

「Association between regional cerebral blood flow and  
Mini-Mental State Examination score in patients with  
Alzheimer's disease」

アルツハイマー型認知症における局所脳血流と  
Mini-Mental State Examination Score の関連性

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## 略語一覧

AD:	アルツハイマー病 (Alzheimer's disease)
AG:	角回 (Angular gyrus)
BA:	ブロードマン領野 (Brodmann's area)
CBF:	脳血流 (Cerebral blood flow)
FBP:	フィルタ補正逆投影 (Filtered back projection)
I-IMP:	N- イソプロピル -4- ヨードアンフェタミン ( N-isopropyl-4-[123I] iodoamphetamine)
IOG:	下側後頭回 (Inferior occipital gyrus)
ITG:	下側側頭回 (Inferior temporal gyrus)
LG:	舌状回 (Lingual gyrus)
LS:	大脳辺縁系 (Limbic system)
MMSE:	ミニメンタルステート検査 (Mini-Mental State Examination)
MOG:	中側後頭回 (Middle occipital gyrus)
MOG:	中側側頭回 (Middle temporal gyrus)
OL:	後頭葉 (Occipital lobe)
PCG:	後部帯状回 (Posterior cingulate gyrus)
S.E.E.	定位抽出推定 (Stereotactic extraction estimation)
SOG:	上側後頭回 (Superior occipital gyrus)
SPECT:	単光子放射線断層撮影 (Single-photon emission computed tomography)
STG:	上側側頭葉 (Superior temporal gyrus)
3D-SSP:	3 次元 定位 脳 表面 投影 法 ( Three-dimensional stereotactic surface projection)
TL:	側頭葉 (Temporal lobe)
WB:	全脳 (Whole brain)

## 序 論

認知症は、世界規模で年々増加傾向にあり、3 秒に 1 人が認知症に罹っているとされている。また 2050 年には 1 億 3 千万人が認知症であると推定されている<sup>1)</sup>。認知症には、アルツハイマー型認知症 (Alzheimer's disease, AD)、血管性認知症 (Vascular dementia, VD) やレビー小体型認知症 (Dementia with Lewy bodies, DLB) などの様々な認知症疾患がある。その中で、日本人の高齢者に発症する認知症のほとんどは、加齢に伴う脳実質の変性によるものであり、その約半数が AD であるとされている<sup>2)</sup>。AD は性別の影響を受け、男性では頭頂と後部帯状皮質で脳血流が減少し、女性は、内側側頭葉と前頭葉でより重度な低下を示す<sup>3)</sup>。また AD の発症した年齢により血流低下領域が変化し、高齢者では、内側前頭葉、内側側頭葉で血流量が低下してくることが知られている<sup>4)</sup>。さらに、AD の発症は、教育歴、発症年齢、バイリンガルなど様々な因子の影響を受けるとされている<sup>5-7)</sup>。AD の特徴的な脳血流所見として、頭頂葉から側頭連合皮質での脳血流・代謝低下が見られ、進行に伴い、前頭葉皮質に広がっていくとされている<sup>8-10)</sup>。臨床において脳血流の測定方法には、コンピュータ断層撮影灌流画像 (Computer Tomography Perfusion Imaging, CTP)、核磁気共鳴灌流画像 (Magnetic Resonance Perfusion Imaging, MRP) やシンチカメラを用いた脳血流シンチグラフィ (単光子放射線断層撮影 Single Photon Emission Computed Tomography, SPECT) 検査が行われる。この中で、認知症疾患の局所脳血流のスクリーニング画像検査として、最も古くから行われているのが、脳血流 SPECT 検査であり、脳血流用トレーサーには、<sup>123</sup>I-IMP (N-isopropyl-4-[<sup>123</sup>I] iodoamphetamine)、<sup>99m</sup>Tc-HMPAO ([<sup>99m</sup>Tc-] hexamethyl propylene amine oxime)、<sup>99m</sup>Tc-ECD ([<sup>99m</sup>Tc-] ethyl cysteinate dimer) の 3 種類がある。<sup>123</sup>I-IMP トレーサーを用いることで、他の 2 種類のトレーサーよりも高血流領域でも直線性が良好であるとされている<sup>11)</sup>。最近では、健常群のデータベースと比較することにより、血流低下部位を客観的に表示する統計学的画像解析である 3 次元定位脳表面投影法 (three-dimensional stereotactic surface projection, 3D-SSP) 解析が一般的に用いられている<sup>12)</sup>。これは、Michigan 大学の Minoshima らにより開発された解析であり、形、大きさの違う個々人の脳を Talairach の標準脳に変形してボクセル単位で画像を処理する概念を用いている<sup>13, 14)</sup>。3D-SSP は

次式で表される Z-score を用いて、血流低下部位を算出し、Z-score map で表示することが可能である。

$$Z\text{-score} = (\text{健常群平均カウント} - \text{患者データカウント}) / \text{正常群標準偏差}$$

3D-SSP の解析手順として最初に定位解剖的標準化を行う。原画像である

$^{123}\text{I}$ -IMP-SPECT のデータをバイナリー形式に変換し、それらのデータは、3D-SSP の基礎である Neurostat プログラムを用いて標準 Talairach 空間へと変換される<sup>15)</sup>。個人の脳と標準テンプレート間のサイズの違いは、線形スケーリングで除かれる。個人の脳と標準テンプレート間の局所解剖の違いは自動非線形湾曲により最小化される。次に、脳のピーク大脳皮質活性は、解剖学的標準化後、あらかじめ定義されているベクトル方向、つまり深さ方向に 3 次元的検索を行い各定位脳表ピクセルへと投影される。投影されたピーク値は、原画の脳表面ピクセルに割り当てられる。投影と割り当ては脳の全皮質をカバーするピクセル毎に行われる。Neurostat にある 3D-SSP プログラムを用いて全脳、視床、橋、小脳のピクセル値を基準として正規化されたピクセル値で算出される。各ベクトルに沿ってピークピクセル値が算出されたあと、左右の内側面と外側面、上面、下面、前、後ろの表示形式に転送される。これらの脳表面投影画像は、群間比較のために参照画像と比較される。これらの脳表面投影画像のピクセル毎の比較は、t または z 統計値との群間比較で使用される<sup>12)</sup>。さらに定位抽出推定法 (Stereotactic Extraction Estimation, S.E.E.) 解析は、3D-SSP により作成された脳表面画像のピクセル数、血流低下領域のピクセル割合を表示することが可能であり、全脳表に対する血流低下領域の割合、つまり、障害面積割合を算出することが可能である。3D-SSP を用いることにより後部帯状回、楔前部、頭頂部等で局所脳血流低下を認めることが報告されている<sup>14, 15)</sup>。

一方、日常診療では認知症の重症度を評価する方法として、精神状態短時間検査 (Mini-mental State Examination, MMSE) が一般的に使用される。MMSE は、認知障害の検出のために作成されたスケールである<sup>16)</sup>。元々は、精神疾患の中で認知障害を有する患者を検出することを目的として考案されたものである。この検査は、実施が容易なことや、臨床的有用性の高さから、その後、神経疾患や認知症疾患の認知機能テストとして広く用いられている。MMSE の認知機能低下に対する感度は 80%-95%

と非常に高く、23 点以下で認知機能低下が疑われるとされている<sup>16-18)</sup>。杉下らは<sup>19)</sup>、MMSE の信頼性と妥当性について検討し、感度 83%、100%とし、MMSE が認知症のスクリーニング検査として十分に使用可能であることを報告している。

AD における脳血流低下と MMSE-score の関連性について Rodriguez らは<sup>20)</sup>、海馬の血流と MMSE-score に相関があるとしている。しかし、この報告では、統計解析を用いず、関心領域 (Region of interest, ROI) をマニュアル設定し解析を行っているため、操作者による違いを含んでいるために再現性に問題があると考えられる。Ikeda らは<sup>21)</sup> The easy Z score system (eZIS) を用いて、左側頭葉や前頭葉と MMSE-total score に相関があるとしている。しかし、脳血流低下の重症度の指標である Z-score のみであり、脳血流低下の範囲、つまり障害面積割合を考慮していない。また、陽電子断層撮影 (Positron Emission Tomography, PET) や<sup>99m</sup>Tc-ECD 用いた研究でも、側頭葉と前頭葉で MMSE-score と相関があるとされているが、これらも脳血流低下の重症度と広がりをも別々に解析し、脳血流低下の重症度と広がりをも考慮していない<sup>22, 23)</sup>。脳血流量低下とは、脳血流低下領域が狭い範囲でも重症の場合や、脳血流低下が軽度でも、脳血流低下領域が広範囲の場合など、様々な状態が考えられる。つまり、脳血流量低下を考える場合、重症度と障害面積割合を一緒に考慮する必要がある。また、脳血流量低下の様々な状態によって、臨床症状の表れ方に違いがある。これまでに脳血流低下を Z-score および脳血流の障害された脳表面積の両方から考慮した評価法は無く、また局所脳血流低下をブロードマン領野 (Brodmann's area, BA) まで細分化し、MMSE-score との関連性について検討した報告は少ない<sup>22, 23)</sup>。

そこで本研究では、AD 患者の脳血流低下をより正確に評価するために、自動解析である 3D-SSP および脳血流低下領域が算出できる S.E.E. 解析を用いて、Z-score および脳表面積の両者を反映させた新しい指標を定義し、MMSE-score との関連性について検討した。

## Materials and methods

*Subjects.* This study was approved by the Committee of Medical Ethics of the Hirosaki University Graduate School of Medicine (Hirosaki, Japan, approval number: 2015-024). We retrospectively evaluated 40 consecutive patients who underwent brain perfusion single-photon emission computed tomography (SPECT) scintigraphy at the Department of Radiology at Hirosaki University Hospital (Hirosaki, Japan) between April 2008 and April 2012. The inclusion criteria were the availability of the Mini-Mental State Examination (MMSE) total score and subscores. On the basis of the results of the MMSE performed within 3 months of brain perfusion SPECT scintigraphy, we selected 13 patients with Alzheimer's disease (AD) for this study. The mean age of the 13 patients was  $71.9 \pm 10.6$  years (mean  $\pm$  SD), with a range of 47-85 years. Four males and 9 females were included. Brain perfusion SPECT scintigraphy was performed on all subjects as a specific test prior to three-dimensional stereotactic surface projection (3D-SSP) (version 1.0; Nihon Medi-Physics Co Ltd, Tokyo, Japan) and stereotactic extraction estimation (S.E.E.) (version 2.0; Nihon Medi-Physics Co Ltd) analyzes based on the 3D-SSP findings. The severity of cognitive and functional impairment was simultaneously assessed by using the MMSE. The mean period between SPECT and MMSE was  $35 \pm 42$  days (5 days-3 months). Ten healthy participants, matched for age and sex with the AD group, were evaluated as control subjects. The control subjects were study volunteers and were used as the Normal Data Base (NDB) in the 3D-SSP program.

*SPECT imaging.* All SPECT studies were performed by using a two-headed rotating gamma camera (Infinia Hawkeye 4; GE Healthcare Life Sciences, Little Chalfont, UK) with an extended low-energy general-purpose collimator. SPECT imaging was initiated 20 min after the intravenous injection of 222 MBq N-isopropyl-4-[ $^{123}\text{I}$ ]iodoamphetamine ( $^{123}\text{I}$ -IMP), and was completed in 45 steps containing 90 projections. The matrix size and slice thickness of the SPECT images were 128x128

(pixel size, 3.88 mm) and 7.75 mm, respectively. The images were reconstructed via filtered back- projection using a Butterworth filter (order, 10; cutoff frequency, 0.42 cycles/pixel), and a ramp filter with attenuation correction by using the Chang method.

*3D-SSP and S.E.E. analysis.* The Neurological Statistical Imaging Analysis Software program (Neurostat; Nihon Medi-Physics Co Ltd) was used to determine the area of cerebral blood flow (CBF) decrease in patients with AD. Clinically, a Z-score >2 is considered as demonstrating impairment associated with a decrease in CBF. In the present study, a Z-score map was created for each case, and the maximum value of the Z-score in the entire brain surface area was measured. In addition, the area of the Z-score zone was measured and divided step by step ( $0 \leq x < 1$ ,  $1 \leq x < 2 \dots$ ), according to the Z-score, which itself is based on the number of pixels, and the ratio of these values was calculated. One radiological technologist analyzed all brain data to eliminate the differences between observers. The pixel size for the 3D-SSP analysis was 3.88mm.

*Definition of a novel indicator of CBF decrease.* The previous maximum Z-score, which represents a certain pixel and thus shows the degree of CBF decrease on the brain surface, was taken to be an indicator of severity. The area ratio of the Z-score > x ( $x = 0, 1, 2 \dots$ ) was used as an indicator of the area of CBF decrease relative to the entire brain surface area. Therefore, a weighted coefficient based on the Z- score zone was introduced, and a novel indicator was defined as  $\Sigma zS$ . The  $\Sigma zS$  comprehensively evaluates the extent of CBF decrease according to the following equation, which integrates the Z-score and the area ratio of the Z-score zone.

$$\Sigma zS = \sum_{z=0}^N z \times f(z)$$



where  $N$  = maximum Z-score,  $K$  = integer number (0.1.2 ...  $N$ ), and when  $K \leq \text{Z-score} < K + 1$ ,  $Z = K + 1$ . The  $f(z)$  function represents the ratio of the area of the Z-score zone divided step by step ( $0 \leq \text{Z-score} < 1$ ,  $1 \leq \text{Z-score} < 2$  ...), according to the Z-score. The Z-score obtained via 3D-SSP analysis was used as a continuous variable; whereas “z” was used as a discrete variable that describes an interval corresponding to a certain Z-score zone ( $0 \leq \text{Z-score} < 1$ ,  $1 \leq \text{Z-score} < 2$  ...). Hence, the  $\Sigma zS$  parameter, which combines 2 factors associated with the maximum Z-score and the area of rCBF decrease, was used as an indicator that takes into consideration the entire brain surface, as shown in Figure 1.

*MMSE.* The MMSE is one of the most common tools for screening of cognitive impairment in older adults. The MMSE was developed to distinguish between older individuals with or without neuropsychiatric disorders early in the disease processes. Folstein et al<sup>16)</sup> reported that the MMSE was highly reliable on 24-hr ( $r = 0.89$ ) and 28-day ( $r = 0.99$ ) retests by single examiners. They also reported good inter-rater reliability for the MMSE ( $r = 0.83$ ) when the MMSE was administered by 2 different examiners 24 hours apart. O'Connor et al<sup>17)</sup> reported that the 86% of respondents judged to have organic mental disorders scored  $< 23$  on the MMSE and that 92% of those judged to be cognitively intact scored  $> 24$  (sensitivity:  $r = 0.86$ , specificity:  $r = 0.92$ ). Table I details the subject and content of each question in the MMSE. The MMSE, with a maximum score of 30, contains 11 subtests that are used to assess the cognitive function of each subject. Assessment is achieved by evaluating the 5 domains of cognitive function: orientation, contributing- maximum of 10 points; memory, 6 points; attention/calculation, 5 points; language, 8 points; and design copying, 1 point.

More specifically, in AD and mild cognitive impairment (MCI), there are different sensitivities of the MMSE subtests. In 86 AD patients, it has been reported that the most sensitive subtests in the “early” phase were delayed recall, temporal orientation, and

serial 7 calculation, while the other subtests were more “sensitive” to the middle and advanced phases<sup>24</sup>). These different subset sensitivities have led to the proposal of short versions of the MMSE that only include spatial orientation and delayed recall that has been claimed to have a accuracy similar to that of the global MMSE score in predicting AD in 29 out of 165 patients followed for 2 years<sup>25</sup>). Regarding multidimensionality, 2 factors were identified in 63 AD patients<sup>26</sup>): the first included copying a drawing, delayed recall, time and space orientation and subtraction; the second included denomination, obeying a command, naming of objects, writing a sentence, repeating a sentence, obeying a three-stage command and space orientation. It should be noted that a substantial part of this first factor (i.e., delayed recall, temporal orientation, and attention/concentration) overlaps with the subtests used on previous reports<sup>24</sup>) that had been reported to be sensitive in the early phase of AD.

Within the first factor used in previous reports<sup>24~26</sup>), the serial 7 calculation has been shown to be the only subtest able to distinguish between converters to AD and non-converters in a series of 73 MCI patients<sup>27</sup>). Moreover, the 35 converters showed a specific score decline in the s orientation subtests (temporal and spatial) and in delayed recall during the 6 months following the basal evaluation. Therefore, the sensitivities and their multidimensionality in both MMSE subtests seem to have specific features in AD. Brugnolo et al<sup>28</sup>) reported that the main subsets in the first and more important factor were time orientation, delayed recall, attention/concentration, constructional praxis (design copying), comprehension (verbal instruction), and spatial orientation<sup>28</sup>). Furthermore, Shigemori et al<sup>29</sup>) reported that the percentages of correct answers in the MMSE subsets were < 90% for time orientation, delayed recall, attention/concentration, constructional praxis (design copying), comprehension (verbal instruction) and spatial orientation. To assess the pathology of the AD group, the total scores of the 6 lowest-scoring subtests (time and spatial orientation, attention/calculation, delayed recall, verbal instruction, design copying) were extracted and evaluated.

*Statistical analysis.* Statcel3 (OMS Publishing Ltd. Tokyo, Japan) analysis software was used to perform the following statistical analyzes: unpaired and paired t-tests, the  $\chi^2$  test and the Mann–Whitney U test. Tests of correlation were performed by using Pearson's coefficient and Spearman's coefficient by rank test.  $P < 0.05$  was considered as indicating a statistically significant difference.

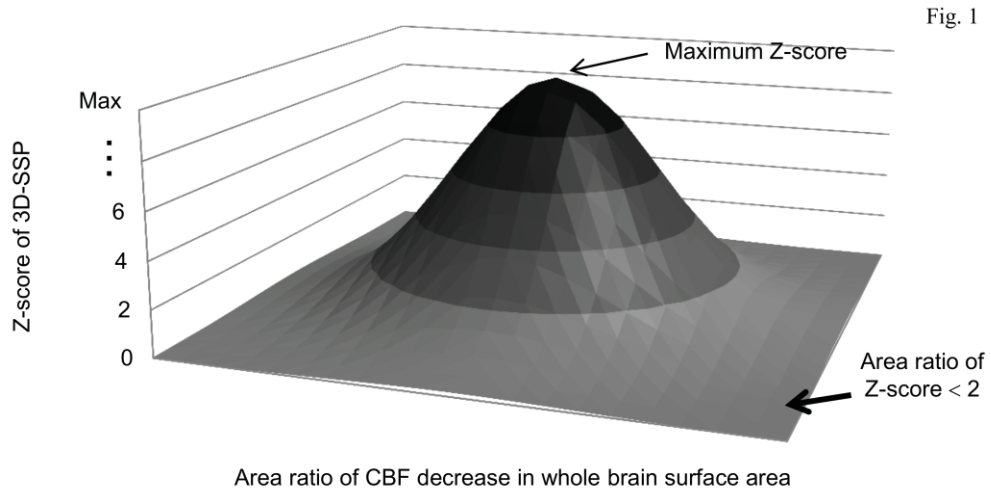


Figure 1. The concept of  $\Sigma zS$ . The vertical axis represents the  $Z$ -score of three-dimensional stereotactic surface projection (3D-SSP), which reflects disease severity; whereas the horizontal axis represents the degree of cerebral blood flow (CBF) decrease in the entire brain surface area, with each  $Z$ -score zone exhibiting a CBF decrease. Therefore, the  $Z$ -score is a 1 pixel indicator, the area of CBF decrease is the extent indicator, and the  $\Sigma zS$ , which combines these 2 parameters with the  $Z$ -scores in different locations, is an indicator that takes the entire brain surface into consideration.

Table I. Mean subscores for the MMSE parameters in patients with Alzheimer's disease (n=13).

No	MMSE parameter	Mean $\pm$ SD
1	Temporal orientation, 1 point for each correct answer Ask the patient for: the year, season, date, day, and month..	2.69 $\pm$ 1.94
2	Spatial orientation, 1 point for each correct answer Ask the patient for: the prefecture, city, address, hospital, and floor	3.46 $\pm$ 1.26
3	Registration: 1, 2, or 3 points according to how many are repeated Name 3 unrelated objects. The patient has 1 sec to say each. After all 3, ask the patient to repeat.	2.92 $\pm$ 0.27
4	Attention and calculation, 1 point for each correct subtraction Ask the patient to begin with 100 and count backward by 7. Stop after 5 subtractions (93, 86, 79, 72, 65).	2.46 $\pm$ 1.85
5	Recall, 1 point for each correct answer Ask the patient to recall the 3 words you previously asked them to remember in the registration section.	0.53 $\pm$ 0.96
6	Naming, 2 points Show the patient a wrist watch and ask them what it is. Repeat with a pencil.	2
7	Repetition - 1 point Ask the patient to repeat the sentence after you. Allow only 1 trial.	1
8	Verbal instruction, 1 point for each part correctly performed Ask the patient to take a piece of paper in their right hand, fold it in half, and put it on the floor.	2.76 $\pm$ 0.59
9	Reading, 1 point Ask the patient to read and obey the command "Close your eyes."	0.84 $\pm$ 0.37
10	Writing, 1 point Hand the patient a blank piece of paper and ask them to write a sentence for you.	0.76 $\pm$ 0.43
11	Copying, 1 point Ask the patient to copy a complex diagram of 2 interlocking pentagons.	0.53 $\pm$ 0.51
MMSE, Mini- Mental State Examination; SD, standard deviation		

## Results

*Clinical background.* Table II outlines the clinical history of the subjects in the control and AD groups. In the AD group, the median disease duration was 2 years (mean,  $2.36 \pm 0.6$  years; range, 4 months–8 years). Four patients with AD presented with complications of diabetes and hypertension or both, whereas four patients with AD had a family history of dementia. Two patients in the AD group had previously received donepezil hydrochloride (Aricept) as a therapeutic agent for dementia. In the control group, the distributions of age and sex were as follows:  $66.8 \pm 7.5$  (mean  $\pm$  SD; range, 56–76 years) and 3:7 (male:female), respectively. No significant differences were noted between the AD and control groups in terms of age or sex. In the AD group, the median total MMSE score was 21 points (mean  $\pm$  SD,  $20 \pm 1.5$ ), with a range of 9–27 points. Notably, all patients in the AD group demonstrated maximum scores for subtests 6 and 7. In addition, 11/13 patients scored maximum points for subtest 8 and 9, whereas 10/13 scored maximum points for subtest 10. For subtest 11, which is a test of design copying, a total of 6 subjects (46% of the group) scored zero.

Table II. Clinical characteristics of control subjects and patients with Alzheimer's disease (AD).

Characteristics	Control subjects (n=10)	AD patients (n=13)
Age (years)	$66.8 \pm 7.5$	$71.9 \pm 10.6$
Sex (male /female)	3/7	4/9
Duration of disease (years)	-	2.0 (0.25–8.0)
Complication (yes / no)	-	4/9
Family history (yes / no)	-	4/9
Aricept (yes / no)	-	2/11

Data are presented as the mean  $\pm$  standard deviation, or median (range).

*3D-SSP and S.E.E. analysis.* Table III details the mean values of the maximum Z-scores for the entire brain surface area and the brain lobe segments. The mean maximum Z-score in the entire brain was  $8.27 \pm 2.76$  in the AD group and  $2.72 \pm 0.54$  in the control group. Furthermore, for all brain lobe levels, the maximum Z-score were higher in the AD group than the control group. In the AD group, the various brain areas that had the maximum Z-score included the limbic system (LS;  $n = 1$ ) and the parietal ( $n = 9$ ), temporal ( $n = 2$ ), and occipital lobes ( $n = 1$ ). Therefore, the AD group had significantly increased maximum Z-scores across the entire brain surface area and in specific brain lobe segments. Table III presents the area ratio for a Z-score  $> 2$  associated with a clinical CBF decrease based on the number of pixels. The mean area ratio for a Z-score  $> 2$  in the entire brain was  $15.4 \pm 5.43$  in the AD group and  $0.93 \pm 0.1$  in the control group. The AD group exhibited significantly higher area ratios than those in the control group. Furthermore, the mean area ratios for a Z-score  $> 2$  were consistently higher across all brain lobe levels in the AD group than in the control group. In the AD group, the brain areas demonstrating an area ratio for a Z-score  $> 2$  included the LS ( $n = 1$ ) and the parietal, ( $n = 4$ ), temporal ( $n = 5$ ), occipital ( $n = 2$ ) and frontal ( $n = 1$ ) lobes. Decreased CBF was notable in both the parietal and temporal lobes.

Table III. Mean maximum Z-scores and area ratios for a Z-score > 2 in the respective brain areas

Index	Area	Control subjects (n=10)	AD patients (n=13)
Maximum Z-score	Whole	2.72 ± 0.54	8.27 ± 2.76*
	Frontal	2.66 ± 0.51	4.56 ± 1.58*
	Parietal	2.23 ± 0.68	7.85 ± 2.89*
	Temporal	1.95 ± 0.27	6.8 ± 2.87*
	Occipital	1.83 ± 0.41	4.8 ± 3.06*
	Limbic system	2.18 ± 0.43	5.06 ± 0.93*
Area ratio of Z-score > 2 (%)	Whole	0.93 ± 0.10	15.4 ± 5.43*
	Frontal	0.76 ± 0.97	7.54 ± 7.86*
	Parietal	0.84 ± 1.44	32.8 ± 22.95*
	Temporal	0.72 ± 1.94	25.23 ± 14.32*
	Occipital	1.65 ± 5.12	12.87 ± 18.57*
	Limbic system	1.31 ± 2.69	15.27 ± 6.18*

Data are presented as the mean ± standard deviation. \*P < 0.05.

*Associations between the MMSE score and rCBF decrease.* The brain areas in the entire brain and at the cerebral lobe, cerebral gyrus, and Brodmann's area (BA) levels were classified by using 3D-SSP. The association between the MMSE score and the rCBF decrease in these areas was evaluated on the basis of the maximum Z-score, the area ratio for a Z-score > 2, and a novel indicator,  $\Sigma zS$ . The MMSE scale was evaluated according to the MMSE total score and each subtest score, evaluation item, and pathological finding. As shown in Table IV, there were significant differences in the area of rCBF decrease across all indicators, the total MMSE, and the subtest scores. Negative correlations were determined among the scores for subtest 11, which evaluates design copy, the indicators in the majority of the brain areas. In addition, negative correlations were found between the total MMSE score and the area ratio for a Z-score > 2 and the  $\Sigma zS$  in the posterior cingulate gyrus (PCG). Furthermore, negative correlations were demonstrated among all indicators in the BA30 and the total MMSE score (Figs. 2A–C).



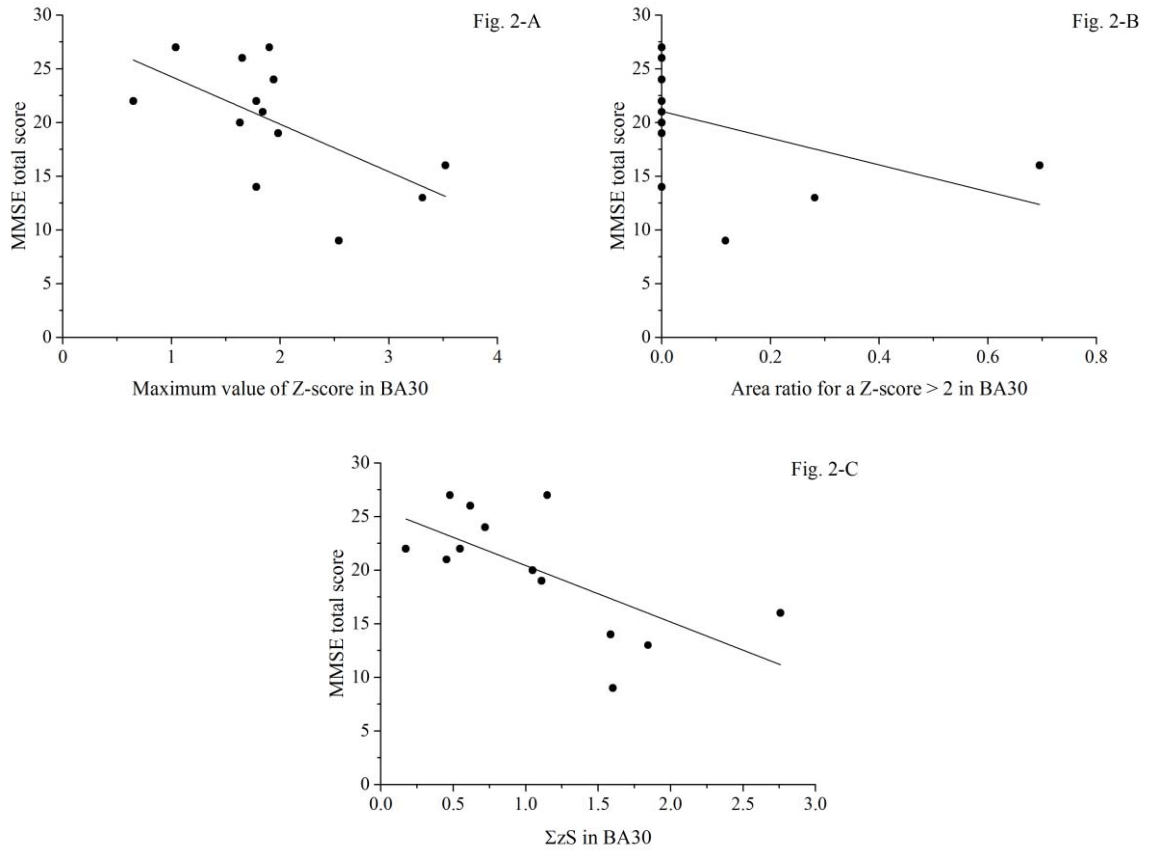


Figure 2. Correlation between the  $\Sigma zS$  value and the Mini-Mental State Examination (MMSE) total score in Brodmann area 30 (BA30). (A) In the BA30 area, negative correlations were determined among the maximum Z-score and the MMSE total score ( $r = -0.61$ ,  $P < 0.05$ ), (B) the area ratio of a Z-score  $> 2$ , and the MMSE total score ( $r = -0.65$ ,  $P < 0.05$ ), and (C) between the  $\Sigma zS$  and the MMSE total score ( $r = -0.67$ ,  $P < 0.05$ ). Tests of correlation were performed by using Pearson's coefficient and Spearman's coefficient by rank test.

In MMSE subtest 5, which assesses delayed recall, negative correlations were observed among the LS, PCG, BA23, BA24, BA30, and BA33 brain areas and the novel  $\Sigma zS$

indicator; in addition to each brain classification level (Figs. 3A–F). However, no correlation was determined between subtests 3, 8, 9, and 10 for any of the indicators assessed. As outlined in Table V, there were significant differences in the rCBF areas among the MMSE scores and 3 other indicators. Furthermore, negative correlations were determined among all of the evaluation items and the novel  $\Sigma zS$  indicator. In the LS, negative correlations were determined among  $\Sigma zS$  and memory evaluation and delayed recall parameters. Furthermore, in both the PCG and BA30 brain areas, negative correlations were determined among the language evaluation parameters and  $\Sigma zS$ . In both the PCG and BA30 areas,  $\Sigma zS$  was determined to be negatively correlated with the scores of the 6 subtests (time and spatial orientation, attention/calculation, delayed recall, verbal instruction, design copying) in AD pathology<sup>28, 29)</sup> (Fig. 4).

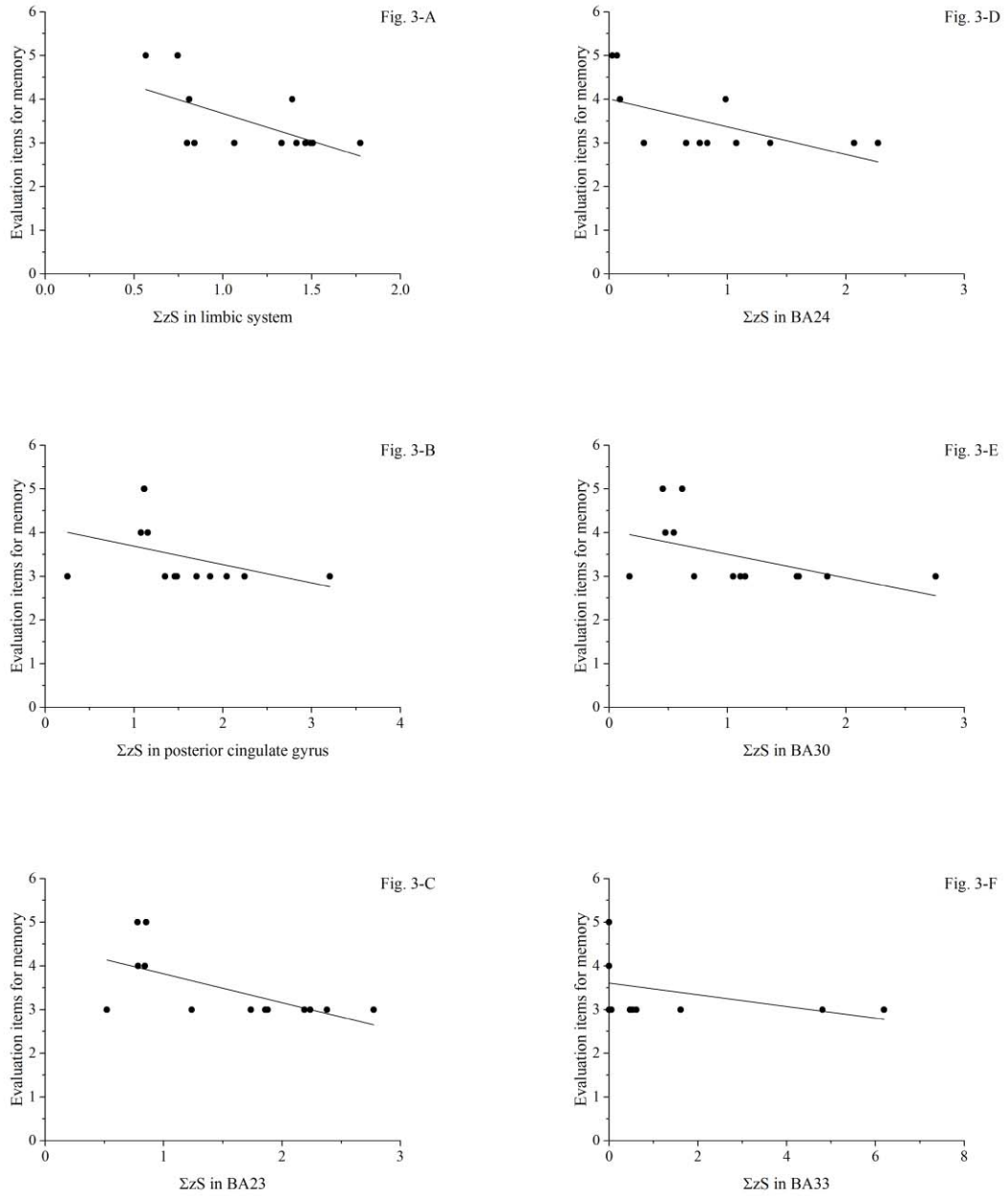


Figure 3. Correlations among the evaluation items for memory and  $\Sigma zS$ . Negative correlations were detected among the  $\Sigma zS$  and the evaluation items for memory in (A) the limbic system ( $r = -0.63$ ,  $P < 0.05$ ), (B) the posterior cingulate gyrus ( $r = -0.61$ ,  $P < 0.05$ ), (C) Brodmann area (BA)23 ( $r = -0.61$ ,  $P < 0.05$ ), (D) BA24, ( $r = -0.63$ ,  $P < 0.05$ ), (E) BA30 ( $r = -0.61$ ,  $P < 0.05$ ) and (F) the BA33 ( $r = -0.72$ ,  $P < 0.05$ ). Tests of correlation were performed by using Pearson's coefficient and Spearman's coefficient by rank test.

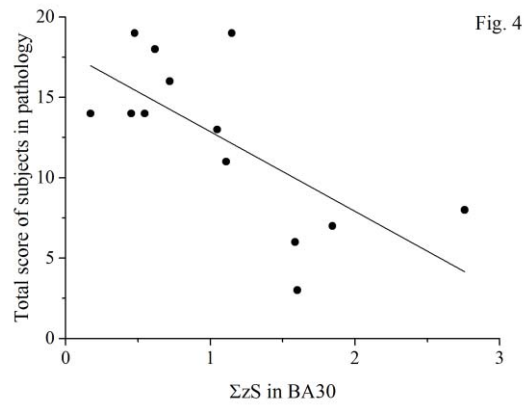


Figure 4. Correlation between the  $\Sigma zS$  values in Brodmann area (BA)30 and the total score of 6 Mini-Mental State Examination subsets with low scores in the Alzheimer's disease group (orientation, attention/calculation, delayed recall, verbal instruction, design copying) ( $r = -0.62$ ,  $P < 0.05$ ). Tests of correlation were performed by using Pearson's coefficient and Spearman's coefficient by rank test.

Table IV. Negative correlations between the MMSE scores and brain uptake, as measured by various indicators.

Subsets	Level	Maximum Z-score	Area ratio of Z-score > 2	New indicator $\Sigma zS$
MMSE Total score	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ND	PCG	PCG
	BA	30	30	30
1	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ND	AG	PCG
	BA	30	30	30
2	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ND	AG	PCG
	BA	30	30	30
4	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ITG, MOG	MTG, MOG	ND
	BA	ND	37, 39	37
5	WB	ND	ND	ND
	Lobe	ND	ND	LS
	Gyrus	ND	ND	PCG
	BA	ND	ND	23, 24, 30, 33
11	WB	ND	ND	ND
	Lobe	Temporal	Parietal	Parietal
	Gyrus	STG, ITG, MOG, LG, PCG	MOG, LG, PCG, Precuneus	MTG, SOG, MOG, IOG, Cuneus, LG
	BA	17, 18, 37	17, 18, 19, 37	17, 18, 19, 37

No significant differences were observed in subtests 3, 8, 9 and 10. Correlation coefficients were calculated by using Pearson's test and Spearman's coefficient by rank test. MMSE, Mini- Mental State Examination; AG, angular gyrus; BA, Brodmann area; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; LG, lingual gyrus; LS, limbic system; MOG, middle occipital gyrus; MTG, middle temporal gyrus; ND, not detected; PCG, posterior cingulate gyrus; SOG, superior occipital gyrus; STG, superior temporal gyrus; WB, whole brain. Tests of correlation were performed by using Pearson's coefficient and Spearman's coefficient by rank test.

Table V. Negative correlations between the MMSE score and brain uptake, as measured by various indicators.

MMSE evaluation item (Subtest)	Level	Maximum value of Z-score	Area ratio of Z-score > 2	New indicator $\sum zS$
Orientation subset (1 + 2)	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ND	AG, PCG	PCG
	BA	30	30	30
Memory subset (3 + 5)	WB	ND	ND	ND
	Lobe	ND	ND	LS
	Gyrus	ND	AG	PCG
	BA	30	30	23, 24, 30, 33
Calculation subset (4)	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ITG, MOG	MTG, MOG	ND
	BA	ND	37, 39	37
Language Subset (6 + 7 + 8 + 9 + 10)	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ND	ND	PCG
	BA	ND	ND	30
Design subset (11)	WB	ND	ND	ND
	Lobe	Temporal	Parietal	Parietal
	Gyrus	STG, ITG, MOG, LG, PCG	MOG, Precuneus, LG, PCG	MTG, SOG, MOG, IOG, Cuneus, LG
	BA	17, 18, 37	17, 18, 19, 37	17, 18, 19, 37
Alzheimer Pathology Subset (1 + 2 + 4 + 5 + 8 + 11)	WB	ND	ND	ND
	Lobe	ND	ND	ND
	Gyrus	ND	ND	PCG
	BA	30	30	30

Correlation coefficients were calculated by using Pearson's test and Spearman's coefficient by rank test. AG, angular gyrus; BA, Brodmann area; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; LG, lingual gyrus; LS, limbic system; MOG, middle occipital gyrus; MTG, middle temporal gyrus; ND, not detected; PCG, posterior cingulate gyrus; SOG, superior occipital gyrus; STG, superior temporal gyrus; WB, whole brain. Tests of correlation were performed by using Pearson's coefficient and Spearman's coefficient by rank test.

## Discussion

In this study, patients with AD were analyzed by using 3D-SSP/S.E.E., and compared with control subjects, to accurately assess the extent of CBF reductions observed in this population. In addition, decreased rCBF at the BA level was evaluated by using the maximum Z-score, area ratio for a Z-score  $> 2$ , and a novel indicator,  $\Sigma zS$ , with the latter facilitating consideration of both the brain surface area and the Z-score. Negative correlations were demonstrated between the total MMSE scores and various indicators in the PCG and BA30 areas. The maximum Z-score was defined as the maximum value determined when 1 pixel was visible outside of the specified decreased rCBF. Therefore, it is not reasonable to determine the severity of dementia on the basis of 1 pixel. In addition, the area ratio for a Z-score  $> 2$  demonstrated significant statistical correlations in numerous areas; however, this parameter does not indicate severity, and a large degree of polarization was observed in the scatter diagram. Furthermore, previous studies have reported that the level of rCBF decrease in the PCG was not directly associated with the severity of AD, whereas it was in the hippocampus and frontal lobe are<sup>20, 22)</sup>. However, these previous studies investigated the Z-score without considering the  $\Sigma zS$  used in the present study. We hypothesized that the  $\Sigma zS$  value would enable more quantitative evaluation of the Z-score correlation with PCG. The results of this study showed that, in patients with AD, the  $\Sigma zS$  value provided a more quantitative assessment of the association between the rCBF and cognitive function than was possible by using existing indicators.

Causative diseases of dementia account for most cases of AD. Diagnostic imaging examinations, such as magnetic resonance imaging (MRI) and nuclear medicine studies with positron emission tomography and SPECT may be performed to detect AD-associated morphology. A previous study demonstrated a decrease in rCBF in the parietotemporal association cortex in addition to hypoperfusion and atrophy of the hippocampus as a characteristic of decreased rCBF<sup>3-7)</sup>. Furthermore, Minoshima et al<sup>14)</sup> documented a decrease in rCBF in the PCG by using a statistical brain function analysis;

the results of which have become widely recognized. As previous studies have demonstrated, the PCG is an important area in the pathology of AD because the CBF and metabolic rate are decreased in patients with early onset AD<sup>30, 31)</sup>. In addition, the PCG has a distant effect on the entorhinal cortex and hippocampus and is associated with the earliest signs of neurodegenerative disease<sup>32)</sup>. Furthermore, in the present study, BA30 in the PCG was determined to be an area of cognitive function by subdividing according to the BA level (Tables IV and V). As a part of the retrosplenial cortex, the BA30 has important neural connections with the entorhinal cortex, and previous studies have demonstrated that damage results in memory impairment<sup>33-35)</sup>. A reduction in CBF in the retrosplenial cortex has been reported in amnesic prodromes of AD and may be a useful parameter for discriminating between patients progressing to AD<sup>36)</sup>. Therefore, in the present study, BA30 was detected on the basis of  $\Sigma zS$ , which exhibits agreement with the area of CBF decrease and previously reported areas and suggests that the  $\Sigma zS$  value may be a useful indicator.

Memory impairment is a core symptom of AD. Previous studies have demonstrated that memory impairment appears following injury to areas along the Papez circuit, which is a neural circuit involved in memory processing<sup>34, 35)</sup>. In the present study,  $\Sigma zS$  values were considered to reflect the degree of rCBF decrease along the neural circuit, as negative correlations were exclusively demonstrated between  $\Sigma zS$  and memory evaluation items (Tables IV and V). However, BAs corresponding to the parahippocampal gyrus were not detected. This finding may be attributed to diluted relevance because the area may have become too small after subdividing the brain surface area. Furthermore, the average duration of disease was 2 years in the AD group, and 6/13 patients presented with disease duration < 2 years. Therefore, the decrease in CBF may have appeared to be lower in the parahippocampal gyrus due to a weak association with the MMSE score, since these areas exhibit a less noticeable rCBF decrease in the early stages of AD. In addition, the results of the present study demonstrated a negative correlation between the  $\Sigma zS$  values in both the BA24 and BA33 areas, which are located



in the anterior cingulate gyrus (ACG) (Fig. 3). The ACG is an area associated with responses to noxious stimuli, and visceromotor and skeletomotor control<sup>37)</sup>. Therefore, in association with the progression of AD, these areas are expected to show a decrease in CBF in the frontal lobe<sup>30)</sup> and thus, may correlate with the severity of MMSE changes and of CBF in the basal forebrain and orbital gyrus<sup>22)</sup>. Because the lower portions of the BA24 and BA33 areas are located in the basal forebrain, the potential for neurodegeneration from the medial direction should also be considered. Notably, the maximum Z-score and the area ratio for a Z-score > 2 did not detect a slight CBF decrease, whereas  $\Sigma zS$  did. The  $\Sigma zS$  is thought to have detected an increase in the area of decreased CBF and Z-score by taking into account the area of impairment in that stage.

The voxel-based specific regional analysis system (VSRAD) using MRI for AD, which targets the medial temporal lobe, was developed as a sensitive diagnostic tool to detect early stages of AD<sup>38)</sup>. VSRAD enabled evaluation of the degree of entorhinal cortex and parahippocampal volume loss by comparing a given subject's gray matter volume with that of the original healthy individual database template. The Z-score obtained from the VSRAD became an indicator of the degree of gray matter atrophy of the hippocampal region in the diagnosis of early AD<sup>39)</sup>. These areas were not detected in the present study because these areas were very small regions (BA level). This finding could be explained by the differences in resolution; MRI had high spatial resolution (pixel size, 1.0–1.5 mm), whereas SPECT had lower spatial resolution (pixel size, 3.88 mm). However, in MMSE subtest 5 and memory evaluation, negative correlations were observed between the limbic system (brain lobe level) and the  $\Sigma zS$  indicator (Tables IV and V) by increasing the amount of analysis data for the brain surface area. Morphological analysis of VSRAD and CBF analysis of 3D-SSP were considered to be equivalent.

Minoshima et al<sup>40)</sup> used a three-dimensional brain phantom to demonstrate that the quantitative accuracy of 3D-SSP data extraction was less biased by the region size caused by cortical atrophy than was standard volume of interest (VOI) analysis. Furthermore, the influence of image noise on 3D-SSP data extraction was no worse than that on VOI

extracted data, and tracer kinetic estimation of rate constants in a neuroreceptor study was improved by using 3D-SSP data extraction because of less contamination from the white matter and cerebrospinal fluid space<sup>40)</sup>.

Therefore, the results of the present study using 3D-SSP suggest that  $\Sigma zS$  may be a useful cerebral flow indicator for assessing the progression and severity of cognitive decline in patients with AD. In the future, the study findings should be confirmed by more detailed analysis in a larger number of subjects.

### Limitation

Our study demonstrated for the first time that  $\Sigma ZS$  in BA 30 was correlated with MMSE subtest 5. However, the hippocampus regions did not show correlations with MMSE subtest 3 or 5 related to memory. Compared with previous studies, the present study had the limitation of requiring more subjects and thus, we could not assess if the activity in the hippocampus regions was associated with MMSE subtest 3 or 5. In addition, further studies will be needed to confirm that our result was useful as a cerebral blood flow indicator in AD patients.

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## References

- 1) Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M: World Alzheimer Report 2015: The Global Impact of Dementia An analysis of prevalence, incidence, cost and trend. Alzheimer's Disease International, London, 2015
- 2) Akatsu H, Takahashi M, Matsukawa N, Ishikawa Y, Kondo N, Sato T, Nakazawa H, Yamada T, Okada H, Yamamoto T and Kosaka K: Subtype analysis of neuropathologically diagnosed patients in a Japanese geriatric hospital. *J Neurol Sci*, 196: 63- 69, 2002.
- 3) Hanyu H, Shimizu S, Tanaka Y, Takahashi M, Koizumi K, Abe K: Differences in regional cerebral blood flow patterns in male versus female patients with Alzheimer's disease. *Am J Neuroradiol*, 25:1199-1204, 2004.
- 4) Hanyu H, Shimizu T, Tanaka Y, Takasaki M, Koizumi K, Abe K: Effect of age on regional cerebral blood flow patterns in Alzheimer's disease patients. *J Neurol Sci*, 209:25-30, 2003.
- 5) Hanyu H, Sato T, Shimizu S, Kanetaka H, Iwamoto T, Koizumi K: The effect of education on rCBF changes in Alzheimer's disease: a longitudinal SPECT study. *Eur J Nucl Med Mol Imaging*, 35:2182-2190, 2008.
- 6) Hirano K, Hanyu H, Kanetaka H, Shimizu S, Sato T, Iwamoto T: Regional cerebral blood flow patterns in extremely elderly patients with Alzheimer's disease. *Nihon Ronen Igakkai Zasshi*, 45 (4): 408-13, 2008.
- 7) Craik F I, Bialystok E, Freedman M: Delaying the onset of Alzheimer's disease: Bilingualism as a form of cognitive reserve. *Neurology*, 75: 1726-1729, 2010.
- 8) Matsuda H: Cerebral blood flow and metabolic abnormalities in Alzheimer's disease. *Ann Nucl Med*, 15: 85-92, 2001.
- 9) Nestor PJ, Fryer TD, Smielewski P, Hodges JR: Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol*, 54 (3): 343-351, 2003.
- 10) Silverman D H, Small G W, Chang C Y, Lu C S, Kung De Aburto M A, Chen W,

- Czernin J, Rapoport SI, Pietrini P, Alexander G E, Schapiro M B: Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome, JAMA 286: 2120-2127, 2001.
- 11) Iida H, Akutsu T, Endo K, Fukuda H, Inoue T, Ito H, koga S, Komatani A, kuwabara Y, Momose T, Nishizawa S: A Multicenter Validation of Regional Cerebral Blood Flow Quantitation Using [123I]Iodoamphetamine and Single Photon Emission Computed Tomography. J Cereb Blood Flow Metab, 16: 781-793, 1996.
  - 12) Matsuda H: Role of Neuroimaging in alzheimer's disease, with emphasis on brain perfusion SPECT. J Nucl Med, 48:1289-1300, 2007.
  - 13) Talairach J Tournoux P: Co-planar stereotaxic atlas of the human brain. Thieme, NewYork, 1988.
  - 14) Minoshima S, Foster N L, Kuhl D E: Posterior cingulated cortex in Alzheimer's disease. Lancet, 344: 895, 1994.
  - 15) Minoshima S, Kirk A F, Koeppe R A, Foster N L, Kuhl D E: A Diagnostic approach in alzheimer's disease using three-dimentional stereotactic surface projections of Fluorine-18-FDG-PET. J Nucl Med, 36:1238-1248, 1995.
  - 16) Folstein M F, Folstein S E , McHugh P R: Mini-mental state; a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 12 (3):189-198, 1975.
  - 17) O'Connor DW, Pollitt PA, Hyde JB, Fellows JL, Miller ND, Brook CP, Reiss BB: The reliability and validity of the Mini-Mental State in a British community survey. J Psychiatr Res, 23 (1): 87-96, 1989.
  - 18) Tombaugh TN, McIntyre NJ: The mini-mental state examination: a comprehensive review. J Am Geriatr Soc,40(9):922-35, 1992.
  - 19) Sugishita M, Hemmi I: Validity and reliability of the mini mental state examination-Japanese (MMSE-J). A preliminary report. Japanese Journal of Cognitive Neuroscience, 12: 186-190, 2010.
  - 20) Rodriguez G, Vitali P, Calvini P, Bordoni C, Girtler N, Taddei G, Mariani G, Nobili F:

- Hippocampal perfusion in mild alzheimer's disease. *Psychiatry Research Neuroimaging*, 100 (2): 65-74, 2000.
- 21) Ikeda E, Shiozaki K, Takahashi N, Togo T, Odawara T, Oka T, Inoue T, Hirayasu Y: Total Mini-Mental State Examination score and regional cerebral blood flow using Z score imaging and automated ROI analysis software in subjects with memory impairment. *Ann Nucl Med*, 22: 539-542, 2008.
  - 22) Kawasaki Y, Ohataki J, Toba K, Koga Y: Relationship of alzheimer disease serverity and <sup>99m</sup>Tc-ECD SPECT brain blood flow imaging. *J kyorin Med Soc*, 38: 21-28, 2007.
  - 23) Mishina M, Ishii K, Kitamura S, Suzuki M, Kobayashi S, Ishiwata K, Katayama Y: Correlation between each task of the Mini-Mental State Examination and regional glucose hypometabolism in at-rest Alzheimer's disease patients. *Geriatr Gerontol Int*, 7; 124-130, 2007.
  - 24) Ashord J W, Kolm P, Colliver J A, Bekian C, Hsu L N: Alzheimer patient evaluation and the mini-mental state: item characteristic curve analysis. *J Gernontol*, 44: 139-146, 1989.
  - 25) Tierney M C, Szalai J P, Snow W G, Fisher R H, Dunn E: Domain specificity of the subtests of the mini-mental state examination. *Arch Neurol*, 54: 713-716, 1997.
  - 26) Tinklenberg J, Brooks J O, Tanke E D, Khalid K, Poulsen S L, Kraemer H C, Gallagher D, Thornton J E, Yesavage J A: Factor analysis and preliminary validation of the mini-mental state examination from a longitudinal perspective. *Int Psychogeriatr*, 2: 123-134, 1990.
  - 27) Meyer J, Xu G, Thornby J, Chowdhury M, Quach M: Lognitudinal analysis of abnormal domains comprising mild cognitive impairment (MCI) during aging. *J Neurol Sci*, 201: 19-25, 2002.
  - 28) Brugnolo A, Nobili F, Barbieri MP, Dessi B, Ferro A, Girtler N, Palummeri E, Partinico D, Raiteri U, Regesta G, Servetto G, Tanganelli P, Uva V, Mazzei D, Donadio S, De Carli F, Colazzo G, Serrati C, Rodriguez G: The factorial structure of

- the mini mental state examination (MMSE) in alzheimer's disease. *Archives of Gerontology and Geriatrics*, 49: 180-185, 2009.
- 29) Shigemori K, Ohgi S, Okuyama E, Shimura T, Schneider E: The factorial structure of the mini mental state examination (MMSE) in Japanese dementia patients. *BMC Geriatrics*, 10: 36, 2010.
  - 30) Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE: Metabolic reduction in the posterior cingulate cortex in very early alzheimer's disease. *Ann Neurol*, 42: 85-94, 1997.
  - 31) Kogure D, Matsuda H, Ohnishi T, Asada T, Uno M, Kunihiro T, Nakano S, Takasaki M: Longitudinal evaluation of early alzheimer's disease using brain perfusion SPECT. *J Nucl Med*, 41: 1155-1162, 2000.
  - 32) Delacourte A, David JP, Sergeant N, Buée L, Wattez A, Vermersch P, Ghazali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C: The biochemical pathway of neurofibrillary degeneration in aging and alzheimer's disease. *Neuropathology*, 52: 1158-1165, 1999.
  - 33) Morris R, Petrides M, Pandya D N: Architecture and connections of retrosplenial area 30 in the rhesus monkey (*macaca mulatta*). *Eur J Neurosci*, 11: 2506-2518, 1999.
  - 34) Lee K, Maeda Y, Shintani Y, Matsuura M, Yamaguchi K, Takayama Y: A case of poststroke dementia after the left medial occipitoparietal lesion. *Clin Neurol*, 48: 43-47, 2008.
  - 35) Rudge P, Warrington E K: Selective impairment of memory and visual perception in splenial tumors. *Brain*, 114: 349-360, 1991.
  - 36) Nestor P J, Fryer T D, Ikeda M, Hodges J R: Retrosplenial cortex (BA29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). *Eur J Neurosci*, 18: 2663-2667, 2003.
  - 37) Vogt B A, Finch D M, Olson C R: Functional Heterogeneity in Cingulate Cortex: The Anterior Executive and Posterior Evaluative Regions. *Cerebral cortex*, 2: 435-443,



1992.

- 38) Hirata Y, Matsuda H, Nemoto K, Ohnishi T, Hirao K, Yamashita F, Asada T, Iwabuchi S, Samejima H: Voxel-based morphometry to discriminate early Alzheimer's disease from controls. *Neurosci Lett*, 382(3):269-74. 2005.
- 39) Shimoda K, Kimura M, Yokota M, Okubo Y: Comparison of regional gray matter volume abnormalities in Alzheimer's disease and late life depression with hippocampal atrophy using VSRAD analysis: A voxel-based morphometry study. *Psychiatry Research: Neuroimaging*, 232: 71-75, 2015.
- 40) Minoshima S, Ficard E P, Frey K A, Koeppe R A, Kuhl D E: Data extraction from brain PET images using three-dimensional stereotactic surface projections . *Quantitative Functional Brain Imaging with Positron Emission Tomography, Section VIII Chapter18*, 1998.

## Abstract

### Association between regional cerebral blood flow and Mini- Mental State Examination score in patients with Alzheimer's disease

Hitoshi Saito

In patients with Alzheimer's disease (AD), cerebral blood flow (CBF) is decreased from the early stages. CBF in AD is currently estimated from Z-scores by using statistical analysis. However, the Z-score is not considered to be an impaired area ratio. In this study, a novel indicator,  $\Sigma zS$ , which is associated with brain surface area and Z-scores, was defined and the association with regional CBF was examined by using Mini-Mental State Examination (MMSE) scores, which indicate the severity of cognitive impairment in patients with AD. We found negative correlations among  $\Sigma zS$  in the posterior cingulate gyrus and the subtest numbers 1, 2, and 5 of the total MMSE scores. Furthermore, a negative correlation was found between the total MMSE score and  $\Sigma zS$  in Brodmann area 30, which is a subdivided area of the brain. The study results indicated that  $\Sigma zS$  may be a useful indicator of CBF metabolism, and thus may improve the current understanding of cognitive function in patients with AD.

## 和文要旨

齊藤 仁

アルツハイマー病患者の脳血流は早期段階から減少している。現在、アルツハイマー病の脳血流は、統計解析を用いた Z-score で評価されている。しかしながら、Z-score は、脳血流の障害領域を考慮していない。本研究では、脳表面領域と Z-score を考慮した  $\Sigma zS$  を定義し、アルツハイマー病患者の認知障害の重症度を示すミニメンタルステート検査を使用して測定した局所脳血流との関連性を調べた。本研究において、後部帯状回の  $\Sigma zS$  とミニメンタルステート検査の下位項目 1、2、5 で負の相関が認められた。さらに、ミニメンタルステート検査の合計スコアと脳の細分化された領域のブロードマン領野 30 で負の相関が認められた。本研究の結果は、局所脳血流代謝の指標として有用であり、アルツハイマー病患者の認知機能の解釈を深めることができるかもしれない。