Original Article

Characteristics of Agraphia in Chinese Patients with Alzheimer's Disease and Amnestic Mild Cognitive Impairment

Jiong Zhou[1], Biao Jiang[2], Xian-Hong Huang[3], Lin-Lin Kong[1], Hong-Lei Li[1]

[1]Department of Neurology, The Second Affiliated Hospital of Zhejiang University, Medical School, Hangzhou, Zhejiang 310009, China
[2]Department of Radiology, The Second Affiliated Hospital of Zhejiang University, Medical School, Hangzhou, Zhejiang 310009, China
[3]Department of Health Service Management, Hangzhou Normal University, Hangzhou, Zhejiang 310036, China

Abstract

Background: Patients with Alzheimer's disease (AD) manifest progressive decline in writing abilities. Most studies on agraphia in AD have been performed in the alphabetic system, such as English. However, these findings may not be applicable to other written language systems. The unique features of the Chinese written script could affect the patterns of agraphia in Chinese AD patients. The aim of this study was to explore the features of writing errors in Chinese patients with AD and amnestic mild cognitive impairment (a-MCI), as well as to study the relationship between their writing errors and neuropsychological functions.

Methods: In this study, we performed an observational study in a group of subjects including 17 AD patients, 14 patients with a-MCI, and 16 elderly healthy controls. We analyzed the writing errors in these subjects and also studied the relationship between their writing errors and neuropsychological functions.

Results: Our study showed that in patients whose mother tongue is Chinese, writing ability was comparatively well preserved in the MCI phase but significantly impaired when the disease progressed to the stage of AD. The writing errors showed corresponding increase with the severity of cognition decline, both in the types of errors and rate of occurrence. Analysis of the writing errors showed that word substitution and unintelligible words were the most frequent error types that occurred in all the three study groups. The occurrence rate of unintelligible words was significantly higher in the AD group compared with the a-MCI group ($P = 0.024$) and control group ($P = 0.018$). In addition, the occurrence rates of word substitution were also significantly higher in AD ($P = 0.013$) and a-MCI groups ($P = 0.037$) than that of control group. However, errors such as totally no response, visuospatial impairment, paragraph agraphia, ideograph, and perseverative writing errors were only seen in AD group. Besides, we also found a high occurrence rate of visuoconstructional errors (13.3%) in our AD group.

Conclusions: Our study confirmed that agraphia is an important feature in patients with AD. The writing error profile in patients whose native language is Chinese was unique compared to patients using the alphabetic language system.

Key words: Agraphia; Alzheimer's Disease; Amnestic Mild Cognitive Impairment; Chinese

Introduction

Patients with Alzheimer's disease (AD) manifest progressive decline in language abilities.[1] Among these language disorders, the most frequently studied disorder was anomia. It is well known that naming ability is impaired even at an early stage of the disease process.[2] However, although language disability has been extensively studied in AD, less attention has been devoted to agraphia. It is generally accepted that writing impairment invariably appears during the clinical course of AD, mostly in the later stages.[3] However, some studies have reported that agraphia is also manifested at a fairly early stage of the disease.[4] Moreover, it was suggested that writing impairment is a more sensitive indicator of language deficits in AD than anomia.[4] Studies on characteristics of language impairment associated with the earlier stages of AD are important since language impairment appears at a very early stage of the disease

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.184467

Address for correspondence: Dr. Hong-Lei Li, Department of Neurology, The Second Affiliated Hospital of Zhejiang University, Medical School, No. 88, Jiefang Road, Hangzhou, Zhejiang 310009, China
E-Mail: Honglei2015@foxmail.com

Received: 29-02-2016 **Edited by:** Xin Chen
How to cite this article: Zhou J, Jiang B, Huang XH, Kong LL, Li HL. Characteristics of Agraphia in Chinese Patients with Alzheimer's Disease and Amnestic Mild Cognitive Impairment. Chin Med J 2016;129:1553-7.

and, hence, it can have diagnostic value and can be used as a marker of disease progression.

Most studies on agraphia in AD have been performed in the alphabetic system, such as English. In the classic cognitive model, agraphia is classified into a central or peripheral type.[5] The central processes are involved in the generation of spelling. These processes are linguistic in nature and include two routes: the lexical-semantic route, in which spelling is derived by accessing stored orthographic information and the phonological route, in which spelling is derived by applying phoneme-to-grapheme conversion rules. The peripheral processes, on the other hand, are restricted to converting orthographic representations into motor commands for writing movements. Writing errors such as upper and lowercase substitution of a letter, letter formation, and stroke placement will be generated if these processes are impaired. However, these findings could not be applied to all written language systems.

There are some unique features of the Chinese written script that could affect the patterns of agraphia in AD patients. Unlike alphabetic scripts, such as English, where letters are associated with individual phonemes, Chinese is generally considered to be logographic.[6] Each character represents a morpheme and maps to a syllable of sound. In other words, each Chinese character represents a combination of morpheme, phoneme, and semanteme. From the perspective of the central process, the visual-sound correspondence that resembles the grapheme to phoneme conversion used in alphabetic scripts may not exist in Chinese. Moreover, from the peripheral aspect, there are remarkable differences between the two writing systems, especially the visuoconstructional perspective. English scripts may require less visuoconstructional ability because the letters are made up of one to three strokes and are written in a linear fashion. In contrast, the Chinese scripts are unique with regard to combination and construction. The Chinese characters can be classified as either simple or compound. Simple characters are made up of spatial arrangement of strokes and compound characters are made up of combination of simple characters (radicals) that are arranged in a square pattern to form a word. Simple characters make up about 5% of the total characters in modern Chinese and compound characters constitute about 95% of all Chinese characters.[7]

Patients with AD may exhibit writing errors with respect to linguistic aspects as well as visuoconstructional aspects because AD is a disease that can result in both language and visuoconstructional dysfunction due to bilateral involvement of the temporoparietal areas. Since Chinese is a written language system that could better reflect the visuoconstructional aspect of writing, we hypothesized that Chinese patients with AD might exhibit both linguistic and visuoconstructional errors in writing and would show more diverse visuoconstructional errors compared to AD patients who use the Roman alphabet. To verify this hypothesis, we performed an observational study in a group of patients with AD or amnestic mild cognitive impairment (a-MCI). We analyzed the writing errors in these subjects and also studied the relationship between their writing errors and neuropsychological functions. Since knowledge of the characteristic of agraphia in patients with AD or MCI is still lacking, this study could provide some baseline data in this field.

Methods

Subjects

The participants of this study included 17 AD patients, 14 a-MCI patients, and 16 elderly healthy controls. The AD and a-MCI patients were recruited from the Memory Disorder Clinic, The Second Affiliated Hospital of Zhejiang University from March 2009 to December 2012. All participants underwent clinical assessment, neuropsychological testing, and 1.5-T structural magnetic resonance imaging. In addition to routine medical examination and neurological examination, each subject was evaluated using a broad battery of neuropsychological tests including the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS), clinical dementia rating (CDR), and the Aphasia Battery of Chinese in the First affiliated Hospital of Peking University. All AD patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision and NINCDS-ADRDA criteria for a clinical diagnosis of probable AD, and the Peterson criteria were applied for the diagnosis of a-MCI.[8] Briefly, for inclusion, subjective and objective evidence was required for progressive cognitive impairment over a period of more than 6 months (verified by an informant). With a CDR score of 0.5, the ability of daily life was within the normal range. Subjects without cognitive symptoms or CDR = 0 were not included since their cognitive impairment was considered too benign, and neither were subjects with more than two cognitive symptoms or a score below 25 on the MMSE, as they were considered to fulfill criteria for dementia.

For AD patients, evaluation also included routine blood tests (biochemistry, Vitamin B12, foliate, thyroid function, and syphilis serology). The detailed exclusion criteria were described previously.[9] The healthy controls were recruited from community epidemiological investigations or spouses of patients from March 2009 to October 2011. All participants were of Han descent, with more than 5 years of education, speaking Chinese (Mandarin) as their first language, and all had visual acuity sufficient to read newsprint. Written informed consent was obtained from the patients or their guardians. The study protocol was approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University.

Statistical analysis

The gender and education distributions in the AD, a-MCI, and control groups were examined with Kruskal-Wallis test. One-way analysis of variance (ANOVA) was employed to compare the age, educational level, MMSE, and ADAS scores (the total score and specific cognitive domain scores).

The classification variables were expressed using the frequency and composition ratio; the continuous variables with the normal distribution were shown as mean ± standard deviation (SD), and data with non-normal distribution were shown as median (interquartile range). To compare the writing subtest scores among the three groups, one-way ANOVA was used to test the differences with normal distribution while nonparametric analysis was used to test the data with abnormal distribution. The statistical analyses were performed with the SPSS 18.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed, and a $P < 0.05$ was considered statistically significant.

Results

Demographic data

The demographic data of all participants are shown in Table 1. No statistically significant differences were observed for age (df = 2, $F = 1.35$, $P = 0.27$), gender (df = 2, $F = 0.50$, $P = 0.78$), and education level (df = 6, $F = 7.80$, $P = 0.25$) among normal controls, a-MCI, and AD groups.

Neuropsychological data

As shown in Table 2, although there was no statistically significant difference between normal controls and a-MCI group in MMSE score, the a-MCI group scored higher in total scores of cognition and ADAS. The other statistically significant differences could be found in the fields of word recall, naming, word recognition, and total memory score. In other words, the MCI group showed changes in the field of memory, yet other cognitive domain was rarely involved. Normal controls performed significantly better than the AD group in all aspects of the neuropsychological test scores, except the psychological factor score, whereas AD group achieved significantly lower scores in MMSE and higher in most aspects of the ADAS, including word recall, following commands, construction praxis, orientation, word recognition, and recall of test instructions, compared with the a-MCI group. Factor points represented different areas of higher cortical functions. On comparison of the factor points between the a-MCI and AD groups, the AD group scored higher in the memory, language, and practical ability factor points; however, there were no statistically significant differences for the mood and psychological factor points. Based on these results, it was concluded that differences between a-MCI and AD groups covered all cognitive domains. This implied that mood and mental disorders appeared in the late stage(s) of the disease.

We compared the performance of the healthy controls and patients with a-MCI or AD on the sections of the writing task. Details are shown in Table 3. These results showed that the AD group differed from a-MCI group and healthy controls for all written tasks, especially in the aspect of name and address, dictation, written description of pictures, and spontaneous writing. However, differences between a-MCI group and healthy controls were not statistically significant. These results suggested that in patients whose native language was Chinese, writing ability might comparatively be preserved in the MCI phase but significantly impaired in AD phase.

Writing error analyses

We studied the profiles of each of the recruited subjects, sorted by the error analysis for each single subject. Details are listed in Supplementary Tables 1-3, respectively. We also conducted a comparison of the symptom occurrence rate of different writing errors between the three study groups and results are shown in Table 4. The writing errors occurred could be classified as single-word level, paragraph level, and those that could not be classified. Errors of single-word level were the most frequent error type, which could be divided into five subtypes as unintelligible word, word substitution, ideograph (picture drawing), mirror writing, and visuospatial impairment. The classification and definition of error types of single-word level are listed in Supplementary Table 4. Writing errors on paragraph level included paragraph agraphia and perseverative writing. Paragraph agraphia meant that the study subjects reserved the ability to write single-word but were unable to write meaningful paragraph or even a sentence. Perseverative writing referred to repeated writing of words that had the same meaning without proper extension. It may be noted here that some study subjects showed absolutely no response to the writing mission; thus, we were unable to classify their writing error.

Based on the results shown in Table 4, it can be concluded that the number of writing errors corresponded with the severity of cognition decline. Thus, there were more errors in the AD group than the a-MCI group compared to the control subjects, both in the errors types and occurrence

Table 1: Demographic data of all participates in this study

Characteristics	NC (n = 16)	a-MCI group (n = 14)	AD group (n = 17)	*P*		
				NC versus a-MCI	NC versus AD	a-MCI versus AD
Age (years), mean ± SD	64.1 ± 9.1	69.1 ± 10.6	68.9 ± 10.0	0.95	0.15	0.17
Male/female, *n*	10/6	7/7	10/7	0.62	0.82	0.49
Education level, *n*				0.09	0.71	0.16
5 years ≤ time <8 years	3	5	2			
8 years ≤ time <11 years	6	8	9			
11 years ≤ time <15 years	6	1	6			
Time ≥15 years	1	0	0			

NC: Normal controls; a-MCI: Amnestic mild cognitive impairment; AD: Alzheimer's disease; SD: Standard deviation.

Table 2: Neuropsychological test scores among NC, a-MCI and AD groups in this study

Tasks	NC (n = 16)	a-MCI group (n = 14)	AD group (n = 17)	*P*		
				NC vs. a-MCI	NC vs. AD	a-MCI vs. AD
MMSE	27.50 ± 2.00	25.57 ± 2.79	14.41 ± 6.96	0.259	0.000	0.000
Word recall	4.69 ±1.29	6.33 ±1.70	8.05 ±1.54	0.007	0.000	0.004
Naming	0.00 (0.00)	1.00 (0.50)	1.00 (2.00)	0.007	0.015	0.842
Following commands	1.00 (0.25)	1.00 (2.50)	4.00 (7.50)	0.435	0.000	0.003
Constructions	0.00 (0.25)	0.00 (1.00)	1.00 (1.50)	0.587	0.000	0.001
Ideational praxis	0.00 (0.25)	0.00 (2.00)	1.00 (5.00)	0.139	0.017	0.214
Orientation	0.00 (0.00)	1.00 (1.50)	4.00 (3.00)	0.0038	0.000	0.000
Word recognition	1.30 (1.48)	5.00 (5.30)	7.70 (5.90)	0.009	0.000	0.013
Recall of test instructions	0.00 (1.00)	0.00 (2.00)	2.00 (2.00)	0.377	0.008	0.062
Spoken language ability	0.00 (0.00)	0.00 (1.00)	0.00 (1.50)	0.121	0.028	0.340
Word-finding difficulty	0.00 (0.00)	0.00 (1.00)	1.00 (1.00)	0.052	0.003	0.240
Comprehension of spoken language	0.00 (0.25)	1.00 (1.50)	0.00 (2.50)	0.023	0.056	0.789
Total score of memory	7.11 ± 3.54	12.12 ± 4.92	18.49 ±5.81	0.012	0.000	0.001
Language factor points	1.43 ± 1.16	4.85 ± 3.26	9.29 ±7.16	0.075	0.000	0.017
Practical ability factor points	0.00 (1.00)	1.00 (2.50)	3.00 (6.00)	0.081	0.001	0.051
Mood factor points	0.00 (0.00)	0.00 (1.00)	1.00 (3.50)	0.152	0.008	0.131
Agitation factor points	0.00 (0.00)	0.00 (0.00)	0.00 (2.50)	0.299	0.016	0.062
Psychological factor points	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.299	0.056	0.246
Total score of non-cognition	0.00(0.00)	0.00 (1.50)	2.00 (6.00)	0.037	0.001	0.030
Total score of cognition	9.40 ± 4.40	20.09 ±8.41	37.08 ± 18.22	0.032	0.000	0.001
Total score of ADAS	9.61± 4.33	20.86 ± 8.47	41.02 ± 21.25	0.047	0.000	0.000

Data are shown as mean ± SD or median (IQR). Total score of memory = word recall + word + word recognition + recall of test instructions; Language factor points = naming + following command + spoken language ability + word-finding difficulty + comprehension of spoken language; Practical ability factor points = constructions + ideational praxis. NC: Normal control; a-MCI: Amnestic mild cognitive impairment; AD: Alzheimer's disease; ADAS: Alzheimer's Disease Assessment Scale; SD: Standard deviation; IQR: interquartile range.

Table 3: Writing tests scores among NC, a-MCI and AD groups in this study

Tasks names	NC	a-MCI	AD	*P*		
				NC vs. a-MCI	NC vs. AD	a-MCI vs. AD
Name and address	1.00 ± 0.00	1.00 ± 0.00	0.67 ± 0.42	1.000	0.001	0.001
Transcribe/copy	1.00 ± 0.00	1.00 ± 0.00	0.79 ± 0.34	1.000	0.006	0.011
Serial writing	1.00 ± 0.00	1.00 ± 0.00	0.76 ± 0.40	1.000	0.008	0.011
Dictation	0.92 ± 0.08	0.82 ± 0.13	0.59 ± 0.38	0.304	0.000	0.013
Written description of pictures	0.92 ± 0.12	0.86 ± 0.24	0.49 ± 0.42	0.542	0.000	0.003
Spontaneous writing	0.87 ± 0.14	0.81 ± 0.14	0.44 ± 0.35	0.472	0.000	0.000

Data are shown as mean ± SD. NC: Normal control; a-MCI: Amnestic mild cognitive impairment; AD: Alzheimer's disease; SD: Standard deviation.

Table 4: Comparison of writing errors among AD, a-MCI, and NC groups in this study

Error types	Symptom occurrence rate (%)			*P*		
	AD	a-MCI	NC	NC versus a-MCI	NC versus AD	a-MCI versus AD
No response	18.8	0	0	1.000	1.000	1.000
Paragraph agraphia	12.5	0	0	1.000	1.000	1.000
Perseverative writing	13.3	0	0	1.000	1.000	1.000
Word substitution	81.3	76.9	43.8	0.037	0.013	0.779
Unintelligible character	100	100	87.5	0.186	0.018	0.024
Picture drawing	12.5	0	0	–	–	–
Mirror writing	0	0	0	–	–	–
Visuoconstructional impairment	13.3	0	0	–	–	–

NC: Normal control; a-MCI: Amnestic mild cognitive impairment; AD: Alzheimer's disease; –: Not applicable.

rate. For example, word substitution and unintelligible words were the most frequent error types that occurred in all the three study groups. However, the occurrence rate of unintelligible words was significantly higher in the AD group compared with the a-MCI group (P = 0.024) and control group (P = 0.018). In addition, the occurrence

rates of word substitution were also significantly higher in AD (P = 0.013) and a-MCI groups (P = 0.037) than that of control group. Besides, we found that error types such as totally no response, visuospatial impairment, paragraph agraphia, picture drawing, and perseverative writing were only seen in AD group, indicating that these error types may be characteristics of patients with AD.

Discussion

AD is a chronic neurodegenerative disease characterized by progressive deterioration of all the aspects of the higher cortical functions. Language ability, which is the most unique intelligence of human beings, is not exempt from disease progression. It was reported that language impairments occurred in 8–10% of individuals during the disease's early stages and became severe during its later stages.[10] Individuals with AD may experience deficits in various linguistic domains including the written language abilities. In this study, we explored writing impairments in patients with AD and a-MCI whose native language is Chinese and provide some baseline data in this field.

Compared with alphabetic writing, the process of reading and writing in Chinese is much more complex. From the results of our study, we hypothesized that the classic model of the central or peripheral writing process that was arrived at based on the studies performed using the alphabetic system was only partially applicable to the Chinese writing system. As discussed above, each Chinese character represents a combination of morpheme, phoneme, and semanteme, thus there may be only one major route for the central process, the lexical-semantic route. The visual-sound correspondence that resembles the grapheme to phoneme conversion used in alphabetic scripts may not exist in Chinese. This could explain why errors in the use of word substitution and unintelligible words were seen at a higher degree in our study. It was possible that there were some phonological substitutions in our writing error samples. However, we tended to attribute it to another important feature of the Chinese language, which is the commonness of homophones. Based on the results obtained in the aspect of the peripheral writing process, the occurrence rate of visuoconstructional errors in our AD group was 13.3%, much higher than in the MCI (0%) and control group (0%), indicating that visuoconstructional impairment was a very important character of AD that can be detected in patients whose native language is Chinese by the application of writing test.

Moreover, in the present study, we observed that writing ability was comparatively well preserved in the MCI phase but significantly impaired once the disease progressed to the stage of AD. This indicated that writing impairment may not serve as a sensitive indicator of language deficits in AD. However, because the study sample of this current study was quite limited, we were unable to compare the characteristic in different stages of AD subjects as well as other subtypes of dementia such as frontal lobe degeneration, Lewy body dementia, thus a larger sample size is required to verify these results. Besides, in this study, analysis of the features of writing errors on single-word level was comparatively sketchy, more detailed study is needed in the future.

In conclusion, this study confirmed that agraphia is an important feature in patients with AD. The writing error profile in patients whose Mother tongue is Chinese was quite unique compared to patients using the alphabetic language system.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Financial support and sponsorship

This study was supported by a grant from the National Natural Science Foundation of China (No. 81500908).

Conflicts of interest

There are no conflicts of interest.

References

1. Lambert J, Eustache F, Viader F, Dary M, Rioux P, Lechevalier B, *et al.* Agraphia in Alzheimer's disease: An independent lexical impairment. Brain Lang 1996;53:222-33. doi: 10.1006/brln.1996.0045.
2. Small JA, Sandhu N. Episodic and semantic memory influences on picture naming in Alzheimer's disease. Brain Lang 2008;104:1-9. doi: 10.1016/j.bandl.2006.12.002.
3. Hughes JC, Graham N, Patterson K, Hodges JR. Dysgraphia in mild dementia of Alzheimer's type. Neuropsychologia 1997;35:533-45. doi: 10.1016/S0028-3932(96)00102-9.
4. Croisile B, Brabant MJ, Carmoi T, Lepage Y, Aimard G, Trillet M. Comparison between oral and written spelling in Alzheimer's disease. Brain Lang 1996;54:361-87. doi: 10.1006/brln.1996.0081.
5. Yoon JH, Suh MK, Jeong Y, Ahn HJ, Moon SY, Chin J, *et al.* Agraphia in Korean patients with early onset Alzheimer's disease. Int Psychogeriatr 2011;23:1317-26. doi: 10.1017/s1041610211000822.
6. Law SP, Or B. A case study of acquired dyslexia and dysgraphia in Cantonese: Evidence for nonsemantic pathways for reading and writing Chinese. Cogn Neuropsychol 2001;18:729-48. doi: 10.1080/02643290143000024.
7. Wu XQ, Liu XJ, Sun ZC, Chromik L, Zhang YW. Characteristics of dyslexia and dysgraphia in a Chinese patient with semantic dementia. Neurocase 2015;21:279-88. doi: 10.1080/13554794.2014.892621.
8. Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med 2011;364:2227-34. doi: 10.1056/NEJMcp0910237.
9. Li HL, Shi SS, Guo QH, Ni W, Dong Y, Liu Y, *et al.* PICALM and CR1 variants are not associated with sporadic Alzheimer's disease in Chinese patients. J Alzheimers Dis 2011;25:111-7. doi: 10.3233/jad-2011-101917.
10. Emery VO. Language impairment in dementia of the Alzheimer type: A hierarchical decline? Int J Psychiatry Med 2000;30:145-64. doi: 10.2190/X09P-N7AU-UCHA-VW08.

Supplementary Table 1: Single-case analysis of the AD patients: Symptoms of agraphia

Patient number	CDR	Type of errors							
		Unclassifiable	Paragrap level		Single-word level				
		No response	Paragraph agraphia	Perseverative writing	Word substitution	Unintelligible character	Picture drawing	Mirror writing	Visuoconstructional impairment
1	3	−	−	−	3/29	24/29	−	−	−
2	1	−	−	−	2/154	6/154	−	−	−
3	2	−	−	+	9/158	1/158	−	−	−
4	2	−	−	+	7/274	17/274	−	−	−
5	2	−	−	−	0	44/93	−	−	−
6	2	−	−	−	6/69	34/69	−	−	−
7	1	−	−	−	4/71	38/71	−	−	−
8	3	−	NA	NA	3/26	23/26	NA	NA	NA
9	2	+	+	−	1/92	3/92	−	−	+
10	1	−	−	−	1/13	5/13	−	−	−
11	2	−	−	−	1/136	4/136	+	−	+
12	1	−	−	+	NA	NA	−	−	−
13	1	−	+	−	0	3/42	−	−	−
14	3	+	−	−	2/85	6/85	−	−	−
15	2	NA	NA	NA	4/169	12/169	NA	NA	NA
16	3	+	−	−	0	7/13	+	−	−
17	1	−	−	−	1/89	7/89	−	−	−
SOR (%)	−	18.8	12.5	13.3	81.3	100	12.5	0	13.3

SOR: Symptom occurrence rate; +: Mild; −: Negative; NA: Not applicable; AD: Alzheimer's disease; CDR: Clinical dementia rating.

Supplementary Table 2: Single-case analysis of the MCI patients: Symptoms of agraphia

Case	CDR	Type of error							
		Unclassifiable	Paragraph level		Single-word level				
		No response	Paragraph agraphia	Perseverative writing	Word substitution	Unintelligible character	Picture drawing	Mirror writing	Visual constructional impairment
1	0.5	−	−	−	0	10/80	−	−	−
2	0.5	−	−	−	2/114	3/114	−	−	−
3	0.5	−	−	−	4/116	5/116	−	−	−
4	0.5	−	−	−	0	3/81	−	−	−
5	0.5	−	−	−	3/156	5/156	−	−	−
6	0.5	−	−	−	1/79	5/79	−	−	−
7	0.5	−	−	−	0	11/94	−	−	−
8	0.5	−	−	−	NA	NA	−	−	−
9	0.5	−	−	−	1/147	5/147	−	−	−
10	0.5	−	−	−	1/73	5/73	−	−	−
11	0.5	−	−	−	2/69	10/69	−	−	−
12	0.5	−	−	−	3/71	18/71	−	−	−
13	0.5	−	−	−	4/167	15/167	−	−	−
14	0.5	−	−	−	1/120	16/120	−	−	−
SOR (%)	−	0	0	0	76.9	100	0	0	0

SOR: Symptom occurrence rate; −: Negative; NA: Not applicable; CDR: Clinical dementia rating; MCI: Mild cognitive impairment.

Supplementary Table 3: Single-case analysis of the control subjects: Symptoms of agraphia

Case	CDR	Type of error							
		Unclassifiable	Paragraph level		Single-word level				
		No response	Paragraph agraphia	Perseverative writing	Word substitution	Unintelligible character	Picture drawing	Mirror writing	Visual constructional impairment
1	0	−	−	−	0	3/157	−	−	−
2	0	−	−	−	1/149	2/149	−	−	−
3	0	−	−	−	2/120	9/120	−	−	−
4	0	−	−	−	1/66	3/66	−	−	−
5	0	−	−	−	0	2/52	−	−	−
6	0	−	−	−	0	3/54	−	−	−
7	0	−	−	−	3/57	4/57	−	−	−
8	0	−	−	−	0	0	−	−	−
9	0	−	−	−	2/231	15/231	−	−	−
10	0	−	−	−	2/89	9/89	−	−	−
11	0	−	−	−	0	1/139	−	−	−
12	0	−	−	−	2/93	9/93	−	−	−
13	0	−	−	−	0	6/117	−	−	−
14	0	−	−	−	0	1/111	−	−	−
15	0	−	−	−	0	0	−	−	−
16	0	−	−	−	0	6/101	−	−	−
SOR (%)		0	0	0	43.8	87.5	0	0	0

SOR: Symptom occurrence rate; −: Negative; NA: Not applicable; CDR: Clinical dementia rating.

Supplementary Table 4: Definition of writing errors on single-word level

Errors	Subtypes	Definition
Unintelligible word	Stroke error	Stroke adding, omission, reforming, and moving
	Radical error	Radical substitution, adding, omission, deforming and moving
	Unreadable	A unreadable sample that cannot be classified as stroke error/radical error
Word substitution	Semantic substitution	Substitution of another meaningful word, whose meaning is close to the target word
	Phonological substitution	Another word with similar pronunciation to the target word
	Number substitution	Use of an arabic number as substitute for a Chinese number word
Ideograph		Use of a picture or the part of a picture to substitute
Mirror writing		Writing in the direction that is the reverse of the natural way, such that the result is the mirror image of normal writing
Visuospatial impairment		The improper organization of the direction, relative size, position, and order of the characters