

Regional Cerebral Blood Flow in [123]I-IMP Single-photon Emission Computed Tomography and the Wechsler Memory Scale-revised in Nondemented Elderly Subjects with Subjective Cognitive Impairment

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Abstract

Objective Regional cerebral blood flow (rCBF) imaging with single-photon emission computed tomography (SPECT) is useful in the early diagnosis of dementia. We aimed to investigate the association between the rCBF and various domains related to the memory function in elderly subjects with subjective cognitive impairment (SCI).

Methods Thirty-two subjects with SCI were included in the present study. Patients with dementia and mild cognitive impairment (MCI) were excluded based on the presence of logical memory impairment. N-isopropyl-p-[¹²³I]-iodoamphetamine SPECT was performed and Wechsler Memory Scale-Revised (WMS-R) was administered to all subjects (mean age, 68.4 years; average Mini-Mental State Examination score, 27.6). The SPECT results were analyzed using the easy Z-score imaging system and the voxel-based stereotactic extraction estimation method. Correlation analyses were performed to investigate the correlation between the mean positive Z-scores in the decrease of the rCBF and the WMS-R indices.

Results The SPECT study indicated marked hypoperfusion in some areas, including the bilateral temporal areas, the caudate, and the thalamus, in these subjects in comparison to the normal database. The decrease in the rCBF that was observed in several regions, including the left precuneus and left inferior frontal gyrus (LIFG), showed a significant negative correlation with several indices of the memory function, particularly visual memory.

Conclusion The regional hypoperfusion observed in the study using the voxel-based stereotactic extraction estimation method suggest that the regional cerebral dysfunction is associated with the memory function of patients with SCI, even though the subjects in the present study were cognitively intact. The correlation analysis with the WMS-R suggested the contribution of the LIFG to the memory function and indicated the significance of visual memory dysfunction in the neuropsychological assessment to determine the stage of SCI.

Key words: left inferior frontal gyrus (LIFG), single-photon emission computed tomography (SPECT), subjective cognitive impairment (SCI), visual memory, wechsler Memory Scale (WMS)

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Introduction

Regional cerebral blood flow (rCBF) imaging by single-photon emission computed tomography (SPECT) or positron emission tomography (PET) plays an important role in the early diagnosis of Alzheimer's disease (AD) (1, 2). Several investigations using SPECT or PET have indicated the presence of hypoperfusion or reduced metabolism in the medial parietal portion, including the posterior cingulate gyrus and precuneus, in the transitional stage of AD (1, 2). The diagnostic findings from SPECT perfusion and PET imaging are biomarkers that are indicated in the new criteria for the diagnosis of AD (3).

The Japan Cooperative SPECT Study on Assessment of Mild Impairment of Cognitive Function (J-COSMIC) assessed the prediction of outcomes in mild cognitive impairment (MCI) using rCBF imaging (4). Moreover, in Japan, a multicenter study (5) was performed to determine whether a computer-assisted diagnostic system Z-score summation analysis method (ZSAM) using three-dimensional stereotactic surface projections (3D-SSP) could differentiate AD/dementia with Lewy bodies (DLB) from non-AD/DLB. However, the automated region of interest (ROI) analyses of both the J-COSMIC and ZSAM only focused on the pattern of hypoperfusion in AD, DLB, and frontotemporal dementia.

The relationship between cerebral perfusion and the psychometric performance of patients with dementia has been investigated. However, a quantitative assessment of the association between cerebral perfusion and the memory function, as assessed by a memory examination such as by the Wechsler Memory Scale-Revised (WMS-R) (6), has not been well studied. The WMS is a neuropsychological examination that is designed to measure multiple memory functions in an individual. The WMS-R consists of 13 subtests: information and orientation, mental control, figural memory, logical memory (LM) I/II, visual paired associates I/II, verbal paired associates I/II, visual reproduction I/II, digit span, and visual memory span. An individual's performance is reported in terms of five index scores: verbal memory, visual memory, general memory (sum of verbal and visual memory), attention/concentration, and delayed recall. A memory examination produces notable results because memory dysfunction generally precedes other cognitive domains dysfunctions in the prodromal phase of AD (7), which is also known as MCI. The purpose of the present study was to assess the association of the rCBF with the functions of various memory domains in elderly individuals with the use of the WMS-R. This association corresponds with the contribution of local neural activity, as reflected by significant changes in the rCBF, to the various memory functions. Thus, this study only included elderly subjects who were cognitively intact, but who had some subjective cognitive complaints (SCCs).

The importance of SCCs has been emphasized as a core feature of MCI in recent consensus reports (8). However,

cognitive complaints are frequent in elderly individuals and not all patients with MCI or dementia complain of memory problems. SCCs or subjective cognitive impairment (SCI) are also considered to be associated with depression and personality traits (9). Studies on the relationship between SCI and cognitive performance have given inconclusive results, and these results have aroused great interest. In this study, we included subjects in whom any memory dysfunction was negligible and did not warrant a diagnosis of AD, this included individuals who had been diagnosed with MCI, because our secondary purpose was to investigate the background pathophysiology of SCI using the subjects' CBF and WMS-R scores and to determine whether the pathophysiology is associated with MCI in prodromal AD.

Materials and Methods

Subjects

We prospectively included 40 elderly subjects with SCCs (for example, "becoming forgetful") at Ayabe City Hospital between 2008 and 2010. All of the subjects were right-handed (as checked by interview). Patients with dementia and MCI were excluded based on the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (10), as were those who showed LM impairment. The criteria for exclusion based on LM impairment were as follows: any subject with <8 years of education whose WMS-R LM II part A index score was <3; any subject with 8-15 years of education whose LM II index score was <5; and any subject with >15 years of education whose LM II index score was <9. We also excluded all subjects with a Mini-Mental State Examination (MMSE) of <24. These criteria were based on the subject selection described in the AD Neuroimaging Initiative (ADNI) profile report (11). Based on a clinical examination by a neurologist, patients with Parkinsonism or other movement disorders were excluded from this study.

A pre-assessment was performed with magnetic resonance imaging (MRI) of the head, to identify severe cerebral vascular disease (Fazekas grade >2) (12), brain tumors, or any other organic abnormalities. Patients with these findings were excluded. To exclude subjects with extreme hippocampal atrophy, we used the voxel-based specific regional analysis system for AD (VSRAD) software program (2, 13), which can assess the degree of atrophy of the entorhinal cortex. Any subject with a VSRAD Z-score of >3.0 (severe level) (14) was excluded.

Finally, a total of 32 subjects were included in the study. The study was approved by the ethics committee of Meiji University of Integrative Medicine. The project details were explained to each subject, and all subjects provided their written informed consent.

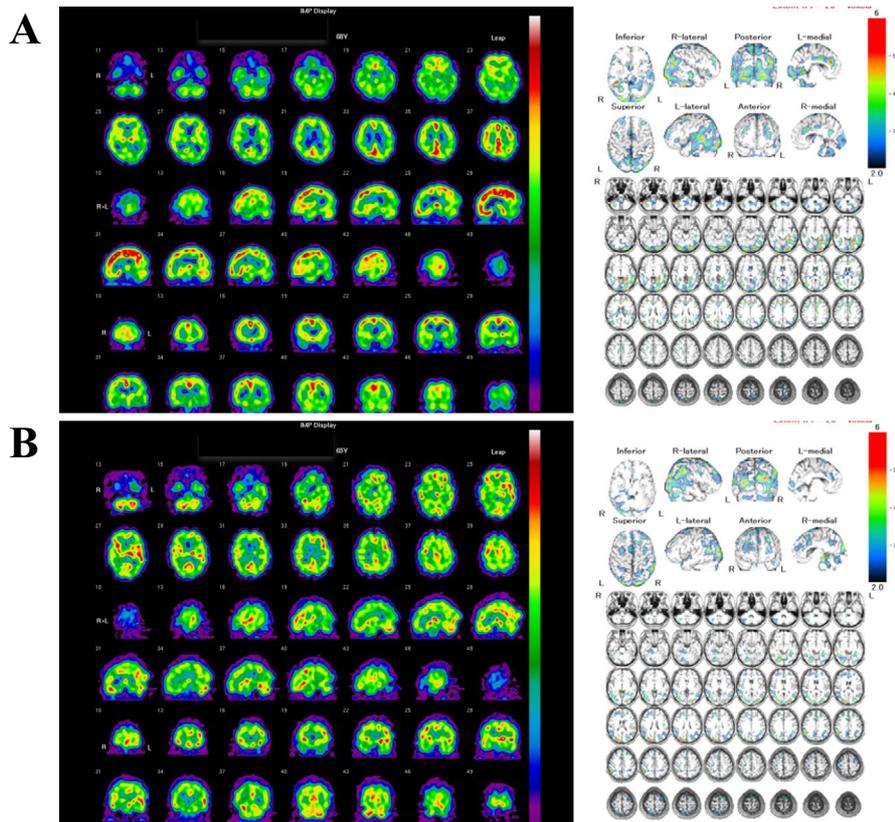


Figure 1. Transaxial N-isopropyl-p-¹²³I-iodoamphetamine single-photon emission computed tomography (SPECT) images (left) and the easy Z-score imaging system (eZIS) mapping of the decrease (right) in two of the study subjects. A: A 68-year-old woman with a Mini-Mental State Examination (MMSE) score of 27/30; B: A 65-year-old man with an MMSE score of 29/30. The images show a relative decrease in the rCBF in several areas, including the temporal area.

Examinations

N-isopropyl-p-[¹²³I]-iodoamphetamine ([¹²³I]-IMP) SPECT scans were performed and the MMSE and WMS-R were administered for all subjects.

All of the subjects were injected with 111 MBq of [¹²³I]-IMP while in a supine resting state with their eyes closed. After 20 minutes, brain SPECT scanning was performed for 20 minutes using an E.CAM system, an LMEGP collimator, and a GMS-5000 WorkStation (Toshiba, Tokyo, Japan). Transaxial images were obtained by filtered back-projection methods, and attenuation correction was performed using Chang's method. Projection data were obtained at 45 s × 45°/step × 4 steps. An attenuation correction coefficient of 0.146 was used. The matrix and pixel sizes of the SPECT images were 128×128 and 3.3×3.3 mm, respectively. The SPECT imaging data were analyzed using the easy Z-score imaging system (eZIS) (2, 15), which uses statistical parametric mapping processing for normalization and smoothing. The Z-scores of the decrease in the rCBF were displayed on the standardized template of the Montreal Neurological Institute (Fig. 1).

The severity of cerebral hypoperfusion was quantified based on the mean decrease in the rCBF using voxel-based stereotactic extraction estimation (vbSEE) (16), a software

program for voxel-based morphometry that was developed by Matsuda et al. The cerebral ROI in the vbSEE software program was based on the Talairach atlas (17). The results were analyzed with reference to the segmentation in the Talairach atlas level 3 (gyrus).

Statistical analysis

In this eZIS study, no healthy subjects without SCCs were enrolled as controls. However, the analysis using eZIS included a comparison with healthy subjects. Unfortunately, the detailed demographics of the normal subjects in eZIS using [¹²³I]-IMP SPECT have not been disclosed, nor have they been published in English-language journals. To the best of our knowledge, these cognitively normal controls, who were ≥60 years of age, included 22 healthy elderly subjects (mean age, 71.8 years) without cerebral vascular disease or other organic abnormalities.

The Pearson's correlation coefficients between the Z-scores of the principal volume of interest (VOI) in the rCBF and the WMS-R indices (age- and reference-scaled percentiles) were calculated. All of the statistical analyses were performed using PASW (formerly SPSS) Statistics (version 18.0J) software program.

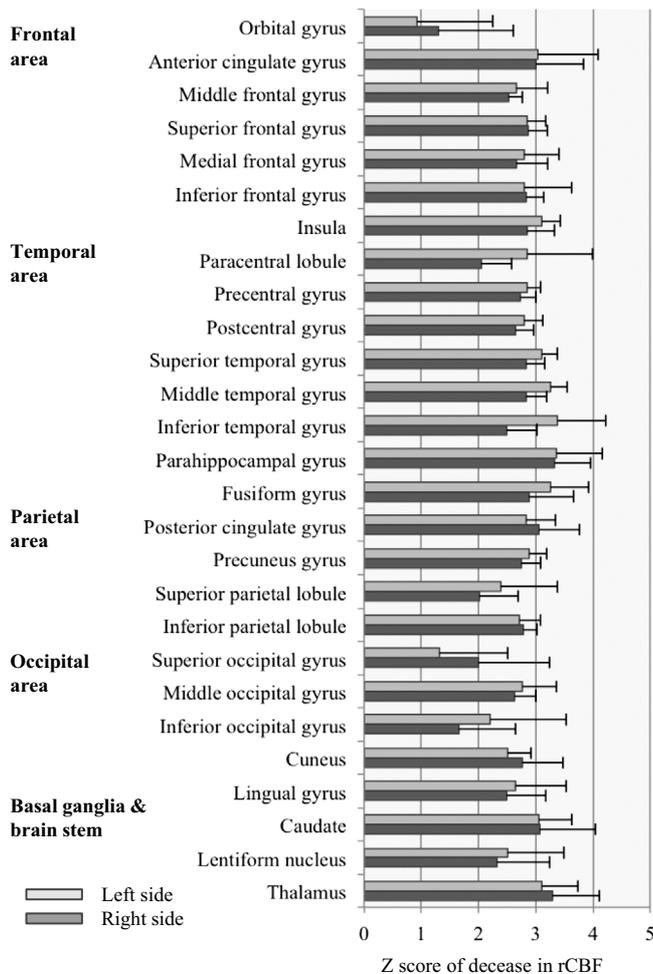


Figure 2. The mean decrease in the regional cerebral blood flow in all subjects. The Z-scores were calculated using the voxel-based stereotactic extraction estimation method.

Results

Subject demographics

The study population included 17 men and 15 women (mean age, 68.4 years; range, 59-75 years); the mean MMSE score was 27.6 (range, 24-30); the mean duration of education 12.7 years (range, 9-16 years). The average percentiles (\pm standard deviation) for the WMS-R were as follows: verbal memory, 102.4 ± 12.7 ; visual memory, 105.3 ± 13.7 ; general memory, 103.6 ± 13.0 ; attention/concentration, 102.6 ± 11.7 ; and delayed recall, 103.7 ± 11.8 . The average percentiles were within the normal range for their age.

Regional cerebral blood flow

Representative images of the CBF in two subjects are shown in Fig. 1. The neuropsychological test scores and indices of subjects A (a 68-year-old female) and B (a 65-year-old male), respectively, were as follows: MMSE, 27 and 29; verbal memory, 94 and 112; visual memory, 95 and 125; general memory, 93 and 118; attention and concentration,

105 and 114; and delayed recall, 95 and 118.

Relative hypoperfusion, mainly in the temporal area, was indicated in the eZIS images of all of the subjects who were included in the study. These findings were also demonstrated by a Z-score analysis using bvSEE. The Z-score of the mean decrease in the rCBF, as measured by bvSEE, showed marked hypoperfusion in some areas (Fig. 2). The areas with a mean Z-score of >3.0 included the bilateral anterior cingulate gyrus, left insula, left superior/middle/inferior temporal gyrus, left fusiform gyrus, bilateral parahippocampal gyrus, right posterior cingulate gyrus, bilateral caudate, and the bilateral thalamus.

The correlation between regional cerebral blood flow and the Wechsler Memory Scale-Revised score

The correlation analysis indicated that the WMS-R indices were most strongly correlated with the CBF in the left inferior frontal gyrus (Table). The decrease in the rCBF of several left-side regions, including the left inferior frontal gyrus and left precuneus, was negatively correlated with the visual memory index. In contrast, no definite trend was observed in the right brain.

Discussion

The regional cerebral blood flow in subjects with subjective cognitive impairment

The group analysis using the Z-score indicated a relative decrease in the rCBF in several areas, including the temporal area. A decrease in the rCBF in the temporal and parietal areas is frequently observed in patients with AD and MCI (1, 2). Although the decreases in the frontal area (the anterior cingulate gyrus and insula) were relatively prominent (Fig. 2), those in the posterior (the temporal and parietal areas) circulation appeared to be even more prominent. Interestingly, the Z-score, as shown in Fig. 2, indicated that decreases in the bilateral parahippocampal gyrus, responsible for memory encoding and retrieval, were relatively stronger than those in other regions in the temporal area. These decreases may reflect the beginning of cognitive impairment in the subjects with SCI. However, the pattern of hypoperfusion in SCI cannot be interpreted as an AD-like pattern, and we could not conclude that most subjects with SCCs showed the potential for AD or MCI because similar temporal-lobe-dominant hypoperfusion can also be observed in patients with cognitive disorders other than AD, such as frontotemporal dementia. In fact, SCI may be associated with heterogeneous disease entities that include depression and personality traits (9). In our study, even after excluding the subjects with MCI and dementia based on a memory assessment and a clinical examination, we found it difficult to distinguish or exclude any subjects with a potential non-AD pathophysiological condition, including non-AD tauopathy and synucleinopathy (Lewy body disease).

A decrease was also observed in other areas, including

Table. The Pearson's Correlation Coefficients between the Wechsler Memory Scale-Revised Indices (Age- and Reference-scaled Percentiles) and the Mean Decrease in the Regional Cerebral Blood Flow in All Subjects.

VOI on left hemisphere	Verbal memory	Visual memory	General memory	Attention/ Concentration	Delayed recall
Orbital gyrus	0.371*	0.224	0.344	0.159	0.336
Anterior cingulate gyrus	-0.147	-0.119	-0.17	-0.237	-0.146
Middle frontal gyrus	0.063	-0.062	-0.005	-0.19	0.014
Superior frontal gyrus	0.291	0.431*	0.357*	0.095	0.312
Medial frontal gyrus	0.168	0.078	0.123	0.214	0.11
Inferior frontal gyrus	-0.414*	-0.462**	-0.479**	-0.106	-0.408*
Insula	-0.108	-0.173	-0.17	-0.354*	-0.044
Precentral gyrus	-0.172	-0.107	-0.158	-0.128	-0.123
Postcentral gyrus	-0.077	0.038	-0.047	-0.252	0.043
Superior temporal gyrus	-0.091	-0.037	-0.098	0.082	0.013
Middle temporal gyrus	0.047	-0.022	0.03	0.167	0.081
Inferior temporal gyrus	-0.277	-0.176	-0.259	-0.011	-0.232
Parahippocampal gyrus	-0.14	-0.118	-0.169	0.066	-0.057
Fusiform gyrus	-0.348	-0.275	-0.372*	-0.147	-0.234
Posterior cingulate gyrus	-0.011	-0.099	-0.05	0.142	0.232
Precuneus gyrus	-0.275	-0.406*	-0.329	0.127	-0.185
Superior parietal lobule	0.115	0.043	0.111	-0.089	-0.022
Inferior parietal lobule	-0.011	-0.261	-0.084	-0.136	-0.051
Superior occipital gyrus	0.264	-0.09	0.155	0.03	0.177
Middle occipital gyrus	-0.15	-0.418*	-0.258	-0.124	-0.294
Inferior occipital gyrus	-0.177	-0.335	-0.266	-0.073	-0.369*
Cuneus	-0.086	-0.297	-0.13	0.082	-0.186
Lingual gyrus	-0.272	-0.399*	-0.365*	0.144	-0.225
Caudate	0.281	0.113	0.254	-0.203	0.221
Lentiform nucleus	0.144	0.025	0.139	-0.016	0.185
Thalamus	0.257	0.088	0.211	0.076	0.345

VOI on right hemisphere	Verbal memory	Visual memory	General memory	Attention/ Concentration	Delayed recall
Orbital gyrus	0.137	-0.107	0.075	-0.071	0.126
Anterior cingulate gyrus	0.041	0.074	-0.003	-0.081	0.111
Middle frontal gyrus	-0.179	-0.063	-0.177	-0.308	-0.15
Superior frontal gyrus	-0.014	0.109	0.024	-0.136	0.062
Medial frontal gyrus	-0.292	-0.046	-0.277	-0.07	-0.144
Inferior frontal gyrus	-0.269	0.007	-0.197	0.011	-0.044
Insula	-0.166	-0.173	-0.197	-0.013	-0.162
Precentral gyrus	0.084	0.301	0.189	-0.034	0.093
Postcentral gyrus	0.278	0.303	0.315	0.109	0.411*
Superior temporal gyrus	0.045	0.137	0.042	0.161	0.12
Middle temporal gyrus	0.155	0.027	0.068	0.391*	0.183
Inferior temporal gyrus	0.122	-0.012	0.088	0.037	0.12
Parahippocampal gyrus	-0.304	-0.272	-0.344	-0.162	-0.296
Fusiform gyrus	-0.309	-0.208	-0.31	-0.169	-0.351*
Posterior cingulate gyrus	-0.011	-0.114	-0.052	-0.023	-0.046
Precuneus gyrus	0.02	-0.119	-0.02	0.188	-0.041
Superior parietal lobule	-0.07	-0.17	-0.12	-0.377*	-0.191
Inferior parietal lobule	-0.121	0.004	-0.126	0.193	0.125
Superior occipital gyrus	0.361*	-0.046	0.26	-0.179	0.113
Middle occipital gyrus	-0.011	0.063	0.021	0.125	0.082
Inferior occipital gyrus	0.062	0.021	0.051	0.022	0.165
Cuneus	0.211	-0.077	0.13	-0.074	0.058
Lingual gyrus	-0.222	-0.011	-0.176	0.279	0.001
Caudate	0.145	-0.069	0.079	0.028	0.049
Lentiform nucleus	0.264	0.021	0.171	-0.08	0.238
Thalamus	0.077	-0.115	0.007	-0.064	0.076

*: p<0.05; **: p<0.01

VOI: Voxel of Interest

the bilateral caudate and thalamus. As a secondary effect, the CBF in the caudate and thalamus may be influenced by that in the frontal area or hippocampus. The thalamic nuclei have multiple reciprocal connections with the cerebral cortex via the putamen or caudate (18, 19). Significant functional

connectivity between the thalamus and hippocampus was also found in a study using functional MRI (20, 21).

The most important characteristic of eZIS is that it corrects for differences between SPECT systems by mediation with brain phantom images. Thus statistical image process-

ing can be performed using a normal age-matched database that is attached to the program (2, 15). Although Z-scores of >2 in many areas of our results may suggest the presence of global cerebral dysfunction causing diffuse hypoperfusion, eZIS is considered to be suitable for assessing relative hypoperfusion. However, the decrease in the rCBF cannot be completely explained — for example, the reason for the observed regional laterality of the decrease remains unclear. To evaluate the severity of regional resting state hypoperfusion, the mean decrease in the rCBF was quantified. This assessment might not have included the increase in the rCBF associated with cerebral activation. Moreover, a potential weakness of this study was that no subjects without SCCs were enrolled as controls. A further group comparison of the absolute rCBF or eZIS data between strictly selected subjects with and without SCCs should be performed.

The correlations between the memory function and regional cerebral blood flow

Although the MMSE is used appropriately for the screening of cognitive impairment and dementia in primary care, the WMS-R is suitable for the systematic examination of memory function. To the best of our knowledge, the association of the WMS-R with a decreased CBF in healthy subjects or subjects with SCI has not been well evaluated or reported. The mean values of the memory indices were within the normal range in this study; however, correlations were observed between the decreases in indices and rCBF in all of the elderly subjects, from the subjects with high scores to those with low scores.

The correlation analysis suggested that hypoperfusion in several areas, but mainly the left cerebral cortex, is responsible for some types of memory dysfunction. Interestingly, the levels of hypoperfusion in the left inferior frontal gyrus (LIFG) were correlated with the function of verbal memory and with the functions of visual memory and delayed recall. The LIFG, which includes the Broca's area, is an important site of syntactic and semantic language processing (22). The nonlinguistic functions of the LIFG have recently attracted attention based on evidence from several neuroimaging studies (21). The activity in the LIFG may substantially contribute to the memory function. A functional MRI study by Neuner et al. indicated that a fronto-parieto-occipital network was activated with left frontal lateralization in an encoding task during the visual paired associates subtest in WMS-R (21). In both Neuner's study and our own study, the findings for the left hemisphere might have been associated with its role as the dominant brain hemisphere, given that all of the subjects were right-handed. In addition, it is known that the LIFG (Broca's area) includes mirror neurons, which are responsible for the understanding and acquisition of actions as well as language acquisition (22). The activity of the mirror-neuron system may be associated with visual or auditory perception and processing in memory.

The visual memory function, the score for which was correlated with hypoperfusion in several areas, such as the

LIFG, plays an important role in the neuropsychological assessment of transitional cognitive decline. A previous study using the Benton visual retention test suggested that the visual memory test could predict AD preclinically (23). Hori et al. found that visual reproduction in WMS-R was important as a predictor of AD in subjects with MCI (24). To the best of our knowledge, the visual working memory capacity differs across individuals (25). Thus, there is individual variation in the storage capacity of the human brain or in the ability to efficiently use the memory capacity. Thus, even when subjects performed the visual tasks in the WMS-R examination, the variation in the storage capacity may have caused variation in the visual memory score, which was probably correlated with the rCBF parameters.

Other than the memory function, cerebral perfusion also reflects other components of the higher cognitive functions, such as the executive and language functions. The results of this study do not account for the association between frontal cerebral perfusion and the higher cognitive functions, including attention and concentration. Further neuropsychological examinations that are designed to assess the other cognitive functions should reveal the correlation between the rCBF (including frontal perfusion) with the various domains of the higher cognitive functions in elderly individuals. However, the association between the WMS-R score with a decreased rCBF may be important with respect to the cognitive assessment of elderly individuals because memory dysfunction precedes other cognitive dysfunctions in patients with prodromal AD (7).

A detailed follow-up study investigating the subjects' background pathologies (such as by amyloid or tau PET imaging) is still needed because some of the subjects in this study may have been affected by amyloid- β or tau for many years. We were able to find some amyloid PET imaging studies involving SCI subjects (26-29). A 2015 study by Amariglio et al. (29) indicated that 68 amyloid deposition-positive subjects were observed among 257 subjects with SCCs. The authors proposed that the presence of SCCs was an early indicator of the detectability of AD pathology prior to the development of significant objective impairment. However, the SCI group with potential AD pathology accounted for only one fourth of the subjects with SCCs, indicating that SCI occurs in patients with different pathological conditions. Further studies may show that a SCI subgroup with a potential non-AD pathophysiology would experience alterations that differ from SCI patients with AD pathophysiology. J-COSMIC yielded multivariate logistic regression analyses for predictors for AD converter (4), which did not show a strong, predictable value in SPECT imaging. To confirm that SCI leads to MCI in prodromal AD, SPECT imaging in SCI subjects with potential non-AD should be longitudinally compared with that in subjects with potential AD. Moreover, to precisely confirm whether the memory function and the CBF are synchronized, a longitudinal investigation of each individual's clinical course is also necessary.

The present study is associated with another limitation in

the form of a statistical problem. eZIS is certainly advantageous in that it quantitatively and conveniently reveals the severity of cerebral hypoperfusion. However, the Z-score is mathematically different from the absolute rCBF value. Thus the same statistical significance of correlations may not be observed in another study using the absolute rCBF value or other modalities, although the same trends may be observed.

We therefore investigated the levels of regional hypoperfusion in elderly subjects with SCI and without dementia using eZIS and vbSEE and the correlations between the rCBF and the memory indices. We found it difficult to conclude that the subjects showed an increased potential for AD or MCI. However, the results suggest that regional cerebral dysfunction in subjects with SCI is associated with their memory function, despite the values being within the normal range. Moreover, a correlation analysis suggested that the left brain hemisphere, particularly the LIFG, was responsible for several memory function domains. Among these, the visual memory function may be important in the neuropsychological assessment of transitional cognitive decline.

The authors state that they have no Conflict of Interest (COI).

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