

# A 3D Vision Transformer-Mixture Density Network for Continuous Centiloid Value Prediction from Amyloid-PET Images

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| BACKGROUND                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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| <ul style="list-style-type: none"><li>Quantification of brain amyloid-beta (Aβ) burden is essential for diagnosing and monitoring clinical progression in patients with Alzheimer’s disease (AD).</li><li>The Centiloid (CL) scale is the gold standard for harmonization, but quantification typically relies on multi-step pipelines involving structural MRI co-registration and ROI extraction.</li><li>The vision transformer (ViT) architecture, a recent innovation in computer vision, has shown promising results in medical imaging analysis due to its scalability, explainability, and capacity to view a whole image in context.</li><li><b>We propose ViT-MDN: a deep learning approach using a 3D (ViT) integrated with a Mixture Density Network (MDN) to predict CL values directly from PET scans.</b></li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |          |         |          | <p>ViT-MDN demonstrated excellent performance in quantifying continuous CL values and binary amyloid classification in ADNI holdout data as well as in SCAN and IDEAS.</p> <p>Figure 1 (below): Predicted vs true CL values across all datasets with corresponding R-squared values. The points are colored by the MDN component with the higher weight, with the point representing that component’s mean and the error bars as its variance.</p> <table><thead><tr><th></th><th>ADNI</th><th>SCAN</th><th>IDEAS</th></tr></thead><tbody><tr><td>Mean absolute error</td><td>10.47</td><td>13.68</td><td>17.17</td></tr><tr><td>Accuracy</td><td>0.94</td><td>0.90</td><td>0.92</td></tr><tr><td>PPV</td><td>0.98</td><td>0.98</td><td>0.99</td></tr><tr><td>NPV</td><td>0.91</td><td>0.86</td><td>0.84</td></tr><tr><td>Sensitivity</td><td>0.91</td><td>0.76</td><td>0.88</td></tr><tr><td>Specificity</td><td>0.98</td><td>0.99</td><td>0.99</td></tr><tr><td>F1 Score</td><td>0.94</td><td>0.86</td><td>0.93</td></tr></tbody></table> |      |             | ADNI  | SCAN        | IDEAS | Mean absolute error | 10.47 | 13.68               | 17.17 | Accuracy | 0.94 | 0.90 | 0.92     | PPV     | 0.98     | 0.98      | 0.99 | NPV | 0.91 | 0.86                        | 0.84 | Sensitivity | 0.91 | 0.76                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0.88 | Specificity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.98 | 0.99 | 0.99 | F1 Score | 0.94 | 0.86 | 0.93 | <ul style="list-style-type: none"><li>ViT-MDN consistently produced accurate CL predictions across tracers and cohorts without the need for re-training or fine-tuning.</li><li>Qualitative analysis of attention maps showed the model prioritizes cortical regions known to be associated with early amyloid deposition.</li><li>By leveraging the feature extraction abilities of the ViT and the probabilistic nature of the mixture density head, this approach offers a scalable and MRI-independent alternative to traditional ROI-based analysis.</li></ul> |  |
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| <table><thead><tr><th></th><th>ADNI</th><th>SCAN</th><th>IDEAS</th></tr></thead><tbody><tr><td>Sample size</td><td>4150</td><td>1256</td><td>9732</td></tr><tr><td># distinct subjects</td><td>1980</td><td>1256</td><td>9732</td></tr><tr><td>Age</td><td>74 ± 7.9</td><td>71 ± 10</td><td>76 ± 6.2</td></tr><tr><td>Sex (% F)</td><td>51%</td><td>63%</td><td>51%</td></tr><tr><td>Amyloid status (% positive)</td><td>29%</td><td>46%</td><td>61%</td></tr></tbody></table> <p>Table 1: Cohort characteristics across all datasets.</p> <p><b>Preprocessing.</b> All data underwent a standard PET preprocessing pipeline and linear registration to a generic amyloid-PET template to minimize spatial heterogeneity, shown above. CL values were scaled by 100 during training for numerical stability</p> <p><b>Architecture.</b> ViT-MDN architecture is shown to the right. The ViT backbone included a patch dropout module (rate=10%) for regularization. The model was trained using negative log likelihood loss to optimize the MDN head.</p> <p><b>Evaluation.</b> The model’s CL prediction was determined as the mean of the highest-weighted component from the MDN’s output. We also evaluated amyloid status as a binary variable using CL=24 as the cutoff for amyloid positivity for the predicted and true values.</p> <p><b>Datasets.</b> The training and internal validation dataset consisted of amyloid PET images collected using Florbetapir (FBP/AV45) and Florbetaben (FBB) tracers from the ADNI database. We validated the model with AV45 and FBB data from SCAN, and IDEAS.</p> <p><b>Flowchart:</b> Co-register &amp; average PET frames → Resample to standard image and voxel size → Normalize to reference region - cerebellum → Smooth to uniform 6mm resolution → Registration to generic amyloid PET template</p> <p><b>Diagram:</b> PET image → ViT backbone (Patch embedding with 10% dropout, Attention blocks + MLP, CLS embedding + tracer embedding) → MDN head → <math>\pi_0, \pi_1</math>, <math>\mu_0, \mu_1</math>, <math>\sigma_0, \sigma_1</math></p> |          |         |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ADNI | SCAN        | IDEAS | Sample size | 4150  | 1256                | 9732  | # distinct subjects | 1980  | 1256     | 9732 | Age  | 74 ± 7.9 | 71 ± 10 | 76 ± 6.2 | Sex (% F) | 51%  | 63% | 51%  | Amyloid status (% positive) | 29%  | 46%         | 61%  | <p>Table 2: Continuous and binary metrics across all datasets.</p> <p><b>ViT-MDN: Predicted vs True Centiloid Values</b></p> <p>ADNI: <math>R^2 = 0.9104</math></p> <p>SCAN: <math>R^2 = 0.8083</math></p> <p>IDEAS: <math>R^2 = 0.7496</math></p> <p><b>Figure 2 (above):</b> An example attention map for an ADNI subject with CL=100 at five axial slices. Hotspots (bright yellow) spatially correspond with visible amyloid plaques.</p> |      | <p>Bishop, C. 1994, “Mixture Density Networks.” <i>Mixture Density Networks</i>.</p> <p>Bourgeat, P., et al. Feb. 2026, <a href="https://doi.org/10.1002/alz.71162">https://doi.org/10.1002/alz.71162</a>.</p> <p>Bourgeat, P., et al. Dec. 2025, <a href="https://doi.org/10.1002/alz70856_104230">https://doi.org/10.1002/alz70856_104230</a>.</p> <p>Chiu, S. et al. Mar. 2026, <a href="https://doi.org/10.1186/s40658-026-00854-8">https://doi.org/10.1186/s40658-026-00854-8</a>.</p> <p>Choi, Y., et al. May 2024, <a href="https://doi.org/10.1093/radadv/umae019">https://doi.org/10.1093/radadv/umae019</a>.</p> <p>Dosovitskiy, A., et al. Oct. 2020, <a href="https://arxiv.org/abs/2010.11929v2">https://arxiv.org/abs/2010.11929v2</a>.</p> <p>Fan, S., et al. June 2024, <a href="https://doi.org/10.1148/radiol.231442">https://doi.org/10.1148/radiol.231442</a>.</p> <p>Iaccarino, L. et al. Feb. 2022, <a href="https://www.sciencedirect.com/science/article/pii/S1053811921010478?via%3Dihub">https://www.sciencedirect.com/science/article/pii/S1053811921010478?via%3Dihub</a></p> <p>Kang, Y., et al. July 2025, <a href="https://doi.org/10.3390/tomography11080086">https://doi.org/10.3390/tomography11080086</a>.</p> <p>Klunk, W., et al. Jan. 2015, <a href="https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2014.07.003">https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2014.07.003</a></p> <p>Landau, S. et al. Nov. 2024, <a href="https://pmc.ncbi.nlm.nih.gov/articles/PMC11772732/">https://pmc.ncbi.nlm.nih.gov/articles/PMC11772732/</a></p> <p>Takahashi, S., et al. Sept. 2024, <a href="https://doi.org/10.1007/s10916-024-02105-8">https://doi.org/10.1007/s10916-024-02105-8</a>.</p> <p>Tosun, D., et al. July 2013, <a href="https://doi.org/10.1016/j.jalz.2013.08.005">https://doi.org/10.1016/j.jalz.2013.08.005</a>.</p> <p>Yamamoto, T., et al. Apr. 2024, <a href="https://doi.org/10.3390/brainsci14040406">https://doi.org/10.3390/brainsci14040406</a>.</p> <p>Yoon, Y., et al. Sept. 2025, <a href="https://doi.org/10.1186/s13195-025-01860-1">https://doi.org/10.1186/s13195-025-01860-1</a></p> |      |      |      |          |      |      |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |
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