Akita J Med **43** : 65-78, 2016

NEUROPSYCHOLOGICAL CORRELATES OF REGIONAL CEREBRAL BLOOD FLOW IN ALZHEIMER'S DISEASE USING CORRELATION IMAGING PLOTS (CIPS)

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(received 3 March 2016, accepted 17 August 2016)

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Abstract
[Background]
Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) is widely used for the assessment of Alzheimer's disease (AD), however little is known concerning the spatial correlation of the brain regions to the performance in ADAS-cog. By using a newly developed 3-D statistical imaging research software, Correlation Imaging Plots (CIPS), which visualizes the spatial correlation of regional cerebral blood flow (rCBF) with any numerical parameters within a group, we tried to elucidate the relationship between rCBF and the Japanese version of the ADAS-cog score (ADAS-Jcog).
[Methods]
The present study was based on 55 patients with early stage AD, 51 mild cognitive impairment patients and 32 age-matched normal controls. Subjects underwent 99mTc-ECD SPECT and ADAS-Jcog assessment. We analyzed these data using the CIPS program and compared to results obtained using statistical parametrical mapping (SPM).
[Results]
CIPS analysis revealed that the ADAS-Jcog total score correlated with hypoperfusion in the bilateral dorsolateral parietal and posterior cingulate cortices, and the precuneus. Among the ADAS-Jcog subscales, orientation, recall and recognition scores correlated with rCBF in similar regions. Only a small difference was observed in these areas when comparing high (ADAS-Jcog > 10) and low (ADAS-Jcog < 10) performance groups using SPM.
[Conclusions]
ADAS-Jcog reflects bilateral parietal rCBF which is predominantly associated with recall and orientation ability. CIPS is suitable for correlation analysis between rCBF and quantitative data.

Key words : Alzheimer's disease (AD), single photon emission computed tomography (SPECT), Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), statistical image analysis, Correlation Imaging Plots (CIPS)

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Backgrounds and Objectives

The current diagnosis of Alzheimer's disease (AD) is based on clinical history, neuropsychological assessment, and neuroimaging evaluation. AD patients usually present with not only memory disturbance but also other cognitive dysfunctions including disorientation, executive

dysfunction, visuospatial dysfunction, aphasia, apraxia and agnosia as American Psychiatric Association Diagnostic and Statistical Manual of mental disorders, 5th edition (DSM-V) or International Classification of Disease 10th revision (ICD-10) defined. Several neuropsychological batteries are available for the assessment of cognitive function in AD patients such as the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale cognitive subtest (ADAS-cog)[1]. ADAS-cog has a high sensitivity to slight differences in cognitive function and is often used to measure the severity and/or therapeutic effect of treatment in AD patients. Although these test batteries are widely employed, there have been only a few reports concerning the relationship between the cerebral localization of cognitive function and the results of these neuropsychological test batteries.

Evaluation of brain atrophy has been used as a surrogate maker of AD pathology in clinical trials and longitudinal studies, and has been linked to cognitive deficits in AD patients. Magnetic resonance imaging (MRI) can be used for routine structural neuroimaging, as it allows for accurate measurement of brain volume structures, especially the medial temporal lobe and related regions. In contrast, functional neuroimaging including positron emission tomography (PET) and single photon emission computed tomography (SPECT) can provide metabolic and hemodynamic measurements of brain activity. 18F-fluorodeoxyglucose (FDG) is the most extensively used PET tracer in whole-brain measurements of glucose metabolism in the clinical diagnosis of AD. There are characteristic reductions in the regional glucose metabolism of AD patients in the posterior cingulate, parietal, temporal and prefrontal regions. These reductions are progressive and have been shown to be correlated with dementia severity. Although having less resolution than PET, SPECT imaging has received widespread clinical application because of its simplicity and the lack of a need for an in-house cyclotron. The measurement of regional cerebral blood flow (rCBF) with SPECT reveals a characteristic pattern of hypoperfusion in the temporal and parietal cortices of AD patients that precedes the evolution of clinical symptoms and is consistent with the reductions in glucose metabolism observed with FDG PET[2,3]. Although SPECT is useful for the early diagnosis of AD in the clinical setting, the ability to recognize patterns of hypoperfusion consistent with AD is highly dependent on the observer's experience and the quality of SPECT images[4]. In contrast, statistical image analysis provides an automated methodology the enables the interpretation of SPECT images with greater accurately and improved inter-rater reliability. Statistical parametric mapping (SPM)[5], 3D stereotactic surface projection (3D-SSP)[6] and easy Z-score Imaging System (eZIS)[7,8] are three such software packages that can visualize the differences between patient cohorts and project onto 3D brain surfaces. Additionally, 3D-SSP and e-ZIS, can analyze a single patient's SPECT data in comparison with the mean values from a normative database, while SPM can correlate imaging measures with any physiological parameter. However, SPM and MATLAB (The Mathworks, Natick, MA, USA) require significant training for the uninitiated researcher. Additionally, it has not been easy to assess the correlation between rCBF and neuropsychological variables in the analysis of SPECT data from AD patients.

Although we understand that total MMSE and ADAS-cog scores decline with progressive global hypoperfusion in AD patients, the spatial significance of the subscores of those neuropsychological batteries remains uncertain, as does the association with cortical hypoperfusion in SPECT images. We developed a new 3D statistical imaging software program, Correlation Imaging Plots (CIPS) in collaboration with Fuji Film RI Pharma Co, Ltd. (Tokyo, Japan). CIPS visualizes the voxel-based spatial correlation of rCBF data with any group parameters such as neuropsychological test scores, or other biomarker data. CIPS research software runs on personal computers operating Windows (Microsoft Corporation, Redmond, WA, USA). The purpose of this study is to elucidate the spatial relationship between rCBF and neuropsychological performance in MMSE and ADAS-cog by using CIPS program.

Methods

Subjects :

The present study was based on early AD patients, mild cognitive impairment (MCI) patients and normal

cognitive subjects in order to assess the slope of cognitive decline. Using NIA-AA criteria we recruited 55 cases with probable AD[9], 51 cases with clinical MCI[10], and 32 cognitive normal elderly subjects. All subjects were right-handed and none had a history of severe head trauma or cerebrovascular disease. All subjects underwent neuropsychological batteries including MMSE and the Japanese version of ADAS-cog (ADAS-Jcog)[11], 1.5 Tesla MRI, brain perfusion SPECT with 99mTc-ethyl cysteinate dimer (ECD), and laboratory testings. Those who had large infarcts on MRI, significant arterial stenosis on MRA which may affect cerebral perfusion state, or other physical or mental diseases which may affect cognitive function were excluded from our analysis. The neuropsychological evaluation was carried out by experienced clinical neuropsychologists who did not participate in the analysis of the results.

Assessment of cerebral blood flow :

Using 99mTc ECD, SPECT was carried out within three months of neuropsychological evaluation. A ring-type SPECT camera (Headtome SET080, Shimadzu CO., Kyoto, Japan) was used to measure radioactivity distribution in the brain. The rCBF data obtained from SPECT were normalized, smoothed and converted to Z score maps by comparing to a database of rCBF images obtained from age-matched Japanese normal volunteers scanned at the National Center of Neurology and Psychiatry[8].

Ethics :

This study protocol was conducted according to the principles of the Declaration of Helsinki and approved by the institutional ethics committee.

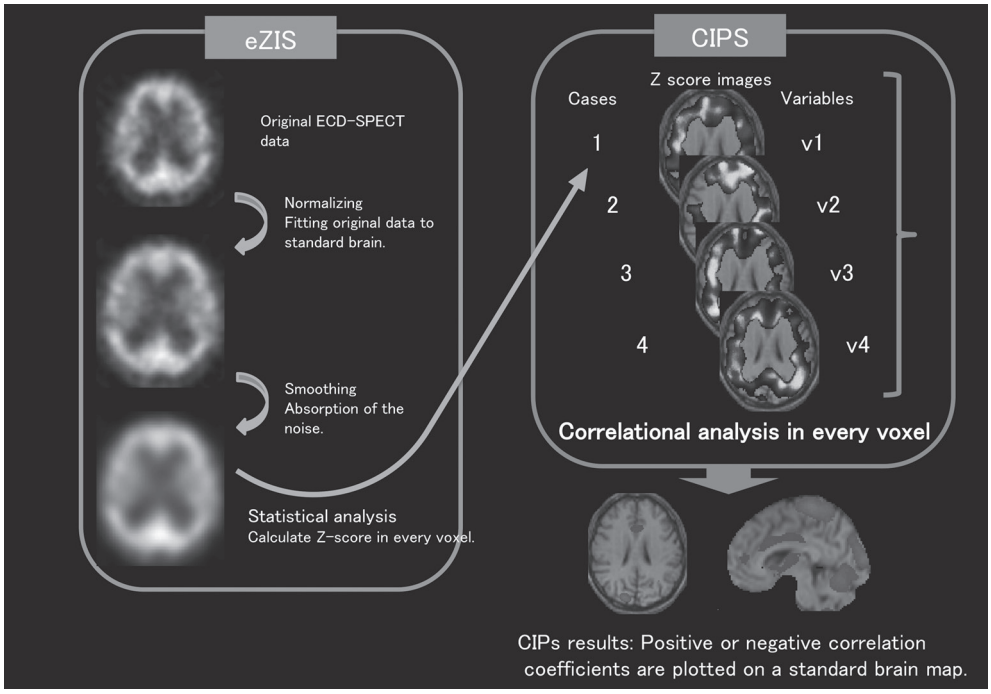

Fig. 1. Process of Correlation Imaging Plots ; CIPS.
The process of CIPS is above. CIPS works together with eZIS. Each SPECT image of the subject is converted to a Z score image by eZIS. CIPS program perform correlation analysis voxel by voxel between the Z-score images of the subjects and their corresponding variables. Significant correlation coefficients were plotted on the standard brain maps and 3-D CIPS images were produced. 1) eZIS, easy Z-score Imaging System.

Statistical image analysis :

CIPS works together with eZIS. In eZIS, each subject's SPECT image was compared to the mean and standard deviation of rCBF in SPECT images acquired from healthy volunteers grouped into 10 year age groups. The process is based on voxel-by-voxel Z score analysis after anatomic standardization of individual scans to a standardized brain volume template.

The CIPS program is based on two processes [Fig. 1]. Firstly, a voxel-wise Pearson's correlation analysis was performed between the Z-score images of subjects produced by eZIS and each subject's variable of interest at an arbitrary threshold. Secondly, significant correlation coefficients were mapped to 3D standard brain maps in Talairach space and output in analyze format for viewing with "eZIS viewer" or "voxel based Stereotactic Extraction Estimation (vbSEE)".

In the present study, rCBF was compared to the to both the MMSE and ADAS-Jcog total scores as well as the following ADAS-Jcog subtests : "word recall", "commands", "construction praxis", "ideational praxis", "orientation", and "word recognition". The resulting CIPS images were evaluated in eZIS viewer ver.3. The CIPS images include correlation coefficients from -1 to $+1$ in those voxels showing significance ($p < 0.01$). The plotted images were shown in unilateral coefficients by either a positive or negative axis according to the scoring system in the neuropsychological battery. A negative axis was used for the correlation with MMSE total score, whereas the ADAS-Jcog total and subscores were shown on a positive axis.

To evaluate the performance of ADAS-Jcog we performed an additional analysis on rCBF using statistical parametrical mapping (SPM). In the SPM analysis, patients were classified into two groups according to their ADAS-Jcog score : those with high performance ($\geqq 10$) and those with low performance (<10). A previous ADAS-Jcog study showed that a score of 10 was the optimal cut off point to distinguish AD from normal cognition[12].

Results

Demographic characteristics are shown in Table 1. The subjects' mean age was 74.0 ± 7.3 years old. The mean scores for ADAS-Jcog and MMSE were 10.62 ± 6.20 and 23.6 ± 4.3, respectively. ADAS-Jcog scores for each cognitive subgroup are shown in Fig. 2. Significant differences were found in "word recall", "commands", "constructional praxis", "ideational praxis", "orientation" and "word recognition" tasks.

Our CIPS analysis revealed that the ADAS-Jcog total score correlated positively with rCBF in the bilateral dorsolateral parietal and posterior cingulate cortices, and the precuneus [Fig. 3A]. Analysis of ADAS-Jcog subtests

Table 1. Characteristics of Subjects.

Characteristics	Mean ± SD / No(%)			
	AD (n=55)	MCI (n=51)	Normal subjects (n=32)	All (n=138)
Age, y	75.3 ± 7.3	74.8 ± 7.3	70.5 ± 7.4	74.0 ± 7.3
Female gender (%)	30 (54.5)	25 (49.0)	20 (62.5)	75 (54.3)
Education, y	11.2 ± 2.5	11.6 ± 2.5	12.4 ± 2.5	11.6 ± 2.5
MMSE[1] total score	20.1 ± 4.4	25.0 ± 4.4	27.4 ± 4.3	23.6 ± 4.3
ADAS-Jcog[2] total score	15.53 ± 6.22	9.14 ± 6.20	4.54 ± 6.23	10.62 ± 6.20

Basic characteristics of each cognitive subgroup and all subjects are shown. Scheffe's multiple comparison revealed the significant differences in age [p=0.0108(AD vs NC), p=0.0295(MCI vs NC)], MMSE total score [p<0.0001(AD vs MCI, AD vs NC), p=0.0048(MCI vs NC)] and ADAS-Jcog total score [p<0.0001(AD vs MCI, AD vs NC), p=0.0001(MCI vs NC)].
Abbreviations : 1) MMSE, Mini-Mental State Examination ; 2) ADAS-Jcog, Japanese version of Alzheimer's Disease Assessment Scale cognitive subscale.

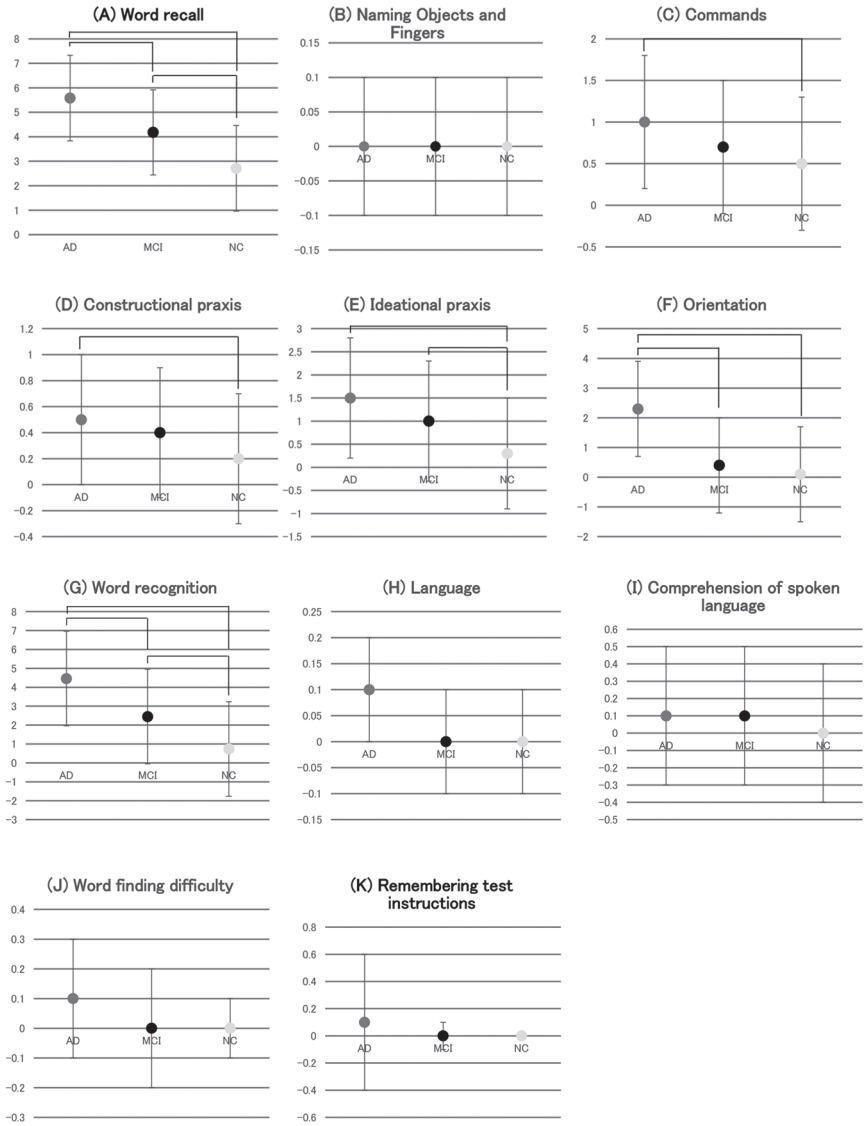

Fig. 2. ADAS-Jcog subscore of cognitive subgroups.
This graph illustrated ADAS-Jcog subscore which each cognitive subgroup got. One-way analysis of variance revealed the significant differences in "(A) word recall"($p<0.0001$[AD vs MCI, MCI vs NC and AD vs NC]), "(C) commands"($p=0.0335$[AD vs NC]), "(D)constructional praxis"($p=0.0139$[AD vs NC]), "(E)ideational praxis"($p=0.0275$[MCI vs NC] and $p<0.0001$[AD vs NC]), "(F)orientation"($p<0.0001$[AD vs MCI and AD vs NC]), "(G)word recognition"($p<0.0001$[AD vs MCI, MCI vs NC and AD vs NC]). "(B)naming objects and fingers", "(H) language", "(I)comprehension of spoken language", "(J)word finding difficulty" and "(K)remember test instructions" have not shown differences among each group.

revealed a significant correlation for "word recall" in the bilateral posterior cingulate and dorsolateral parietal cortices [Fig. 3B] and for "word recognition" in the bilateral posterior cingulate, left dorsolateral parietal cortices and in the left temporal cortices with a weaker significance [Fig. 3C]. The "commands" subtest of ADAS-Jcog was

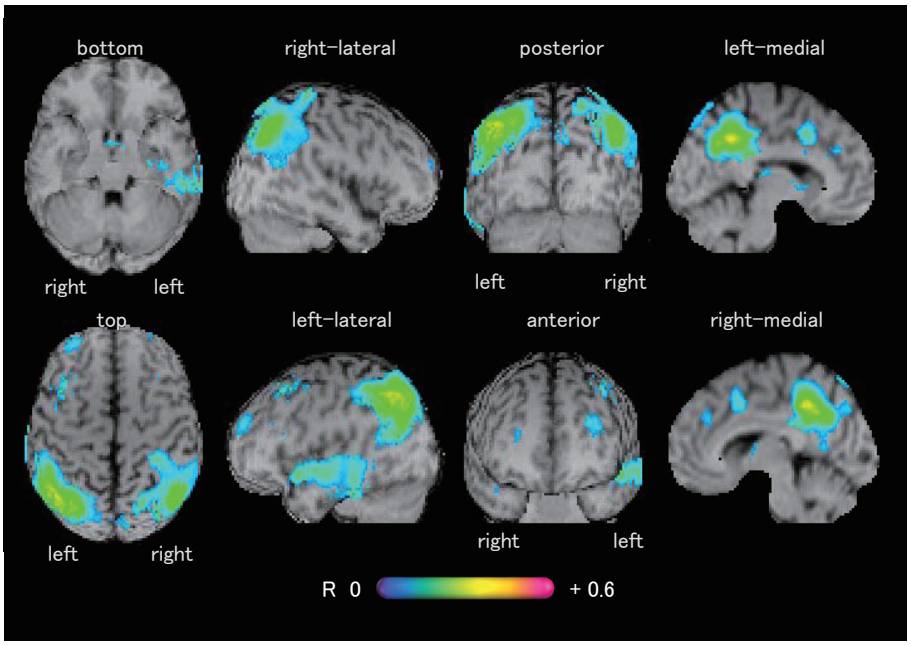

Fig. 3A. CIPS result of ADAS-Jcog total score

Fig. 3. CIPS result of ADAS-Jcog and MMSE score.
CIPS analysis revealed ADAS-Jcog total score correlated with rCBF decrease in bilateral dorsolateral parietal, posterior cingulate cortices and precuneus (A). Significant correlation for "word recall" was seen in similar regions (B). That for "word recognition" was seen in left temporal cortex in addition to similar regions (C) That for "commands" was seen dominantly in left hemisphere (D). That for "constructional praxis" was seen in left temporal and bilateral dorsolateral parietal and anterior and posterior cingulate cortices (E). That for "Ideational praxis" was seen in bilateral posterior cingulate and dorsolateral parietal cortices and left temporal and inferior frontal cortex (F). That for "orientation" was seen in bilateral posterior cingulate and the right parietal corteces.

correlated with rCBF from the left temporal, inferior parietal, dorsolateral prefrontal and inferior frontal cortices [Fig. 3D]. "Construction praxis" was correlated weakly with rCBF from the left temporal and bilateral dorsolateral parietal, anterior and posterior cingulate cortices [Fig. 3E] while "ideational praxis" was correlated with rCBF from the bilateral posterior cingulate, dorsolateral parietal, and the left temporal and inferior frontal cortices [Fig. 3F]. Finally, "orientation" was correlated with rCBF from the bilateral posterior cingulate and the right parietal cortices [Fig. 3G].

The MMSE total score correlated negatively with rCBF in the dorsolateral parietal cortices and posterior cingulate gyri of both hemispheres [Fig. 3H].

SPM analysis revealed a similar but non-significant ($p < 0.3$) pattern of hypoperfusion in the bilateral dorsolateral parietal and posterior cingulate cortices, and the precuneus [Data not shown]. Additionally, there were no significant differences in rCBF data when compared to the ADAS-Jcog subtests.

Discussion

To our knowledge this is the first report investigating the localization of cognitive function associated with total ADAS-Jcog and its subtests in AD patients using SPECT. Our results showed that cognitive decline, as reflected by the total ADAS-Jcog score, was significantly correlated with a reduction in rCBF in the bilateral dorsolateral parietal and posterior cingulate cortices, and the precuneus, areas regarded as hallmarks in the early detection of AD as shown in previous FDG-PET[13,14] and perfusion

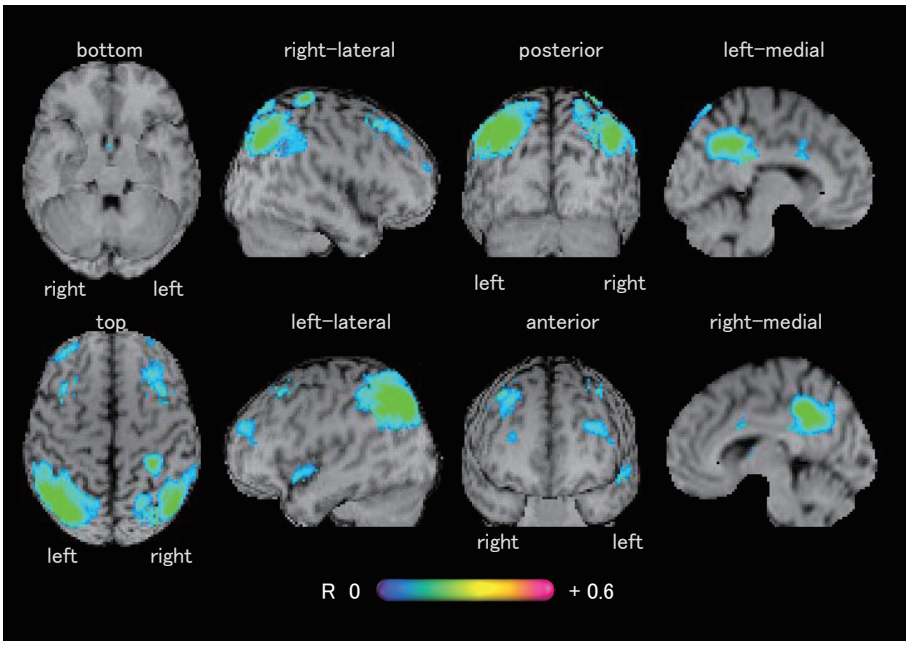

Fig. 3B. CIPS result of ADAS-Jcog word recall score

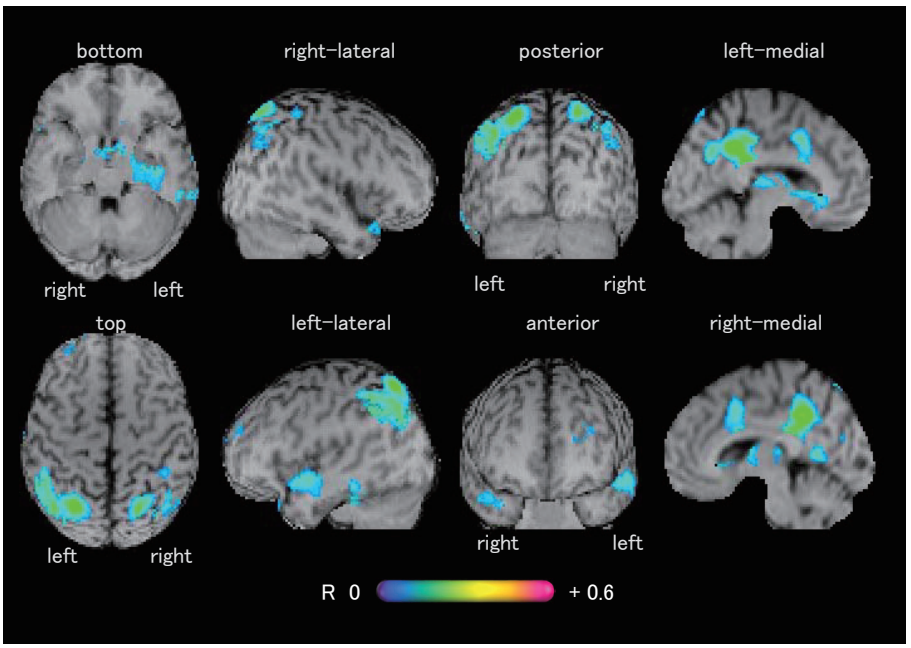

Fig. 3C. CIPS result of ADAS-Jcog word recognition score

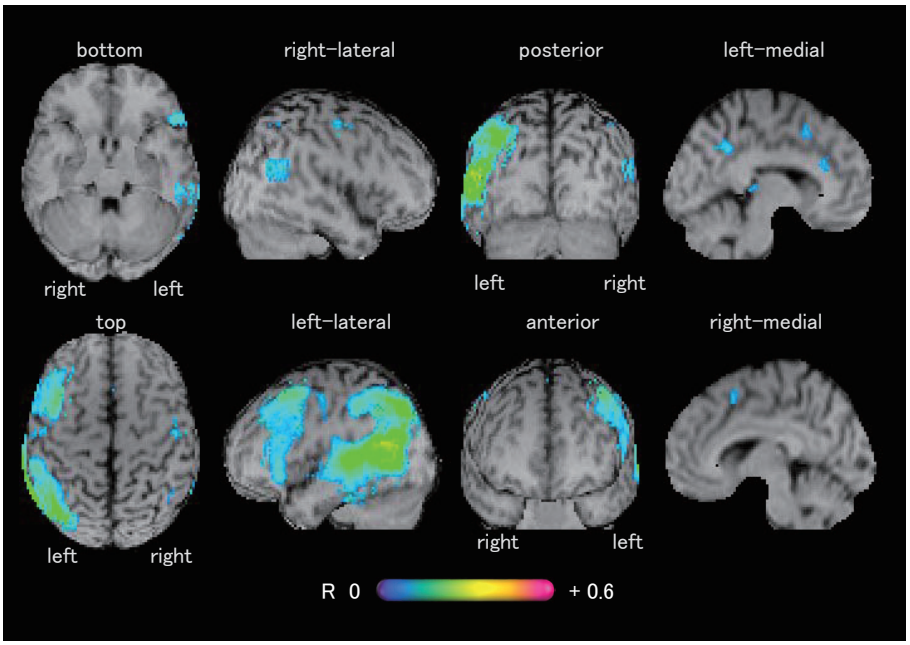

Fig. 3D. CIPS result of ADAS-Jcog commands score

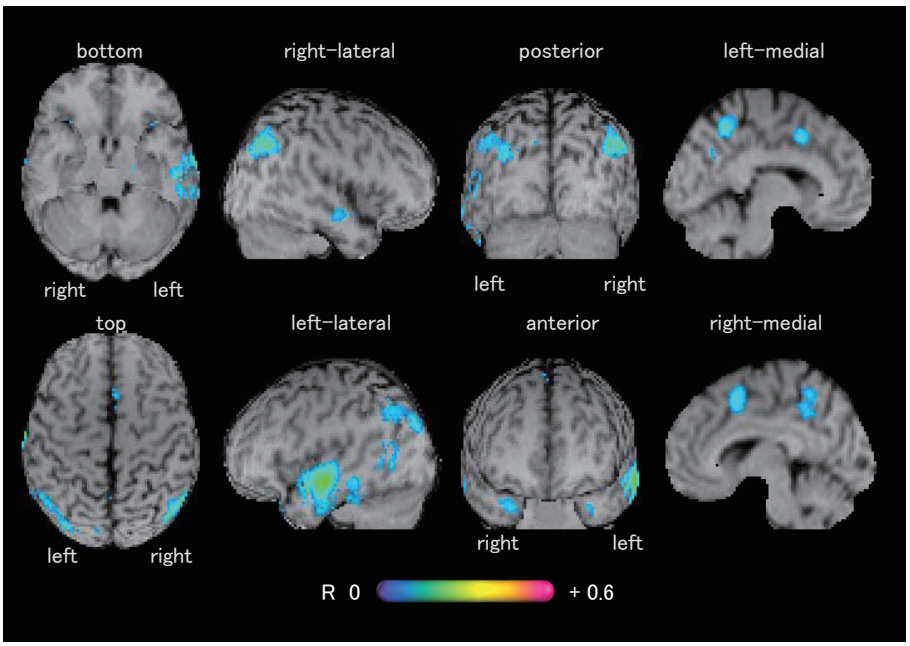

Fig. 3E. CIPS result of ADAS-Jcog constructional praxis score

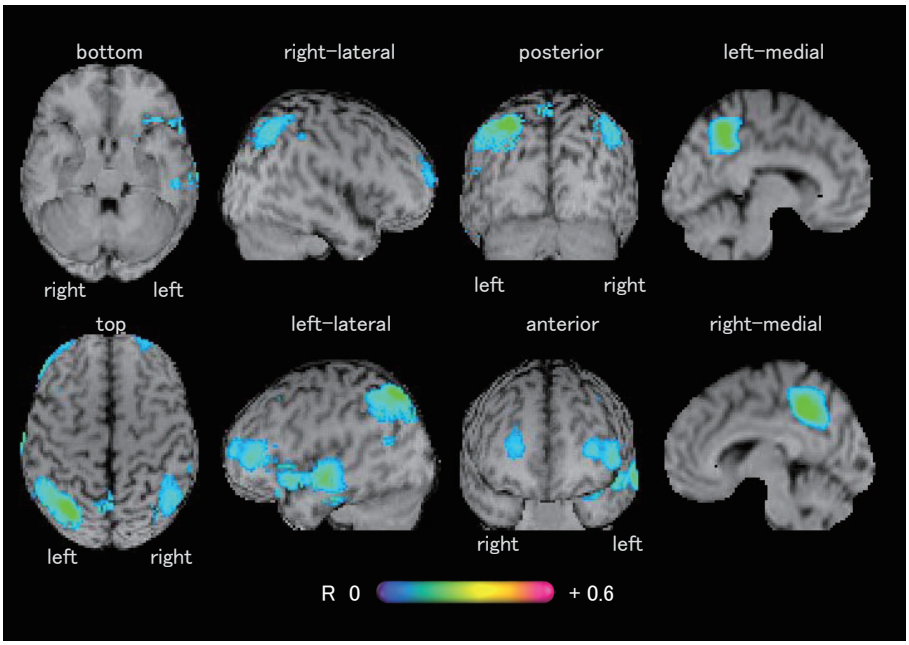

Fig. 3F. CIPS result of ADAS-Jcog ideational praxis score

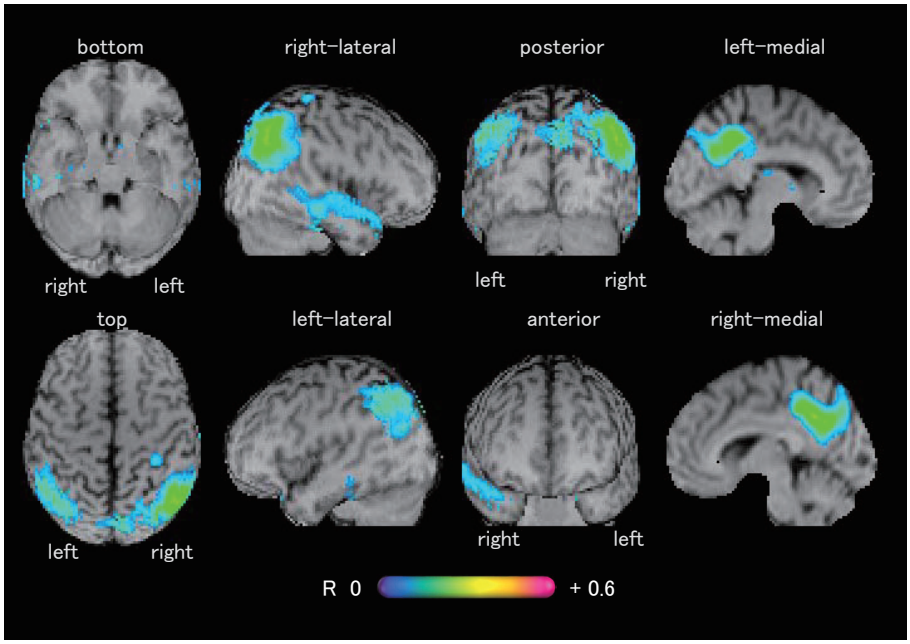

Fig. 3G. CIPS result of ADAS-Jcog orientation score

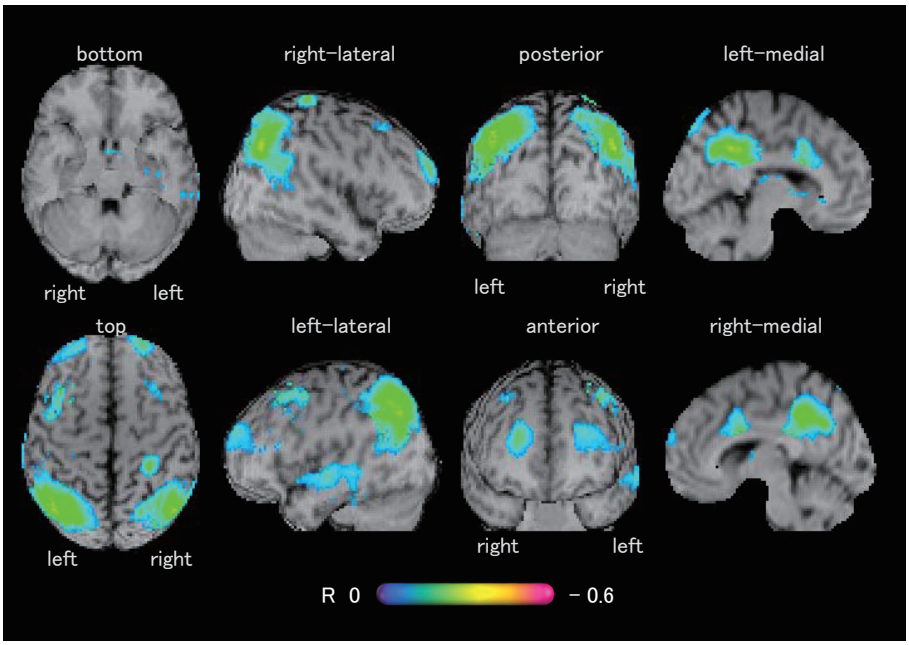

Fig. 3H. CIPS result of MMSE total score

SPECT studies[15]. Consequently, the present results may endorse the appropriateness of ADAS-cog in the evaluation of early AD patients. In the analysis of ADAS-Jcog subtests, impaired "word recall" was correlated with hypoperfusion in regions similar to those observed for the total ADAS-Jcog score, likely due to the fact that the "word recall" score accounts for a substantial proportion of the ADAS-Jcog total score. "Word recognition" was found to be associated with hypoperfusion in the bilateral posterior cingulate, and left dominant dorsolateral parietal cortices, while a milder correlation was seen in the left temporal cortex. However, parietal hypoperfusion was more weakly correlated than "word recall". Previous studies claimed that there were differences in localization between "word recall" and "word recognition" in the temporal and parietal lobes[16,17]. The latter study demonstrated that the dorsal part of the lateral parietal cortex was closely linked to familiarity, whereas the ventral part was associated with recollection. Our results may support these findings and provide further evidence to explore the neural substrates of word recall and recognition in AD patients. With regard to the ADAS-Jcog subtests, "commands" was associated with the superior temporal, inferior parietal, dorsolateral prefrontal and inferior frontal cortices on the left side. These regions, including Wernicke's and motor association areas are consistent with the verbal comprehension and programming of purposeful movement, required by the "commands" task. "Constructional praxis" was correlated with the left temporal and bilateral parietal cortices and is consistent with previous results showing that this subtest is associated with the parietal lobe of the dominant hemisphere[18]. "Ideational praxis" was correlated with dorsolateral parietal, posterior cingulate, left temporal and inferior frontal cortices. Although there has been some dispute concerning the presence of ideational apraxia as a nonspecific manifestation of global mental deterioration in AD patients in the light of executive dysfunction, it is thought to be associated with the function of the left hemisphere, in particular, the left temporoparietal cortices as shown in previous neuropsychological observations of predominantly stroke cases[19,20]. "Orientation" was associated with hypoperfusion in both the posterior cingulate and the right lateral parietal cortex. We hypothesize that orientation is not an independent single-domain function, but instead con-

sists of composite multiple domain functions associated with attention, short-term memory, and visuospatial abilities. Previous reports focusing on the localization of orientation claimed that the orientation for time was associated with the bilateral posterior cingulate[21], while the orientation for place was associated with the right posterior parietal[22] or posterior regions in the right hemisphere[23]. A neuropathological study revealed that the amount of neurofibrillary tangles in the superior parietal cortex was correlated with the orientation of time and place[24]. These areas are also regarded as parts of the default mode network (DMN)[25]. The activation of the DMN is increased in resting and awaking state and is thought to be involved in self-reflection. Greicius *et al*., reported that DMN activity was decreased in AD patients and dysfunctional self-reflection might also be associated with disorientation[26].

In our CIPS image results, the MMSE total score was associated with the bilateral dorsolateral and medial parietal cortices, but no significant correlation was obtained in the medial temporal regions including the hippocampus in the coronal section. These results were considered in regards to previous reports using PET. Ishii and co-workers reported that hippocampal rCBF measured by PET was preserved in mild-to-moderate AD patients as compared with normal controls, whereas rCBF was significantly lower in the temporoparietal cortex in AD patients. Additionally, the parietal perfusion correlated well with MMSE and ADAS-Jcog scores in their AD patients[27]. Using 123I-IMP SPECT, Ikeda *et al*., reported that the total MMSE score was associated with rCBF in the left hippocampus in AD patients[28]. In contrast, Nebu *et al*., compared rCBF measured by SPECT in 90 AD patients who were divided into 5 groups according to their ADAS-Jcog score and found no significant differences in rCBF in the medial temporal cortex among the patient groups. They concluded that rCBF in the medial temporal cortex had already reached a plateau even in the early stage of AD[15]. However, this might be confounded by the possible overestimation of rCBF and by partial voluming due to the advanced brain atrophy seen in AD patients.

CIPS correlation in the left superior temporal lobe was more apparent for the ADAS-Jcog total score than MMSE and may have been influenced by the "commands" subtest result. Although MMSE also includes the "three stage commands" task, the "commands" task in ADAS-Jcog requires greater language comprehension ability.

In this report, we also compared our CIPS maps to SPM-based statistical maps in which AD patients were classified into 2 groups based on their ADAS-Jcog score : those having more than 10 points and those having less than 10 points. As with our CIPS maps, differences between the two groups were observed in the bilateral dorsolateral and medial parietal cortices, but only when the statistical threshold was set at $p < 0.3$. This may suggest that CIPS is more sensitive for the investigation of topographical localization of brain function than the SPM-based group analysis as it evaluates the entire trend as opposed to detecting a cut-off point.

CIPS is a unique program for performing correlation analyses of rCBF within a group and takes only a few minutes to run. Our study shows that CIPS can reliably detect correlating brain areas that are consistent with previous reports and may also have higher sensitivity than conventional approaches. CIPS is able to investigate correlations between rCBF and any numerical variable, e.g. neuropsychological test batteries, serum or cerebrospinal fluid markers, cardiac output or carotid artery stenosis rate.

Age was differentiated among the cognitive subgroups in our study, because we registered subjects consecutively without adjustment for age. The effect of age has to be considered when analyzing rCBF data because rCBF varies according to age not only in AD patients[29] but also healthy subjects[30,31]. CIPS avoids this issue by using Z score maps which are generated from the average rCBF of normal data. CIPS can also adjust for age effects not linearly but in a practical manner as eZIS utilizes normal rCBF databases with 10 year age intervals.

One limitation of our study is that subjects only included cognitive normal to early stage AD. We excluded patients with advanced stage AD from this study because attention deficit or reduced arousal might affect the scores of test batteries and made it difficult to analyze specific functions. Therefore there were few cases who lost point in "language", "comprehension of spoken language", "word finding difficulty", "naming objects and

fingers" and "remembering test instructions" subtests. Future work will investigate how the hypoperfusion areas expand in the advanced stage of AD.

Conclusions

We developed a new 3D statistical imaging program, CIPS which visualizes correlation coefficients between rCBF and arbitrary variables plotted on standard brain maps. This study revealed two main results. Firstly, that the ADAS-Jcog total score was associated with rCBF in the dorsolateral and medial parietal cortices of both hemispheres in the progressive course from cognitive normal to early stage AD. Secondly, those brain areas were also closely related with the "word recall" and "orientation" subtests which are crucially dependent on short-term memory. CIPS can be used to assess correlations between rCBF and any quantitative variable of interest.

Acknowledgements :

Development of CIPS was performed in collaboration with the Fuji Film RI Pharm Company. The Technical support of Mr. Tsutomu Souma is gratefully acknowledged. We are grateful to Dr. David Wright, the Florey Institute of Neuroscience and Mental Health for careful proofreading the manuscript.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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