# Neuroanatomical Correlates of Error Types on the Clock Drawing Test in Alzheimer's Disease Patients

**Hirotaka Nakashima[1], Hiroyuki Umegaki[1], Taeko Makino[1], Katsuhiko Kato[2], Shinji Abe[3], Yusuke Suzuki[4] and Masahumi Kuzuya[1]**

Departments of [1]Community Healthcare and Geriatrics, [2]Radiological and Medical Laboratory Sciences, and [4]Comprehensive Community Care Systems, Nagoya University Graduate School of Medicine, Nagoya, Japan

[3]Department of Radiological Technology, Nagoya University Hospital, Nagoya, Japan

Correspondence: Hiroyuki Umegaki, Department of Community Healthcare & Geriatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya city, Aichi, 466-8550, Japan.
Tel.: +81-52-744-2364; fax: +81-52-744-2371
E-mail: umegaki@med.nagoya-u.ac.jp

**Running title:** Neural Correlates of Error Types on the CDT

**Abstract**

**Aim:** We sought to identify the relation between regional cerebral blood flow (rCBF) and error types on the Clock Drawing Test (CDT) in patients with Alzheimer's disease (AD).

**Method:** The CDT was administered to 142 patients with AD. We used the Mendez scoring method. Their rCBF values were measured by single photon emission computed tomography. The correlation between the CDT total score and rCBF was examined on a voxel-by-voxel basis. After we excluded 37 patients whose drawings were inappropriate for assessing the CDT error types, we examined the relations between each error type on the CDT and rCBF.

**Results:** Total score on the CDT was positively correlated with rCBF in the left posterior middle temporal lobe. We also found relations between the error "non-existence of number 2, or not pointing toward number 2" and the left frontal lobe; the error "uneven number spacing" and the bilateral frontal lobe; "deviation of the clock center" and the left frontal lobe; "missing numbers" and the right parietal lobe; "uneven number distance from edge" and the right parietal and the temporal lobes; "same length hands" and the bilateral temporal lobe; and "unclosed circle" and the left temporal lobe.

**Conclusions:** Each error type on the CDT appears to relate to a different brain region. These findings will be useful in the understanding of CDT performances and the underlying neuropsychological pathology.

**Keywords**

dementia, executive function, functional neuroimaging, single photon emission computed tomography, spatial ability

## Introduction

The Clock Drawing Test (CDT) is widely used in cognitive assessment. It is simple, time-saving, and well accepted by cognitively impaired patients. The CDT is regarded as a good screening instrument for a wide range of cognitive dysfunctions from mild cognitive impairment to sever dementia.[1,2] It reflects many cognitive functions such as executive function,[3,4] visuospatial ability,[3,5] and semantic memory,[4] which have been estimated by comparisons between the performance on the CDT and that of other neuropsychological tests.

Several recent studies investigated the neuroanatomical correlates of CDT performance using functional neuroimaging, but their findings are inconsistent. Potential reasons for the inconsistencies are as follows: A wide range of cognitive functions is necessary to complete the CDT. There are many scoring methods[1] and different scoring methods may evaluate different cognitive functions.[6] In addition, CDT performance probably reflects functions of different brain regions depending on the clinical stages of Alzheimer's disease (AD).[7,8]

There are some patterns of errors on the CDT. In order to examine associations between brain regions and cognitive correlates on the CDT, it might be useful to use not only the total score of the CDT but also its error types. However, there are only a few studies about error types on the CDT and brain regions, and their classifications of error types or brain regions were relatively broad-brush.[5,9,10] In the present study, we aimed to identify associations between regional cerebral blood flow (rCBF) and specific error types on the CDT in patients with AD.

## Methods

### *Patients*

One hundred and forty-two patients with AD who attended the memory clinic of the Nagoya University Hospital between January 2010 and May 2013 participated. The criteria for patient inclusion were as follows: (1) no present serious medical or psychiatric disorders, (2) right-handed (ambidextrous patients were excluded), (3) no significant focal lesion on magnetic resonance imaging (MRI) of the brain, (4) both single photon emission computed tomography (SPECT) and neuropsychological tests were performed, (5) the period between the SPECT and the neuropsychological tests was $\leq$ 2 months. All patients were Japanese.

The diagnosis of AD was made according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR)[11] criteria for dementia.

*Clinical Assessments*

Each patient's medical history, social history, and changes in cognitive and functional status were extensively reviewed by attending geriatricians at the memory clinic. These histories were confirmed by family members or other caregivers, if necessary. General physical and neurological examinations were performed, as well as routine laboratory tests and MRI of the brain. At a case conference, a team of experienced geriatricians reviewed the information obtained from these diagnostic evaluations.

The Ethics Committee of the Nagoya University Graduate School of Medicine approved this study, and informed consent was obtained from all patients or their primary caregivers.

*Clock Drawing Test*

A clinical psychologist administered the CDT as a part of a clinical evaluation at the memory clinic. The patient was presented with a blank sheet of paper and verbally instructed to "Draw a 10-cm-diameter clock that says 11:10, with all numbers" in Japanese. We used the Mendez method to score the CDT performances.[12] The Mendez method, also called the Clock Drawing Interpretation Scale, is a 20-point scoring system. Twenty items are assessed individually (1 point per item). Higher points indicate fewer errors and better performance. There are three components: general impression (3 items), clock numbers (12 items), and hands (5 items). We scored the drawings according to the original description (Appendix 1), but we named each item after their errors, for convenience (Table 1). We chose the Mendez method because most items assess one error each, whereas in many other scoring methods, one item assesses multiple errors. The rater was not informed about the patients except for their clinical diagnosis.

*Other Neuropsychological Tests*

The clinical psychologist performed the Mini-Mental State Examination (MMSE) and the Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-J cog) as a part of the clinical evaluation.

*SPECT Imaging*

The SPECT studies were performed on a system with five gamma cameras. Camera 1 (core camera; Symbia T, Siemens Medical Solutions, Hoffman Estates, Illinois, USA), camera 2 (Symbia T6, Siemens Medical Solutions) and camera 3 (Symbia S, Siemens Medical Solutions) were dual-headed cameras equipped with low-energy high-resolution collimators. Camera 4 was a triple-headed camera (GCA-9300A, Toshiba Medical Systems, Tokyo, Japan) equipped with low-energy super high-resolution fan beam collimators. Camera 5 was a dual-headed camera (E.CAM, Toshiba Medical Systems) equipped with low-energy fan beam collimators.

The patient laid on the scanner bed with eyes closed; 600 MBq of 99mTc-ethyl cysteinate dimer (FUJIFILM RI Pharma, Tokyo, Japan) was administered intravenously. After 5 min of injection, the SPECT image was acquired over a period of 25 min in camera 5 and 30 min in the other cameras. The projection data, collected in a 128 × 128 matrix, were prefiltered with a Butterworth filter. In cameras 1 and 2, the transaxial images were reconstructed using a filtered back projection algorithm and an ordered subset expectation maximization method with 15 iteration and six subsets. In cameras 3, 4 and 5, only a filtered back projection algorithm was used. The resulting voxel was 3.3 × 3.3 × 3.3 mm in cameras 1, 2 and 3, but 1.72 × 1.72 × 1.72 mm in camera 4 and 1.95 × 1.95 × 1.95 mm in camera 5. To correct differences among these cameras, we adopted a method using Hoffman 3-D Brain Phantom (Biodex Medical Systems, Shirley, NY).[13,14] As a consequence, 51 of 142 SPECT data were converted to the core SPECT data.

*Image Data Analysis*

The acquired SPECT image data were converted from DICOM to Analyze format using MRIcro 1.37 (http://www.mricro.com). These images were analyzed using statistical parametric mapping 8 (SPM8; Wellcome Trust Centre for Neuroimaging, University College of London, UK) in Matlab 7.14 (Mathworks, Natick, Massachusetts, USA). Before the statistical analysis, the images were transformed into the standard stereotactic anatomical space using the ECD template (Fujifilm RI Pharma) matched to the Montreal Neurological Institute (MNI) template (McGill University, Montreal, Canada). The images were then smoothed using a 12-mm full-width at half-maximum Gaussian filter to reduce the variance due to individual anatomical variability. Global normalization was performed using proportional scaling.

First, for a comparison with previous studies, we analyzed the relationship between the patients' CDT total scores and their rCBF on a voxel-by-voxel basis using "multiple regression" design of SPM 8 (first analysis). We included age, gender, and education as covariates by reference to the similar previous studies.[7,8,9] The statistical threshold was set to a family-wise error uncorrected p-value of 0.001 at the voxel level.

Second, we analyzed the relationships between each error type and the rCBF (second analysis). In this analysis, we excluded patients whose drawings had no clock hands or no numbers, because it was difficult to assess error types using such drawings. For example, a drawing without clock numbers loses all of the points of clock numbers (12 points), which does not mean there are all types of the errors. Eventually 37 patients were excluded, and the remaining 105 patients were subjected to the analyses. Then, we divided the subjects into two groups based on their performances on each item by Mendez scoring (correct or incorrect) for the "two-sample t-test" design of SPM 8. We included Geriatric Depression Scale (GDS) score as a covariate in analyses on Mendez item 5 and 14, because there were intergroup (correct versus incorrect) differences in those Mendez items as we will describe later. Statistical thresholds were set to a family-wise error uncorrected p-value of 0.005 at the voxel level.

We used MNI stereotactic coordinates to examine and report the brain areas.[15] In order to describe the anatomical location, we converted MNI coordinates into Talairach coordinates using Lancaster's calculating formula[16] and used the Talairach Daemon (http://www.talairach.org/daemon.html).

*Other statistical analyses*

In the second analysis, differences in demographic and clinical variables between groups (correct or incorrect) on each Mendez item were computed using 2 sample t-test. Analyses were performed using SPSS software, version 22 (IBM, Chicago, Illinois, USA).

## Results

*Characteristics of patients*

As shown in Table 2, the patients' cognitive dysfunction was mild to moderate. The elimination of subjects whose drawing of the clock had no clock hands or numbers had no significant influence on the characteristics except for total score on the CDT ($p<0.001$).

*First analysis: CDT total score and rCBF*

We found a positive relationship between the left posterior temporal lobe and the CDT total score (Table 3).

*Second analysis: CDT error types and rCBF*

There was a great variability among the percentages of patients who failed on each item (25% on Mendez item 3; 27% on item 4; 39% on item 5; 19% on item 10; 21%

on item 14; 19% on item 16; 31% on item 17; 13% or low on the other items). We analyzed only items 3, 4, 5, 10, 14, 16, and 17 because they had relatively high proportions of failure that were eligible for statistical procedures to examine the associations between erroneous performance on the CDT and the corresponding areas of the brain. The brain areas with reduced cerebral blood flow in the incorrect group compared to the correct group on each item of the CDT are shown in Table 3 and Figure 1. There were some intergroup (correct versus incorrect) differences in Mendez item 4, 5, 10 and 14 (Table 4).

## Discussion

We found a positive association between total score on the CDT and rCBF in the left posterior middle temporal lobe. We also found brain regions related to errors on the CDT in seven of the CDT's 20 items.

In the first analysis, total score on the CDT was positively correlated with rCBF in the left posterior middle temporal lobe. Various studies have reported brain regions which relate to the performance on the CDT.[6,7,8,9,17,18] The left temporal lobe is one of the most frequently reported regions in those studies.[8,9,17,18] In particular, one study using the executive clock drawing task (CLOX) showed that, in patients with less severe AD, regional dysfunction in the left temporal cortex was associated with CDT performance.[8] The severity of dementia of the patients in our study was also relatively mild.

On the other hand, another study using the Mendez method showed a relationship between the right parietal lobe and CDT performance.[7] The study also reported that the results were almost the same regardless of scoring methods (the study compared four scoring methods including the Mendez method). However, the patients in that study were in a more severe stage of dementia compared with the patients in the present study. Thus, the severity of AD might explain the observed difference.

In the second analysis, we found relationships between the error types on the CDT and rCBF. Item 4 of Mendez scoring (i.e., non-existence of number 2, or not pointing toward number 2) was found to be related to the frontal lobe. There were mainly two error types identified for item 4. In one error, the patients set the hands at 11:50 instead of 11:10, presumably affected by the direct auditory input of hearing "11" and "10" when instructed. This error is called a "stimulus-bound response",[19,20] and this response is thought to occur as a consequence of frontal lobe dysfunction.[21] In the other error, the patient set the minute hand to a completely different time (the hour hand was set to 11 in most cases). This error probably reflects impaired abstract thinking such as number-time relation,[10] which is also believed to occur due to frontal lobe dysfunction.[22]

Some studies suggested that "uneven number spacing" (Mendez item 5) corresponds to visuospatial difficulty or planning deficit,[19,20] and that this relates to the parietal or frontal lobe,[22,23] whereas in our study, the association of errors in Mendez item 5 was found only with the frontal lobe.

An earlier study classified "missing numbers" (Mendez item 10) into conceptual deficits of clock[24] (loss or impairment in accessing knowledge of the attributes, features, and meaning of a clock) and it was reported to be related to the left temporal lobe.[22] In contrast, another study classified "missing numbers" as a visuospatial difficulty[10] for which the right parietal lobe dysfunction was proposed to be responsible.[23] Our result supports the findings of the latter study by having shown the association between Mendez item 10 (missing numbers) and right parietal lobe dysfunction. In our study, numbers 4, 5, 7 and 8 on the clock face were frequently omitted, whereas most of the patients rarely failed to draw the numbers 11, 2, and/or the anchoring numbers (12, 3, 6 and 9), except in one case which was apparently caused by left hemineglect. This feature of error on Mendez item 10 also suggests the association between "missing numbers" and visuospatial difficulty.

Mendez item 14 (uneven number distance from edge) is thought to reflect visuospatial difficulties,[19,20] related to right parietal lobe dysfunction. Our study revealed the same association between the error and the responsible region of the brain in this regard.

One study reported a relation between the "deviation of the clock center" (Mendez item 16) and low scores on tests of frontal lobe function.[25] Our findings are consistent with this knowledge since we found an association between this error and reduced CBF in the left middle frontal gyrus.

Some studies classified inadequate representation of the clock hands as a conceptual deficit.[19,20] Accordingly, Mendez item 17 (clock hands of the same length) may be due to conceptual deficits of a clock, presumably related to left temporal lobe dysfunction. As expected, we observed the relationship between Mendez item 17 and temporal lobe in the present study.

We originally thought that Mendez item 3 (an unclosed circle) may reflect visuospatial difficulty, thus item 3 may be related to parietal lobe dysfunction. However, we observed the relationship between Mendez item 3 and the temporal lobe. We were unable to find any previous studies that include a neuropsychological interpretation about the "unclosed circle." The neuroanatomical correlates of the Mendez item 3 type of error remain to be identified.

These outcomes suggest that each error type on the CDT reflects a different regional cerebral dysfunction. A determination of all of these relationships would be useful to interpret the CDT performances and to understand the underlying neuropsychological pathology. Only AD patients were included in the present study, and the evaluation of patients with other medical conditions could be informative. Because the outcomes in this study may indicate the relationships purely between the error types on the CDT and rCBF, the same or similar results may be obtained in other patient groups.

Our study has some limitations. First, we did not assess correlations between the CDT and other neuropsychological tests or between neuropsychological tests and rCBF, although we were able to confirm our results referring to previous studies. Second, we did not collect data about neuropsychiatric symptoms except for GDS. Some studies reported relationships between brain regions and neuropsychiatric symptoms such as depression, apathy, agitation, delusion.[26] Thus, these symptoms may affect the results of the present study and further researches are required. Third, the Mendez method is not necessarily a perfect scoring method to investigate error types on the CDT. For example, according to the Mendez method, the creation of a clock indicating 2:50 instead of 11:10 (i.e., the hour hand is longer than the minute hand) can be judged as correct. Fourth, we combined the SPECT images obtained by different cameras using Hoffman 3-D Brain Phantom experiments, and the statistical thresholds in the second analysis were relatively high. However, this correction method is widely used in clinical settings as an easy Z-score imaging system,[27,28] and given the exploratory aspect of the present research, we believe that the results are reasonable evidence of the significance of this simple instrument as a surrogate for regional cerebral dysfunction in dementia.

In conclusion, the results of the present study suggest that each error type on the CDT relates to a different brain region. These findings could be useful in the interpretation of CDT performances and the understanding of the underlying neuropsychological pathology.

**Acknowledgment**

The author thanks Ms. Yukie Kobayashi for office work assistance.

**Disclosure statement**

No potential conflicts of interest were disclosed.

## References


1 Pinto E, Peters R. Literature review of the Clock Drawing Test as a tool for cognitive screening. *Dement Geriatr Cogn Disord* 2009; 27: 201–213.

2 Yamamoto S, Mogi N, Umegaki H, et al. The clock drawing test as a valid screening method for mild cognitive impairment. *Dement Geriatr Cogn Disord* 2004; 18: 172–179.

3 Freedman M, Leach L, Kaplan E, Winocur G, Shulman KI, Delis DC. Normative Study. In: Freedman M, eds. *Clock Drawing: A neuropsychological analysis*. New York: Oxford University Press, 1994; 9–43.

4 Libon DJ, Malamut BL, Swenson R, Sands LP, Cloud BS. Further analyses of clock drawings among demented and nondemented older subjects. *Arch Clin Neuropsychol* 1996; 11: 193–205.

5 Suhr J, Grace J, Allen J, Nadler J, Mckenna M. Quantitative and qualitative performance of stroke versus normal elderly on six clock drawing systems. *Arch Clin Neuropsychol* 1998; 13: 495–502.

6 Matsuoka T, Narumoto J, Shibata K *et al.* Neural correlates of performance on the different scoring systems of the clock drawing test. *Neurosci Lett* 2011; 487: 421–425.

7 Lee DY, Seo EH, Choo IH *et al.* Neural correlates of the Clock Drawing Test performance in Alzheimer's disease: a FDG–PET study. *Dement Geriatr Cogn Disord* 2008; 26: 306–313.

8 Shon JM, Lee DY, Seo EH *et al.* Functional neuroanatomical correlates of the executive clock drawing task (CLOX) performance in Alzheimer's disease: a FDG–PET study. *Neuroscience* 2013; 246: 271–280.

9 Matsuoka T, Narumoto J, Okamura A *et al.* Neural correlates of the components of the clock drawing test. *Int Psychogeriatr* 2013; 25: 1317–1323.

10 Tranel D, Rudrauf D, Vianna EP, Damasio H. Does the Clock Drawing Test have focal neuroanatomical correlates? *Neuropsychology* 2008; 22: 553–562.

11 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders Text Revision*, 4th edn. Washington: American Psychiatric Association, 2000.

12 Mendez MF, Ala T, Underwood KL. Development of scoring criteria for the clock drawing task in Alzheimer's disease. *J Am Geriatr Soc* 1992; 40: 1095–1099.

13 Matsuda H, Mizumura S, Soma T, Takemura N. Conversion of brain SPECT images between different collimators and reconstruction processes for analysis using statistical parametric mapping. *Nucl Med Commun* 2004; 25: 67–74.

14 Nagafusa Y, Okamoto N, Sakamoto K, et al. Assessment of cerebral blood flow findings using 99mTc-ECD single-photon emission computed tomography in patients diagnosed with major depressive disorder. *J Affect Disord* 2012; 140: 296–299.

15 Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J. A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). *Neuroimage* 1995; 2: 89–101.

16 Lancaster JL, Tordesillas–Gutiérrez D, Martinez M *et al.* Bias between MNI and Talairach coordinates analyzed using the ICBM–152 brain template. *Hum Brain Mapp* 2007; 28: 1194–1205.

17 Nagahama Y, Okina T, Suzuki N, Nabatame H, Matsuda M. Neural correlates of impaired performance on the clock drawing test in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2005; 19: 390–396.

18 Ueda H, Kitabayashi Y, Narumoto J *et al.* Relationship between clock drawing test performance and regional cerebral blood flow in Alzheimer's disease: a single photon emission computed tomography study. *Psychiatry Clin Neurosci* 2002; 56: 25–29.

19 Cahn DA, Salmon DP, Monsch AU *et al.* Screening for dementia of the alzheimer type in the community: the utility of the Clock Drawing Test. *Arch Clin Neuropsychol* 1996; 11: 529–539.

20 Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain Cogn* 1992; 18: 70–87.

21 Tanabe H, Ikeda M, Komori K. Behavioral symptomatology and care of patients with frontotemporal lobe degeneration — based on the aspects of the phylogenetic and ontogenetic processes. *Dement Geriatr Cogn Disord* 1999; 10 Suppl 1: 50–54.

22 Hodges JR. Distributed Cognitive Functions. In; Hodges JR, eds. *Cognitive Assessment for Clinicians*, 2nd edn. New York: Oxford University Press, 2007; 1–28.

23 Thiebaut de schotten M, Urbanski M, Duffau H, Volle E, Lévy R, Dubois B, Bartolomeo P. Direct evidence for a parietal–frontal pathway subserving spatial awareness in humans. *Science* 2005; 309: 2226–2228.

24 Eknoyan D, Hurley RA, Taber KH. The clock drawing task: common errors and functional neuroanatomy. *J Neuropsychiatry Clin Neurosci* 2012; 24: 260–265.

25 Nakatani K, Takahashi H, Miyazaki M, Yamamoto S, Tanaka Y. Vertical

deviation of center on the clock drawing test. *Neurological Medicine* 2008; 69: 166–170 (in Japanese).
26 Li XL, Hu N, Tan MS, Yu JT, Tan L. Behavioral and psychological symptoms in Alzheimer's disease. *Biomed Res Int* 2014. doi: 10.1155/2014/927804.
27 Matsuda H, Mizumura S, Nagao T, et al. An easy Z-score imaging system for discrimination between very early Alzheimer's disease and controls using brain perfusion SPECT in a multicentre study. *Nucl Med Commun* 2007; 28: 199–205.
28 Matsuda H, Mizumura S, Nagao T, et al. Automated discrimination between very early Alzheimer disease and controls using an easy Z-score imaging system for multicenter brain perfusion single-photon emission tomography. *AJNR Am J Neuroradiol* 2007; 28: 731–736.

## Figure Legends

**Figure 1** Examples of errors on the Clock Drawing Test based on the Mendez scoring method, and images showing regions of reduced cerebral blood flow in the incorrect group in the second analysis (n = 105)

**There is a supplementary material**

**Appendix 1**

The original description of the Mendez scoring method.

**Figure 1** Examples of errors on the Clock Drawing Test based on the Mendez scoring method, and images showing regions of reduced cerebral blood flow in the incorrect group in the second analysis (n = 105)

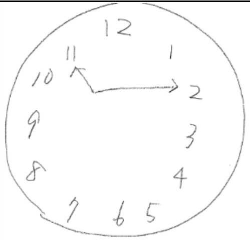
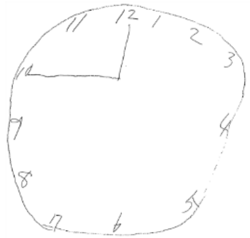
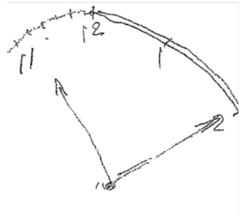
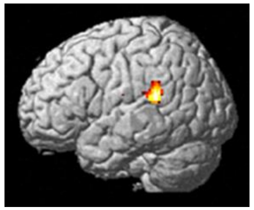
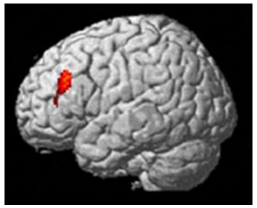
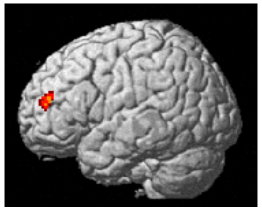
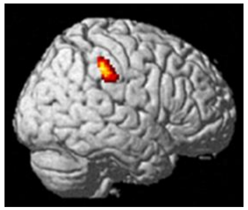
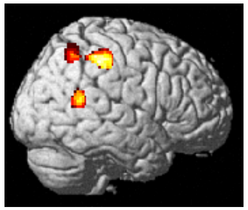
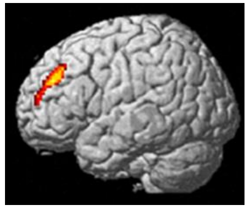
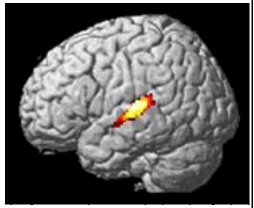
| | Item 3 | Item 4 | Item 5 | Item 10 | Item 14 | Item 16 | Item 17 |
|---|---|---|---|---|---|---|---|
| Mendez item | Unclosed circle | Non-existence of number 2, or not pointing toward number 2 | Uneven number spacing | Missing numbers | Uneven number distance from edge | Deviation of the clock center | Same length hands |
| Examples of errors |  |  |  |  |  |  |  |
| Region of reduced cerebral blood flow in the incorrect group |  |  |  |  |  |  |  |
| | Left temporal lobe | Left frontal lobe | Bilateral frontal lobe | Right parietal lobe | Right parietal and temporal lobe | Left frontal lobe | Bilateral temporal lobe |

Table 1 Clock drawing errors based on the Mendez scoring method

| Mendez item number | |
|---|---|
| General impression | |
| 1 | No attempt to idicate a time |
| 2 | Extra marks, symbols, or figures |
| 3 | Unclosed circle |
| Numbers: Score only if clock numbers are present | |
| 4 | Non-existence of number 2, or not pointing toward number 2 |
| 5 | Uneven number spacing |
| 6 | Two or more clock quadants having no appropriate numbers |
| 7 | Numbers counterclockwaise |
| 8 | Numbers outside of circle |
| 9 | Non-existence of number 11, or not pointing toward number 11 |
| 10 | Missing numbers |
| 11 | Repeated numbers |
| 12 | Substitution of numbers or hands |
| 13 | Number beyond 12 |
| 14 | Uneven number distance from edge |
| 15 | Six or less of the same type symbols |
| Hands: Score only if one or more hands are present | |
| 16 | Deviation of the clock center |
| 17 | Same length hands |
| 18 | More than 2 hands, or only one hand |
| 19 | Hands extended over ciecle |
| 20 | No attempt to point to any numbers |

*Notes:* The original Mendez article assesses the correctness of the drawings, and we scored drawings according to the original descriptions, but we named each item after their errors for convenience. The original descriptions of the Mendez scoring method are shown in Appendix 1.

**Table 2** Clinical characteristics of the patients

| | First analysis (n = 142) | Second analysis (n = 105) |
|---|---|---|
| Age, years | 77.2 ± 7.5 | 77.2 ± 6.9 |
| Gender, % female | 64.8 | 66.7 |
| Education, years | 11.3 ± 2.7 | 11.4 ± 2.7 |
| Duration of dementia, years | 2.3 ± 2.3 | 2.3 ± 2.4 |
| MMSE score | 21.4 ± 3.8 | 22.2 ± 3.4 |
| ADAS-J cog score | 16.2 ± 7.0 | 14.6 ± 5.1 |
| CDT score (Mendez) | 15.0 ± 4.8 | 17.6 ± 2.1 |
| GDS score | 5.1 ± 3.4 | 4.8 ± 3.4 |

*Notes*: MMSE = Mini-Mental State Examination; ADAS-J cog = Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale; CDT = Clock Drawing Test; GDS = Geriatric Depression Scale.

**Table 3** Location, expanse, and significance of detected brain area correlates with CDT total score in the first analysis (n = 142). And brain areas with reduced cerebral blood flow in the incorrect group compared to the correct group on each item of the Clock Drawing Test in the second analysis (n = 105).

| | Brain region (BA) | MNI coordinates | | | Voxels, | z-score | Voxel p-value |
|---|---|---|---|---|---|---|---|
| | | x | y | z | n | | (uncorrected) |
| First analysis | | | | | | | |
| | Left middle temporal gyrus (BA 39) | −46 | −64 | 22 | 383 | 3.86 | <0.001 |
| Second analysis | | | | | | | |
| Item 3 | Left superior temporal gyrus (BA 13) | −54 | −40 | 22 | 189 | 3.10 | 0.001 |
| Item 4 | Left middle frontal gyrus (BA 9) | −46 | 32 | 30 | 87 | 3.06 | 0.001 |
| Item 5 | Left middle frontal gyrus (BA 10) | −36 | 50 | 18 | 57 | 2.93 | 0.002 |
| | Right middle frontal gyrus (BA 10) | 30 | 56 | −4 | 72 | 2.92 | 0.002 |
| Item 10 | Right inferior parietal lobule (BA40) | 56 | −34 | 46 | 130 | 3.18 | 0.001 |
| Item 14 | Right inferior parietal lobule (BA40) | 48 | −32 | 48 | 369 | 3.83 | <0.001 |
| | Right superior temporal gyrus (BA 39) | 54 | −50 | 16 | 170 | 3.18 | 0.001 |
| | Right superior parietal lobule (BA7) | 36 | −58 | 54 | 109 | 3.09 | 0.001 |
| Item 16 | Left middle frontal gyrus (BA 9) | −34 | 42 | 34 | 191 | 3.02 | 0.001 |
| Item 17 | Left superior temporal gyrus (BA 42) | −62 | −22 | 8 | 593 | 3.84 | <0.001 |
| | Right transverse temporal gyrus (BA 41) | 58 | −12 | 8 | 638 | 3.20 | 0.001 |

*Notes*: BA = Brodmann area; MNI = Montreal Neurological Institute.
The statistical thresholds were $p < 0.001$ on the first analysis and $p < 0.005$ on the second analysis, uncorrected at the voxel level.
Each coordinate indicates the voxel location with the highest z-score within each brain region.

**Table 4** Differences in demographic and clinical variables between groups (correct or incorrect) on each item of the Clock Drawing Test.

| Mendez item | | correct | incorrect | p-value |
|---|---|---|---|---|
| Item 3 | n | 79 | 26 | |
| | Age, years | 76.6 ± 6.9 | 78.9 ± 6.6 | 0.146 |
| | Gender, % female | 69.6 | 57.7 | 0.267 |
| | Education, years | 11.3 ± 2.7 | 11.5 ± 2.4 | 0.713 |
| | MMSE score | 22.0 ± 3.6 | 22.9 ± 2.8 | 0.212 |
| | GDS score | 5.0 ± 3.5 | 4.3 ± 3.1 | 0.326 |
| Item 4 | n | 77 | 28 | |
| | Age, years | 77.0 ± 7.1 | 77.8 ± 6.3 | 0.589 |
| | Gender, % female | 68.8 | 60.7 | 0.440 |
| | Education, years | 11.4 ± 2.5 | 11.4 ± 3.0 | 0.895 |
| | MMSE score | 22.6 ± 3.5 | 21.0 ± 2.8 | 0.024 |
| | GDS score | 5.1 ± 3.5 | 4.1 ± 3.0 | 0.206 |
| Item 5 | n | 64 | 41 | |
| | Age, years | 76.7 ± 7.2 | 77.9 ± 6.3 | 0.409 |
| | Gender, % female | 60.9 | 57.0 | 0.113 |
| | Education, years | 11.7 ± 2.9 | 10.9 ± 2.2 | 0.148 |
| | MMSE score | 22.6 ± 3.2 | 21.5 ± 3.7 | 0.097 |
| | GDS score | 5.4 ± 3.8 | 4.0 ± 2.4 | 0.031 |
| Item 10 | n | 85 | 20 | |
| | Age, years | 77.5 ± 6.8 | 75.7 ± 7.3 | 0.287 |
| | Gender, % female | 72.9 | 40.0 | 0.005 |
| | Education, years | 11.1 ± 2.5 | 12.5 ± 3.1 | 0.043 |
| | MMSE score | 22.4 ± 3.6 | 21.3 ± 2.0 | 0.068 |
| | GDS score | 4.9 ± 3.5 | 4.6 ± 3.0 | 0.729 |
| Item 14 | n | 83 | 22 | |
| | Age, years | 77.8 ± 6.4 | 74.8 ± 8.2 | 0.070 |
| | Gender, % female | 65.1 | 72.7 | 0.502 |
| | Education, years | 11.3 ± 2.7 | 11.5 ± 2.3 | 0.870 |
| | MMSE score | 22.5 ± 3.1 | 21.0 ± 4.1 | 0.103 |
| | GDS score | 4.4 ± 3.2 | 6.5 ± 3.5 | 0.011 |
| Item 16 | n | 85 | 20 | |
| | Age, years | 77.6 ± 6.7 | 75.3 ± 7.3 | 0.187 |
| | Gender, % female | 65.9 | 70.0 | 0.728 |
| | Education, years | 11.5 ± 2.7 | 10.7 ± 2.2 | 0.210 |
| | MMSE score | 22.5 ± 3.3 | 21.1 ± 3.7 | 0.092 |
| | GDS score | 4.7 ± 3.6 | 5.4 ± 2.6 | 0.455 |
| Item 17 | n | 72 | 33 | |
| | Age, years | 77.1 ± 7.4 | 77.4 ± 5.8 | 0.808 |
| | Gender, % female | 72.2 | 54.5 | 0.091 |
| | Education, years | 11.6 ± 2.6 | 10.9 ± 2.7 | 0.199 |
| | MMSE score | 22.4 ± 3.4 | 21.8 ± 3.5 | 0.475 |
| | GDS score | 4.8 ± 3.6 | 4.9 ± 2.9 | 0.885 |

*Notes:* MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale.

**Appendix 1:** The original description of the Mendez scoring method.

CLOCK DRAWING INTERPRETATION SCALE
(Score "1" per item):

1. There is an attempt to indicate a time in any way.
2. All marks or items can be classified as either part of a closure figure, a hand, or a symbol for clock numbers.
3. There is a totally closed figure without gaps (closure figure).

Score Only if Symbols for Clock Numbers Are Present:

4. A "2" is present and is pointed out in some way for the time.
5. Most symbols are distributed as a circle without major gaps.
6. Three or more clock quadrants have one or more appropriate numbers: 12-3, 3-6, 6-9, 9-12 per respective clockwise quadrant.
7. Most symbols are ordered in a clockwise or rightward direction.
8. All symbols are totally within a closure figure.
9. An "11" is present and is pointed out in some way for the time.
10. All numbers 1-12 are indicated.
11. There are no repeated or duplicated number symbols.
12. There are no substitutions for Arabic or Roman numbers.
13. The numbers do not go beyond the number 12.
14. All symbols lie about equally adjacent to a closure figure edge.
15. Seven or more of the same symbol type are ordered sequentially.

Score Only if One or More Hands Are Present:

16. All hands radiate from the direction of a closure figure center.
17. One hand is visibly longer than another hand.
18. There are exactly two distinct and separable hands.
19. All hands are totally within a closure figure.
20. There is an attempt to indicate a time with one or more hands.