60-Min Amyloid PET Standardized to a 90-Min Centiloid Reference on SiPM PET/CT

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Disclosure of Conflict of Interest

Name of first author: Koji Sohara

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- PI: Koji Sohara
- Acceptance of researchers: None
- Personal COI (first author): None

Background (1): Clinical need for a shorter amyloid PET protocol

• ^{18}F-flutemetamol amyloid PET supports diagnosis, differential diagnosis, and selection for anti-Aβ therapy.

• The conventional delayed static protocol is acquired at approximately 90 min post-injection.

• Reducing the waiting interval may decrease patient burden and improve scanner workflow, especially in elderly or cognitively impaired patients.

• Any shortened protocol must preserve the clinical visual read, because visual assessment remains the primary basis of routine interpretation.

Minoshima S. J Nucl Med. 2016; Collij LE. Eur J Nucl Med Mol Imaging. 2021; Takemoto S. Ann Nucl Med. 2025

Background (2): Why VA and CL validation are both required

- **Visual assessment:** captures the clinically decisive global amyloid status but can be vulnerable in borderline regional uptake.
- **Centiloid quantification:** complements VA near thresholds and enables harmonized reporting across scanners, sites, and processing pipelines.
- **SiPM PET/CT:** offers high sensitivity and image quality, making a shorter delayed acquisition plausible.
- **Methodological gap:** a 60-min acquisition must be validated against the 90-min reference for both VA concordance (Analysis 1) and CL bridging (Analysis 2).

Klunk WE. Alzheimers Dement. 2015; Collij LE. Eur J Nucl Med Mol Imaging. 2021; van Sluis J. J Nucl Med. 2019; Takemoto S. Ann Nucl Med. 2025

Study Objective

To determine whether 60-min delayed 18F-flutemetamol PET on digital SiPM PET/CT is interchangeable with conventional 90-min imaging by evaluating:

- **Analysis 1:** visual assessment agreement across readers and between 60- and 90-min images.
- **Analysis 2:** quantitative agreement between converted CL_{90}(est.60) and measured CL_{90} on the conventional 90-min Centiloid scale.

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Study population and design

Single-center retrospective observational study.

Participants: **63 consecutive** patients who underwent **^{18}F-flutemetamol amyloid PET** at the Nippon Medical School Clinical Imaging Center for Healthcare between February and September 2025, using **a semiconductor (SiPM) PET system**.

For the present analysis, we included cases in which both 60-min and 90-min post-injection images were available.

The study protocol was approved by the institutional review board (approval No. M-2025-428), and informed consent was obtained using an opt-out procedure.

Pre-treatment brain imaging to exclude:

Major cerebrovascular lesions　Intracranial hematoma　CSF distribution imbalance (e.g., hydrocephalus)　Brain tumors

Encephalopathy / encephalitis　Other findings contraindicating anti-Aβ antibody therapy

Modalities: screening MRI or same-day low-dose CT

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Participant characteristics

Characteristic	Overall (n = 63)
Participants, n	63
Age, years, mean ± SD	77.7 ± 7.8
Female, n (%)	44 (69.8%)
Education, years, mean ± SD	13.2 ± 2.4 (n = 53)
MMSE, mean ± SD	24.9 ± 2.6 (n = 57)
Global CDR, median [IQR]	0.5 [0.5, 0.5] (n = 57)
Exam type, n (Insurance/Checkup)	57/6

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Imaging conditions

Radiotracer	^{18}F-flutemetamol
Injected dose	Mean 223.3 ± 23.8 MBq (range 172.4–268.0 MBq)
Uptake time (60-min images)	59.9 ± 1.7 min (range 55–67 min)
Uptake time (90-min images)	89.9 ± 1.1 min (range 88–96 min)
Acquisition time	20 min per static scan
PET scanners	Siemens Biograph Vision 450 (38 cases) Canon Cartesion Prime PCD-1000 (25 cases)

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Imaging conditions

Biograph Vision 450（BV, Siemens）/Cartesion Prime PCD-1000A（CP, Canon）

CT-AC (for attenuation correction)
kVp: 120 / 120　　mA (AEC / fixed): AEC / 300
Slice thickness (mm): 2 / 2　　Pitch: 0.55 / 0.813
Reconstruction kernel: Hf38 / FC07　　MAR: OFF / OFF
PET Reconstruction
Method: 3D OSEM / 3D OSEM　Iterations / subsets: 4 × 5 / 5 × 12
TOF: ON (214 ps / 238 ps)　Gaussian post filter (FWHM): 2.5 mm / 4.0 mm
Matrix / Voxel
Matrix: 440 × 440 / 128 × 128　Pixel size (mm): 0.825 / 2.11
QC & EARL
Normalization updated by QC with Ge calibration source (both)
Cross-calibration: 2023/3/20 (SIEMENS), 2025/8/4 (CANON)
Latest QC: Pass / Pass　　EARL 18F/11C brain PET/CT: No / No

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Key terminology

VA_{60} / VA_{90}: Visual assessment on the 60-min and 90-min images, respectively

$SUVR_{60}$ / $SUVR_{90}$: Standardized uptake value ratios referenced to the whole cerebellum

CL_{90}: Centiloid derived from the 90-min image

CL_{90}(est.60): 90-min-equivalent Centiloid estimated from the 60-min image using the study-derived calibration

CL_{90}(pub.60): 90-min-equivalent Centiloid estimated from the 60-min image using the published conversion formula

Takemoto ANM. 2025

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Quantification (SUVR and CL) and Statistical analysis

$SUVR_{60}$ and $SUVR_{90}$ denote whole-cerebellum–referenced SUVR [SUVR(WC)] measured from the 60- and 90-min images, respectively.

CL_{90} was derived from $SUVR_{90}$ using the vendor-implemented SUVR-to-CL transformation (VIZcalc in medi+FALCON).

Analyses were performed using SPSS (version 29.0.2) and Python (version 3.11.2).

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Analysis overview and statistical methods

Analysis 1: Robustness of the visual reference standard across readers and time points

- Inter-reader agreement was assessed using Fleiss' κ (three experienced readers)
- Between-time-point agreement was assessed using Cohen's κ and McNemar's exact test

Analysis 2: Quantitative agreement between CL_{90}(est.60) **and** CL90

- Linear regression was used to estimate 90-min CL from 60-min SUVR, overall and by platform.
- Agreement between estimated and observed 90-min CL was evaluated using Pearson correlation and Bland–Altman analysis.

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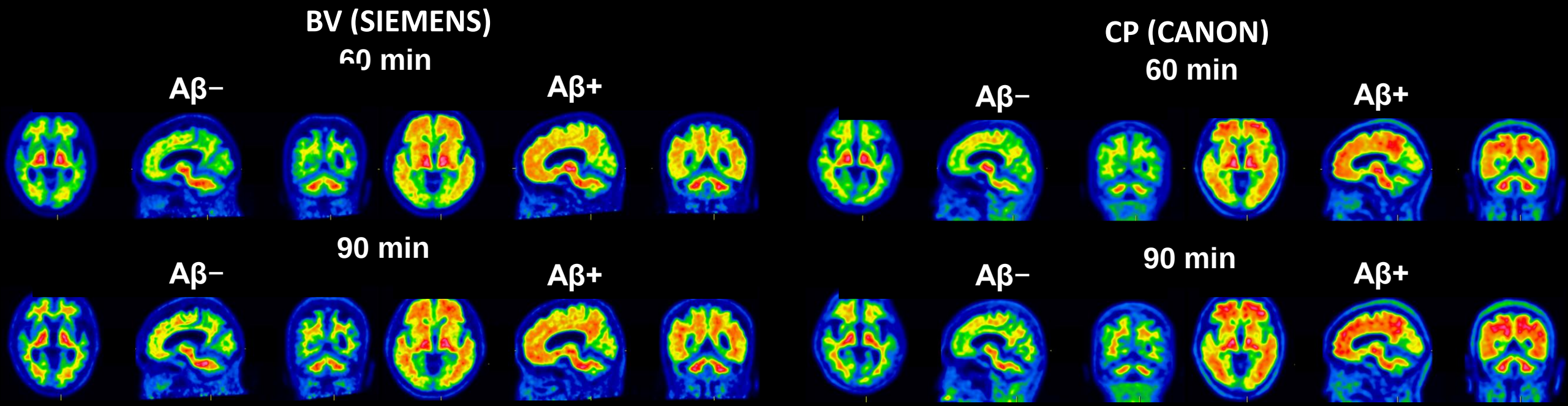
RESULTS:Participant characteristics (majority VA at 60 min)

Characteristic	Overall	Aβ–	Aβ+	p
Participants, n	63	30	33	
Age, years, mean ± SD	77.7 ± 7.8	77.0 ± 9.2	78.2 ± 6.3	0.549
Female, n (%)	44 (69.8%)	21 (70.0%)	23 (69.7%)	1.000
Education, years, mean ± SD (available n)	13.2 ± 2.4 (n = 53)	12.7 ± 2.5 (n = 24)	13.6 ± 2.4 (n = 29)	0.175
MMSE, mean ± SD (available n)	24.9 ± 2.6 (n = 57)	24.8 ± 2.6 (n = 24)	25.1 ± 2.6 (n = 33)	0.702
Global CDR, median [IQR] (available n)	0.5 [0.5, 0.5] (n = 57)	0.5 [0.5, 0.5] (n = 24)	0.5 [0.5, 0.5] (n = 33)	0.870
Scanner (BV/CP), n	BV: 38; CP: 25	BV: 16; CP: 14	BV: 22; CP: 11	0.313
Exam type (insurance/checkup), n	57/6	24/6	33/0	

Analysis 1: Visual Assessment （Readers and Gold Standard）

- Three nuclear medicine physicians (A: 47 years, B: 37 years, C: 12 years of reading experience).
- All are board-certified radiologists and nuclear medicine specialists focusing on brain imaging.
- Dedicated Vizamyl Viewer was used under blinded conditions (randomized anonymized IDs).
- Global amyloid status (positive / negative) was evaluated independently for 60-min and 90-min images.
- Final global visual judgment was defined as positive or negative when at least two of the three readers agreed.

Visual Read Criteria and Representative Cases (60 vs 90 min)



Negative: Cortical gray matter uptake lower than white matter with preserved gray–white contrast; uptake limited to white matter/choroid plexus/meninges is not positive.

Positive: Loss of gray–white matter contrast due to increased cortical uptake in ≥1 key 5 key regions (frontal, parietal, lateral temporal, or posterior cingulate/precuneus).

Vizamyl® (flutemetamol F 18) Prescribing Information; Matsuda H et al., Front Neurol. 2021.

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Analysis 1: Visual Agreement and Gold Standard

- Inter-reader agreement was evaluated for both 60-min and 90-min images.
- Complete agreement among all three readers was recorded, as well as pairwise agreement (A–B, A–C, B–C).
- Agreement was quantified using Cohen's κ (pairwise) and Fleiss' κ (overall).
- Consensus (gold standard) was defined by majority rule (≥2 of 3 readers positive or negative).
- The numbers of visually positive and negative cases were used as the reference for subsequent ROC analyses.

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Result1-1 Per-Reader Visual Calls (60 vs 90 min)

60-min

Reader	Positive (n)	Positive (%)	Negative (n)	Negative (%)
A	35	55.6	28	44.4
B	34	54.0	29	46.0
C	32	50.8	31	49.2
Consensus	**30**	**47.6**	**33**	**52.4**

90-min

Reader	Positive (n)	Positive (%)	Negative (n)	Negative (%)
A	34	54.0	29	46.0
B	31	49.2	32	50.8
C	28	44.4	35	55.6
Consensus	**31**	**49.2**	**32**	**50.8**

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Result1-2 Inter-reader Agreement (60-min images)

Pair / All readers	**Agreements (n / 63)**	**Agreement (%)**	**κ**
A vs B	60 / 63	95.2	0.904
A vs C	60 / 63	95.2	0.905
B vs C	61 / 63	96.8	0.936
A, B, C all	59 / 63	93.7	0.915

*κ was calculated using Cohen's kappa for pairwise agreement and Fleiss' kappa for three-reader agreement.

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Result1-3 Inter-reader Agreement (90-min images)

Pair / All readers	**Agreements (n / 63)**	**Agreement (%)**	**κ**
A vs B	60 / 63	95.2	0.905
A vs C	57 / 63	90.5	0.811
B vs C	58 / 63	92.1	0.841
A, B, C all	56 / 63	88.9	0.852

*κ was calculated using Cohen's kappa for pairwise agreement and Fleiss' kappa for three-reader agreement.

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Result1-4
Agreement of Consensus Reads Between 60-min and 90-min images

Consensus	Positive (n)	Positive (%)	Negative (n)	Negative (%)
60-min	30	47.6	33	52.4
90-min	31	49.2	32	50.8

*Consensus (gold standard) was defined by majority rule (≥2 of 3 readers positive or negative).

Concordant consensus
between 60-min and 90-min scans: 62 / 63 (**98.4%**)
Cohen's κ between 60-min and 90-min consensus reads: **0.97**

Discordant cases: 1 / 63 (1.6%)

Therefore, majority visual assessment was used as the reference standard for subsequent analyses.

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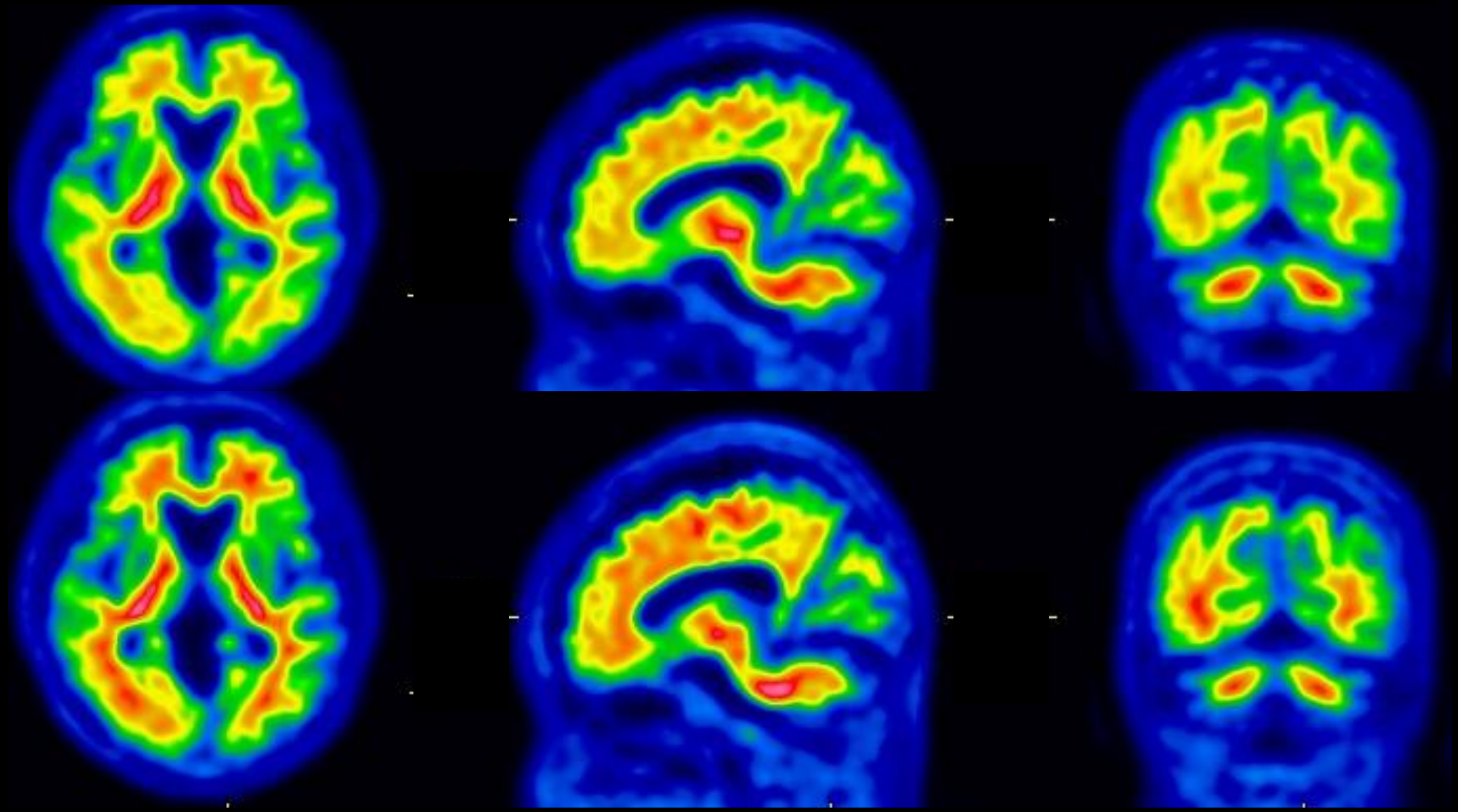
Result 1-5: Discordant Case Between 60-min and 90-min Reads

60-min

90-min



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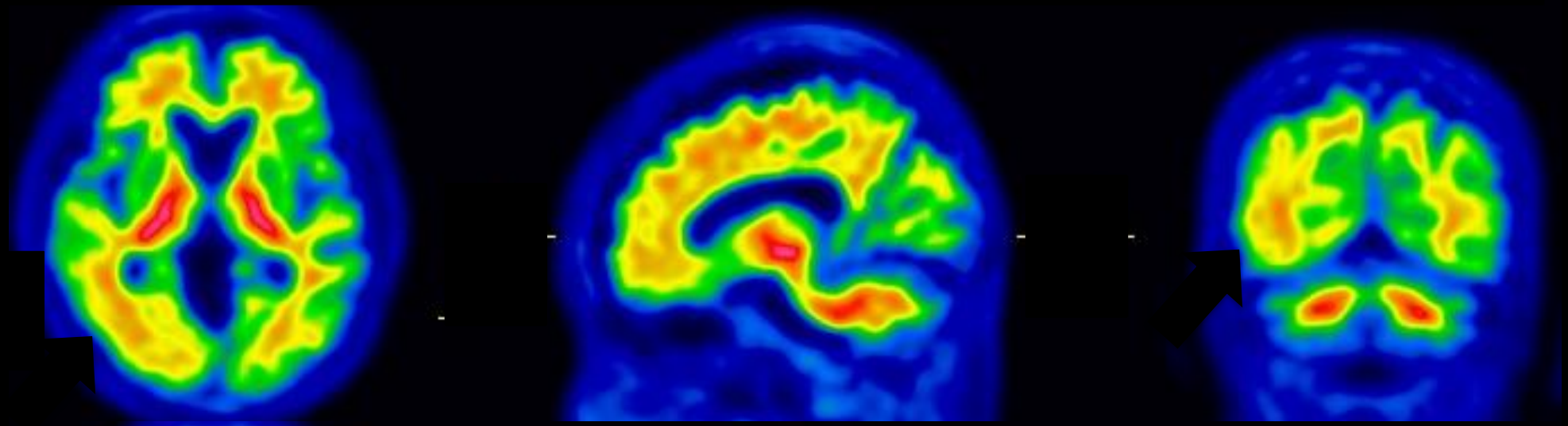
Result 1-5: Discordant Case Between 60-min and 90-min Reads

60-min

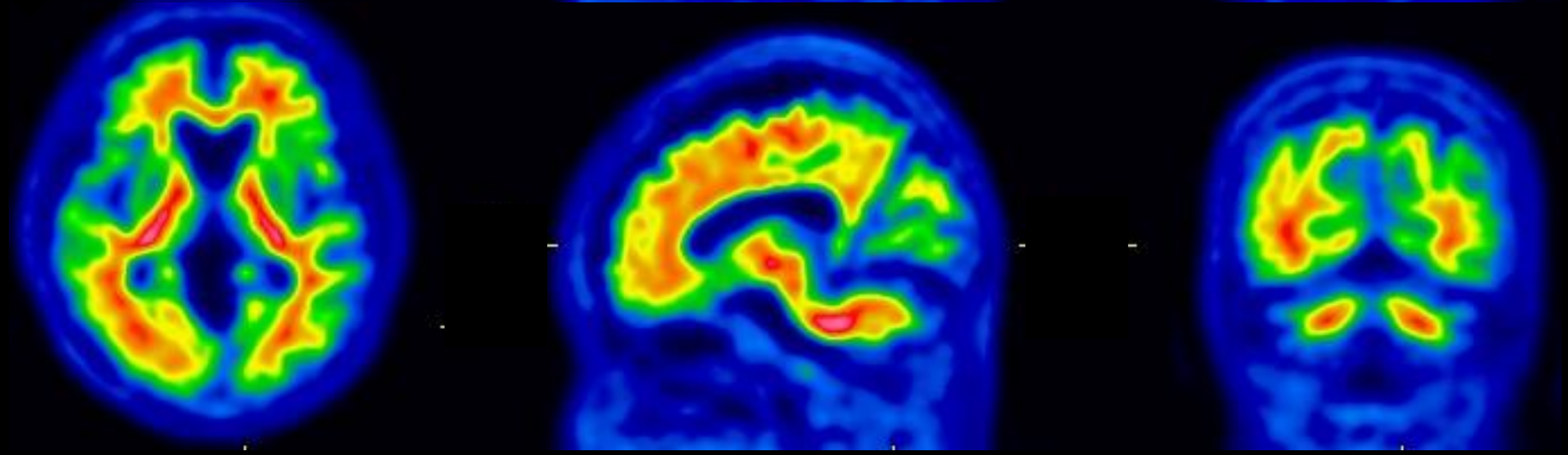
2 out of 3 readers positive
→ **positive**

Right temporal
lateral temporal



90-min

All readers negative
→ **negative**



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Analysis 2: Agreement Between CL60_SiPM and CL90_SiPM

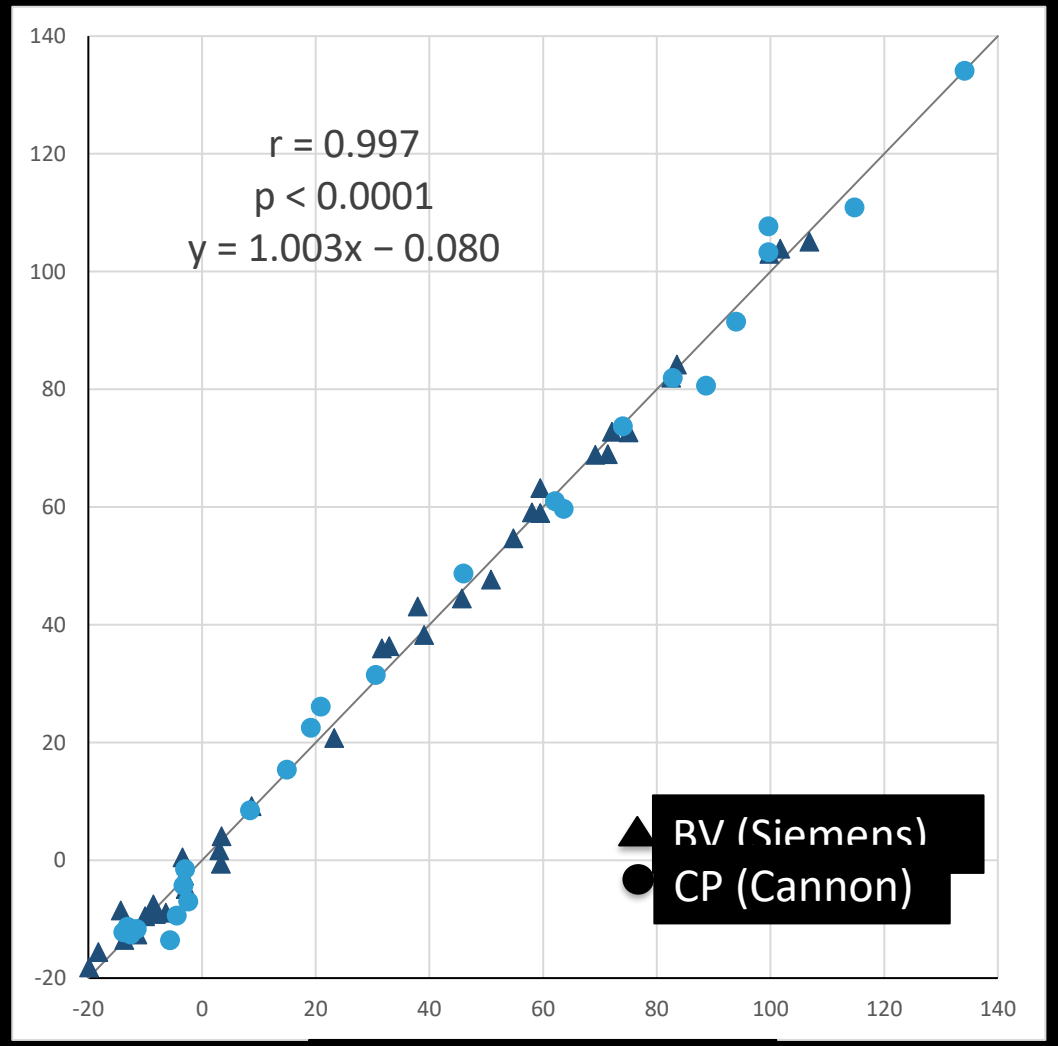
Aim: To evaluate the agreement between CL60_SiPM and CL90_SiPM.

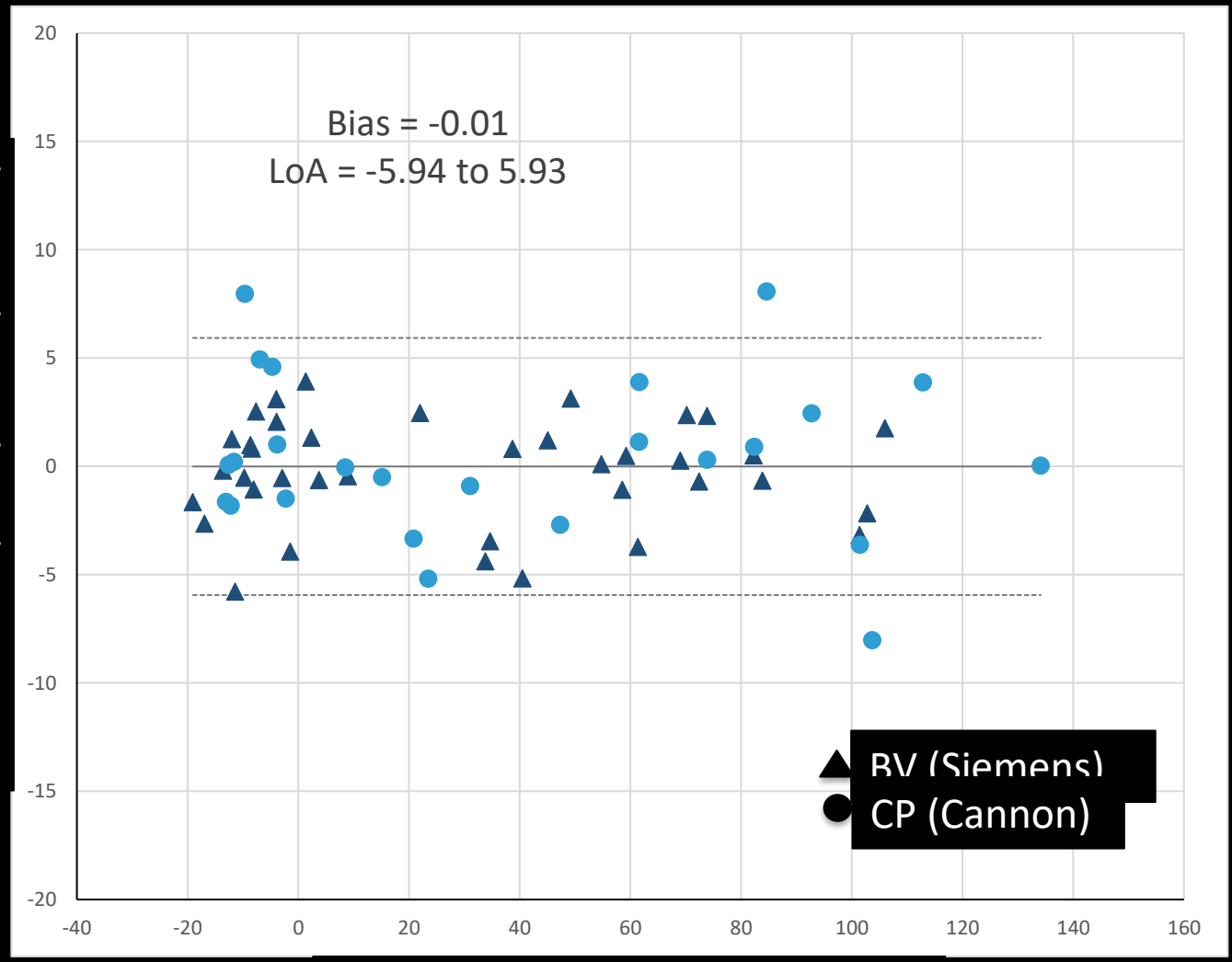
Imaging indices:
SUVR60 / SUVR90: Standardized uptake value ratios from 60- and 90-min images.
CL90_SiPM (reference CL): Centiloid from the 90-min SiPM image.
CL60_SiPM (standardized CL): Centiloid from the 60-min SiPM image, standardized from SUVR60 using an institutional regression model.

Correlation analyses:
Pearson correlations for CL60 vs SUVR60 and CL90 vs SUVR90.

Agreement analyses:
Scatter plot (x: CL60_SiPM, y: CL90_SiPM) with the identity line (y = x).
Bland–Altman plot using mean CL (x-axis) vs difference (CL60_SiPM − CL90_SiPM) (y-axis); report bias and 95% limits of agreement.

Analysis 2_1: Quantitative agreement between Centiloid values derived from 60- and 90-min images.





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Analysis 2_2: Quantitative agreement between CL_{90}(est.60) and CL_{90} (overall and scanner-stratified)

Overall (SiPM, n = 63)

CL_{90}(est.60) = 146.66 × $SUVR_{60}$ −152.73

CL_{90} = 1.00 × CL90(est.60) + 0.01 (r = 0.998)

BV (n = 38)

CL_{90}(est.60) (BV) = 146.61 × $SUVR_{60}$ −152.39

CL_{90} = 1.00 × CL_{90}(est.60) + 0.29 (r = 0.998)

CP (n = 25)

$CL_{90}(\text{est.60})\ (\text{CP}) = 146.98 \times SUVR_{60} - 153.55$

CL_{90} = 1.00 × CL_{90}(est.60) − 0.49 (r = 0.997)

Analysis 2_3: Quantitative agreement between CL_{90}(pub.60) and CL_{90}

Overall (SiPM, n = 63)

CL_{90}(pub.60) = 143.330 × $SUVR_{60}$ − 150.151

CL_{90} = 1.02 × CL_{90}(pub.60) + 0.91 (r = 0.997)

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Discussion: Integrated interpretation of Analysis 1 and 2

- **Core finding:** 60-min SiPM 18F-flutemetamol PET preserved both clinically anchored VA and quantitative CL agreement with the 90-min reference.
- **Analysis 1 - VA:** Majority reads were concordant in 62/63 cases (98.4%; κ = 0.968), with high inter-reader reliability at both time points.
- **Analysis 2 - CL:** After conversion, CL_{90}(est.60) closely matched measured CL_{90} (slope 1.003; r = 0.997; CCC = 0.997; bias −0.01 CL; LoA ≈ ±6 CL).
- **Clinical use:** A 60-min protocol can reduce waiting time, but near-threshold cases should integrate VA, converted CL, and clinical context; conversion remains pipeline- and site-specific.

Collij LE. Eur J Nucl Med Mol Imaging. 2021; Klunk WE. Alzheimers Dement. 2015; Takemoto S. Ann Nucl Med. 2025; Sohara K et al. submitted

Limitations

This was a single-center within-subject study using two SiPM systems; generalizability to other scanners, reconstructions, and sites remains to be established.

The study assessed comparative concordance, not diagnostic accuracy against an independent biological or neuropathological reference standard.

The conversion formulas were pipeline-specific, and interpretation near the positivity boundary may shift with acquisition timing and processing details.

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Conclusions

- **Visual agreement:** 60- and 90-min majority VA showed almost perfect concordance (62/63, 98.4%; κ = 0.968).
- **Quantitative agreement:** Converted 60-min CL values were essentially interchangeable with measured CL_{90} (CCC = 0.997; bias −0.01 CL).
- **Practical conclusion:** With protocol-specific CL conversion, 60-min delayed SiPM amyloid PET can serve as a practical alternative to the conventional 90-min protocol.
- **Caution:** Borderline cases near positivity thresholds should be interpreted using both VA and converted CL, together with clinical context.

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Mange tak for jeres opmærksomhed.