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A simple index derived from cerebral blood flow SPECT for differentiating Alzheimer's disease and frontotemporal lobar degeneration

Koji Fujita

priuskf@gmail.com

Naga Municipal Hospital https://orcid.org/0000-0001-9586-0588

Chikako Watson

Naga Municipal Hospital

Tomohiro Shizuka

Naga Municipal Hospital

Masami Okumoto

Naga Municipal Hospital

Fumie Kuriyama

Naga Municipal Hospital

Tetsuya Nokami

Naga Municipal Hospital

Naoki Tsuji

Naga Municipal Hospital

Emi Kuriyama

Naga Municipal Hospital

Katsuhisa Hirayama

Naga Municipal Hospital

Megumi Mori

Wakayama Medical University

Shinichiro Maeshima

Naga Municipal Hospital

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Authors: Koji Fujita [*1,2], Chikako Watson [2,3], Tomohiro Shizuka [2,4], Masami Okumoto [2,5], Fumie Kuriyama [2,3], Tetsuya Nokami [6], Naoki Tsuji [1], Emi Kuriyama [1], Katsuhisa Hirayama [1], Megumi Mori [2,7], Shinichiro Maeshima [1,2]

Affiliations:

[1] Department of Neurological Surgery, Naga Municipal Hospital, 1282 Uchita, Kinokawa, 649-6414, Japan

[2] Dementia Medical Center, Naga Municipal Hospital, 1282 Uchita, Kinokawa, 649-6414, Japan

[3] Department of Nursing, Naga Municipal Hospital, 1282 Uchita, Kinokawa, 649-6414, Japan

[4] Department of Rehabilitation, Naga Municipal Hospital, 1282 Uchita, Kinokawa, 649-6414, Japan

[5] Department of Pharmacy, Naga Municipal Hospital, 1282 Uchita, Kinokawa, 649-6414, Japan

[6] Department of Radiology, Naga Municipal Hospital, 1282 Uchita, Kinokawa, 649-

6414, Japan

[7] Department of Neurology, Wakayama Medical University, 811-1 Kimiidera, Wakayama, 641-8509, Japan

***Corresponding author:** Koji Fujita, Department of Neurological Surgery, Naga Municipal Hospital, 1282 Uchita, Kinokawa, 649-6414, Japan. Tel: +81-736-77-2019; Fax: +81-736-77-4659; E-mail: priuskf@gmail.com

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Manuscript

Abstract

Objective Anti-amyloid-β (Aβ) antibody therapy requires confirmation of Aβ pathology, but cerebrospinal fluid testing is invasive and amyloid positron emission tomography (PET) is costly. Differentiating Alzheimer's disease (AD) from frontotemporal lobar degeneration (FTLD) is also essential for treatment planning. We evaluated whether a simple index derived from cerebral blood flow single-photon emission computed tomography (SPECT), namely the difference in hypoperfusion between disease-specific and non-specific regions, could differentiate AD from non-AD and FTLD from non-FTLD.

Methods We retrospectively analyzed 46 patients who underwent N-isopropyl-p-[123I]iodoamphetamine (123I-IMP) SPECT: 27 with AD (9 with mild cognitive impairment due to AD and 18 with mild AD dementia; 9 amyloid PET-positive), 9 with FTLD, 7 with vascular dementia, and 3 with other diagnoses. Using 10 cortical regions from three-dimensional stereotactic surface projection (3D-SSP), we calculated the mean Z-score of AD-specific regions (parietal lobe, precuneus, and posterior cingulate gyrus; specific AD), that of the remaining 7 regions (outside AD), and their difference. FTLD indices were calculated similarly from FTLD-specific regions (frontal and temporal lobes) and the remaining 8 regions. Groups were compared using the Mann-Whitney U test and receiver operating characteristic analysis.

Results The median specific AD − outside AD value was 2.55 in AD and −1.26 in non-AD ($p < 0.001$; area under the curve [AUC] 0.836). The AUC was 0.871 for mild cognitive impairment due to AD, 0.819 for mild AD dementia, and 0.895 for amyloid

PET-positive AD, whereas specific AD alone yielded AUCs of 0.713–0.760. The median specific FTLD − outside FTLD value was 5.11 in FTLD and 0.185 in non-FTLD ($p < 0.001$; AUC 0.856); specific FTLD alone yielded an AUC of 0.886. No index correlated with Mini-Mental State Examination scores or medial temporal atrophy.

Conclusions The difference in hypoperfusion between disease-specific and non-specific regions differentiated AD and FTLD independently of disease severity. This index can be easily calculated from routine 3D-SSP analysis and may help select candidates for Aβ testing.

Keywords Alzheimer's disease · Frontotemporal lobar degeneration · Cerebral blood flow SPECT · 3D-SSP · Amyloid PET

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, and its early diagnosis and treatment are major challenges in aging societies such as Japan. Recently, the anti-amyloid-β (Aβ) antibodies lecanemab and donanemab were shown to slow clinical progression in early AD [1, 2]. In Japan, lecanemab was approved in 2023 and donanemab in 2024 for mild cognitive impairment (MCI) and mild dementia due to AD.

Eligibility for these drugs requires confirmation of Aβ pathology by amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) testing [3, 4]. However, CSF testing requires lumbar puncture, and amyloid PET is expensive and available only at a limited number of facilities. Moreover, a substantial proportion of patients clinically suspected of having AD turn out to be Aβ-negative [5]. A simple, objective method is therefore needed to identify patients with a high likelihood of Aβ positivity before Aβ testing.

Frontotemporal lobar degeneration (FTLD) is another important degenerative dementia, particularly in patients with early or presenile onset. FTLD is not an indication for anti-Aβ antibodies and requires different clinical management and caregiver support, including management of behavioral symptoms. Accurate early differentiation between AD and FTLD is therefore directly relevant to treatment decisions.

Cerebral blood flow single-photon emission computed tomography (SPECT) is widely available and commonly used in the differential diagnosis of dementia [6]. AD shows hypoperfusion in the posterior cingulate gyrus, precuneus, and parietal lobe from an early stage [7, 8], whereas FTLD is characterized by hypoperfusion in the frontal and anterior temporal lobes [9]. Statistical image analyses such as three-dimensional

stereotactic surface projection (3D-SSP) and the easy Z-score imaging system (eZIS) allow these disease-specific patterns to be assessed objectively [7, 10]. In clinical practice, however, we often encounter patients with only mild hypoperfusion in the disease-specific regions, or with widespread hypoperfusion beyond these regions that obscures the characteristic pattern. Such cases are difficult to classify when only the degree of hypoperfusion in the disease-specific regions is considered.

At our institution, patients whose SPECT suggests hypoperfusion in AD-specific regions are prioritized for Aβ testing to increase the positive rate. To make this selection more objective, we focused on a relative index that compares hypoperfusion in disease-specific regions with that in the remaining regions. We hypothesized that whether hypoperfusion is stronger in the disease-specific regions than in the non-specific regions reflects the likelihood of the disease more sensitively.

The aim of this study was to calculate the mean Z-scores of disease-specific and non-specific regions and their difference from 3D-SSP analysis of N-isopropyl-p-[123I]iodoamphetamine (123I-IMP) SPECT, and to evaluate their usefulness for differentiating AD from non-AD and FTLD from non-FTLD. We also examined the associations of these indices with cognitive function (Mini-Mental State Examination [MMSE]) and medial temporal atrophy assessed with the Voxel-based Specific Regional analysis system for Alzheimer's Disease (VSRAD).

Materials and methods

Patients

We retrospectively studied 46 patients who visited the Medical Center for Dementia at our institution between April 2024 and March 2026 and underwent cerebral blood flow SPECT for the diagnosis of dementia. Patients with dementia with Lewy

bodies (DLB) were excluded, because the diagnostic criteria for DLB rely on dopamine transporter SPECT and 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy as indicative biomarkers, and cerebral blood flow SPECT plays a different role in its diagnosis [11].

AD was diagnosed clinically according to the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria [12, 13]. The AD group comprised 27 patients: 9 with MCI due to AD and 18 with mild AD dementia. Aβ positivity was confirmed by amyloid PET in 9 of them (7 with MCI due to AD and 2 with mild AD dementia). Amyloid PET was performed with 18F-flutemetamol (Vizamyl) in 5 and 18F-florbetapir (Amyvid) in 4 of these patients. Positivity was determined by visual assessment by nuclear medicine physicians, and Centiloid values were calculated for reference. For florbetapir, using the whole cerebellum, including white matter, as the reference region can lower the standardized uptake value ratio in patients with high non-specific cerebellar uptake. This can lead to underestimated Centiloid values despite visually evident cortical deposition [14]. In the present study, 2 patients examined with florbetapir showed clear cortical deposition on visual assessment but low Centiloid values (4.9 and 21.5); they were classified as positive based on visual assessment.

The non-AD group comprised 19 patients: 9 with FTLD [15, 16] (3 each with behavioral variant frontotemporal dementia [bvFTD], semantic dementia [SD], and progressive non-fluent aphasia [PNFA]), 7 with vascular dementia (VaD) [17], and 3 with other diagnoses. The other diagnoses were primary age-related tauopathy (PART) in 2 patients [18] and corticobasal degeneration (CBD) in 1 [19]. Both patients with PART were amyloid PET-negative (1 examined with flutemetamol and 1 with florbetapir), which formed the basis of their diagnosis. For the analysis of FTLD, the 9

patients with FTLD formed the FTLD group, and the remaining 37 patients (27 AD, 7 VaD, 2 PART, and 1 CBD) formed the non-FTLD group.

Clinical assessment

Cognitive function was assessed with the MMSE [20] and the Revised Hasegawa's Dementia Scale (HDS-R) [21]. Daily living function was assessed with the Instrumental Activities of Daily Living (IADL) scale and the Physical Self-Maintenance Scale (PSMS) [22], and caregiver burden with the Zarit Burden Interview [23, 24]. Atrophy of the medial temporal lobe (parahippocampal gyrus) was evaluated on brain MRI using VSRAD [25].

Cerebral blood flow SPECT

After intravenous injection of 167 MBq of 123I-IMP, images were acquired with a Discovery NM830 (GE Healthcare) equipped with extended low-energy general-purpose (ELEGP) collimators. A 2-min dynamic acquisition was performed immediately after injection, and SPECT acquisition started 13 min after injection. SPECT data were acquired over 30 min (6 rotations) with a zoom factor of 1.28. The matrix size was 128 × 128 for all acquisitions. Images were analyzed with 3D-SSP [7] and compared with a normal database. For each of 10 cortical regions (parietal lobe, precuneus, posterior cingulate gyrus, lateral occipital lobe, medial occipital lobe, frontal lobe, temporal lobe, inferior frontal gyrus, precentral gyrus, and postcentral gyrus), the deviation from the normal mean (Z-score) was obtained.

Calculation of indices

The same 10 regions were divided into disease-specific and non-specific regions for each disease (Table 1, Fig. 1). The Z-scores in each set of regions were summed and divided by the number of regions to obtain the mean Z-score:

specific AD = (Z1 + Z2 + Z3) / 3; outside AD = (Z1 + … + Z7) / 7

specific FTLD = (Z1 + Z2) / 2; outside FTLD = (Z1 + … + Z8) / 8

The difference was then calculated by subtracting the value of the non-specific regions from that of the specific regions (specific AD − outside AD; specific FTLD − outside FTLD). Higher Z-scores indicate stronger hypoperfusion. A positive difference means that hypoperfusion in the disease-specific regions is relatively stronger than in the non-specific regions.

Statistical analysis

For AD, each of 4 groups—all patients with AD (n = 27), MCI due to AD (n = 9), mild AD dementia (n = 18), and amyloid PET-positive AD (n = 9)—was compared with the non-AD group (n = 19). For FTLD, the FTLD group (n = 9) was compared with the non-FTLD group (n = 37).

Group comparisons were performed with the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was used to obtain sensitivity, specificity, cutoff values, and the area under the curve (AUC). Cutoff values were determined by the maximum Youden index. Correlations of each index with MMSE and VSRAD were assessed with Spearman's rank correlation coefficient: AD-related indices in the 4 AD groups and FTLD-related indices in the FTLD group. A p value < 0.05 was considered statistically significant. All analyses were performed with EZR (version 1.70) [26].

Results

Patient characteristics

Patient characteristics are shown in Table 2. The median age was 77 years (range 52–88) in the AD group, 74 years (65–85) in the FTLD group, and 79 years (63–82) in

the VaD group. Women accounted for 19 patients (70.3%) in the AD group, 7 (77.8%) in the FTLD group, and 3 (42.9%) in the VaD group. The median MMSE score was 22 in the AD group (25 in MCI due to AD and 20 in mild AD dementia), 19 in the FTLD group, and 24.5 in the VaD group. The median VSRAD score was 1.80 in the AD group, 2.14 in the FTLD group, and 1.04 in the VaD group. Of the 9 amyloid PET-positive patients, 7 had MCI due to AD. The FTLD group comprised 3 patients each with bvFTD, SD, and PNFA.

Distribution of AD-related indices

The median specific AD value was 3.73 in the AD group and 1.11 in the non-AD group. The median outside AD value was 0.834 in the AD group and 2.56 in the non-AD group, with particularly strong non-specific hypoperfusion in FTLD (3.15) and VaD (2.51). The median specific AD − outside AD value was 2.55 in the AD group and −1.26 in the non-AD group. It was positive in all AD subgroups: 3.48 in MCI due to AD, 2.41 in mild AD dementia, and 2.55 in amyloid PET-positive AD. Among non-AD patients, it was negative in FTLD (−1.33) and VaD (−1.39), but high in the 3 patients with other diagnoses (PART and CBD; median 4.77) (Table 3A).

Comparison between AD and non-AD and ROC analysis

Comparisons between each AD group and the non-AD group are shown in Table 4. All 3 indices differed significantly between all patients with AD and the non-AD group. The specific AD − outside AD value showed the smallest p value ($p = 0.0000556$). Its AUC was 0.836, with a sensitivity of 74.1% and a specificity of 84.2% at a cutoff of 0.297.

In the comparison with MCI due to AD, the specific AD − outside AD value showed the highest AUC (0.871; $p = 0.00105$; sensitivity 88.9%, specificity 84.2%). It

also showed the highest AUC in the comparison with mild AD dementia (0.819; p = 0.000611).

In the comparison with amyloid PET-positive AD, specific AD alone did not differ significantly (p = 0.0763; AUC 0.713). In contrast, both outside AD (p = 0.000316; AUC 0.901) and the specific AD − outside AD value (p = 0.000408; AUC 0.895) differed significantly, with comparable discriminative ability. The cutoff of the specific AD − outside AD value was 0.609, with a sensitivity of 88.9% and a specificity of 89.5%.

The AUC of specific AD alone ranged only from 0.713 to 0.760 across all comparisons. ROC curves of each index are shown in Fig. 2.

Comparison between FTLD and non-FTLD and ROC analysis

The distribution of FTLD-related indices is shown in Table 3B, and the group comparison in Table 6. The median specific FTLD value was 6.29 in the FTLD group and 2.35 in the non-FTLD group. The median outside FTLD value was 1.18 and 1.84, respectively. The median specific FTLD − outside FTLD value was 5.11 in the FTLD group and 0.185 in the non-FTLD group.

The specific FTLD − outside FTLD value showed the smallest p value (p = 0.0000529). Its AUC was 0.856, with a sensitivity of 88.9% and a specificity of 83.8% at a cutoff of 3.02. Specific FTLD alone also differed significantly (p = 0.000127), with an AUC of 0.886 and a sensitivity of 88.9% and specificity of 81.1% at a cutoff of 5.315. In contrast, outside FTLD did not differ between the groups (p = 0.782; AUC 0.532). ROC curves of each index are shown in Fig. 3.

By subtype, the median specific FTLD − outside FTLD value was 5.86 in bvFTD, 5.64 in SD, and 4.84 in PNFA (Table 3B). The median outside FTLD value was 0.213

in bvFTD, 1.22 in SD, and 2.67 in PNFA, indicating relatively strong non-specific hypoperfusion in PNFA. The single FTLD patient below the cutoff of 3.02 (−0.105) had PNFA.

When the AD and FTLD indices were plotted together for each patient, the AD and FTLD groups were distributed in different areas (Fig. 4). Using the cutoff of each index, 20 of 27 patients with AD (74.1%) were located in the area where only the AD index was positive, and 8 of 9 patients with FTLD (88.9%) in the area where only the FTLD index was positive. No patient was positive for both indices. All 7 patients with VaD were negative for the AD index, but 4 of them were positive for the FTLD index. All 9 amyloid PET-positive patients with AD were located in the area where only the AD index was positive. However, the patient with CBD and 1 amyloid PET-negative patient with PART were also located in this area.

Correlations with clinical measures

Correlations of the AD-related indices with MMSE and VSRAD are shown in Table 5. No significant correlations were found in any group. In the MCI due to AD group, the specific AD − outside AD value tended to correlate positively with VSRAD, but this did not reach significance ($r = 0.69$, $p = 0.069$). Correlations of the FTLD-related indices are shown in Table 7. In the FTLD group, none of the indices correlated significantly with MMSE or VSRAD (specific FTLD − outside FTLD value vs. MMSE: $r = 0.349$, $p = 0.357$; vs. VSRAD: $r = -0.167$, $p = 0.678$).

Discussion

This study showed that the difference in hypoperfusion between disease-specific and non-specific regions on cerebral blood flow SPECT was useful for differentiating both AD from non-AD and FTLD from non-FTLD. For AD, the specific AD − outside

AD value discriminated AD from non-AD more accurately than hypoperfusion in AD-specific regions alone, and this finding was consistent across MCI due to AD, mild AD dementia, and amyloid PET-positive AD. For FTLD, the specific FTLD − outside FTLD value showed the smallest p value and discriminative ability comparable to that of specific FTLD alone.

Why a relative index is useful

When only hypoperfusion in AD-specific regions was assessed, the median specific AD value was 1.11 even in the non-AD group, showing considerable overlap with the AD group (3.73). FTLD and VaD can cause hypoperfusion over wide areas, including the AD-specific regions. Therefore, the absolute degree of hypoperfusion in AD-specific regions alone may not capture the distribution pattern characteristic of AD.

In contrast, the difference between specific and non-specific regions removes the effect of overall hypoperfusion and indicates whether hypoperfusion is relatively stronger in particular regions. This can be regarded as a numerical version of the process by which readers judge whether hypoperfusion is posterior- or anterior-dominant when viewing the whole image. With eZIS, a ratio comparing hypoperfusion in a volume of interest with that in the whole brain has also been reported to be useful for identifying AD [10], which is consistent with our findings. A feature of our method is that indices for several diseases can be calculated within the same framework simply by allocating the same 10 regions differently for each disease.

Significance of outside AD

In the comparison with amyloid PET-positive AD, outside AD alone showed a high AUC of 0.901. The median outside AD value in amyloid PET-positive AD was as low as 0.264, suggesting that perfusion in non-specific regions is relatively preserved in

early AD with confirmed Aβ pathology. In contrast, non-specific hypoperfusion was prominent in the non-AD group. The specific AD − outside AD value integrates 2 pieces of information, hypoperfusion in AD-specific regions and preserved perfusion in non-specific regions, into a single value. This may explain its stable discriminative ability regardless of disease stage or target group.

Interpretation of the FTLD index

FTLD is characterized by hypoperfusion in the frontal and anterior temporal lobes [9], and in the present study specific FTLD alone showed a high AUC of 0.886. This indicates that hypoperfusion in FTLD is strongly concentrated in the specific regions, so that FTLD can be differentiated even by the absolute degree of hypoperfusion.

Unlike in AD, outside FTLD did not differ between the groups ($p = 0.782$). Of the 37 non-FTLD patients, 27 had AD, and the marked hypoperfusion of the parietal lobe, precuneus, and posterior cingulate gyrus in AD is included in outside FTLD. As a result, outside FTLD values were also elevated in the non-FTLD group, which probably limited the additional benefit of taking the difference. Nevertheless, the specific FTLD − outside FTLD value showed the smallest p value, and its sensitivity was the same as that of specific FTLD alone (88.9%).

By subtype, the difference index was somewhat lower in PNFA, and the only false-negative FTLD case had PNFA. PNFA mainly affects the left inferior frontal gyrus and the surrounding insular region [16]. Because the inferior frontal gyrus was included in the non-specific regions in this study, outside FTLD may have been higher in PNFA (median 2.67), reducing the difference. In bvFTD and SD, hypoperfusion was concentrated in the specific regions.

The AD and FTLD indices complement each other. In the FTLD group, the

median specific AD − outside AD value was negative (−1.33), in the opposite direction from that in the AD group (2.55). Thus, calculating both indices from a single SPECT analysis allows posterior-dominant AD-type and anterior-dominant FTLD-type patterns to be assessed simultaneously. In the scatter plot (Fig. 4), no patient was positive for both indices, and most patients with AD and FTLD were located in different areas. In particular, all 9 amyloid PET-positive patients with AD were located in the AD-type area.

On the other hand, 4 of 7 patients with VaD were positive for the FTLD index. VaD due mainly to small vessel disease can show frontal hypoperfusion caused by disruption of frontal-subcortical circuits, which may explain this finding. A positive FTLD index therefore does not necessarily indicate FTLD, and vascular lesions should also be assessed on MRI.

Relationship with cognitive function and brain atrophy

None of the AD- or FTLD-related indices correlated significantly with MMSE or VSRAD. These indices therefore appear to reflect the distribution pattern of hypoperfusion rather than dementia severity or the degree of medial temporal atrophy. They may thus be used independently of severity and complement morphological indices such as VSRAD. However, the MCI due to AD group showed a trend toward a positive correlation with VSRAD ($r = 0.69$, $p = 0.069$), which should be examined in a larger sample. The median MMSE score in the FTLD group was 19, lower than that in the AD group (22), raising the possibility that high FTLD index values reflected disease severity. However, within the FTLD group, none of the FTLD-related indices correlated with MMSE or VSRAD (Table 7). This supports the interpretation that the FTLD index also reflects the distribution of hypoperfusion rather than severity. Because the FTLD

group included only 9 patients, the statistical power to detect correlations was limited.

Clinical implications

Confirmation of Aβ pathology is required for anti-Aβ antibody therapy [3, 4], but some patients clinically suspected of having AD are Aβ-negative [5]. Our index can be obtained by simple calculation from routine cerebral blood flow SPECT analysis, which is available at many facilities. It may serve as an auxiliary index for objectively selecting patients who should be prioritized for Aβ testing when visual assessment is inconclusive. In this study, the cutoff for amyloid PET-positive patients was 0.609 (sensitivity 88.9%, specificity 89.5%). In patients with a high FTLD index, it may also support prioritizing an evaluation focused on FTLD rather than Aβ testing. However, this index does not replace Aβ testing and should be regarded as a screening tool for increasing the pretest probability.

Possible false-positive cases

The 3 non-AD patients with other diagnoses (PART and CBD) showed a high median specific AD − outside AD value of 4.77. PART is characterized by tau pathology centered on the medial temporal lobe without Aβ pathology [18], and both patients with PART in this study were amyloid PET-negative. Its clinical features resemble those of AD, and its hypoperfusion pattern may also be similar. CBD often shows asymmetric hypoperfusion extending from the frontal to the parietal lobe [19], and parietal hypoperfusion may have increased the AD index. PART in particular is a typical condition in which the AD index can be positive despite negative Aβ pathology. This index reflects the distribution of hypoperfusion and does not directly indicate the presence of Aβ. For this reason too, Aβ testing remains necessary for the final diagnosis.

Limitations

This study has several limitations. First, this was a single-center retrospective study with a small sample. In particular, the FTLD group and the subgroups included only 9–18 patients each, and the FTLD subtypes (3 patients each) were not compared statistically. Second, Aβ pathology was confirmed in only 9 of the 27 patients with AD, and the others were diagnosed clinically. FTLD was also diagnosed clinically without pathological confirmation. In addition, 2 amyloid PET tracers were used, and positivity was based on visual assessment. Third, CBD belongs pathologically to FTLD-tau, but in this study it was classified as non-FTLD based on clinical diagnosis; results could differ depending on the classification. Fourth, DLB was excluded. DLB shows posterior hypoperfusion, including the occipital lobe, and is a major differential diagnosis of AD [11]; the performance of this index in populations that include DLB is unknown. Fifth, the cutoff values were derived from the same population and may be overestimated, and validation in an independent population is needed. Sixth, differences in AUC between indices were not tested statistically. Finally, the division into disease-specific and non-specific regions was based on previous studies [7–9], and the optimal combination of regions was not examined. For example, the inferior frontal gyrus was included in the non-specific regions in the FTLD analysis; including it in the specific regions may be more appropriate for evaluating PNFA.

Conclusions

In 3D-SSP analysis of cerebral blood flow SPECT, the difference in hypoperfusion between disease-specific and non-specific regions can serve as an index for differentiating AD from non-AD and FTLD from non-FTLD. The specific AD − outside AD value identified AD more accurately than hypoperfusion in AD-specific

regions alone and was also useful for MCI due to AD and amyloid PET-positive AD. The specific FTLD − outside FTLD value identified FTLD with high accuracy. Neither index correlated with cognitive function or medial temporal atrophy. Indices for several diseases can be calculated easily from a single SPECT analysis, and this method may help select candidates for Aβ testing and support the differential diagnosis of degenerative dementias. Validation in larger populations that include DLB is needed.

Declarations

Funding

This study received no specific funding.

Conflict of interest

The authors declare no conflicts of interest.

Ethics approval

This retrospective study was approved by the institutional ethics committee (approval number: 2026013) and was conducted in accordance with the Declaration of Helsinki.

Consent to participate

The requirement for written informed consent was waived because of the retrospective design; patients were given the opportunity to opt out.

Data availability

The data are available from the corresponding author upon reasonable request.

Author contributions

K.F. conceived and designed the study. K.F., C.W., T.S., M.O., F.K., N.T., E.K. and K.H. collected the clinical data. K.F., C.W., T.S., M.O. M.M. and S.M. evaluated the clinical data. K.F. and T.N. collected and curated the imaging data. K.F., M.M. and S.M. and performed the image analysis. K.F. performed the statistical analysis and drafted the manuscript. All authors critically reviewed the manuscript, contributed to its revision, and approved the final version.

References

1. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388:9–21.

2. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330:512–27.

3. Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, et al. Lecanemab: appropriate use recommendations. J Prev Alzheimers Dis. 2023;10:362–77.

4. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024;20:5143–69.

5. Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BN, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA. 2015;313:1939–49.

6. Matsuda H. Role of neuroimaging in Alzheimer's disease, with emphasis on brain perfusion SPECT. J Nucl Med. 2007;48:1289–300.

7. Minoshima S, Frey KA, Koeppe RA, Foster NL, Kuhl DE. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. J Nucl Med. 1995;36:1238–48.

8. 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. 1997;42:85–94.

9. McNeill R, Sare GM, Manoharan M, Testa HJ, Mann DM, Neary D, et al. Accuracy

of single-photon emission computed tomography in differentiating frontotemporal dementia from Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2007;78:350–5.

10. Matsuda H, Mizumura S, Nagao T, Ota T, Iizuka T, Nemoto K, et al. Automated discrimination between very early Alzheimer disease and controls using an easy Z-score imaging system for multicenter brain perfusion single-photon emission tomography. AJNR Am J Neuroradiol. 2007;28:731–6.
11. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology. 2017;89:88–100.
12. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–9.
13. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270–9.
14. Arai H. Underestimated Centiloid values in amyloid PET: a technical report on clinically relevant quantification errors. Cureus. 2025;17:e97398.
15. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456–77.

16. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76:1006–14.

17. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43:250–60.

18. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol. 2014;128:755–66.

19. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013;80:496–503.

20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.

21. Kato S, Shimogaki H, Onodera A, Ueda H, Oikawa K, Ikeda K, et al. Development of the revised version of Hasegawa's Dementia Scale (HDS-R). Jpn J Geriatr Psychiatry. 1991;2:1339–47 (in Japanese).

22. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86.

23. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980;20:649–55.

24. Arai Y, Kudo K, Hosokawa T, Washio M, Miura H, Hisamichi S. Reliability and validity of the Japanese version of the Zarit Caregiver Burden interview. Psychiatry Clin Neurosci. 1997;51:281–7.

25. Matsuda H, Mizumura S, Nemoto K, Yamashita F, Imabayashi E, Sato N, et al. Automatic voxel-based morphometry of structural MRI by SPM8 plus diffeomorphic anatomic registration through exponentiated Lie algebra improves the diagnosis of probable Alzheimer disease. AJNR Am J Neuroradiol. 2012;33:1109–14.

26. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.

Figure legends

Fig. 1 Examples of indices calculated by 3D-SSP analysis of 123I-IMP cerebral blood flow SPECT. (A) AD index. Specific AD is the sum of Z-scores in the AD-specific regions (parietal lobe, precuneus, and posterior cingulate gyrus) divided by 3, and outside AD is the sum of Z-scores in the 7 non-specific regions divided by 7. In this patient (amyloid PET-positive AD; flutemetamol PET, Centiloid 52.8), specific AD was 5.31, outside AD 1.24, and specific AD − outside AD 4.07. (B) FTLD index. Specific FTLD is the sum of Z-scores in the frontal and temporal lobes divided by 2, and outside FTLD is the sum of Z-scores in the 8 non-specific regions divided by 8. In this patient (FTLD, semantic dementia), specific FTLD was 8.09, outside FTLD 1.06, and specific FTLD − outside FTLD 7.03. Red dots, patient values; blue bars, threshold (mean + 1.64 SD of normal controls); gray bars, mean of normal controls; R, right; L, left.

Fig. 2 ROC curves of each index for differentiating AD from non-AD. (A) All patients with AD vs. non-AD. (B) Amyloid PET-positive AD vs. non-AD. Curves for specific AD (dashed line), outside AD (dotted line), and specific AD − outside AD (solid line) are superimposed. The x-axis shows 1 − specificity and the y-axis shows sensitivity. Circles indicate cutoff values determined by the Youden index, and AUCs are given in parentheses in the legend.

Fig. 3 ROC curves of each index for differentiating FTLD from non-FTLD. Curves for specific FTLD (dashed line), outside FTLD (dotted line), and specific FTLD − outside FTLD (solid line) are superimposed. Axes, circles, and AUCs are shown as in Fig. 2.

Fig. 4 Scatter plot of the specific AD − outside AD value (x-axis) and the specific FTLD − outside FTLD value (y-axis) for each patient. Symbols indicate the diagnostic group (AD, n = 27; FTLD, n = 9; VaD, n = 7; PART, n = 2; CBD, n = 1). Filled circles

indicate the 9 amyloid PET-positive patients with AD, and open circles the 18 patients with clinically diagnosed AD. Both patients with PART were amyloid PET-negative. Dashed lines indicate the cutoff values of each index (AD index 0.297; FTLD index 3.02). The lower right area corresponds to the AD-type and the upper left area to the FTLD-type hypoperfusion pattern.

PET-positive patients with AD, and open circles the 18 patients with clinically diagnosed AD. Both patients with PART were amyloid PET-negative. Dashed lines indicate the cutoff values of each index (AD index 0.297; FTLD index 3.02). The lower right area corresponds to the AD-type and the upper left area to the FTLD-type hypoperfusion pattern.

Figure 1(A)

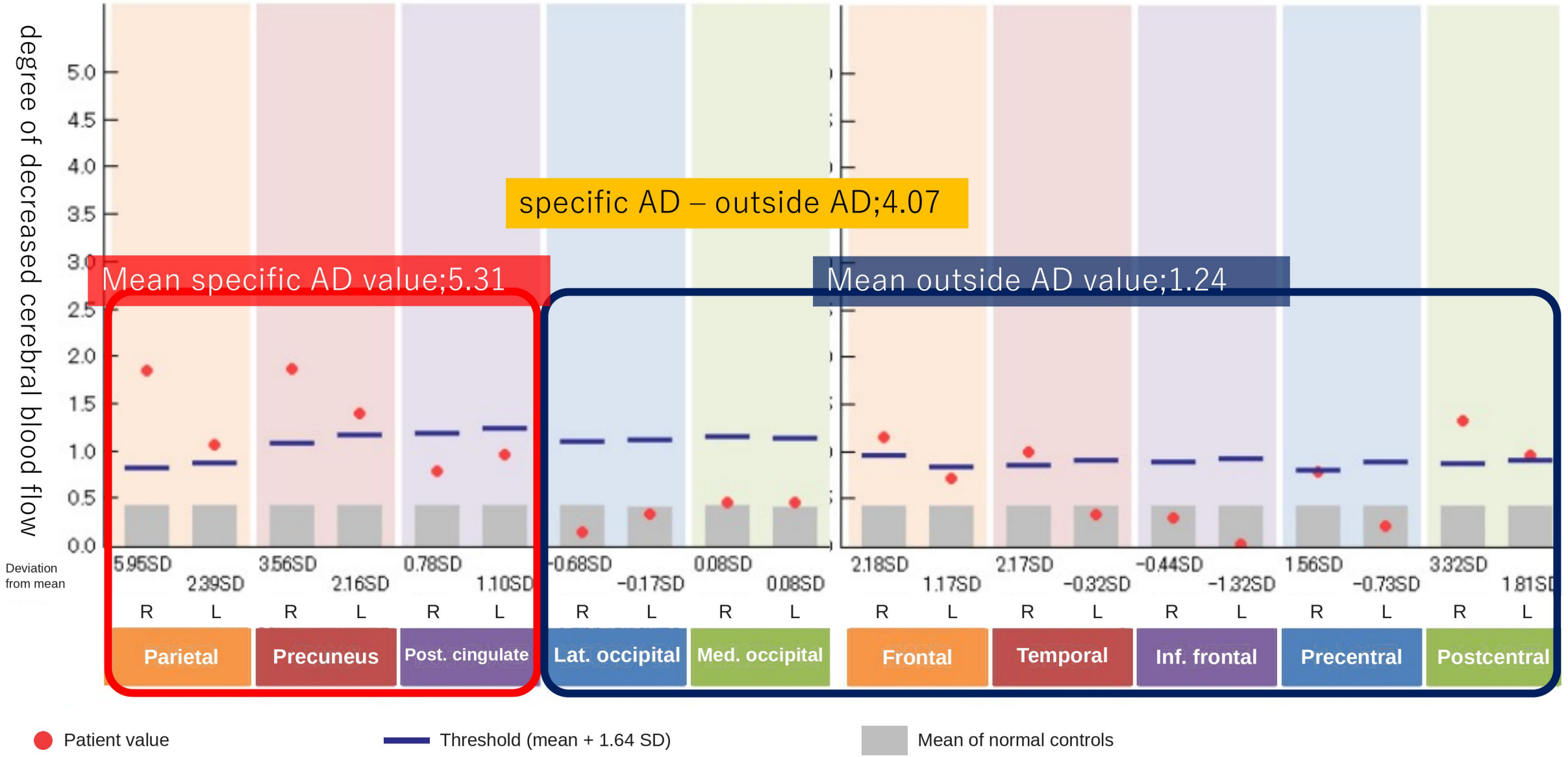
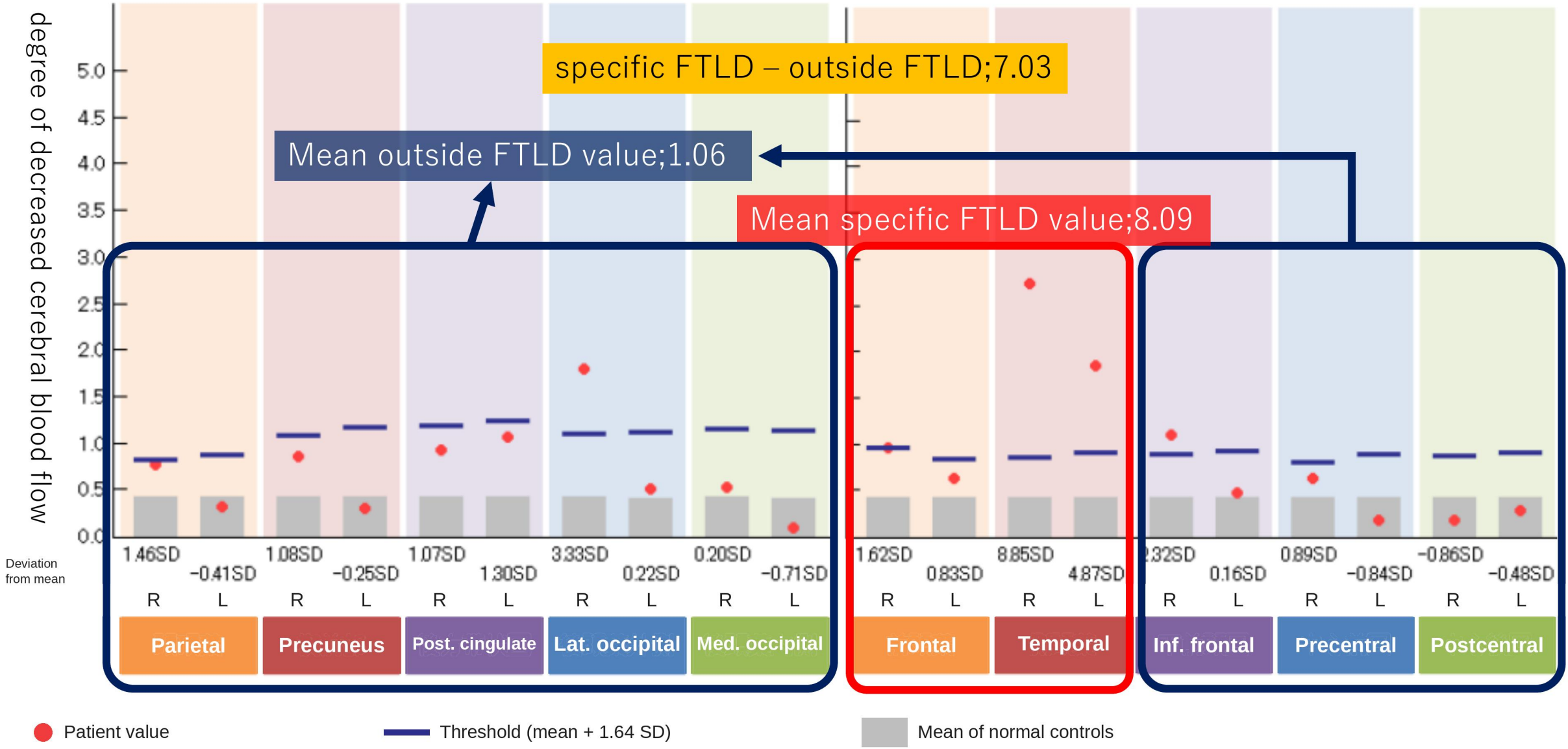
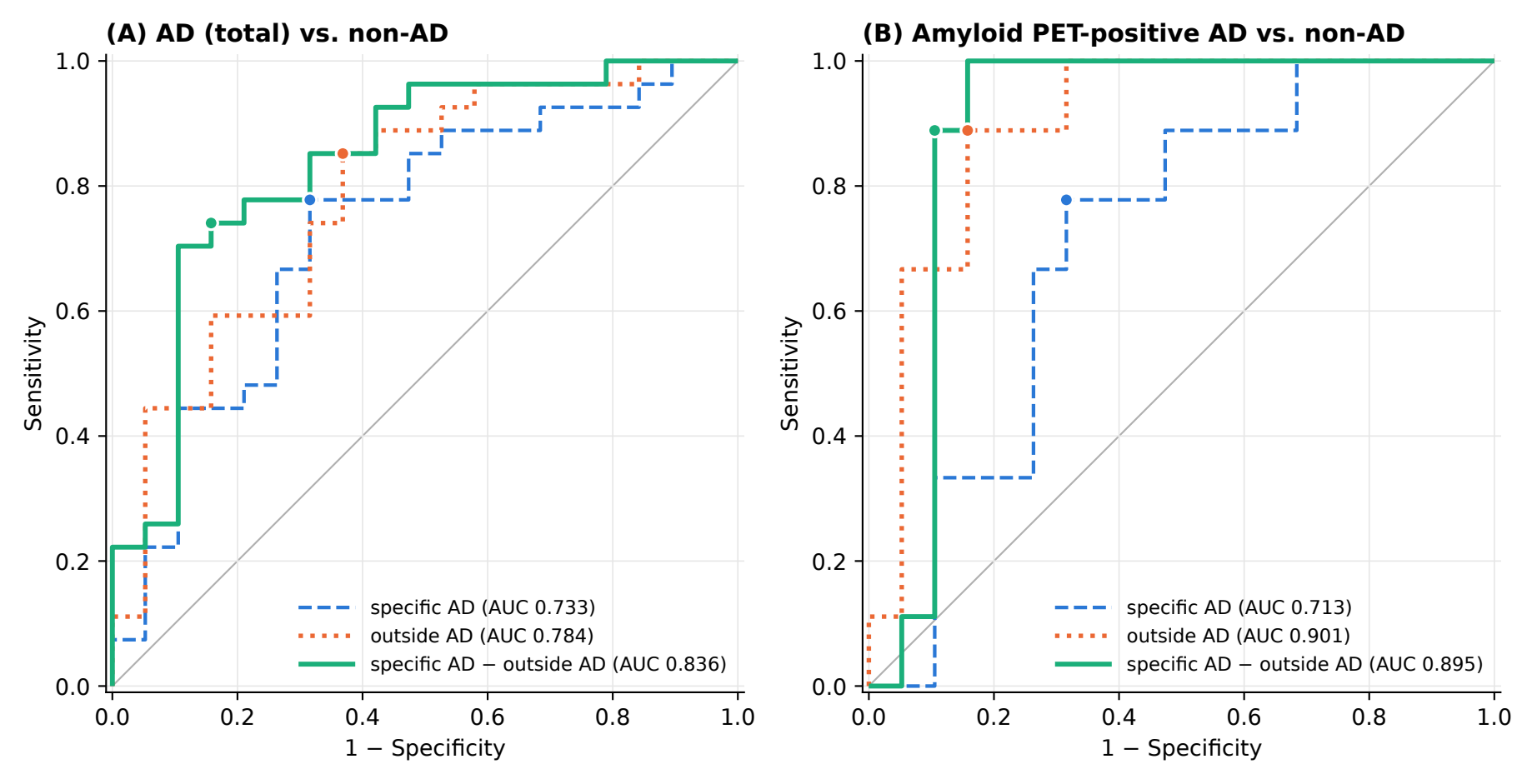
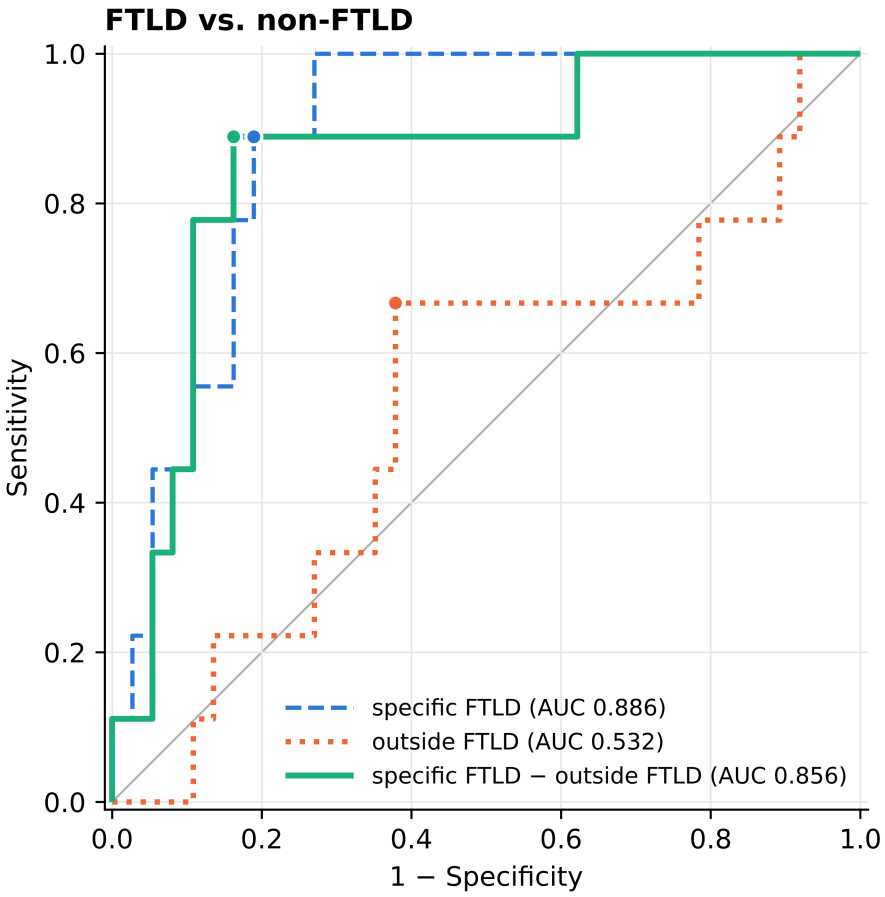
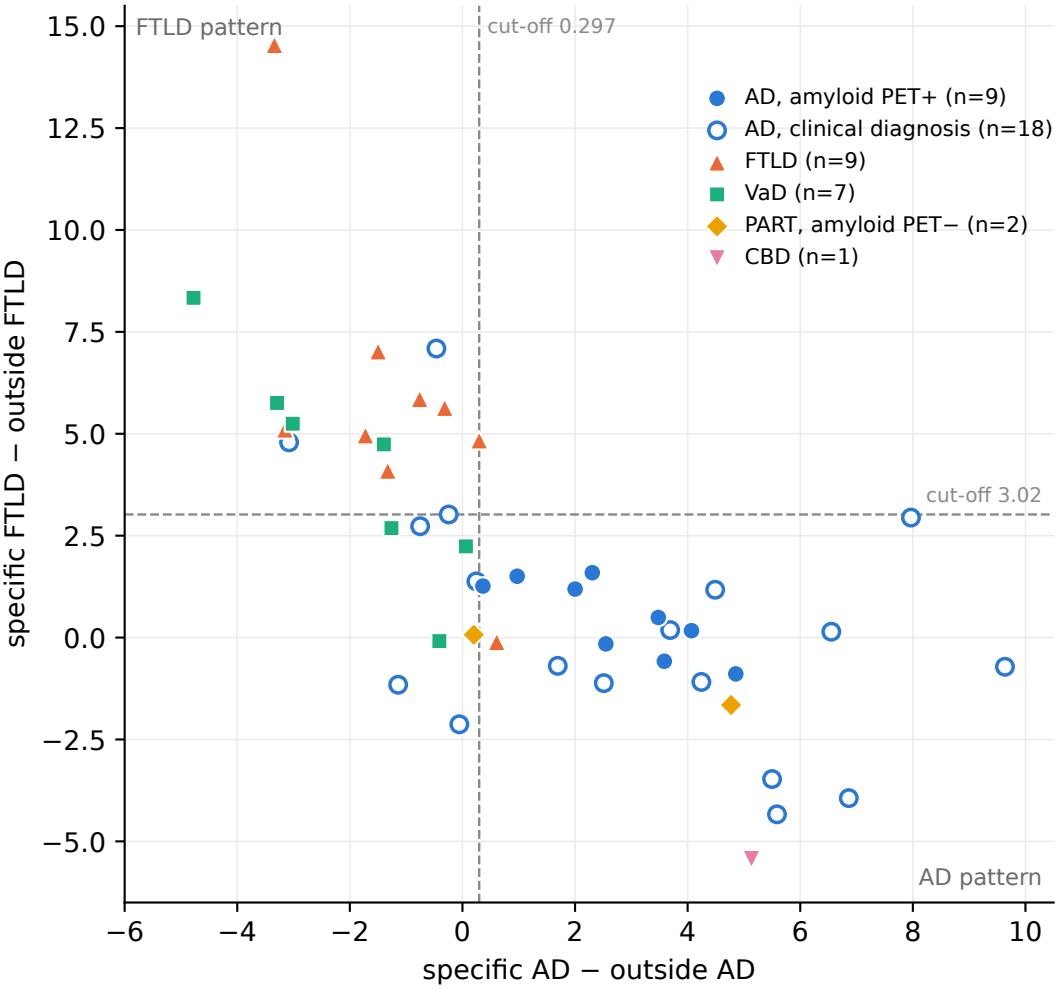

degree of decreased cerebral blood flow
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
specific AD – outside AD;4.07
Mean specific AD value;5.31
Mean outside AD value;1.24
Deviation from mean
5.95SD
2.39SD
3.56SD
2.16SD
0.78SD
1.10SD
-0.68SD
-0.17SD
0.08SD
0.08SD
2.18SD
1.17SD
2.17SD
-0.32SD
-0.44SD
-1.32SD
1.56SD
-0.73SD
3.32SD
1.81SD
R
L
Parietal
Precuneus
Post. cingulate
Lat. occipital
Med. occipital
Frontal
Temporal
Inf. frontal
Precentral
Postcentral
Patient value
Threshold (mean + 1.64 SD)
Mean of normal controls

Figure 1(B)


degree of decreased cerebral blood flow
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
specific FTLD – outside FTLD;7.03
Mean outside FTLD value;1.06
Mean specific FTLD value;8.09
Deviation from mean
1.46SD
-0.41SD
1.08SD
-0.25SD
1.07SD
1.30SD
3.33SD
0.22SD
0.20SD
-0.71SD
1.62SD
0.83SD
8.85SD
4.87SD
2.32SD
0.16SD
0.89SD
-0.84SD
-0.86SD
-0.48SD
R
L
Parietal
Precuneus
Post. cingulate
Lat. occipital
Med. occipital
Frontal
Temporal
Inf. frontal
Precentral
Postcentral
Patient value
Threshold (mean + 1.64 SD)
Mean of normal controls


(A) AD (total) vs. non-AD
Sensitivity
1 − Specificity
0.0
0.2
0.4
0.6
0.8
1.0
specific AD (AUC 0.733)
outside AD (AUC 0.784)
specific AD − outside AD (AUC 0.836)
(B) Amyloid PET-positive AD vs. non-AD
Sensitivity
1 − Specificity
specific AD (AUC 0.713)
outside AD (AUC 0.901)
specific AD − outside AD (AUC 0.895)


FTLD vs. non-FTLD
Sensitivity
1 − Specificity
0.0
0.2
0.4
0.6
0.8
1.0
specific FTLD (AUC 0.886)
outside FTLD (AUC 0.532)
specific FTLD − outside FTLD (AUC 0.856)


FTLD pattern
cut-off 0.297
cut-off 3.02
AD pattern
AD, amyloid PET+ (n=9)
AD, clinical diagnosis (n=18)
FTLD (n=9)
VaD (n=7)
PART, amyloid PET− (n=2)
CBD (n=1)
specific FTLD − outside FTLD
specific AD − outside AD
15.0
12.5
10.0
7.5
5.0
2.5
0.0
−2.5
−5.0
−6
−4
−2
0
2
4
6
8
10