3.2)[a]
WMS-III			
LM I	10.5 (2.5)[a]	7.1 (2.8)[b]	2.6 (.7)[c]
LM II	9.7 (3.4)[a]	6.3 (3.0)[b]	3.1 (.9)[c]
VR I	12.5 (1.6)[a]	7.2 (2.2)[b]	3.2 (1.1)[c]
VR II	10.4 (2.4)[a]	6.8 (1.3)[b]	4.1 (.8)[c]

HC = healthy control participants, aMCI = participants with amnestic mild cognitive impairment, AD = participants with Alzheimer's disease.
WMS-III = Age-corrected scaled score of Wechsler Memory Scale-3rd ed. (Chinese version).
LM = Logical Memory, VR = Visual Reproduction. Analyses reflect differences at the .05 level for comparison of adjacent groups. Same letters (i.e. a, b and c) indicate no significant difference between pairwise comparison.

Table 2
Mean squared error in movement control of drawing straight lines.

	Equivalent	Non- Equivalent	Wrist	Fingers
HC	0.19 (0.17)	0.20 (0.08)	0.27 (0.12)	0.30 (0.23)
aMCI	0.22 (0.31)	0.41 (0.14)	0.55 (0.08)	0.32 (0.18)
AD	0.23 (0.88)	0.38 (0.21)	0.54 (0.17)	0.37 (0.32)
Task effect	$F_{3,153} = 14.647$, $p < .001$, $\eta^2 = 0.473$			
Group effect	$F_{2,51} = 6.251$, $p = .004$, $\eta^2 = 0.197$			
Interaction effect	$F_{6,153} = 2.371$, $p = .035$, $\eta^2 = 0.125$			
Post hoc test	AD > HC** aMCI > HC** AD > HC* aMCI > HC*			

* $p < .05$.
** $p < .01$.

3. Results

3.1. Demographic characteristics

Table 1 shows the demographics and memory measurements of the participants. No significant difference was found in the comparisons of age, education, and gender ratios across the three groups. There was significant difference in the age-corrected scaled score of the Wechsler Memory Scale across the adjacent groups.

Table 2 shows the results in relation to the coordination control of drawing lines for comparing different types of movement. Among the movement types, the MSE's are significantly larger in non-equivalent and wrist movements than those of equivalent and fingers ($p < .05$). The result of repeated-measures ANOVA revealed significant main effect and interaction effect. In a comparison of the three groups, the AD and aMCI groups showed significantly larger MSE than those of the HC group in non-equivalent and wrist movements. In comparing the three groups, no significant difference was found in equivalent and fingers movements.

Table 3 shows the results of temporal and spatial data on the handwriting tasks. Significant difference was found in RAPL and PTS. The AD group showed larger RAPL and PTS than the HC group did. From the post hoc test, the aMCI group showed significantly longer PTS than the healthy control did.

Table 4 summarizes the results of character and stroke placement control in the handwriting tasks. The character sizes in AD and aMCI groups are larger than those in the HC group. From the results concerning CSV and CAC, no significant difference was found in the variation of character size and the linear alignment among the three groups. From the handwriting test, the accuracy of stroke placement was found to significantly differ among the three groups. The AD and aMCI groups showed significantly lower spatial accuracy than the HC group did.

4. Discussion

This study investigated the fine motor control of Chinese handwriting in subjects with varied levels of cognitive dysfunction. From the results of computerized evaluation, subjects with cognitive impairment demonstrated significant differences in handwriting performance when compared to healthy controls. The temporal and spatial parameters showed pauses or hesitation while writing, and these subsequent inactions or actions signified handwriting difficulty in subjects with AD or aMCI. Among the kinematic parameters applied for measuring motor control of handwriting proficiency, our results suggested that pausing on paper (PTS) and the dysfluency of stroke movement (RAPL) were better indicators of writing difficulties than the temporal parameter (RAPT). In subjects with AD or aMCI, the significant deterioration was found in the control of stroke placements but not in the control of character size and alignment.

Table 3
The temporal and spatial measures in handwriting tasks.

	RAPT	RAPL	PTS
HC	0.389 (0.078)	0.567 (0.062)	0.135 (0.091)
aMCI	0.429 (0.092)	0.612 (0.025)	0.239 (0.108)
AD	0.460 (0.107)	0.640 (0.086)	0.227 (0.126)
Main effect	$F_{2,51} = 2.752$ $p = 0.073$ $\eta^2 = 0.097$	$F_{2,51} = 5.879$ $p = .002$ $\eta^2 = 0.187$	$F_{2,51} = 4.576$ $p = .015$ $\eta^2 = 0.152$
Post hoc test		AD > HC**	AD > HC* aMCI > HC*

PTS: Pause time per stroke, RAPT: Ratio of In Air to On Paper time, RAPL: Ratio of In Air to On Paper length.
* $p < .05$.
** $p < .01$.

Table 4
The control of character size, alignment, and stroke placements.

	Characters			Strokes		
	Size	CSV	CAC	SPC	SLC	SOC
HC	1.01 (0.17)	0.15 (0.07)	0.31 (0.10)	1.29 (0.32)	1.61 (0.51)	0.10 (0.04)
aMCI	1.21 (0.31)	0.17 (0.06)	0.31 (0.13)	2.41 (0.94)	2.61 (0.71)	0.25 (0.18)
AD	1.23 (0.38)	0.21 (0.14)	0.39 (0.24)	2.45 (0.57)	2.72 (1.42)	0.30 (0.19)
Main effect	$F_{2,51} = 2.95$ $p = .061$ $\eta^2 = 0.09$	$F_{2,51} = 2.04$ $p = .141$ $\eta^2 = 0.08$	$F_{2,51} = 1.52$ $p = .229$ $\eta^2 = 0.001$	$F_{2,51} = 17.96$ $p < .001$ $\eta^2 = 0.394$	$F_{2,51} = 6.55$ $p = .003$ $\eta^2 = 0.151$	$F_{2,51} = 8.77$ $p = .001$ $\eta^2 = 0.221$
Post hoc test				AD > HC** aMCI > HC**	AD > HC** aMCI > HC*	AD > HC** aMCI > HC*

CSD: Character size variation, CAC: Character alignment control, SPC: Stroke position control, SLC: Stroke length control, SOC: Stroke orientation control.
* $p < .05$.
** $p < .01$.

For clinical realization of computerized evaluation, the measuring parameters of computerized handwriting evaluation should be linked with the handwriting model of motor-control theories. According to Van Galen (1991), the psychomotor system of handwriting includes three components in succession: the motor program, parameterization and regularization of the motor program, and muscular initiation, in order that the task may be performed. In this study, the increased PTS, RAPT and RAPL in subjects with early signs of cognitive dysfunction may be linked with the time needed in parameterization and regularization of the motor program and the initiation of muscle activity in the latter component. These parameters showed promising results in identifying the impaired characteristics independently of task length and complexity. The PTS with its real-time feature may be a more valuable and practical parameter for clinical applications as it can be more easily derived compared to the others.

This study found that the aMCI and AD groups showed similar impairment in temporal and spatial data. Kawa et al. (2017) also found similar results, revealing that subjects with MCI needed more time to complete tasks because their writing was significantly slower. They found a longer time was required to complete a single stroke of written text. The MCI group was found to show a longer pause between strokes. In our study, we not only found a pause between strokes but also a pause within a single stroke. These two delays may contribute to the slowness in the whole handwriting process. Kawa et al. (2017) also noted the written text was noticeably larger in the MCI group. The current study also found larger written characters in the aMCI and AD groups, but the difference did not reach statistical significance. This study noted the inappropriate stroke length (either shorter or longer than expected), which was important for accuracy and legibility. The implication of these findings would be that different clinical features may present in their own language system.

A Chinese character is composed of a certain number of strokes ranging from 1 to 30. Most of the strokes are straight lines (e.g. 正) while some have one or two turning points (e.g. "口") and a few have an arc like "弋." Different from Western or other language systems, the Chinese writing system has no strokes like a circle (e.g. "o"), semicircle (e.g. "c") or cursive coils (e.g. "ℓℓℓ") in its characters. The production of curves or coils is more difficult than straight lines. However, most of the challenge in Chinese handwriting comes from requiring the correct placement of all the strokes in a character. It requires correct position, length and orientation of each individual stroke. For example, the shorter horizontal stroke in "土" should not be at the bottom as in "士"; the three horizontal strokes in "日" are shorter than those in "曰"; the orientation of the uppermost stroke in "夭" is different from that in "天." They are different from their corresponding ones. The difference between characters may be the subtle requirement of fine position control in the stroke placement. These are all important factors that may influence the legibility, and most of them showed their significance in differentiating subjects with different clinical features.

Silveri, Corda, and Di Nardo (2007) studied lexical and phonological dysgraphia in patients affected by mild and severe dementia. Their data suggest that AD dysgraphia is first produced by a reduction of general cognitive resources. Hayashi et al. (2011) found that the ability to write Kana words to dictation and the ability to copy Kanji words were preserved in AD patients, but the ability to write Kanji words to dictation was impaired. Kana words (typical Japanese words), which are based on a phonetic system, are used in addition to Kanji words. Kanji characters are Chinese characters that are also used in the Japanese language system, but these characters, which are without phonetic function, are used less frequently in daily life. Fukui and Lee (2008) found that progressive agraphia may be one of the early symptoms of degenerative dementia such as corticobasal degeneration. They found that agraphia was generally more prominent for Kanji than Kana characters. They surmised this occurred due to later acquisition and due to there being a larger number of Kanji characters leading to a lower frequency of use and familiarity per character. Their results support the clinical significance of Chinese character writing tasks used in this study. A similar result was found by Yoon et al. (2011) in writing Korean letters. Their study revealed that patients with AD, especially early onset AD, can show visuoconstructional dysfunction due to its effect in the parietal areas. Writing errors may be more prominent in early onset AD than in later-onset AD patients because they demonstrate more hypometabolism extending into the frontal region as well as a more severe degree of hypometabolism in the parietal regions (Kim et al., 2005; Yoon et al., 2011), which are known to be involved in processing visuoconstructional function (Lezak, 2004). Their more complex graphic structure increases the challenge and ability required to successfully write the Chinese characters; this heightened difficulty may explain the deterioration of spatial alignment of strokes revealed in AD and aMCI subjects.

This study tried to separate the components related to fluency or accuracy in handwriting and handwriting-like movements. Our findings pertaining to movement fluency are consistent with those of previous studies (Werner et al., 2006; Yu & Chang, 2016), in which researchers found slower movement in subjects with deteriorating memory. However, this study showed significantly lower accuracy and consistency in the AD and aMCI groups. There was no such measurement in previous handwriting research. Accuracy and consistency in handwriting analysis studies require tests for accuracy and legibility. However, these variables are difficult to quantify, especially in Chinese handwriting with numerous strokes and a complex structure within a single character. The design for the current study may be much easier than a handwriting performance test for identifying dysgraphia or agraphia. To reduce the cognitive load, our previous study used straight lines and cursive l loops rather than Chinese handwriting. Besides complex graphomotor tasks with constraints in time and accuracy, pure motor tasks seemed unable to differentiate the difference across the three groups. This suggests that AD and aMCI participants may not show impairments in simple tasks with less cognitive demand or constraint. The precise constraint in Chinese handwriting tasks enhanced the differences among the three groups. This indicates that the impaired fine motor control of patients with aMCI and AD can be revealed in the handwriting task that requires coordination between fine motor skills and visuospatial function. This shows a clinical hallmark for the relationship between aMCI and the risk of AD.

For future application, the clinical meaning of the measuring parameters is important in the early screening or diagnosis of neurodegenerative diseases. This study tried to deconstruct the stroke movements in handwriting into four fundamentals. Movements produced using a nonequivalent manner or finger manipulation were found to deteriorate earlier than equivalent or wrist movements. The data collected for strokes with different orientations and directions may signify their clinical characteristics. In addition, the extent of the impairment is also important information that a clinical test should provide by offering a clear definition. As a parameterized baseline, most measurements used in this study have been normalized with a standard. The normalization procedure can provide a meaningful baseline as a reference for screening, diagnosis or monitoring the deterioration of these sensory motor functions. The deviation from the normal baseline can be presented by a ratio or percentage that signifies the deterioration level with a clearer definition.

5. Limitations

Our study had limitations that should be addressed. First, its cross-sectional design limited its potential to set predictive models of cognitive loss. Our analysis was based on a cross-sectional study, not on a longitudinal study; thus, it did not allow a time course but rather the differences among the three groups. In a longitudinal perspective, we could test whether patients with specific handwriting deficits are more likely to experience long-term cognitive loss. The other possible limitation is the definition of the accumulated pause time. Our definition was different from the work of van Gemmert, Teulings, and Stelmach (1998), in which they recorded pause time as being a period of time of 25 ms or more. What is the optimal period to define a pause? Future study is needed to validate a definition for identifying the pause in handwriting.

For the future clinical application with an aim of early detection, the related domains of the test intended to be measured should be completely identified. Handwriting tasks with a simplex configuration can identify the coordination problem, but may prove difficult in differentiating problems with mixed sensorimotor and cognitive dysfunction. Future studies can address the visuoconstructional features of complex characters and their related perceptuomotor functions. The result of the four movement patterns in the present study may be applied to the analyses of handwriting tasks and their related perceptuomotor functions.

6. Conclusion

Our results suggested that the impairment of cognitive function is associated with longer pause time and larger ratio of in air to on paper trajectory length in handwriting tasks. We also documented differential patterns of association of motor and cognitive functioning with handwriting tasks. Fine motor function seemed severely affected in both AD and aMCI subjects, as assessed in the stroke position, length, and orientation control of handwriting tests. AD and aMCI subjects showing difficulties in nonequivalent and wrist movement in performing strokes reflected the specific impairment in the fine motor control needed for handwriting. It is possible that these features could be used to screen individuals with insidious degeneration, which may improve early diagnosis and intervention protocols for individuals with cognitive dysfunction.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.humov.2018.06.006.

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