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Digital Handwriting Analysis of Characters in Chinese Patients with Mild Cognitive Impairment

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TITLE:

Digital Handwriting Analysis of Characters in Chinese Patients with Mild Cognitive Impairment

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KEYWORDS

cognitive disorder, digital technologies, handwriting analysis, kinematic, movement disorder, small vessel disease

SUMMARY:

This study proposed a digital handwriting analysis of characters in individuals with mild cognitive impairment to find more information than is revealed by traditional pencil–paper handwriting analysis.

ABSTRACT:

An increasing amount of evidence shows that cognitive deficits and movement dysfunctions are not separated. Patients with mild cognitive impairment (MCI) can manifest fine motor disorders of the upper extremities. Handwriting is a complex and unique human activity involving both motor and cognitive coordination. Researchers from western countries have discovered that patients with MCI have abnormal handwriting features. However, no relevant studies have been conducted in the Chinese population. Owing to the cross-culture phenomenon of handwriting, the aim of this study is to find new handwriting tasks to demonstrate the differences in handwriting features between elderly patients with MCI and age-matched healthy individuals.

INTRODUCTION:

Mild cognitive impairment (MCI) is considered as a transitional but progressively degenerative cognitive phase that precedes the onset of Alzheimer's disease (AD)[1]. It has been reported that the AD progression rate per year is 15% while nearly 75% of moderate and severe MCI cases might remain undiagnosed[2]. Recent studies have reported that patients with MCI have difficulty in some aspects of fine motor tasks[3], and those patients who showed motor disorders, such as slow gait, had a high risk of dementia[4].

Handwriting is a complex human activity that entails an intricate blend of cognitive, kinesthetic, and perceptual-motor components including visual and kinesthetic perception, motor planning, eye-hand coordination, visual-motor integration, dexterity, and manual skills[1]. Handwriting analysis has been utilized to detect cognitive and motor dysfunctions in many types of neurodegenerative diseases, such as AD and Parkinson's disease (PD)[5]. In addition, some aspects of handwriting problems have been reported to be an indicator for MCI and related to disease progression[6]. As a majority of the population uses language, studies that investigate handwriting analysis in Chinese speakers (especially simplified Chinese characters) are still lacking.

There have been several articles that have investigated handwriting abnormalities or "agraphia" in individuals with MCI. For example, by utilizing the traditional pencil–paper methods, Zhou and colleagues tried to unveil the distinct writing abilities between patients with MCI and individuals without MCI. The differences between the groups were not obvious, with the exception of writing errors[7]. Kawa et al. found handwriting features in patients with MCI using a smart pen, which could dynamically analyze the stroke and pen speed during writing[2]. WACOM hardware and MovAlyzeR software can detect more real-time information compared with traditional pencil and paper methods and smartpen paper methods. Therefore, dynamic handwriting data, such as pen-down pressure, velocity, acceleration, and jerk, have been found to be a new focus of handwriting analysis relative to static data, such as letter size and space between words[2].

However, another phenomenon that cannot be overlooked is the cross-cultural effect of handwriting. The writing systems of different nations are not always the same (e.g., English letters are written from left to right while Hebrew letters are written from right to left)[8]. In this issue, even reviews have confirmed the effectiveness of handwriting analysis[9,10] in alphabetic languages, and the wide gap between Chinese characters and western letters has hindered the interchange capability of handwriting analysis in the methods and results[11] of these studies.

There exist several major dissimilarities between western languages (e.g., English) and Chinese. First, there are many more horizonal movements of the pen tip during Chinese character writing compared with letter writing[12]. Second, unlike the alphabet language, which is associated with phonemes, Chinese is considered to be logographic[7]. As a result, most Chinese characters have their own unique stroke order, and the width and height of strokes need to be strictly limited. Otherwise, unlimited widths and heights might cause increased illegibility[11] ("日" and "曰" are completely different Chinese characters. Also, "木木昆", "林昆", and "木棍" are different Chinese characters).

"正" (pronounced "Zheng") is a typical, simple, and commonly used Chinese character that nearly every Chinese speaker with a two-year educational level can read and write. It has been selected as a writing task in previous Chinese handwriting analysis studies[6,12]. Researchers decided to use "正" as the writing task because it is "square-like" and composed of five strokes, all of which are horizonal (#1, #3, #5 stroke, from left to right) or vertical (#2, #4 stroke, from up to down) (**Figure 1**). According to many fine motor studies, fulfilling the #3 stroke (horizonal) and the #4 stroke (vertical) requires pure wrist and finger movements, respectively[6,12,13]. As a result, the stroke velocity of both strokes could be a proper manifestation[14].

In addition, pen pressure during handwriting is a handwriting feature that has been shown to outperform other kinematic features in reflecting motor control[5,15]. However, there are no relevant studies in Chinese patients, though positive results have been confirmed by research groups from the Czech Republic, Spain, Israel, and other countries[8,16,17].

The signature has been commonly used as a handwriting task in numerous studies[5]. In general, a signature requires little thinking or in-air time[18]. "In-air" is defined as when the pressure of the pen tip to the screen is 0 during the handwriting, and "in-air time" is the sum of the time "in-air" during the handwriting. Individuals who suffer from many neuropsychiatric disorders might have deficits in psychomotor control, and thus they exhibit increased in-air time of the signature. For example, Rosenblum et al. found that Israeli patients with depression and Parkinson's disease showed longer in-air time compared with healthy controls during writing their own name in Hebrew[8,19]. As Chinese characters have their own shape, in this study, it was decided to use the in-air length tortuosity in segmentation between characters during writing the name as a potential indicative parameter. Tortuosity, defined by the ratio of the arc length to the Euclidean distance between end points, is a measure of curvature, and therefore indexes the smoothness of a specific writing output[20].

PROTOCOL:

Our study was approved by the Academic Ethics Committee of the Biological Sciences Division of the Seventh Medical Center of PLA General Hospital in Beijing, China.

1. **General aspects of method development**

1.1. Use a USB digitizer (e.g., Wacom Cintiq Pro 16) and a handheld stylus pen for the handwriting movements. The detailed specifications of the digitizer are as follows: external dimensions (width x depth x height) 410 x 265 x 17.5 mm, spatial resolution 3840 x 2160 dots, pixel size 0.090 x 0.090 mm, temporal resolution 30 ms, and a pressure level of 8,192.

1.2. Connect a laptop PC to the digitizer to collect and exhibit the handwriting traces.

1.3. Use a software (e.g., Neuroscript MovAlyzeR) for data recording, processing, and analyzing.

1.4. Patient inclusion/exclusion criteria

1.4.1 Recruit MCI participants who present with a memory complaint, an objectively impaired memory function, intact activities of daily living, and the absence of dementia[21]. Besides, they should have the educational level of more than 2 years of preliminary school in mainland China, otherwise, they might have difficulty in writing Chinese characters.

1.4.2. Exclude participants who have obvious visual and upper limb disability.

2. **Handwriting task**

2.1. Run the software and a non-inking stylus pen.

2.2. Create an example of Chinese characters on the writing area of the digitizer (see **Figure 1**).

2.3. Allow the subjects to position the writing area into a comfortable position.

2.4. Allow the subjects to write on the writing area and accommodate the pen and the surface of the writing area.

2.5. Set the sampling rate in the software at 200 Hz.

2.6. Instruct the subjects to write his/her name in Chinese with the dominant hand.

NOTE: A signature in either cursive or a printed version is acceptable, as the subject wished.

2.7. Instruct the subjects to write the Chinese character "正" (pronounced "Zheng") with the dominant hand.

NOTE: The Chinese character "正" in a printed version is acceptable.

2.7.1. Remind the subjects to write in a printed version prior to beginning handwriting.

NOTE: Ensure that the subject sits and writes in an upright position.

2.8. Keep instructions visible during each trial.

2.8.1. Repeat the handwriting trial three times.

2.8.2. If the character "正" was in written in the wrong stroke order, stop the trial and trace and show the subject how to write the character in the correct stroke order.

2.8.3. If any hesitation was derived from a lack of knowledge, stop the trial and show the subject how to write the character correctly.

3. **Data analysis**

3.1. Run the software; right click on **Experiment** and select **Properties**.

3.2. Select **Processing**, and then select **Segmentation**.

3.3. Click on **Add first segmentation at any rate**, **Add last segmentation at any rate**, and **Move segmentation point to nearest pendown if on a penlift** in Segmentation Flags.

3.4. Click on **At pendown trajectories** in **Segmentation Methods**.

NOTE: All of these adjustments for the default mode were done to improve the analysis of the Chinese handwriting.

4. **Parameter calculation**

4.1. Run the software, select the subjects in "正", and click on **Handwriting Trials**.

4.2. Use the tracing system and trace the handwriting process and stroke order of "正" step by step.

4.3. Find the segmentation of stroke #3 of "正" and read out the "Average Absolute Velocity" in "extracted data".

NOTE: The handwriting analysis software will automatically calculate the "Average Absolute Velocity" of each segmentation.

CAUTION: Stroke #3 of "正" is a horizonal movement (from left to right) of the pen tip that is shorter than Character 1 and Character 5 (**Figure 1A**).

4.4. Find the segmentation of stroke #4 of "正" and read out of the "Average Absolute Velocity" in the "extracted data".

CAUTION: Stroke #4 of "正" is a vertical movement (from up to down) of the pen tip that is shorter than Character 2 (**Figure 1**).

4.5. Read out the "Pen Pressure" of each segmentation in the "extracted data" and obtain an "Average Pen Pressure" of "正".

NOTE: The handwriting analysis software will automatically calculate the "Average Pen Pressure" of each segmentation.

4.6. Run the software, select the subjects in "正", and click on **Handwriting Trials**.

4.7. Using the tracing system, trace the handwriting process and stroke order of the signature step by step.

4.8. Find the segmentation of the stroke between the characters and read out the "**Absolute Size**" and "**Road Length**" in the "**extracted data"**.

4.9. Obtain the in-air length tortuosity in the segmentation between characters according to the equation.

NOTE: The segmentation of the stroke between characters was an in-air segmentation (**Figure 2**).

4.9.1. Calculate the in-air length tortuosity: 1-Absolute Size/Road Length %.

NOTE: Tortuosity, defined by the ratio of the arc length to the Euclidean distance between end points, is a measure of curvature, and therefore indexes the smoothness of a specific writing output[20]. A highly tortuous curve has several bends or curves, whereas a low tortuous curve is one with relatively wide loops/curves and more straightness.

CAUTION: Most Chinese names are composed of two or three characters. If the signature has two characters, there is only one segmentation of stroke between characters. If the signature has three characters, there are two stroke segmentations between characters. In-air length tortuosity in the segmentation between characters would be an average value.

5. Statistical analysis

5.1. Evaluate group differences using a Student's *t*-test. A P value less than 0.05 was considered statistically significant. Conduct all statistical analyses using the SPSS 22.0 statistical software package.

REPRESENTATIVE RESULTS:

The demographic data of the subjects demonstrated that all the groups matched well in age, gender, educational level, dominant hand, and other parameters.

As shown in **Table 1**, during the writing of the Chinese character "正", elderly subjects with MCI exhibited a lower average absolute velocity of the #3 (2.46 ± 0.40 vs 1.82 ± 0.55, P = 0.001) and #4 stroke (2.61 ± 0.46 vs 1.93 ± 0.50, P < 0.001) and a higher average pen pressure (237.43 ± 39.77 vs 281.99 ± 37.70, P = 0.001) compared with healthy elderly subjects. Additionally, during the signing of Chinese names, the elderly subjects with MCI exhibited a higher in-air length tortuosity in segmentations between the characters compared with the healthy elderly subjects (12.57 ± 6.96 vs 31.66 ± 7.53, P < 0.001).

Figure 1: Chinese character "正" written in the software. (**A**). The Chinese character "正" with only the in-screen segmentations exhibited. The red circles are the beginnings and ends of the segmentations. The blue lines are the in-screen segmentation traces. (**B**). The Chinese character "正" with both the in-air and in-screen segmentations exhibited. The blue lines are the in-screen segmentation traces. The grey lines are the in-air segmentation traces.

Figure 2: Chinese signatures of healthy elderly subjects and elderly subjects with MCI. (**A**). The Chinese signature "张秀君" (a subject of the healthy elderly group) with only the in-screen segmentations exhibited. The red circles are the beginnings and ends of segmentations. The blue lines are the in-screen segmentation traces. (**B**). The Chinese signature "张秀君" (a subject of the healthy elderly group) with both in-air and in-screen segmentations exhibited. The blue lines are the in-screen segmentation traces. The grey lines are the in-air segmentation traces. The red areas emphasize the in-air length segmentations between characters (tortuosity = 5.34%). The left area is the segmentation between "张" and "秀" (absolute size = 2.2226; road length = 2.4658; tortuosity = 9.98%). The right area is the segmentation between "秀" and "君" (absolute size = 2.9607; road length = 2.9821; tortuosity = 0.71%). (**C**). The Chinese signature "曲丽" (a subject of the elderly with MCI group) with only the in-screen segmentations exhibited. The red circles are the beginnings and ends of the segmentations. The blue lines are the in-screen segmentation traces. (**D**). The Chinese signature "曲丽" (a subject of the elderly with MCI group) with both in-air and in-screen segmentations exhibited. The blue lines are the in-screen segmentation traces. The grey lines are the in-air segmentation traces. The red area emphasizes the in-air length segmentations between characters (absolute size = 1.2100; road length = 1.7072; tortuosity = 29.12%).

Table 1: Demographic and handwriting analysis data of subjects.

DISCUSSION:

The critical steps in the protocol confirm the legibility of "正". In detail, within an entire character, the #3 stroke needs to be shorter than the other horizonal strokes, and the #4 stroke needs to be shorter than the #2 stroke. More specifically, more attentional resources are needed during the writing of the #3 stroke and #4 stroke[6,12], and both strokes have a similar length limit. An inappropriate stroke length might have given rise to a bias in the detection of velocity.

The software with the digitizer screen is an on-line data collecting software without a pencil–paper-like shape. To start and stop writing, subjects needed to follow the instructions of the researchers or the prompting instruments. These explicit conditions could be stressors for subjects, distracting their attentional resources and affecting the performance of the handwriting. The troubleshooting of this method is even more severe in patients from rural areas who are not familiar with electronic devices. Enough warm-up time could be helpful. Another way to minimize the effects of this limitation is to place a paper sheet on top of the digitizer. In addition, devices that can collect off-line data with pencil–paper-like shapes, such as Smartpen plus Livescribe notebook, could be another modification. As far as we know, data from MovAlyzeR software and Smartpen will be compatible in the near future.

First, because the primary focus was on the dynamic analysis of handwriting, static parameters, such as character width and height, were not included and analyzed in the current study. Actually, "正" has been confirmed as a good writing task for detecting micrographia in PD[12]. Second, some researchers chose to limit the size of the character during the handwriting task (e.g., 1 cm, 2 cm, and 4 cm in amplitude)[19]. As has been found, subjects require more time to write in a smaller amplitude relative to a larger one. A definite amplitude was not set in this study while the shape of Chinese characters might be an implicit limit for a particular stroke.

To our knowledge, this is the first study of a digital handwriting analysis for simplified Chinese character users. More handwriting tasks regarding simplified Chinese characters can be used to find cognitive deficits and motor dysfunctions in patients with neuropsychiatric disorders.

A digital handwriting analysis can complement traditional pencil–paper cognitive tests, such as Trail-Making Test, MMSE, Montreal Cognitive Assessment, and others[17,22]. Analyzing handwriting features during a cognitive test is a new paradigm for motor-cognitive dual tasks[23]. This method might be of help for diagnosing motor cognitive risk syndrome and cerebral small vessel disease.

ACKNOWLWDGMENTS:

We thank Professor Hans-Leo Teulings from Neuroscript LLD for the digital technology support.
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DISCLOSURES:

The authors have nothing to disclose.

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Figure1

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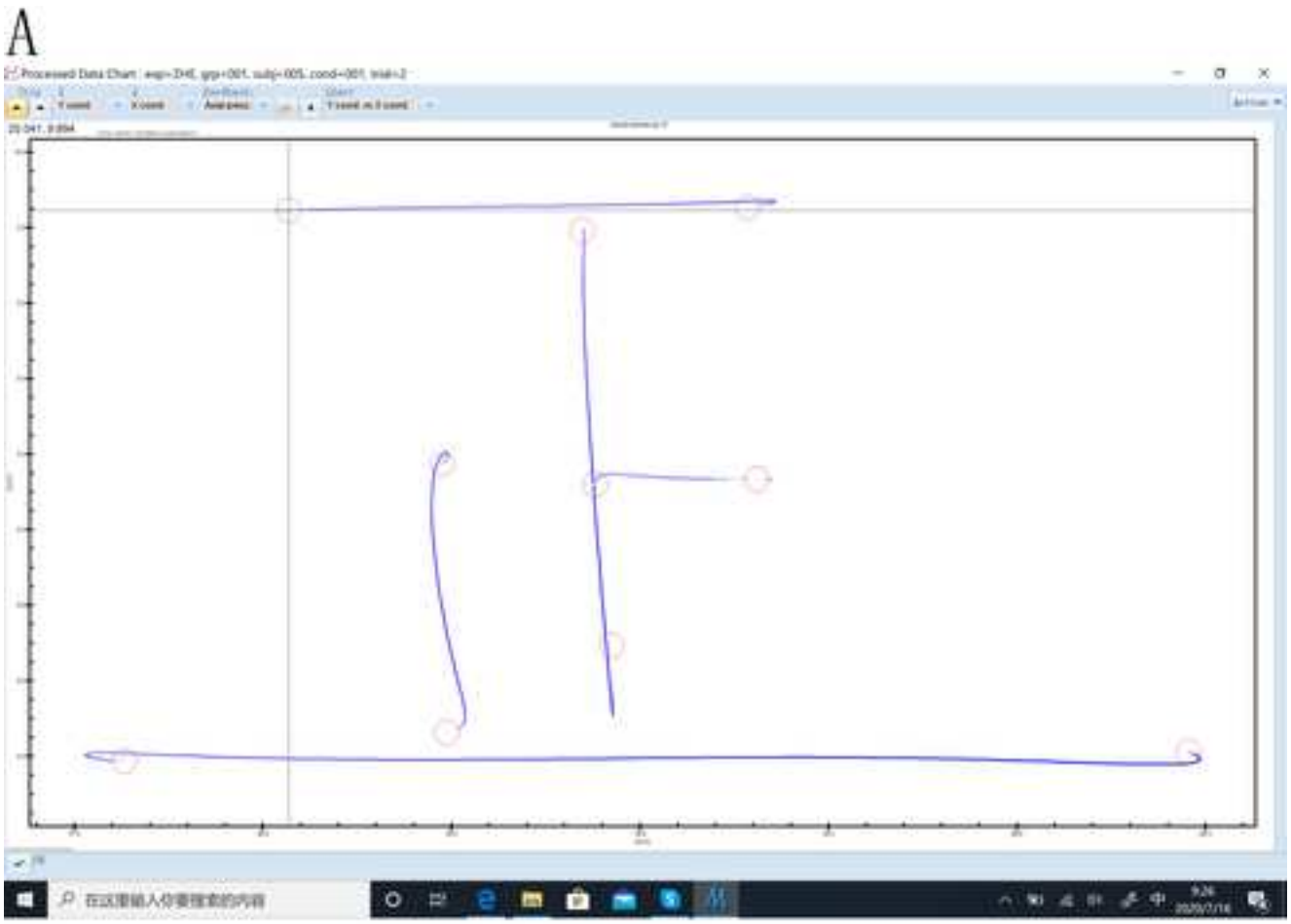

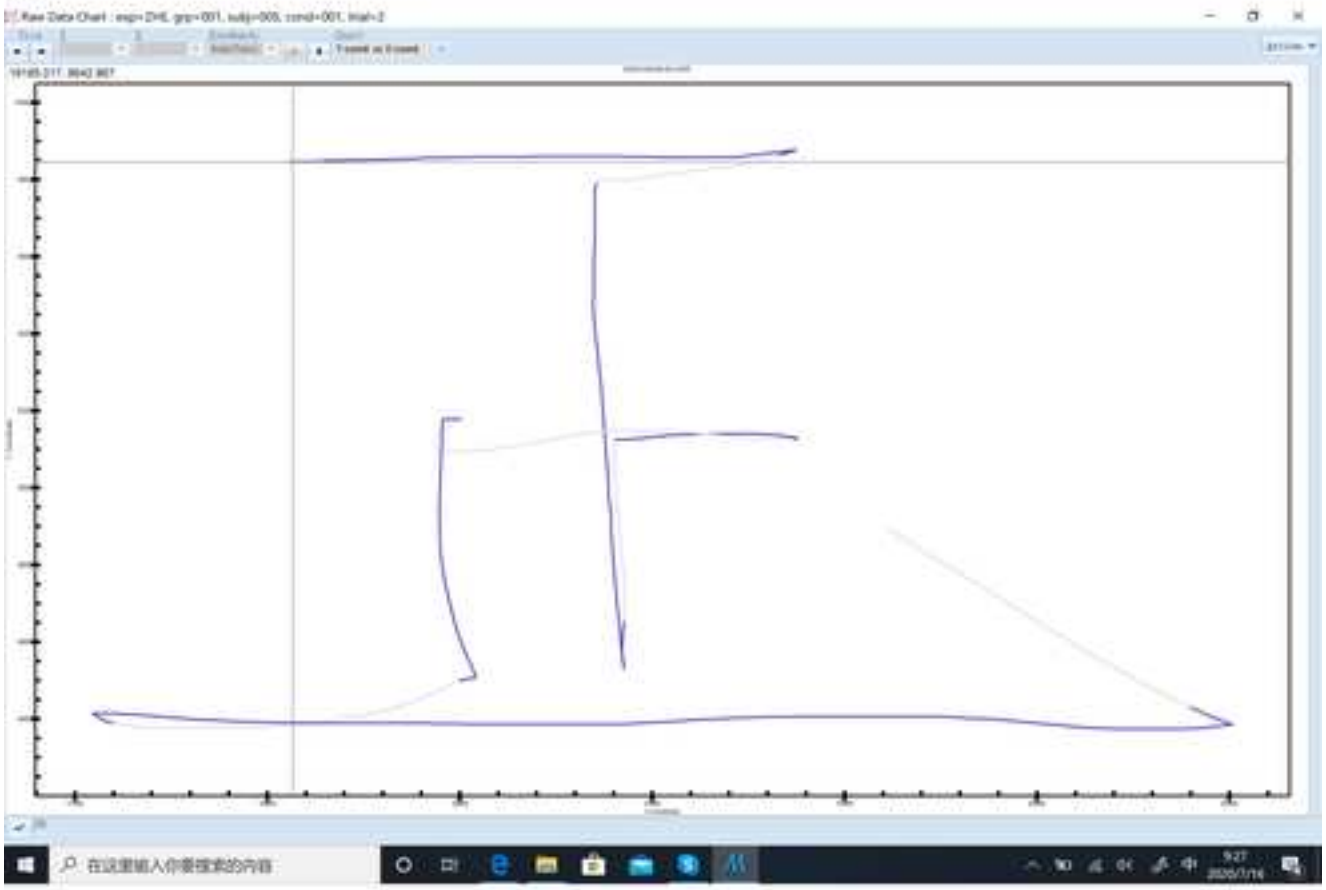

Figure2

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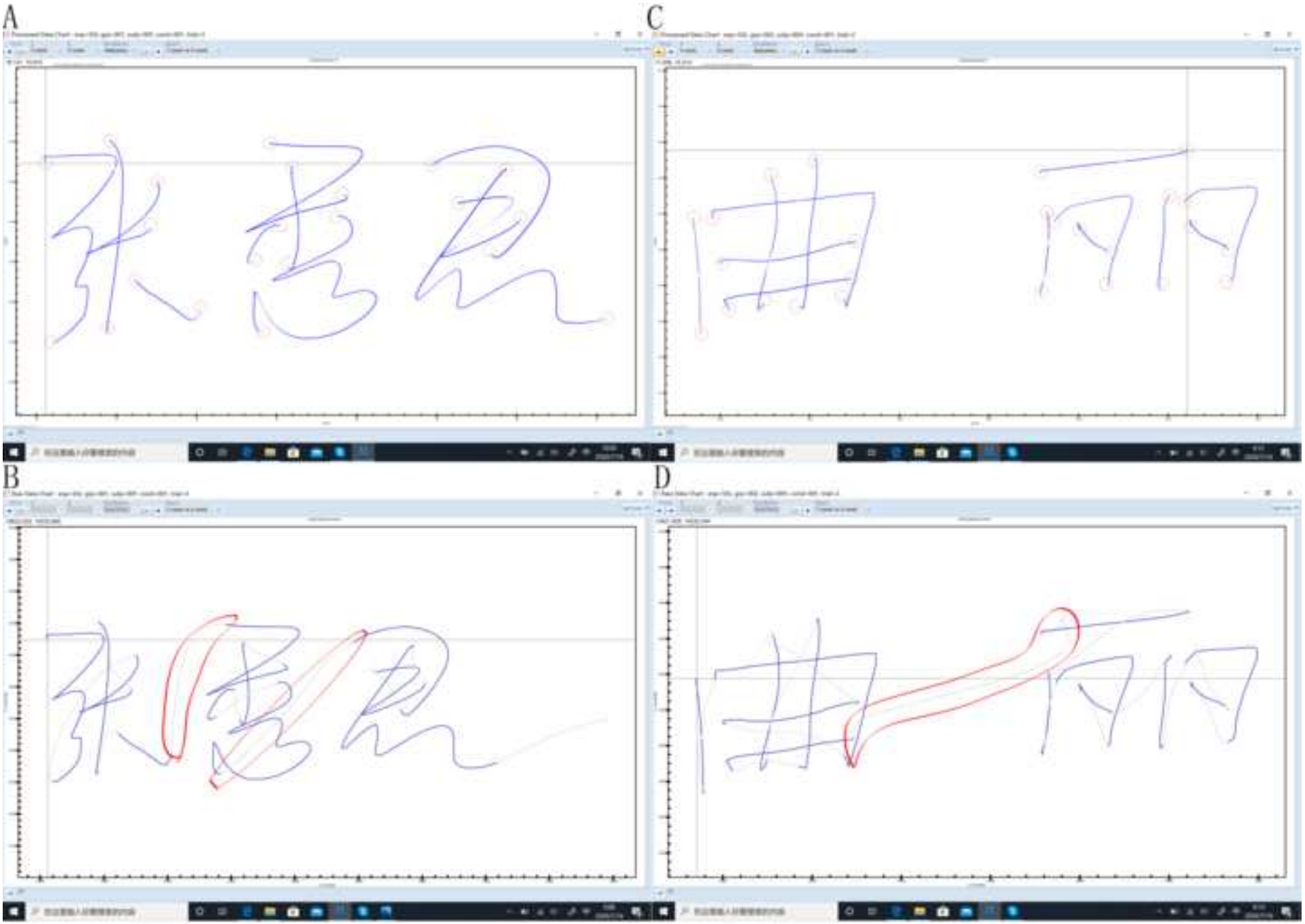

Table 1 Click here to access/download;Table;Table1.xlsx

	Healthy Elderly N=20	Elderly with MCI N=20	P Value
Gender (male/female)	10-Oct	8/104	0.74
Age (years)	69.70±4.51	70.39±3.42	0.602
Dominant hand (Right%)	100	100	
Educational (years)	9.60±3.72	8.22±3.30	0.237
MMSE (score)	28.90±0.79	26.33±0.77	＜0.001
Average absolute velocity of 3#stroke of "正"	2.46±0.40	1.82±0.55	0.001
Average absolute velocity of 4# stroke of "正"	2.61±0.46	1.93±0.50	＜0.001
Average pen pressure of "正"	237.43±39.77	281.99±37.70	0.001
Tortuosity of in air length "Signature" (%)	12.57±6.96	31.66±7.53	＜0.001

MCI: Mild Cognitive Impairment

haracter 3 "正" is a horizonal movement.

:haracter 4 "正" is a vertical movement.

Table of Materials

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Name of Material/ Equipment	Company
	Microsoft
	MovAlyeR
	WACOM

Catalog Number	Comments/Description
Surface Pro 2	computer
3.4	software
Cintiq	digitizer

Reviewers' comments:

Reviewer #1:

Manuscript Summary:

The manuscript concerns a case study about dynamic handwriting analysis for mild cognitive impairment detection. The main assumption of this work is that such a methodology, which may help clinicians instead of using traditional paper and pencil tasks, has been studied extensively in Western countries' cohorts, but few works have been done from a Chinese perspective.

Reply:

Thank you very much for your comments.

Major Concerns:

The very few subjects the authors involved in the study prevent any statistical test from being meaningful. In addition, sometimes the authors report a p-value equals to 0, which is meaningless as the p-value cannot be theoretically 0. The authors made also use of the MovAlyeR tool, which, although effective, is a simple and old tool not taking into account several features at the state-of-the-art on this topic.

Reply:

Thank you very much for your comments, and I need to give some explanations.

First, the subjects are few.

We keep on working on the topic of "Digital Handwriting Analysis of Characters in Chinese Patients with Mild Cognitive Impairment", and the sample size is becoming larger, so we added more subjects in representative results. Actually, the pandemic of COVID-19 influenced our daily life. Patients needed to change the way to see a doctor, doctors needed to change the way to work. As a result, the sample size is not large enough. In our opinion, JoVE is a journal mostly focusing on the methods, and show the procedure of methods step by step. As a result, we did not pay enough attention to the sample size. Thank you for your advice, and we are still working on this topic, and collecting more and more subjects.

Second, a p-value equals to 0.

That's our flaw. Actually, the p-value is <0.0001 rather than theoretically 0, we have changed the way of expression. Thank you for your suggestion.

Third, as has been mentioned, MovAlyeR is a simple and old tool in handwriting research. And many researchers have reported to use this software in detecting handwriting ways of MCI patients. I think the novelty of the present study is that we use it in Chinese patients, and show how to improve the methods in comparing the data of Chinese characters we collected. As we know, MovAlyeR is invented by group from the Netherland and US, and has been confirmed to be a good tool in analyze western language characters. But few researchers in China use this device, and few studies introduce how to analyzed handwriting data of Chinese speakers.

Minor Concerns:

The manuscript need some style and language editing.

Reply:

Thank you very much for your advice. We have improved the language by native English speakers in new-versioned manuscript.

In the abstract, it is not true that only English, Spanish and German researchers have been involved in this field: I would talk about Western countries more in general.

Reply:

Thank you for your suggestion, we have made a mistake, and the sentence in Abstract section has been changed into "Researchers from western countries have discovered that MCI patients have abnormal handwriting features." In new-versioned manuscript.

In addition, some relevant studies on Chinese patients have been carried out in the past: the authors themselves cite them in their manuscript.

Reply:

Thank you for your reminding. Maybe that's because of our poorly expression. There are basically two systems in Chinese characters, "traditional Chinese characters" and "simplified Chinese characters". Several relative studies on Chinese patients are based on traditional Chinese users. That is to say, they wrote traditional Chinese characters. Actually, simplified Chinses characters were used for more than 70 years, although most Chinese users can read in both traditional and simplified Chinese, simplified Chinese user cannot write in traditional Chinese. Also, traditional Chinese cannot write traditional Chinese. As an investigator of handwriting analysis, this is an obvious difference. In fact, more than 2/3 of characters are not written in the same way.

The studies we cited in manuscript, for example "Yu, N.Y., et al. Characterization of the fine motor problems in patients with cognitive dysfunction - A computerized handwriting analysis. Human Movement Science. 65, S0167-9457(17)30841-2 (2019)." and "Ma, H.I., et al. Progressive micrographia shown in horizontal, but not vertical, writing in Parkinson's disease. Behavioural Neurology. 27(2), 169-174 (2013)." were also from traditional Chinese users in Taiwan.

Finally, the meaning of the so-called "tortuosity" measure should be explained.

Reply:

Thank you. We have added the definition of "tortuosity" behind the equation to explain "tortuosity" in new-versioned manuscript.

Reviewer #2:

Manuscript Summary:

The manuscript describes a protocol to analyse kinematic measures of handwriting production using a digitising tablet and the software Neuroscript MovAlyzeR, and more specifically how this was used to investigate potential differences in handwriting between elderly participants with and without Mild Cognitive Impairment. Some of the results obtained showed that there are differences in pen pressure while writing a frequent Chinese character and in pen in-air tortuosity

in a signature task. The procedure is interesting and relatively new, so I think this manuscript will make a valuable contribution once published in JoVE. However, I think there are a number of issues that I think should be addressed before the study is accepted.

Reply:

Thank you for your comments.

Major Concerns:

* The main issue is the quality of the English, which is not sufficient in the current version. I have been asked not to review for grammatical errors, but inaccurate word selection sometimes makes understanding of the message difficult.

Reply:

Thank you very much for your advice. We have improved the language by native English speakers in new-versioned manuscript.

* Introduction, line 83. The authors might want to cite Afonso, Álvarez, Martínez, & Cuetos (2019) here. These authors also explored pen pressure in MCI. Reference to this paper might be worth making in other parts too, as other kinematic measures of AD's and MCI's patients were analysed in this study. The full reference is:

Afonso, O., Álvarez, C. J., Martínez, C., & Cuetos, F. (2019). Writing difficulties in Alzheimer's disease and Mild Cognitive Impairment. Reading and Writing, 32(1), 217-233. doi: 10.1007/s11145-017-9813-6

Reply:

Thank you very much for your suggestion. This reference is quite helpful about pen pressure, and we have added it in our new-versioned manuscript.

* Discussion, line 234. "As far as we know, this is the first study of digital handwriting analysis in simplified Chinese users". I am not sure this is true. At least the following two studies (I think that there should be more) have analysed kinetic measures of handwriting in Chinese. I suggest the authors are more specific (maybe they refer to participants with MCI?) or remove this claim.

Lam SS, Au RK, Leung HW, Li-Tsang CW. Chinese handwriting performance of primary school children with dyslexia. Res Dev Disabil. 2011;32(5):1745-1756. doi:10.1016/j.ridd.2011.03.001

Zham, P., Raghav, S., Kempster, P., Poosapadi Arjunan, S., Wong, K., Nagao, K. J., & Kumar, D. K. (2019). A Kinematic Study of Progressive Micrographia in Parkinson's Disease. Frontiers in neurology, 10, 403. https://doi.org/10.3389/fneur.2019.00403

Reply:

Thank you for your reminding.

I think I need to give some explanations about that. There are basically two systems in Chinese characters, "traditional Chinese characters" (subjects of Lam SS and Li-Tsang used) and "simplified Chinese characters" (subjects of our study used). Several relative studies from Hongkong and Taiwan on Chinese patients are based on traditional Chinese users. That is to say, they wrote traditional Chinese characters. Actually, simplified Chinese characters have been used for more than 70 years in mainland China. Although most Chinese users can read in both traditional and simplified Chinese, simplified Chinese user cannot write in traditional Chinese freely and fluently, and traditional Chinese cannot write traditional Chinese freely and fluently. As an

investigator of handwriting analysis, this is an obvious difference. In fact, more than 2/3 of characters are not written in the same way.

Prof Li-tsang's group is a famous group in handwriting analysis from Hongkong, and they invent a great system of handwriting, called "Chinese Handwriting Assessment Tool (CHAT)", however, it is suitable for traditional Chinese users, but not quite suitable for simplified Chinese users. (Figure S1).

Zham and colleagues are from Australia, and subjects were collected in Australia, too. So, their study is not on simplified Chinese users.

As far as we know, there are few (not more than 4) institutions in mainland China use MovAlyzeR in their study, and most of which are focusing on education and writing disability in children. And other investigators in mainland China still work on non-digitized device, eg paper pen/pencil way [1]. As a result, we mentioned in the discussion like that.

The studies we cited in manuscript, for example "Yu, N.Y., et al. Characterization of the fine motor problems in patients with cognitive dysfunction - A computerized handwriting analysis. Human Movement Science. 65, S0167-9457(17)30841-2 (2019)." and "Ma, H.I., et al. Progressive micrographia shown in horizontal, but not vertical, writing in Parkinson's disease. Behavioural Neurology. 27(2), 169-174 (2013)." were from traditional Chinese users in Taiwan.

* I am not a Chinese speaker, but it is my understanding from the description given by the authors that the examples provided in Figure 2 represent complete signatures by the participants. If this is the case, these signatures are identifying information and should not be included in the article. Specially with signatures, that can be used in many illicit ways, I think these should not be published for ethical reasons. However, I understand that the examples are of interest for the reader. Could the authors provide images of incomplete signature (i.e., a part of the signature that is showing the phenomenon of interest)?

Reply:

Thank you for your reminding. We have manipulated the figures of signature in new-versioned manuscript. In fact, informed consents were given from the subjects in the present study.

Minor Concerns:

* Abstract, line 26: It is unclear what is meant by "cross-cultural effect of handwriting". I would rephrase this.

Reply:

Maybe "cross-culture phenomenon in handwriting" is better. It means the dissimilarities of handwriting manners between people from western countries and China.

* Introduction, line 44. "As the most population used language, researches around handwriting analysis in Chinese (especially simplified Chinese characters) 45 speakers are still lacking". I am not sure what is meant by this.

Reply:

This is a mistake of expression, sorry. It has been changed into "As a majority of the population uses language, studies that investigate handwriting analysis in Chinese speakers (especially simplified Chinese characters) are still lacking."

* Introduction, line 60. "As far as we know, the methods selected by researches from different nations are not the same (eg, English letters are written from left to right, while Hebrew letters are written from right to left)". This does not refer to the methods selected by researchers, but to the characteristics of the writing system. I think some terminology is misleading.

Reply:

Thank you for your advice, we accept the mistake. And this has been changed into "As far as we know, the writing system of different nations are not the same (eg, English letters are written from left to right, while Hebrew letters are written from right to left)".

* "and the width and height of strokes need to be strictly limited". This is not easy to understand if you are not a Chinese speaker. Could authors clarify why they mean by the limits of width and height?

Reply:

Sorry for the difficulty in understanding, we should notice that. In new-versioned manuscript, we give some examples, eg. "日" and "曰" are totally different in Chinese characters. Also, "木木昆", "林昆" and "木棍" are totally different in Chinese characters. These examples may be helpful.

* Introduction, line 74. "selected as writing paradigm in previous Chinese handwriting analysis researches". This is another example of inappropriate use of the terminology. I think the authors meant hat this has been used as a stimulus in previous research conducted in Chinese. Here, and in subsequent instances, I don't think writing paradigm is the term that conveys the meaning intended by the authors.

Reply:

Thank you for your advice. We changed "paradigm" into "task". I think it will be more proper.

* Introduction, line 86. It might be worth clarifying what in-air time (and specify that is pen in-aitr time). JoVE's audience is not necessarily specialist in this field, so a little bit more context to understand the measures would be useful.

Reply:

Thank you for your advice. We have added the explanation about in-air time in new-versioned manuscript. ("in-air" is defined as when the pressure of pen tip to the screen is 0 during the handwriting, and "in-air time" is the sum of the time of "in-air" during the handwriting)

* Introduction, line 91. "we decided to use in-air length Tortuosity in segmentation". I am not sure what this measure refers to. A brief explanation should be given. The formula is included in the protocol, but it should be described here.

Reply:

Thank you for your reminding. We have added explanation of Tortuosity.

* Protocol, line 98. Instead of device, I would replace "device" with "digitizer".

Reply:

Thank you. We accept it, "device" has been changed into "digitizer".

* Protocol, line 104. It is the first time that I review for JoVE, so this might be the standard way to include this in the manuscript, but this seems to be a description of what will be shown in the video? If a description of the protocol is going to be included in the manuscript, then this should be re-written to become a more standard method section.

Reply:

Thank you very much. Protocol will be shown in video, and this section will be reviewed by the photographer.

* Protocol, line 106. I would replace "screen" with "work area" or "writing area", as it may lead to confusion. The first time I read this I though this referred to the screen of a monitor.

Reply:

Thank you, we have changed “screen” into “writing area”.

* Statistical analysis, line 166. It might be that I am not understanding correctly the highlighting (I am assuming that it reflects he content of the video, so this will be demonstrated rather than included in the manuscript), but I do not understand why the statistical analysis section is highlighted.

Reply:

It was our mistake. This section should not be included in video, and the highlighted mode was deleted.

* Discussion, line 210, I think "within" is more accurate than "inside" here.

Reply:

Yes, thank you. It was replaced.

* Discussion, from line 216 onwards. Another way to minimise the effects of this limitation is to place a paper sheet on top of the digitizer. This does not interfere with data collection and increases the external validity of the task. I think this is standard procedure in studies in the field. The authors may want to suggest this possibility besides the sufficient warm-up.

Reply:

Yes, we accept it. A paper sheet placed on top of the digitizer is another helpful way. It has been added in new-versioned manuscript.

* Discussion 238. "Digital handwriting analysis can substitute traditional pencil-paper cognitive tests such as Trail-Making Test, MMSE, Montreal Cognitive Assessment, etc16,20". I would say "complement" instead of "substitute". Pen and paper tasks can be more convenient in a range of circumstances, for example, in those cases in which one is not interested in the dynamics of the production but only in the accuracy of the product.

Reply:

Yes, “complement” is more proper here.

* Discussion, line 241. I would say "might" instead of "will". This possibility must be confirmed experimentally.t

Reply:

Yes, “will” is replaced by “might”.

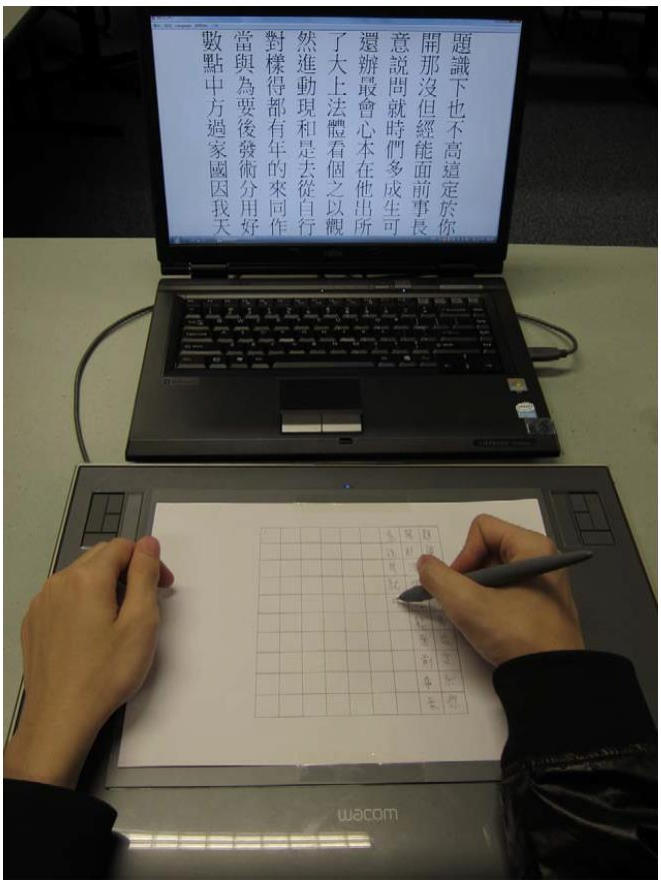

Figure s1 ChaT used in Lam SS and Li-Tsang group.

Reference:

1. Li C, Cai W. Relation between writing characteristic and therapeutic effect in schizophrenia. Journal of Forensic Medicine. 2014;2:93-95.