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Neural Correlates of the Clock Drawing Test Performance in Alzheimer's Disease: A FDG-PET Study

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Key Words
Alzheimer's disease · Clock drawing test · Neural correlate · PET

Abstract
Background/Aim: This study aimed to identify the functional neuroanatomical correlates of impaired clock drawing test (CDT) performance in patients with Alzheimer's disease (AD). ***Method:*** The CDT was administered to 71 patients with AD, and regional cerebral glucose metabolism (rCMglc) was measured by positron emission tomography (PET). Correlations between CDT scores and rCMglc were examined on a voxel-by-voxel basis. ***Results:*** Significant positive correlations were found between CDT performance and rCMglc in the right inferior parietal lobule and right posterior cingulate cortex. ***Conclusion:*** These results provide the first PET evidence that poor CDT performance in patients with AD is closely related to the functional decline in the right hemisphere, especially the right parietal cortex.

Introduction

The Clock Drawing Test (CDT) is a widely used cognitive assessment tool. It is not only simple and easy to administer, but also easily accepted by cognitively impaired patients. Many investigators have reported that the CDT is very useful in detecting and tracking cognitive decline in patients with neurodegenerative disorders, e.g. Alzheimer's disease (AD) [1–4].

Performance on the CDT relies, in general, on visuospatial ability, semantic memory, executive control function, receptive language and even motor ability [5, 6]. Some authors have attributed the poor performance of AD patients on the CDT to impaired visuospatial ability [3, 4], whereas others have argued that it is more heavily influenced by semantic memory and frontal executive functioning [2, 7, 8].

While diverse neuroanatomical lesions could be associated with impaired CDT performance [5], the brain areas that underlie the impaired performance on the CDT in patients with AD are still controversial. Functional neuroimaging studies using single photon emission com-

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puted tomography (SPECT) [6, 9] suggested that CDT performance has a close relationship with the function of the left posterior temporal area. In contrast, a structural neuroimaging study [10] indicated that the CDT performance by AD patients is specifically related to regional volume loss of the right anterior and posterior superior temporal cortex. The parietal cortex is known to be closely related to visuospatial processing and spatial thought [11], and it has been shown to be consistently involved in the process of pathological progression of AD [12]. However, no previous brain imaging study had suggested that the structural or functional involvement of the parietal cortex, especially the right one, is responsible for poor CDT performance. There has also been no suggestion of an association between the frontal lobe and the CDT performance of AD patients, although the frontal lobe is responsible for executive functions and known to be pathologically involved in the later stages of AD [12]. Differences in CDT scoring methods, brain imaging modalities or the clinical severity of AD in the patients included may be the reason of these conflicting reports.

In order to identify the functional neuroanatomical correlates of impaired CDT performance in patients with AD, we investigated the relationship between the CDT scores assessed by four different scoring methods and regional cerebral glucose metabolism measured by positron emission tomography (PET). To explore the overall correlation pattern between diverse brain areas and CDT performances without an a priori hypothesis, we adopted voxel-based analysis instead of region-of-interest approaches.

Patients and Methods

Patients

The study patients included were recruited from patients with AD who visited the Dementia and Age-Associated Cognitive Decline Clinic of the Seoul National University Hospital in Seoul. Seventy-one patients with AD who met both the Diagnostic and Statistical Manual of Mental Disorders criteria for dementia [13] and the criteria for probable AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) [14] were included. Forty cognitively intact healthy normal controls (NC) were also selected from a pool of elderly volunteers with a normal neurologic and psychiatric history and examination, and a normal brain magnetic resonance image. The exclusion criteria for this study were as follows: any present serious medical, psychiatric and neurological disorder that could affect mental function; evidence of focal brain lesions on magnetic resonance imaging; the presence of severe behavioral or communication problems that would make a clinical or PET examination difficult; both- or left-handedness, and absence of a reliable informant. The Institutional Review Board of the Seoul National University Hospital, Korea, approved the study protocol, and informed consent was obtained from all the subjects as well as their relatives.

Clinical Assessments

All the subjects were examined by neuropsychiatrists who had advanced training in neuropsychiatry and dementia research according to the protocol of the Korean Version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) [15, 16]. Psychiatric, general physical and neurological examinations were performed along with routine laboratory tests and MRI of the brain. Reliable informants were necessarily interviewed to acquire the accurate information regarding the cognitive, emotional and functional changes as well as the medical history of the subjects. A panel consisting of four neuropsychiatrists with expertise in dementia research made the clinical decisions including diagnosis and clinical dementia rating (CDR) [17] after reviewing all the available raw data. All clinical assessments were carried out within 3 weeks of the PET examination. None of the subjects were receiving an antidepressant or other psychotropic medication.

Clock Drawing Test

The CDT was administered as a part of clinical evaluation according to the CERAD-K. To perform the CDT, all subjects were presented with a blank sheet of paper (8.5 × 11 inch) and a pencil, and the following instructions were given: 'I want you to draw a clock. Start with a circle and then insert all the numbers. Then set the hands to show the time to be 8:20.' The performance on the CDT was scored by a clinical psychologist according to four different sets of commonly used scoring systems. The rater was unaware of any other information about the participants including their clinical diagnoses, CDR and other neuropsychological test scores. Each of the scoring systems used in this study is described below.

Rouleau. The Rouleau scoring system [8] independently assesses the three components of the drawing (the accuracy of the representation of the clock face, 2 points; the presence and sequencing of numbers, 4 points, and the presence and placement of hands, 4 points), yielding an overall 10-point scale, with higher numbers indicating better performance.

Sunderland. The Sunderland scoring system [4] uses a single 10-point rating, with higher numbers indicating better performance. Clock drawings are matched to 1 of 10 clock descriptions, ranging from 1 (no attempt or an uninterpretable effort to draw a clock) to 10 (clock face and numbers intact and hands in the correct positions). The first 5 points reflect drawing a clock face with circle and numbers intact. The remaining points are assigned for accurately drawing hands to denote the time.

Todds. The Todds scoring system [18] uses a 10-point scale with two points given for each of the following: circle, numbers 1–6, number 7–12, short arm and long arm. Each item is scored for correctness of drawing and location. Higher numbers also reflect better performance.

Mendez. The Mendez scoring system [3] uses a 20-point scale with higher numbers reflecting better performance. The scale is derived from 20 individual items, worth 1 point each. Three items on this scale reflect the general characteristics of the clock, 12

items refer to the presentation and placement of the numbers, and 5 items assess the existence and placement of each hand.

Other Neuropsychological Tests

In addition to the CDT, seven neuropsychological tests, including verbal fluency – 'animal category' (VF), the 15-item Boston Naming Test (BNT), Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), Constructional Praxis (CP) and Constructional Recall (CR) from the CERAD-K [15, 16], were also applied in order to explore which cognitive abilities could explain CDT performance. VF measures semantic memory and verbal production; BNT, naming; WLM, the learning ability for new verbal information; WLR, delayed verbal recall ability; WLRc, verbal recognition ability; CP, visuospatial and constructional ability, and CR, delayed visual recall ability [19].

PET Imaging

PET studies were performed using the ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, Tenn., USA), which has an intrinsic resolution of 5.2-mm full width at half maximum (FWHM) and the images of 47 contiguous transverse planes with a 3.4-mm thickness for a longitudinal field of view of 16.2 cm. Before administering [^{18}F] fluorodeoxyglucose (FDG), transmission scanning was performed using three germanium-68 rod sources to correct the attenuation. Static emission scans began 30 min after the intravenous injection of 370 MBq (10 mCi) [^{18}F]FDG and were continued for 30 min. All of the [^{18}F]FDG PET scans were performed in a dimly lit room with minimal auditory stimulation during both the injection and PET scanning. The subjects were in the supine position with their eyes closed during the scanning in order to minimize the confounding effects of any activity. The transaxial images were reconstructed using a filtered back-projection algorithm employing a Shepp-Logan filter with a cutoff frequency of 0.3 cycles/pixel as 128 × 128 × 47 matrices with a size of 2.1 × 2.1 × 3.4 mm.

PET Data Analysis

Image data were analyzed using statistical parametric mapping 99 (Institute of Neurology, University College of London, UK) implemented in the Matlab (Mathworks, Natick, Mass., USA) [20]. Before the statistical analysis, all of the images were spatially normalized to the Montreal Neurological Institute (McGill University, Montreal, Que., Canada) space in order to correct for intersubject anatomical variability [21]. An affine transformation was performed to determine the 12 optimal parameters essential for registering the brain on the template. Subtle differences between the transformed image and the template were removed by the nonlinear registration method, using the weighted sum of predefined smooth basis functions used in a discrete cosine transformation. The normalized images were smoothed by convolution with an isotropic Gaussian kernel with 16-mm FWHM, both to accommodate intersubject differences in gyral and functional anatomy and to increase the signal-to-noise ratio in the dataset. The glucose metabolism value of each voxel was normalized versus the pontine value, which was extracted for each scan, as glucose metabolism in the pons tends to be relatively preserved in AD [22]. The normalized images were smoothed by convolution with an isotropic Gaussian kernel with 16-mm FWHM. The difference in the regional cerebral glucose metabolism (rCMglc) between the AD and NC group was estimated on a voxel-by-voxel basis using a t test. Positive correlations between the CDT score and rCMglc were examined on a voxel-by-voxel basis with age and education as covariates within AD patients. A height threshold $p < 0.001$ (uncorrected) and an extent threshold of 20 voxels was applied. The Montreal Neurological Institute coordinates of the local maximum of each cluster were converted into Talairach coordinates [23].

Table 1. Demographic and clinical characteristics of the study groups

Characteristics	NC (n = 40)	AD (n = 71)
Age, years	70.6 ± 7.1	68.6 ± 8.4
Education, years	8.4 ± 5.3	7.7 ± 5.6
Sex, % female	60.0	73.2
MMSE	27.0 ± 2.6	16.4 ± 6.1
CDR, n of patients		
0	40	0
0.5	0	25
1	0	26
2	0	18
3	0	2
CDR sum of boxes	0.0	2.0–17.0

MMSE = Mini-Mental State Examination.

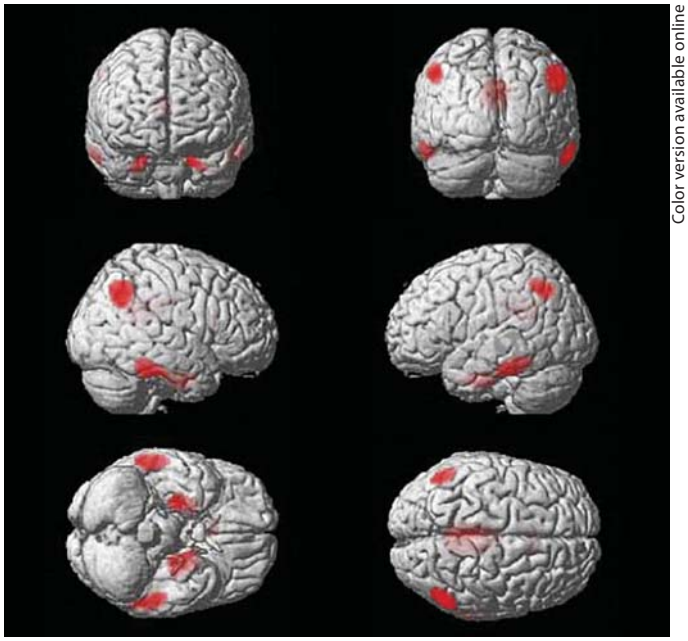
Analysis of Demographic, Clinical and Neuropsychological Data

Differences in demographic and clinical variables between the NC and AD groups were tested using Student's t test or the χ^2 test. Stepwise multiple linear regression analysis was performed to identify which of the seven neuropsychological tests in the CERAD-K could explain the variance of CDT scores in the AD patients. The criteria for entry of the variables were $p < 0.05$ and $p < 0.10$ for removal. All analyses were performed using SPSS software, version 10.0 (SPSS, Cary, N.C., USA).

Results

Demographic and Clinical Characteristics of the Subjects

Demographic and clinical characteristics of the subjects are shown in table 1. There were no significant differences in age, education and gender between the NC and AD groups. The patients with AD showed a significantly lower mean Mini-Mental State Examination score than the NC group ($t = 11.3$, $p < 0.01$). The AD group included 25 very mild (CDR 0.5), 26 mild (CDR 1), 18 moderate (CDR 2) and 2 severe (CDR 3) patients.



Color version available online

Fig. 1. Statistical parametric maps showing decreased metabolism in patients with AD compared with NC elderly (uncorrected $p < 0.001$).

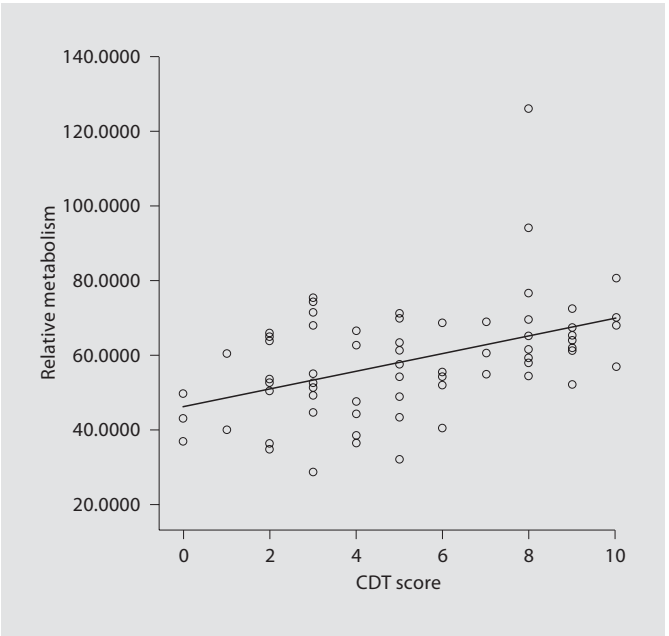


Fig. 3. Illustration of the significant correlation between CDT score according to the Rouleau method and glucose metabolism in the right inferior parietal lobule in AD patients.

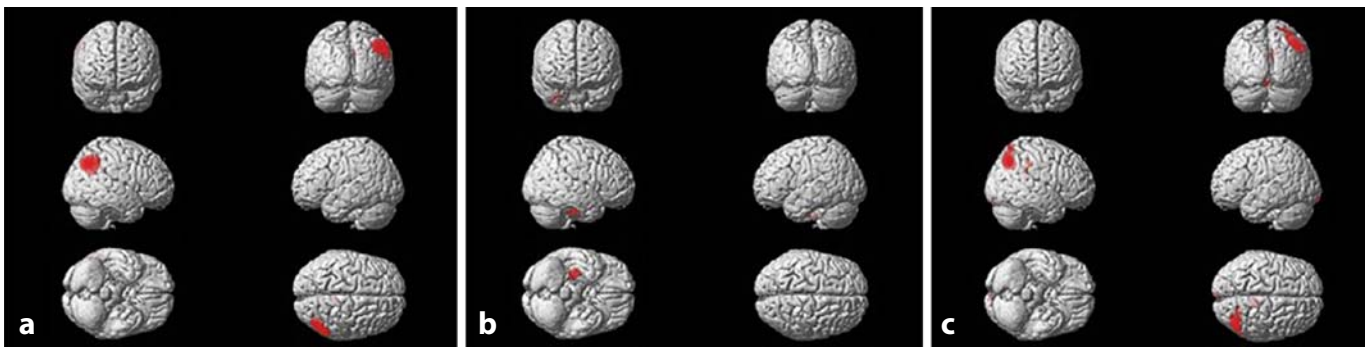


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Fig. 2. Statistical parametric maps showing brain areas with positive correlation between CDT scores according to the Rouleau method and glucose metabolism (**a**) in the total group (uncorrected $p < 0.001$), the subgroup with less severe AD (**b**; uncorrected $p < 0.005$) and the more severe AD subgroup (**c**; uncorrected $p < 0.005$).

Relationship between CDT and Other Neuropsychological Test Scores in AD

Stepwise multiple regression analysis revealed that the CP and VF scores of the seven neuropsychological tests could explain the significant variance in CDT scores using the Rouleau system (CDT_R: $\beta = 0.60$, $R^2 = 0.46$, $p < 0.001$ for CP; $\beta = 0.23$, $R^2 = 0.05$, $p < 0.05$ for VF), CDT scores by the Todd system (CDT_T: $\beta = 0.63$, $R^2 = 0.52$, $p < 0.001$ for CP; $\beta = 0.29$, $R^2 = 0.07$, $p < 0.01$ for VF), CDT scores using the Mendez system (CDT_M: $\beta = 0.62$, $R^2 = 0.53$, $p < 0.001$ for CP; $\beta = 0.32$, $R^2 = 0.09$, $p < 0.001$ for VF), while only CP scores could predict the significant variance in CDT scores using the Sunderland system (CDT_S: $\beta = 0.63$, $R^2 = 0.39$, $p < 0.001$).

Comparison of rCMglu between AD and NC groups

Figure 1 shows the brain areas with significantly ($p < 0.001$, uncorrected) lower rCMglc in the AD group than in the NC group, documenting the expected hypometabolism in the bilateral temporal areas including the me-

Table 2. Brain areas showing a significant positive correlation between CDT scores and cerebral glucose metabolism in the AD patients included in the study (n = 71)

Scoring system for clock drawing	Brain regions (BA)	Coordinates: x, y, z	Voxels n	z score	p value (uncorrected)
Rouleau	right inferior parietal lobule (40)	57, –58, 42	1,104	4.08	<0.001
	right posterior cingulate (31)	8, –37, 30	177	3.52	<0.001
Sunderland	right inferior parietal lobule (40)	57, –58, 42	164	3.62	<0.001
Todds	right inferior parietal lobule (40)	55, –58, 44	469	3.60	<0.001
	right posterior cingulate (31)	8, –35, 28	59	3.35	<0.001
Mendez	right inferior parietal lobule (40)	61, –53, 42	634	3.68	<0.001

Coordinates (x, y and z) refer to a standard stereotactical space [23]. Each coordinate indicates the location of the voxel with the highest z score within each brain region.

Table 3. Brain areas showing positive correlations between CDT scores (Rouleau method) and cerebral glucose metabolism in two AD subgroups (uncorrected $p < 0.005$)

Subgroups	Brain regions (BA)	Coordinates: x, y, z	Voxels n	z score	p value (uncorrected)
Less severe	right parahippocampal gyrus (36)	34, –21, –34	263	3.03	0.001
More severe	right superior parietal lobule (7)	44, –68, 48	676	3.52	0.001
	right posterior cingulate (23)	10, –35, 29	521	3.01	0.001
	right lingual gyrus (18)	0, –100, –12	138	3.23	0.001
	right inferior parietal lobule (40)	67, –31, 40	81	2.87	0.004

Coordinates (x, y and z) refer to a standard stereotactical space [23]. Each coordinate indicates the voxel location with the highest z score within each brain region.

dial temporal areas [Brodmann's area (BA) 28: x, y, z = 22, –9, –28; BA 28: –18, –9, –28; BA 37: 63, –38, –20; BA 37: –55, –32, –19], the bilateral inferior parietal lobule (BA 40: 51, –56, 40; BA 40: –51, –54, 47), the right posterior cingulate cortex (PCC; BA 23: 2, –39, 26) and the right anterior cingulate cortex (BA 33: 6, 11, 22). No voxel was observed with significantly increased rCMglc in AD.

Correlations between CDT Scores and rCMglu in AD

Significant positive correlations between CDT_R and rCMglc were found in the right inferior parietal lobule and the right PCC in patients with AD (table 2, fig. 2). In very similar brain areas, significant positive correlations were also observed between CDT_S, CDT_T or CDT_M and rCMglc (table 2). The normalized metabolism value was extracted at the local maximum of each voxel cluster showing a significant correlation using the voxel of interest module of statistical parametric mapping to estimate the degree of correlation between CDT_R and glucose metabolism. Pearson's correlation coefficient (r) was 0.46 ($p < 0.001$) for the right inferior parietal lobule and 0.33 for the right PCC ($p < 0.01$) in each of the correlations. Figure 3 illustrates the correlation between CDT_R and normalized glucose metabolism in the right inferior parietal lobule in patients with AD.

To explore the effect of global AD severity on the relationship between CDT scores and rCMglc, we divided the patients with AD into two severity subgroups according to the CDR Sum of Boxes score (SOB): less severe subgroup (CDR SOB <5.5, which equals to the median CDR SOB score of overall AD patients) and more severe subgroup (CDR SOB ≥5.5). For subgroup analyses, a less conservative threshold, $p < 0.005$ (uncorrected) was applied, as we were merely attempting to explore, not confirm, the patterns of relationship between CDT scores and rCMglc in a relatively smaller sample. Positive cor-

relations between CDT_R and rCMglc were found in the right parahippocampal gyrus for the less severe subgroup, and in the right inferior parietal lobule, right posterior cingulate and right lingual gyrus for the more severe subgroup (table 3; fig. 2). In almost identical brain areas, significant positive correlations were also observed between the CDT_S, CDT_T or CDT_M and rCMglc.

Discussion

This is the first study using PET to demonstrate that the impairment in CDT performance in patients with AD is closely related to the functional decline in the right hemisphere, including the right inferior parietal lobule, right PCC and right parahippocampal gyrus. Although the right hemisphere (especially the right parietal cortex) is traditionally coupled with visuospatial function and CDT performance has been explained at least partly by this function [3–5], no previous functional imaging study has provided any evidence for the relationship between CDT performance and the right hemisphere function in AD. In a SPECT study adopting the voxel-based analysis, Nagahama et al. [6] reported that the impaired CDT performance in patients with AD is related to the dysfunction in the left posterior temporal cortex, which may be related to semantic memory [24]. On the basis of their results, they suggested that the impaired CDT performance in patients with AD might be associated mainly with their deficit in semantic knowledge. However, the only neuropsychological predictor of CDT score in their study was block design performance, which is not related to semantic memory but mainly reflects visuospatial ability. Another SPECT study using the regions of interest method by Ueda et al. [9] also reported that left posterior temporal blood flow had a close relationship with CDT performance in AD. Although it is not easy to provide actual reasons for the discrepancy between the results of those studies and ours except for the use of different imaging methods (PET versus SPECT), the discrepancy in CDT scoring systems are not likely to contribute to the difference. Nearly identical results were obtained for the four different CDT scoring systems used in our study. The Rouleau method, one of the four scoring systems adopted in our study, was also used in the study by Ueda et al. [9]. In contrast to the functional imaging studies, a structural imaging study using magnetic resonance imaging showed that the CDT score significantly correlated with the regional volume of the right anterior and posterior superior temporal lobe [5, 19].

Because the brain areas involved in AD-related pathologies progressively expand as the clinical severity of AD increases [12], the neuroanatomical substrates related to CDT performance are expected to change from the earlier stage to later stages of AD. Therefore, we divided the patients with AD into two subgroups based on severity, and explored the relationship between CDT performance and regional brain function separately within each subgroup. CDT performance in the more severe patients correlated with the function of the right parietal cortex and lingual gyrus, whereas the right parahippocampal gyrus was related to CDT performance in the less severe patients. There is much evidence that the right parahippocampal gyrus is required for spatial memory, especially the retrieval of object location and schematic spatial representations of familiar environments [25–29]. The impairment in retrieving a schematic clock face accurately is mainly associated with poor CDT performance in the early stage of AD. The relationship between CDT performance and the right parietal areas or right lingual gyrus, observed for the more severe patients with AD in this study, probably indicates that neurodegenerative changes involving both the dorsal and ventral visual processing pathways are progressively more responsible for the failure in CDT performance. Two fundamental pathways for visual information processing have been proposed based on many nonhuman primate researches: the dorsal pathway, which projects from the primary visual cortex to the posterior parietal cortex, is specialized for processing the spatial relationships of objects ('where'), and the ventral pathway, which projects from the primary visual cortex to the inferior temporal cortex, is specialized for object recognition ('what') [30]. Because motor function was globally intact in our subjects with AD, the impairment in the dorsal and ventral pathways seems to underlie the deficits of locating the various components of the clock correctly in space and linking the meaning of a clock to its visual shape, respectively. This change in the responsible areas for a poor CDT score coincide with the general progression pattern of AD-related pathologies, especially neurofibrillary tangles and neuronal loss, which initially appear in the medial temporal areas, including the parahippocampal area, and then progress to the posterior multimodal association cortices. One previous neuropathological study also suggested that CDT performance has a weak but consistent and inverse relationship with both the tangle count in the parietal lobe and parahippocampal gyrus, and the number of neurons in the parahippocampal gyrus [31].

Executive control function, which is closely related to the frontal cortex or frontal-subcortical circuit, was also suggested to be involved in CDT performance. However, no relationship between CDT performance and the frontal region was found in our study. This result is consistent with those of previous imaging studies on CDT suggesting that poor CDT performance in AD more sensitively reflects loss of semantic memory or poor visuospatial ability than executive dysfunction. Moreover, our data on the relationship between the CDT and other neuropsychological test scores revealed that CDT performance taps semantic knowledge and constructional praxis. As previous researchers [9, 10] pointed out, the four scoring systems applied in this study may not be sensitive enough to detect executive dysfunction. To investigate this possibility, further functional neuroimaging studies and qualitative analysis on CDT errors are needed. An alternative explanation, however, may be that the frontal or subcortical involvement of the brain appears in the more advanced stage of AD, compared to parietal involvement. As only 3 patients in this study were in the severe stage (CDR 3) and all of the other patients had mildly or moderately severe AD, this may explain why no relationship between CDT performance and frontal or subcortical hypometabolism was found in our study.

In conclusion, our results provide the first PET evidence that clock drawing performance in AD patients is closely related to the function of the right hemisphere. Regardless of the four CDT scoring systems, poor clock drawing performance was related to the functional decline in the right inferior parietal lobule, right PCC and right lingual gyrus in patients with more severe AD, and the right parahippocampal gyrus in patients with less severe AD.

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