

Original Research Article

Trail Making Test Part A and Brain Perfusion Imaging in Mild Alzheimer's Disease

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Key Words

Alzheimer's disease · Cerebral blood flow · Single photon emission computed tomography · Trail Making Test

Abstract

Background/Aims: The Trail Making Test (TMT) has long been used to investigate deficits in cognitive processing speed and executive function in humans. However, there are few studies that elucidate the neural substrates of the TMT. The aim of the present study was to identify the regional perfusion patterns of the brain associated with performance on the TMT part A (TMT-A) in patients with Alzheimer's disease (AD). **Methods:** Eighteen AD patients with poor performance on the TMT-A and 36 age- and sex-matched AD patients with good performance were selected. All subjects underwent brain single photon emission computed tomography. **Results:** No significant differences between the good and poor performance groups were found with respect to years of education and revised Addenbrooke's Cognitive Examination scores. However, higher z-scores for hypoperfusion in the bilateral superior parietal lobule were observed in the group that scored poorly on the TMT-A compared with the good performance group. **Conclusion:** Our results suggest that functional activity of the bilateral superior parietal lobules is closely related to performance time on the TMT-A. Thus, the performance time on the TMT-A might be a promising index of dysfunction of the superior parietal area among mild AD patients.

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Introduction

Alzheimer's disease (AD) is the leading cause of late-onset dementia worldwide. Patients with AD display a multiplicity of cognitive deficits in domains such as memory, visuospatial cognition, language, and executive function [1]. Therefore, in the dementia clinic, many neuropsychological tests have been used to detect deficits in cognitive function. When evaluating the results of those tests, it is important to know the neural correlates of the tests. The Trail Making Test (TMT) is among the most commonly used neuropsychological tests in clinical practice, including memory clinics [2]. The TMT has long been used to investigate deficits in cognitive processing speed and executive function in humans [3]. However, there is relatively more ambiguity about the neural systems associated with the TMT than with many other tests of comparable clinical use [4], and there have been no studies to investigate the neural substrates of the TMT among patients with AD.

To elucidate the neural substrate of neuropsychiatric symptoms in AD, brain single photon emission computed tomography (SPECT) is often used. Dorsolateral prefrontal hypoperfusion is involved in depression [5–7], whereas medial frontal or orbitofrontal hypoperfusion is devoted to apathy [7–9]. Delusion is closely related to decreased perfusion in the right frontal lobe [10–12], and anosognosia may be a reflection of functional impairment in the orbitofrontal or inferior frontal cortex [13–15]. The neural substrate of neuropsychological tests for patients with dementia has also been disclosed using brain SPECT data. The total Mini-Mental State Examination (MMSE) score is significantly correlated with a reduction of left hippocampal perfusion [16]. The Frontal Assessment Battery score and the category-achieved score from the Wisconsin Card Sorting Test are closely related to functional activity of the dorsolateral prefrontal areas [17, 18].

In this study, we tried to clarify the relationship between TMT time and regional cerebral blood flow (rCBF) using SPECT data. The TMT consists of part A and part B (TMT-A and TMT-B). As a first step, we investigated the cerebral correlates of the TMT-A. Studies of the mutual relationships among various neuropsychological tests report that the TMT-A examines mainly visuospatial abilities and graphomotor speed [3, 19]. However, in another study, participants with frontal brain damage performed significantly more poorly than those with nonfrontal brain damage on the TMT-A but not on the TMT-B [20]. In a study using ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET), the focal brain metabolic rate did not predict the performance of schizophrenia patients ($n = 42$) on the TMT-A [21]. In this study, we aimed to compare the rCBF of AD patients with good and poor performances on the TMT-A, and to investigate the neural substrate involved in the performance of AD patients on the TMT-A. Because mutual relationships among various neuropsychological tests suggest that visuospatial ability is very important for the performance of the TMT-A, and visual attention deficits in AD have been reported to correlate with superior parietal lobe hypoperfusion [1, 22], we predicted a relationship between the TMT-A performance time and rCBF in the parietal region among AD patients.

Methods

The Trail Making Test

The TMT-A and TMT-B were administered by clinical psychologists who were blind to the clinical diagnosis and Clinical Dementia Rating (CDR) score. The tests were conducted according to the standard administration procedure described by Spreen and Strauss [23].

Briefly, the TMT-A requires the patient to link in ascending order a series of 25 numbers (1, 2, 3...) randomly distributed in space [24]. Subjects are instructed to start their trial at the

circle marked 'Begin' and continue linking numbers until they reach the endpoint (circle marked 'End'). In the Japanese version of the TMT-B, the test is modified by changing letters of the Roman alphabet (A, B, C...) to Kana (Japanese phonograms; 'a', 'i', 'u'...) [25]. The TMT-B is similar to the TMT-A, although instead of just linking numbers, the patient must alternately switch between a set of numbers (1–13) and a set of Kana letters ('a' through 'shi'), again linking them in ascending order (1/a/2/i...). During the tests, the examiner corrects each error immediately. At the same time, the subject is also asked to connect the array of circles as fast as possible without lifting the pencil [24]. The time limits for performing the TMT-A and TMT-B are 300 and 600 s, respectively.

The detailed normative TMT data stratified by age and educational level have been reported elsewhere [26]. In this study, patients with a TMT-A time greater than or equal to the mean + 2 SD for the normal elderly were included in the poor performance group on the TMT-A, while patients with a TMT-A time less than or equal to the mean + 1 SD for the normal elderly were included in the good performance group on the TMT-A.

Subjects

Eighteen AD patients with dementia severity of 0.5 (suspicious) or 1 (mild) based on the CDR [27] and whose time on the TMT-A was over the mean + 2 SD were selected from 124 consecutive AD patients who were fully examined at the Memory Clinic of Okayama University Hospital between April 2004 and March 2010. In addition, 36 AD patients from the Memory Clinic with good performance on the TMT-A, matched for age, sex, education, and revised Addenbrooke's Cognitive Examination (ACE-R) scores [28, 29], were also selected.

They all (1) underwent general physical and neurological examinations and extensive laboratory testing, including thyroid function tests, serum vitamin B₁₂, and syphilis serology; (2) took the MMSE [30] and ACE-R within 1 week of scanning; (3) underwent brain SPECT as well as head MRI; (4) were diagnosed with probable AD according to the criteria formulated by the NINCDS-ADRDA [31]; (5) had a dementia severity of 0.5 or 1 on the CDR [27], and (6) they or their nearest relatives gave written informed consent.

The exclusion criteria were (1) complications by other neurological diseases or illnesses; (2) a history of mental illness or substance abuse prior to the onset of dementia; (3) any evidence of focal brain lesions on head MRI; (4) treatment with cholinesterase inhibitors, anti-psychootics, antidepressants, or anxiolytic drugs, and (5) left-handedness or ambidexterity.

Information was also gathered from caregivers familiar with the patient's daily behavior. To serve as an informant, the caregiver must have been living with the patient. The profile of each subject (age, sex, years of education, and years of disease duration) was recorded. The Neuropsychiatric Inventory (NPI) [32], Physical Self-Maintenance Scale (PSMS), and Lawton Instrumental Activities of Daily Living (IADL) scale [33] were scored based on the information from caregivers.

Other Instruments

The ACE-R was developed to provide a brief test sensitive to early-stage dementia and is capable of differentiating between dementia subtypes including AD, frontotemporal dementia, progressive supranuclear palsy, and other parkinsonian syndromes [28]. The ACE-R includes the MMSE but extends it to encompass important areas not covered by the MMSE, such as frontal-executive function and visuospatial skills. For this study, we used the Japanese version of the ACE-R described by Yoshida et al. [29]. The reliability of the Japanese version of the ACE-R is excellent, and its validity is, to some extent, established [29].

Neuropsychiatric symptoms were evaluated by the NPI. The NPI is a valid and reliable instrument for measuring behavior in dementia [32, 34]. It is a caregiver-based tool that assesses 10 common behaviors in dementia. The PSMS and IADL are validated scales for the

assessment of activities of daily living (ADL) [33]. The PSMS is a 6-item scale that rates self-care ability in toileting, feeding, dressing, personal hygiene and grooming, locomotion (physical ambulation), and bathing. The IADL scale assesses a patient's ability to perform 8 complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundry, mode of transportation, responsibility for medications, and ability to manage finances.

Ethics

The study protocol was approved by the Committee of Okayama University Hospital on Human Research. After giving a complete description of the study to the subjects and their relatives, written informed consent was obtained.

Brain Perfusion SPECT

All subjects were examined by brain perfusion SPECT. Patients were examined in a comfortable supine position with their eyes closed in quiet surroundings. First, the passage from the heart to the brain was monitored after intravenous administration of ^{99m}Tc -ethyl cysteinate dimer (ECD, 600 MBq; Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan). Ten minutes after the angiography, SPECT images were obtained using a triple-head, rotating gamma camera interfaced to a minicomputer (GCA9300A/DI; Toshiba, Tokyo, Japan) equipped with a fan beam, low-energy, high-resolution collimator. Sixty projection images over a 360° angle in a 128×128 matrix were acquired. All images were reconstructed using ramp-filtered back projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.12 cycles/cm). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

Data Analysis

Spatial reprocessing and statistical analysis of images were performed on a voxel-by-voxel basis using Statistical Parametric Mapping 2 (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) running on MATLAB (The MathWorks Inc., Natick, Mass., USA). All SPECT images of each subject were normalized to the standard brain of the Montreal Neurological Institute, and spatial normalization was performed with 12-parameter affine and nonlinear transformations [35]. The voxel sizes of the reslice option were $2 \times 2 \times 2$ mm. The nonlinear parameter was set at 25-mm cutoff basis functions and 16 iterations. All normalized SPECT images were then smoothed with an isotropic gaussian kernel filter (12 mm full width at half-maximum). To examine the images for specific regions showing differences in perfusion, two-sample t tests were performed. Global normalization was performed by proportional scaling with the mean voxel value. Masking was applied using the threshold method (0.8 times the global value). The analysis used a threshold of $p < 0.01$ at the voxel level, and results were considered significant at $p < 0.05$ (uncorrected) at the cluster level.

Statistical Analysis

Statistical analysis was performed using the SPSS 14.0J software program (SPSS Inc., Chicago, Ill., USA). The two groups were compared using independent sample t tests. A value of $p < 0.05$ was accepted as significant.

Results

Clinical Characteristics and Neuropsychological Tests

No significant differences were found between the good and poor performance groups on the TMT-A with respect to age ($p = 0.456$) or years of education ($p = 0.638$; table 1).

Table 1. Clinical characteristics and neuropsychological tests

	Bad score	Good score	t	p
Total	18	36		
Males/females	7/11	10/26		
Age, years	72.7±7.9	75.3±6.7	-1.281	0.206
Education, years	11.5±3.3	11.1±2.6	0.473	0.638
ACE-R score	69.2±12.8	69.1±7.4	0.040	0.968
MMSE score	23.2±3.3	23.2±2.5	-0.069	0.945
TMT-A time, s	99±23	50±15	9.605	0.000
TMT-B time, s	406±230	239±144	3.281	0.002
TMT B-A time, s	308±222	189±138	2.426	0.019
TMT B/A ratio	4.1±2.2	4.8±2.3	-1.068	0.290

Values are n or means ± SD. Bad score = AD patients with poor performance on the TMT-A. Good score = AD patients with good performance on the TMT-A.

Table 2. ADL and IADL

	Bad score	Good score	t	p
NPI				
Delusion	0.5±1.6	0.4±1.0	0.457	0.650
Hallucination	0.3±0.8	0.1±0.5	0.911	0.367
Agitation/aggression	0.3±1.0	0.4±1.3	-0.419	0.677
Depression	0.7±1.0	0.4±0.9	1.078	0.287
Anxiety	0.2±0.4	0.1±0.5	0.497	0.621
Euphoria	0±0	0±0	0.000	1.000
Apathy	1.1±1.4	1.1±1.5	0.156	0.877
Disinhibition	0.1±0.3	0.2±0.7	-0.446	0.658
Irritability	0.4±0.9	0.9±1.8	-0.915	0.365
Aberrant motor behavior	0.5±1.2	0.2±1.1	0.941	0.352
PSMS				
Toileting	0.9±0.3	1.0±0.0	-2.052	0.045
Feeding	0.9±0.2	1.0±0.0	-1.408	0.165
Dressing	0.8±0.4	1.0±0.2	-1.825	0.074
Grooming	0.9±0.3	1.0±0.2	-1.226	0.226
Ambulation	0.8±0.4	1.0±0.2	-2.360	0.022
Bathing	0.9±0.4	1.0±0.0	-0.797	0.429
IADL				
Ability to use telephone	0.9±0.2	1.0±0.0	-1.408	0.165
Shopping	0.8±0.4	0.9±0.3	-1.030	0.308
Food preparation	0.7±0.5	0.8±0.4	-0.292	0.772
Housekeeping	1.0±0.0	1.0±0.0	0.000	1.000
Laundry	0.9±0.4	1.0±0.0	-2.018	0.052
Mode of transportation	1.0±0.0	1.0±0.0	0.000	1.000
Responsibility for own medications	0.6±0.5	0.7±0.5	-0.752	0.456
Ability to handle finances	0.9±0.3	1.0±0.0	-2.052	0.045

Values are means ± SD. Bad score = AD patients with a low score on the TMT-A. Good score = AD patients with a high score on the TMT-A.

Table 3. Significant regional uptake differences between AD patients with high and low scores on the TMT-A

Direction of difference	Number of voxels	Peak z-scores	Coordinates (MNI)		
			x	y	z
Decreased uptake in AD patients with low scores on the TMT-A	553	3.44	-10	-70	70
		3.16	0	-76	62
		3.04	-4	-86	48

MNI = Montreal Neurological Institute.

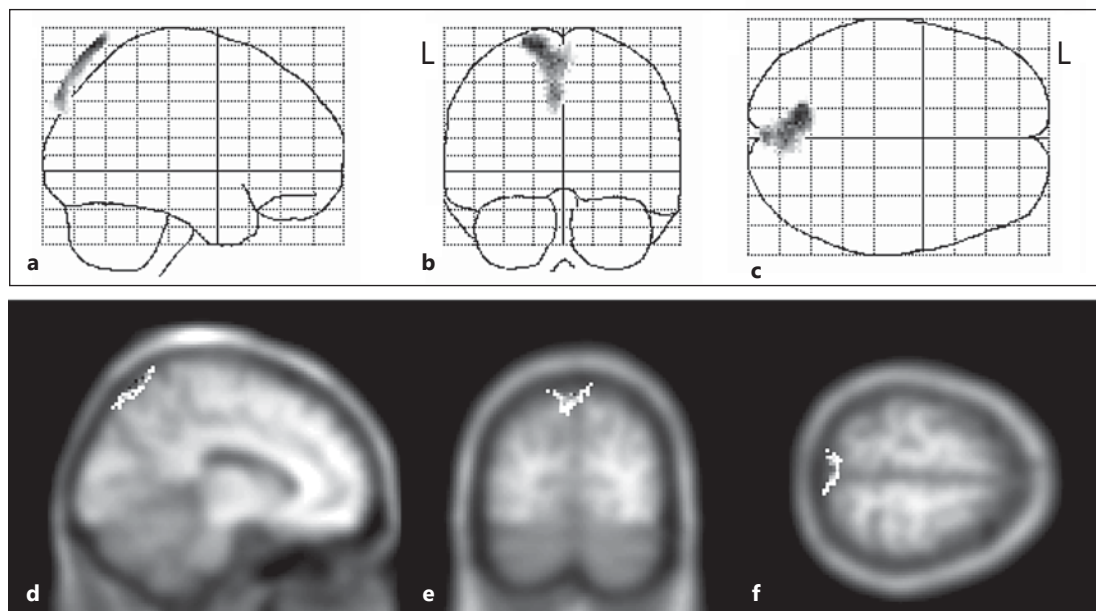


Fig. 1. a–f SPM (z) of rCBF decrease in AD patients with poor performance on the TMT-A compared with AD patients with good performance. Three-way glass view of the area of significant hypoperfusion (a–c), superimposed on head MRI T1-weighted images: x = -10 (d), y = -75 (e), and z = 65 (f). L = Left.

With the exception of the TMT-A, TMT-B, and TMT B-A [(TMT-B time) – (TMT-A time)] times (TMT-A, $p < 0.001$; TMT-B, $p < 0.013$; TMT B-A, $p < 0.019$), no significant differences were found between the good and poor performance groups on the ACE-R ($p = 0.968$), MMSE ($p = 0.945$), TMT B/A ratio [(TMT-B time)/(TMT-A time)] ($p = 0.290$), or NPI subscale scores (table 1, 2). Comparison of the PSMS and IADL scale revealed that AD patients with poor performance on the TMT-A had lower scores than those with good performance on the TMT-A in the subscale scores of toileting, physical ambulation, and ability to handle finances (table 2).

Regional Cerebral Blood Flow

A group comparison between the SPM results of the good and poor performance groups was performed. Specific voxels with a significantly lower perfusion in the poor performance group than in the good performance group are shown in figure 1 and table 3.

Figure 1 shows the z-score for each voxel in this cluster superimposed onto a three-dimensional glass brain view. A significant cluster of voxels in the left superior parietal lobule slightly extending to the right superior parietal lobule can also be seen in figure 1. Table 2 shows the probability results of the Statistical Parametric Mapping analysis and the location of peak z-scores in terms of the Montreal Neurological Institute coordinates.

Discussion

Superior Parietal Lobule and the TMT

We predicted hypoperfusion in the parietal region among AD patients with poor performance on the TMT-A, and this study revealed that rCBF in the bilateral superior parietal lobule of AD patients with poor performance on the TMT-A was lower than that of AD patients with good performance on the TMT-A. Therefore, the results are in accordance with our hypotheses.

Visual attention and visuospatial processing involve the superior parietal lobule [36, 37], and both are impaired in AD [38–42]. As stated above, the TMT-A requires mainly visuoperceptual abilities and graphomotor speed [3, 19]. Therefore, it is not surprising that performance on the TMT-A among AD patients is significantly correlated with rCBF in the superior parietal lobule. However, to our knowledge, this is the first study to show that rCBF in the superior parietal lobule of AD patients with poor performance on the TMT-A is significantly lower than that of AD patients with good performance.

TMT and ADL

Visual attention and visuospatial processing are reported to greatly affect patients' ADL [42, 43]. In this study, AD patients with poor performance on the TMT-A showed lower scores than those with good performance on the TMT-A in the subscale scores of toileting, physical ambulation, and ability to handle finances among PSMS and IADL. Our results suggest that performance on the TMT-A is closely related to several ADL as well as rCBF in the superior parietal lobule, independent of ACE-R and MMSE scores.

Superior Parietal Lobule and AD

At the very early stage of AD, regional cortical atrophy is mainly restricted to the medial temporal structures as well as the posterior cingulate gyrus [44–46]. With the progression of the disease, the atrophic areas extend to the parietal and frontal lobes with the advancement of the disease [47, 48]. Significant decreases of rCBF were detected in the bilateral parietal, angular gyrus, pericallosal, thalamus, right temporal, and left hippocampal regions in mild AD [49].

We found a decrease in rCBF in the superior parietal lobule among mild AD patients with poor performance on the TMT-A compared to those with good performance. Our results suggest that some AD patients suffer from parietal neuropsychological deficits and parietal hypoperfusion in the early stage of the disease.

Limitations of This Study

The TMT is a popular neuropsychological test and is often used to detect executive dysfunction [3]. In those cases, the TMT B-A time or TMT B/A ratio is calculated as a score reflecting executive function [20, 50]. However, in this study we focused on the TMT-A. We selected two groups of patients based on their TMT-A scores. As a result, the AD patients with poor performance on the TMT-A also showed lower scores on the TMT-B time and TMT B-A time but not on the TMT B/A ratio. Therefore, it cannot be denied that the TMT-B time and

TMT B-A time are also significantly related to rCBF in the superior parietal lobule. Further study is needed to clarify the significance of the TMT B-A time or TMT B/A ratio by comparing rCBF between two groups with significantly different scores on the TMT B-A time or TMT B/A ratio but without significantly different scores on the TMT-A time.

The results of this study should be interpreted with some caution. First, the relatively small sample size, comprising only 18 AD patients with poor performance on the TMT-A and 36 AD patients with good performance on the TMT-A, may limit the sensitivity to actual group differences and associations between neuropsychological functions and regional brain hypoperfusion. Second, the low spatial resolution of SPECT scans may limit detection of alterations in small regions, thus increasing the risk of false negatives and interference from surrounding regions [51].

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