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Ludovica Brusaferri

`ludovica.brusaferri@lsbu.ac.uk`

London South Bank University

Alexander Whitehead

London South Bank University

Leonardo Barzon

University of Padua

Lucia Maccioni

University of Padua

Zeynab Alshelh

University of Sydney

Minhae Kim

Harvard Medical School

Antonio Micoli

London South Bank University

Nicola Toschi

University of Rome Tor Vergata

Matteo Ferrante

University of Rome Tor Vergata

Marianna Inglese

<https://orcid.org/0000-0002-9154-8260>

Ciprian Catana

Harvard Medical School

Jodi Gilman

Massachusetts General Hospital <https://orcid.org/0000-0001-5180-6694>

Mattia Veronese

University of Padua

Oliver Howes

King's College London

Tiago Reis Marques

King's College London

Maria Antonietta Nettis

King's College London

Valeria Mondelli

King's College London

Carmine Pariante

King's College London

Federico Turkheimer

King's College London

Enrico Grisan

London South Bank University

Marco Loggia

Harvard Medical School

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Non-invasive full quantification of dynamic $[^{11}\text{C}]$ PBR28 PET imaging with ASTRA

Ludovica Brusaferri^{†1,2}, Alexander C. Whitehead^{1,3}, Leonardo Barzon⁴, Lucia Maccioni^{4, 5}, Zeynab Alshelh⁶, Minhae Kim², Antonio Micoli¹, Nicola Toschi^{7,2}, Matteo Ferrante⁷, Marianna Inglese⁷, Ciprian Catana², Jodi Gilman², Mattia Veronese^{4,8}, Oliver Howes⁹, Tiago Reis Marques⁹, Maria Antonietta Nettis¹⁰, Valeria Mondelli¹⁰, Carmine Pariante¹⁰, Federico E. Turkheimer⁸, Enrico Grisan¹, and Marco L. Loggia^{2,11}

¹College of Technology and Environment, School of Computer Science and Digital Technologies, London South Bank University, London, SE1 0AA, United Kingdom

²Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, 02129, MA, United States

³Department of Computer Science, University College London, London, WC1E 6EA, United Kingdom

⁴Department of Information Engineering, University of Padua, Padua, 35131, Italy

⁵Paris Brain Institute, ICM, CNRS, Inserm, Sorbonne Université, Paris, 75013, France

⁶University of Sydney, Sydney, 2050, Australia

⁷Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, 00133, Italy

⁸Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, London, SE5 8AF, United Kingdom

⁹Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, London, SE5 8AF, United Kingdom

¹⁰Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, London, SE5 8AF, United Kingdom

¹¹Department of Anesthesia, Critical Care And Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, 02114, MA, United States

[†]Corresponding author: ludovica.brusaferri@lsbu.ac.uk

Abstract

Quantitative analysis of dynamic PET imaging requires metabolite-corrected arterial input functions, traditionally obtained through invasive arterial sampling. This limits broader adoption of fully quantitative kinetic modelling, particularly for tracers such as $[^{11}\text{C}]$ PBR28 that generate radiometabolites. Here we demonstrate that metabolite-corrected input functions can be estimated from dynamic PET images alone across heterogeneous scanners and acquisition protocols, enabling full quantification without blood sampling. We developed a deep learning framework, ASTRA, that estimates subject-specific arterial input functions from brain PET data while quantifying predictive uncertainty. Across two independent multi-centre datasets acquired with different scanners and protocols, ASTRA-derived estimates closely matched arterial blood-based quantifi-

40 cation. In a fully held-out clinical cohort without ground-truth blood data, ASTRA
41 reproduced previously reported semi-quantitative SUVR group differences. Finally, in a
42 fourth dataset, ASTRA preserved sensitivity to pharmacological TSPO blockade. This
43 work addresses a longstanding barrier in dynamic PET imaging and establishes a scalable
44 path toward blood-free, fully quantitative [^{11}C]PBR28 PET imaging.

Main Text

Dynamic Positron Emission Tomography (PET) combined with kinetic modelling provides quantitative, in vivo characterisation of brain pathophysiology, with important implications for drug development and precision diagnostics¹. Within this context, [¹¹C]PBR28, a second-generation ligand for 18 kDa Translocator Protein (TSPO) radioligand, has become an important tool for investigating neurodegenerative, psychiatric and chronic pain disorders^{2–7}.

Accurate quantification of [¹¹C]PBR28 is hindered by several factors, including the highly heterogeneous distribution of TSPO in both brain tissue and circulating blood, together with a low plasma free fraction⁸. Although semi-quantitative approaches have been proposed and applied in numerous studies^{9–11}, the calculation of Volume of Distribution (V_T) using radiometabolite-corrected Arterial Input Function (AIF) is still considered to be, in many contexts, the preferred quantification method^{12–14}. However, arterial sampling is invasive, logistically demanding, and burdensome. These challenges have constrained the wider clinical adoption of [¹¹C]PBR28 and other experimental radiotracers¹⁵. Overall, reliance on arterial sampling remains a barrier to quantitative dynamic PET, underscoring the need for more generalizable and less invasive approaches¹⁶.

To address these challenges, several blood-free alternatives have been explored. One widely investigated strategy is the Image Derived Input Function (IDIF), which derives the AIF directly from PET images. However, IDIF-based methods are inherently limited, as they are labour-intensive, heavily operator-dependent and prone to inaccuracies in estimating the parent plasma fraction from image data alone¹⁷. To mitigate some of these limitations, simplified blood-free approaches for [¹¹C]PBR28 have been proposed¹⁴; however, they do not support full kinetic analysis.

More recently, Deep Learning (DL) methods have been applied to the AIF estimation problem¹⁸. Although these approaches offer a promising route towards automation, most efforts have focused on preclinical animal models¹⁹ or have been evaluated only under limited experimental conditions^{20–22}. In particular, although adaptation to individual sources of variability, such as scanner hardware or radiotracer choice, has been explored in the recent literature, these evaluations have been conducted under closely matched acquisition protocols²³. To our knowledge, no previous work has demonstrated blood-free PET quantification evaluated across independent datasets acquired at multiple centres, generalising across heterogeneous scanners, acquisition protocols, and clinical populations within a unified modelling framework.

Here we introduce Autoencoder Signal Transformer for Radiotracer Analysis (ASTRA), a fully non-invasive, data-driven framework for estimating metabolite-corrected AIF directly from dynamic [¹¹C]PBR28 brain PET data. ASTRA comprises three sequential modules: M1, a Spatio Temporal Patched Autoencoder (ST-pAE) that compresses dynamic PET volumes into temporally ordered latent embeddings; M2, a transformer²⁴-based network that extracts the plasma curve; and M3, a dedicated metabolite-correction module that yields the final AIF.

In its current design, the model is intended to be scanner-robust and protocol-flexible, supporting AIF and kinetic parameters estimation without reliance on blood data or manual input. Specifically, the framework was developed and evaluated using four [¹¹C]PBR28

brain PET datasets acquired across two countries, acquisition settings, and reconstruction protocols. Datasets 1 and 2 include scans with ground-truth arterial blood measurements, Dataset 3 comprises scans without arterial blood data, and Dataset 4 consists of scans acquired under TSPO blocking conditions, enabling evaluation under altered target availability.

Results

The performance of ASTRA in estimating metabolite-corrected AIFs was evaluated by comparing four approaches: (1) NN-dPET, a fully end-to-end pipeline using only dynamic PET data; (2) NN-unBlood, in which the metabolite-correction module (M3) was applied to measured uncorrected plasma curves; (3) p-metcorIDIF, an IDIF-based pipeline using population-based metabolite correction, providing a lower-bound reference for NN-dPET; and (4) p-metcorBLOOD, in which the same population-based correction was applied to ground-truth uncorrected plasma curves, providing a lower-bound reference for NN-unBlood. An overview of the ASTRA architecture and processing modes is provided in Figure 1, while the IDIF pipeline is shown in Supplementary Figure 1. Full implementation details, including network configurations and hyperparameters, are given in Supplementary Table 2, and trainable parameter counts are reported in Supplementary Table 3.

The output of the ST-pAE (M1) was visually inspected. Reconstructions from the latent embeddings, subsequently used as input to M2, were found to retain salient anatomical features. Mild spatial smoothing was noted but without detectable loss of TSPO spatio-temporal distribution (Figure 2).

Figure 3 reports an error–uncertainty analysis of NN-unBlood and NN-dPET predictions across Dataset 1 and Dataset 2. For each subject, prediction error with respect to the ground-truth arterial blood curve is evaluated separately for the early uptake (peak) and post-peak decay (tail) phases and related to the corresponding predicted uncertainty. Results are shown both in absolute units and after normalisation by a subject-specific signal scale, defined as the mean value of the ground-truth curve over the central 25–75% portion of the corresponding phase. In both representations, larger predicted uncertainty is generally associated with increased prediction error, with the association more clearly expressed in the scaled analysis and in the peak phase. In the tail phase of Dataset 1, the error spans a relatively narrow dynamic range, which limits the visual expression of this relationship in absolute units. For the absolute uncertainty values, predictions in the highest uncertainty quantile (Q4) correspond to σ ranges of approximately 0.8–1.0 in Dataset 1 and 1.3–1.6 in Dataset 2 during the peak phase, and approximately 0.03–0.05 during the tail phase; these ranges may be considered indicative of reduced prediction reliability in this preliminary uncertainty calibration assessment of ASTRA.

The predicted AIF for each subject was subsequently used to compute V_T values using the Logan graphical method²⁵. Agreement with blood-derived V_T estimates was assessed across cross-validation folds in Datasets 1 and 2. Figure 4 shows scatter plots of predicted versus measured V_T values together with Bland–Altman analyses for all evaluated methods. Displayed results were pooled across all available test subjects, while fold-wise metrics are reported in Supplementary Tables 4–7. Across both datasets, ASTRA-based methods consistently outperformed their conventional counterparts. NN-unBlood

achieved higher concordance with arterial blood-derived V_T than p-metcorBLOOD (population-based), with Concordance Correlation Coefficient (CCC) exceeding 0.8 across both datasets (Figure 4). Similarly, NN-dPET substantially outperformed p-metcorIDIF, achieving CCC values in the range of approximately 0.66–0.81 across both datasets, whereas p-metcorIDIF showed markedly reduced concordance.

Overall, ASTRA predictions retained high accuracy, whereas p-metcorIDIF estimates were systematically biased. It should also be noted that the p-metcorIDIF benchmark relied on population metabolite correction curves derived from the same site as Dataset 1, which may have benefited its performance.

Kinetic microparameter recovery was further assessed using both the full two-tissue reversible compartment model (2T4K) and a reduced single irreversible compartmental model for K_1 (1T1K) model¹⁴. As summarised in Supplementary Tables 5–6, NN-unBlood outperformed population-based metabolite-corrected blood input functions for K_1 across both datasets and modelling approaches, achieving higher concordance in Dataset 1 (2T4K: CCC = 0.959 vs 0.875; 1T1K: CCC = 0.991 vs 0.822) and Dataset 2 (2T4K: CCC = 0.942 vs 0.690; 1T1K: CCC = 0.979 vs 0.703). For V_T estimated using the full 2T4K, NN-unBlood showed improved concordance in Dataset 1 (CCC = 0.877 vs 0.681), while performance was lower but of comparable magnitude in Dataset 2 (CCC = 0.717 vs 0.830). In contrast, recovery of the remaining microparameters (k_2 – k_4) was characterised by higher variability across datasets and modelling approaches. Additionally, NN-dPET consistently outperformed IDIF-based approaches across datasets and parameters, showing substantially reduced bias and improved agreement with blood-derived estimates. Overall, image-based methods (IDIF and NN-unBlood) yielded systematically lower estimates of V_b (fractional blood volume), likely reflecting approximations in the estimation of C_p (plasma tracer concentration) and C_b (whole-blood tracer concentration).

In the blind Dataset 3, ASTRA reproduced the cross-sectional Standardized Uptake Value Ratio (SUVR) differences reported previously²⁶, with Knee Osteo-Arthritis (KOA) patients exhibiting statistically significantly higher values than healthy controls across all regions (all p 's ≤ 0.001 ; Figure 5) except the pituitary gland ($p = 0.12$) (Supplementary Table 10). Dataset 3 was derived from a previously published cohort²⁶ after excluding participants overlapping with Dataset 2. Group SUVR values for both the original sample and the subset in this evaluation are provided in Supplementary Table 10. Of note, pituitary elevations were also not significant in SUVR values within this subset of patients (Supplementary Table 10), likely attributable to reduced sample size and increased measurement noise. No significant group differences were detected in ASTRA-derived V_{TS} , which displayed a markedly higher coefficient of variation (Supplementary Table 10). Across all six regions, SUVR and Distribution Volume Ratio (DVR) were positively correlated (Figure 5), consistent with previous findings²⁷. All statistical comparisons were adjusted for age, TSPO genotype (which determines binding affinity for the radioligand^{28,29}), and Body Mass Index (BMI), in line with the original SUVR analysis²⁶.

Finally, model generalisation under pharmacological TSPO blockade XBD173³⁰ was evaluated in Dataset 4, comprising paired baseline and TSPO-blocking scans from five subjects with schizophrenia. Despite the small sample size ($n = 5$ subjects), within-subject regional comparisons demonstrated significant reductions in V_{TS} following blockade (two-

178 sided paired t-tests across Region Of Interests (ROIs), all $p < 0.001$).

179 At the subject level, after averaging V_T values across ROIs within each subject, the
 180 reduction in V_T remained statistically significant for both arterial blood-derived estimates
 181 (two-sided paired t-test, $n = 5$, $p = 0.0063$) and ASTRA-derived estimates (two-sided
 182 paired t-test, $n = 5$, $p = 0.0343$). These findings indicate preservation of sensitivity to
 183 TSPO blockade and consistency with arterial blood-derived V_T estimates (Figure 6).

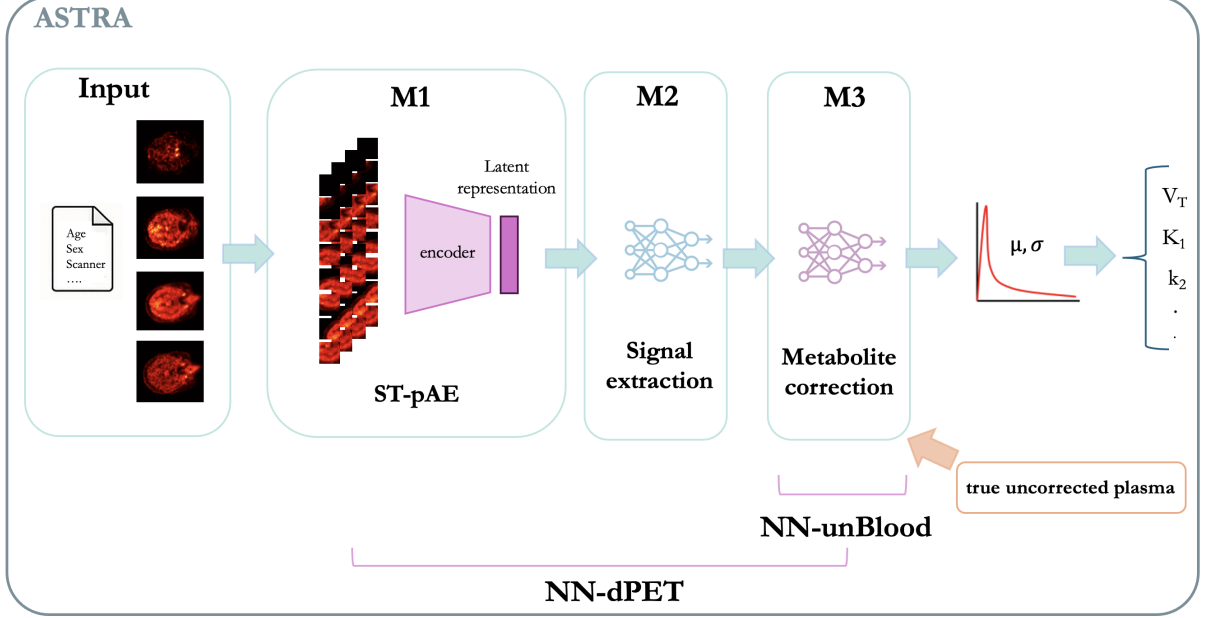


Figure 1. ASTRA architecture and processing modes. The framework combines dynamic PET images with subject-level metadata (e.g., age, sex, scanner type) to estimate the AIF and downstream kinetic parameters. M1: A patched autoencoder encodes spatiotemporal PET information into latent representations; M2: A transformer-based network extracts the plasma curve from the latent sequence; M3: A dedicated metabolite-correction module refines the plasma curve to predict the metabolite-corrected AIF, outputting both the mean and predictive uncertainty (μ, σ). In NN-dPET mode, M1–M3 operate end-to-end directly from PET images; in NN-unBlood mode, only M3 is used, taking the measured uncorrected plasma curve as input.

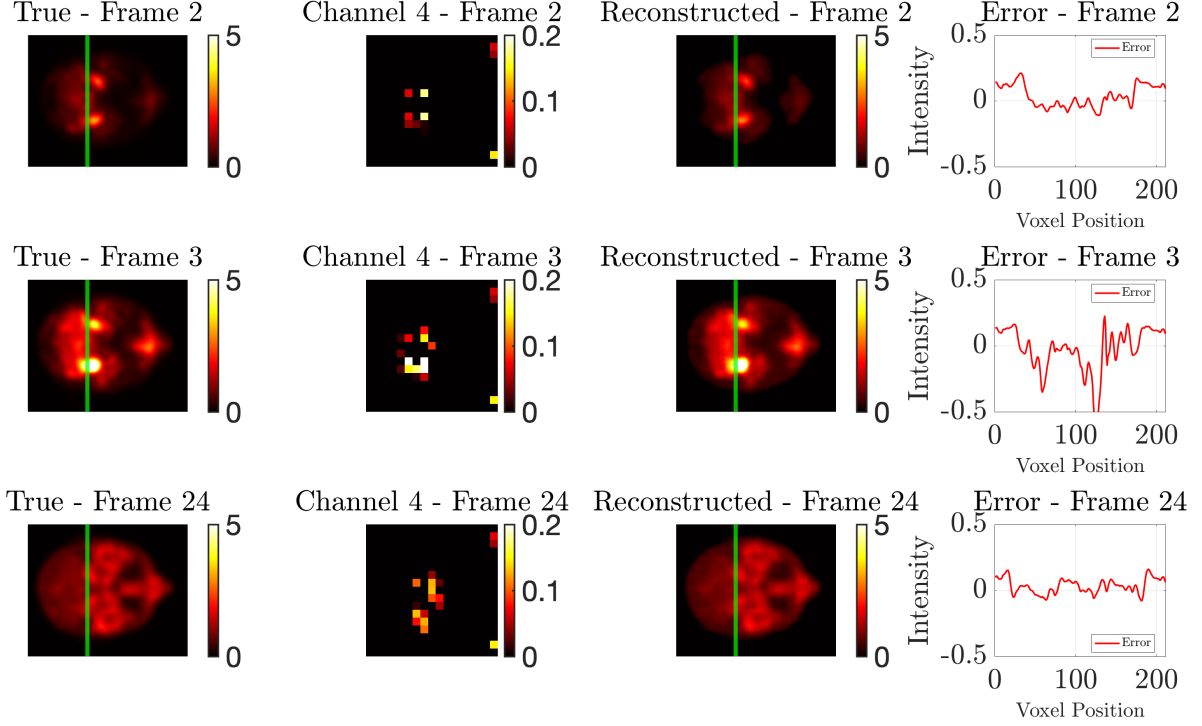


Figure 2. ST-pAE reconstruction and latent feature visualisation. Representative output from the ST-pAE (M1) for an example subject (Dataset 2), shown for three selected time frames (2, 3, and 24). For each frame, the first column shows the true dynamic PET slice with a vertical green line marking the profile extraction position ($x = 96, z = 82$), the second column visualises a single feature channel (channel 4 of 128) from the latent embedding, the third column shows the corresponding reconstructed slice from the decoder. The fourth column plots reconstruction error along the marked vertical line, computed as the difference between the true and reconstructed images.

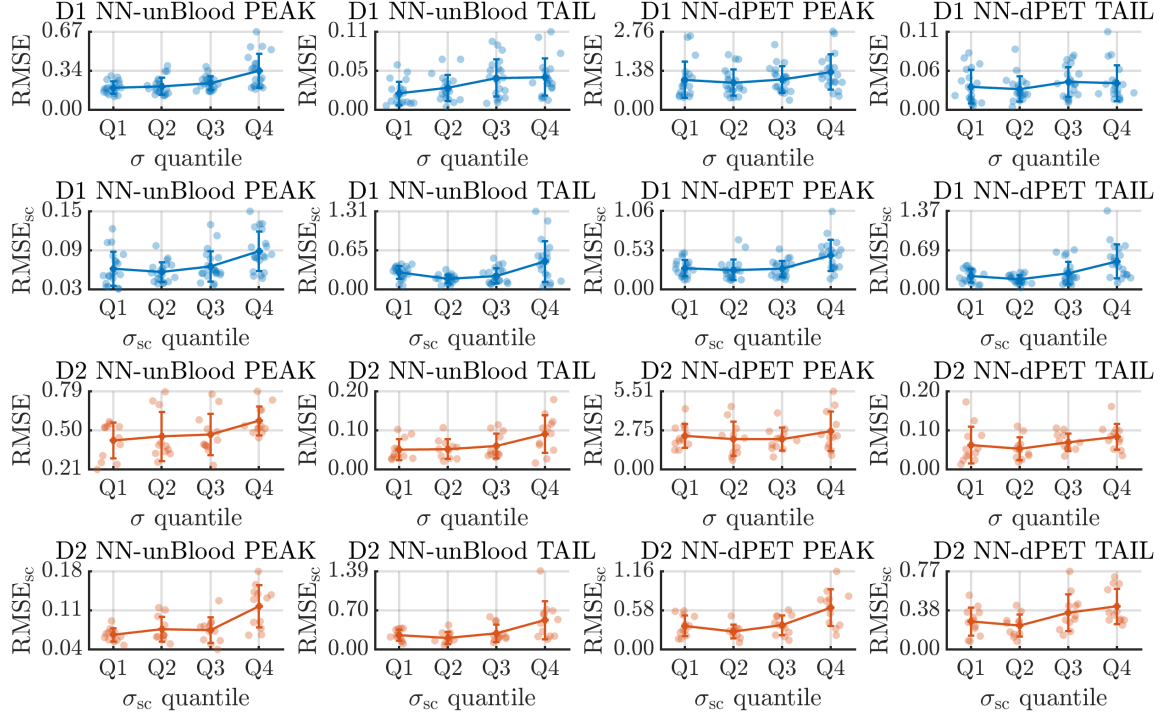


Figure 3. Prediction error and uncertainty analysis. Evaluation of ASTRA performance across Dataset 1 and Dataset 2 for NN-unBlood and NN-dPET modes. Rows correspond to datasets and error normalisation (D1: rows 1–2; D2: rows 3–4), with absolute Root Mean Squared Error (RMSE) and uncertainty (σ) shown in rows 1 and 3, and scaled error (RMSE_{sc}) and scaled uncertainty (σ_{sc}), computed with respect to the true signal scale, shown in rows 2 and 4. Prediction error is plotted as a function of the corresponding predicted uncertainty, with errors grouped into quantiles. Circles represent individual subjects, while coloured markers connected by lines indicate the mean error within each uncertainty bin; vertical bars denote inter-subject variability.

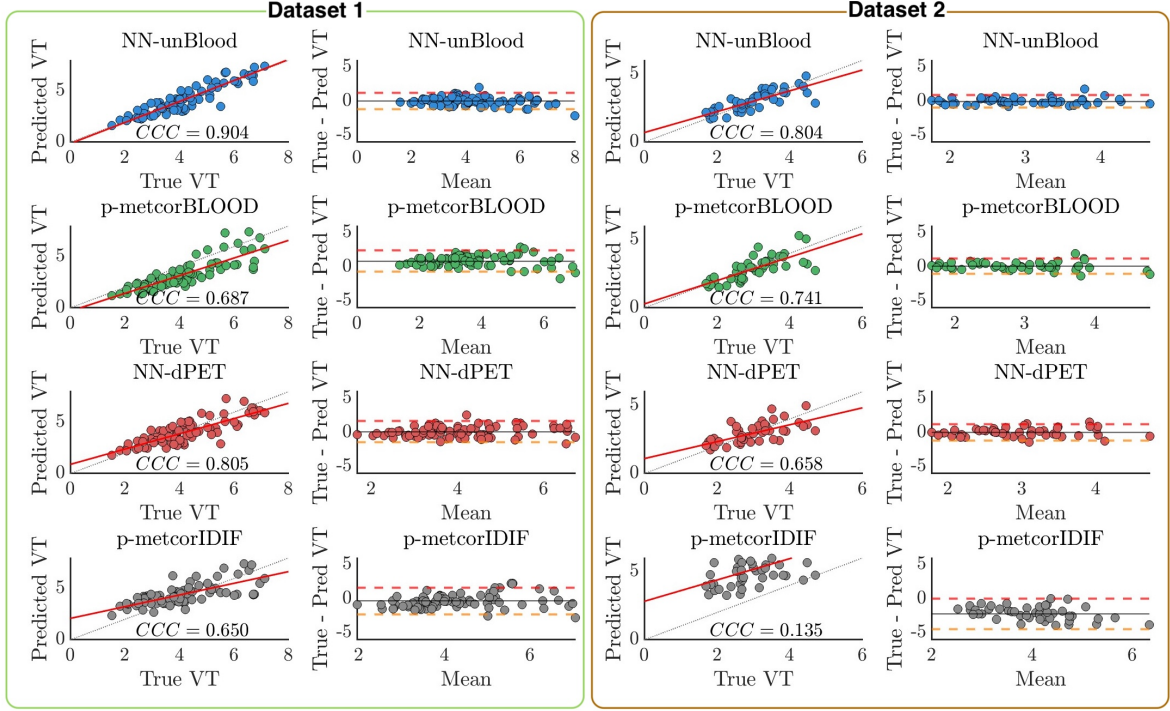


Figure 4. Estimated V_T s: comparison across methods and datasets. Results for Dataset 1 (left box) and Dataset 2 (right box) comparing predicted versus true V_T (Logan) across four methods: NN-unBlood, p-metcorBLOOD, NN-dPET, and p-metcorIDIF (from top to bottom). For each method, scatter plots of predicted versus true V_T values across subjects are shown, with identity lines (grey dotted), linear regression fits (solid red), and CCC reported within each panel, obtained after averaging V_T values across ROIs. Additionally, Bland-Altman plots of the difference (true - predicted) versus the mean V_T are displayed, with mean bias (solid black line) and limits of agreement at ± 1.96 standard deviations (dashed lines).

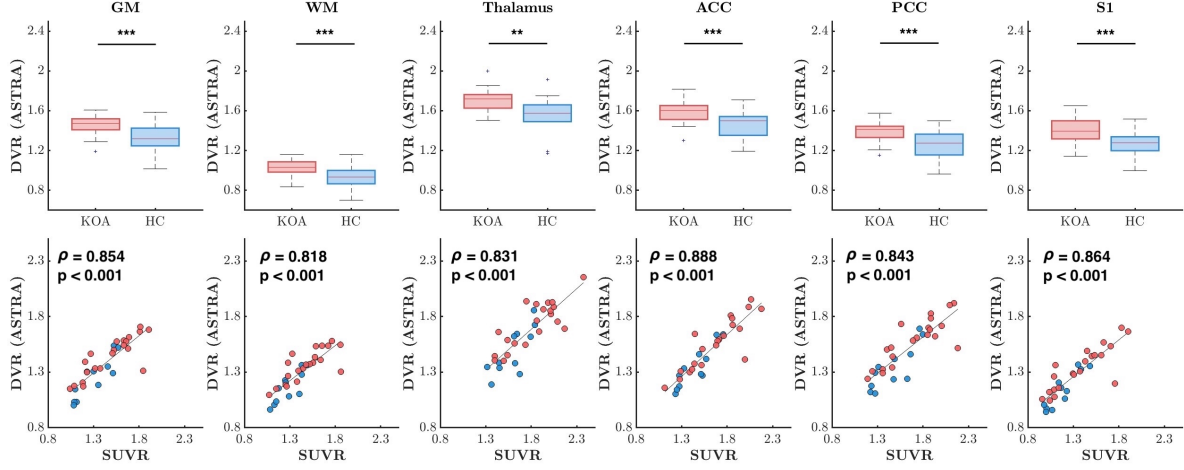


Figure 5. Blind test: ASTRA reproduces cross-sectional clinical findings. First row: Cross-sectional differences in DVR between KOA patients ($n = 21$) and healthy controls ($n = 11$) (Dataset 3) across multiple ROIs showing significant SUVR elevations²⁶. Values are corrected for age, BMI and TSPO genotype as in the SUVR published analysis. Box plots show the median (centre line), and interquartile range (box limits); individual points represent outliers; $**p < 0.01$; $***p < 0.001$. Legend: GM= Gray Matter. WM = White Matter. ACC = Anterior Cingulate Cortex, PCC = Posterior Cingulate Cortex S1 = Primary Somatosensory Cortex. Second row: Correlation between SUVR and ASTRA-derived DVR for each ROI. Pearson's correlation coefficients (ρ) and p -values are shown. Red points: KOA patients; blue points: healthy controls. Solid lines indicate linear fit.

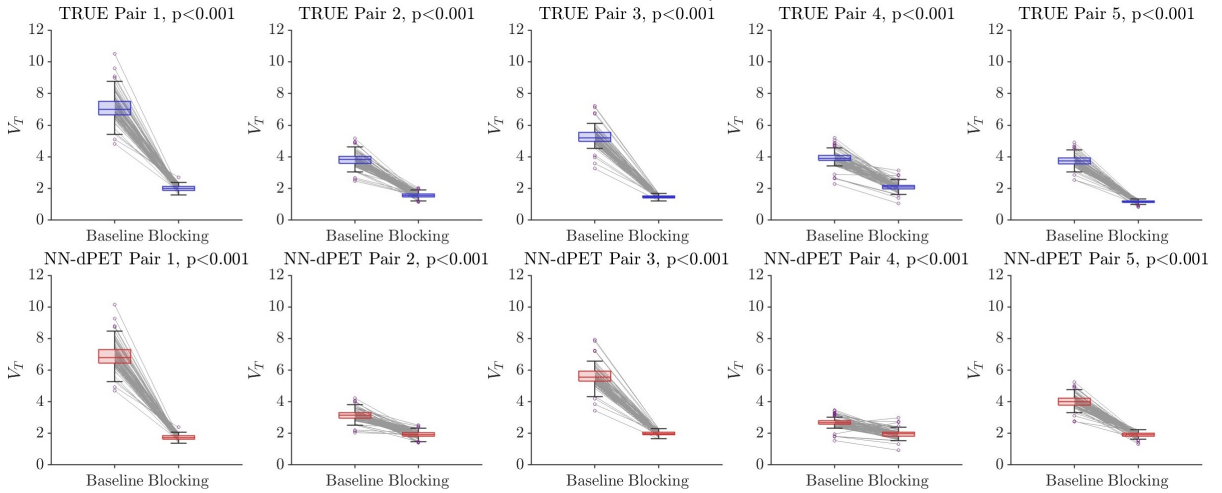


Figure 6. TSPO blocking analysis: baseline versus post-blockade comparisons. Paired comparisons of Logan V_T estimates before (baseline) and after pharmacological TSPO blockade with XBD173 across five subject pairs. Each column corresponds to one subject pair, with baseline and post-blocking values shown for the ground-truth arterial input function (top row) and from NN-dPET (bottom row). Box plots show the median (centre line) and interquartile range (box limits); outliers are shown as individual points. Lines connect matched regional values within each subject, highlighting within-subject changes induced by blockade, while boxplots summarise the distribution across regions.

Discussion

We present ASTRA, a data-driven framework for quantitative analysis of dynamic PET imaging that estimates the metabolite-corrected AIF directly from image data. By integrating Feature-wise Linear Modulation (FiLM)-conditioned latent representations with transformer-based temporal modelling, ASTRA aims to reduce reliance on arterial blood sampling. The framework was evaluated across independent datasets encompassing diverse scanners, acquisition protocols, clinical populations and TSPO genotype distributions, demonstrating scanner-robust performance following partial transfer learning.

The principal advantage of ASTRA is its ability to reconstruct the entire AIF, enabling downstream kinetic modelling beyond a single summary measure such as V_T . The first module (M1) employs a ST-pAE, developed specifically for this application, to compress high-dimensional dynamic PET data into compact latent features, reducing memory demands while preserving local tracer kinetics. This design was motivated mainly by the relatively modest sample sizes available across datasets (reflecting a broader constraint in PET research) which made dimensionality reduction essential for enabling stable performance. Of note, while patched autoencoders have recently emerged in computer vision for efficient representation learning³¹, our approach extends this architecture to dynamic PET imaging. The second module (M2), a transformer conditioned via FiLM, captures both local and global temporal dependencies while adapting to subject-specific and protocol-specific variables including demographic, biological and scanner-related factors. Unlike conventional IDIF methods, ASTRA does not require carotid segmentation or population-based correction factors.

Predictive uncertainty estimates were generated alongside each model prediction. In absolute units, a positive association between predicted uncertainty and prediction error can be observed in the early uptake (peak) phase, whereas the relationship is weaker in the post-peak decay (tail) phase, where errors span a narrower dynamic range. When the same analysis is reported after normalisation by a subject-specific signal scale, the association between predicted uncertainty and error becomes more marked in both phases. In this preliminary evaluation, predicted uncertainty is intended to support Quality Control (QC) assessment. Accordingly, predictions falling within the highest uncertainty quantile (Q4) could be flagged during QC as indicative of reduced prediction reliability. Further validation on larger datasets and the development of explicit calibration strategies will be required to establish robust uncertainty-based QC criteria.

Across the evaluated datasets, ASTRA, in both NN-dPET and NN-unBlood modes, demonstrated improved agreement with blood-derived quantification compared with state-of-the-art IDIF methods and population-based metabolite-corrected approaches, for both input function reconstruction and downstream kinetic parameter estimation. In particular, NN-unBlood showed higher CCC than population-based metabolite-corrected blood input functions for V_T values calculated with graphical methods. NN-dPET substantially outperformed population-based metabolite-corrected IDIF methods in terms of both CCC and reduced bias, as assessed by Bland–Altman analysis. When incorporated into 2T4K analysis, ASTRA-derived AIFs yielded accurate recovery of kinetic microparameters, particularly K_1 , with greater variability observed for k_2 – k_4 . It should be noted that the population used to generate the metabolite-corrected IDIF curves was drawn from the same centre as Dataset 1, which may bias performance estimates and make the method

appear overly optimistic.

The framework also generalised to a blind external test set without blood data and reproduced group differences between clinical and control populations previously reported with SUVR, here demonstrated using DVR²⁶. This ratio-based measure was examined to parallel earlier findings, as such metrics typically show lower variability and greater sensitivity to patient-control differences³². In this subset of patients, DVR showed statistically significant elevations in the same regions where SUVR differences were observed²⁶. No significant effects were observed in V_T . While it is possible that group-level differences in V_T were not detectable due to the higher coefficients of variation (as previously reported in the literature^{27,33}), it is also possible that inter-subject variability from method-estimation errors further compounded the high biological noise, thereby reducing statistical power and obscuring potential effects (see Supplementary Discussion for additional details). Importantly, the ability of ASTRA to reproduce known SUVR-based group differences through DVR, while avoiding arterial sampling, highlights its potential clinical and translational relevance. While further validation in larger and more diverse cohorts will be required to establish its utility in routine practice, the framework offers the prospect of lowering participant burden and facilitating the broader use of dynamic PET in multi-centre studies.

A particularly challenging aspect of this study was the assessment of ASTRA under pharmacological TSPO blockade with XBD173³⁰. TSPO blocking induces profound alterations in tracer kinetics, affecting both tissue uptake and plasma input functions, and therefore represents a stringent test of model generalisability beyond the conditions encountered during training. In this setting, ASTRA preserved sensitivity to blockade-induced changes in V_{TS} , yielding paired baseline and TSPO-blocking differences that were consistent with those obtained using true input functions. The ability of ASTRA to maintain biologically meaningful contrasts under these conditions suggests that the framework captures physiologically relevant features of tracer dynamics.

It should be noted that the framework was evaluated in a transfer learning setting, in which models pre-trained on Dataset 1 were adapted to Dataset 2. While minimal harmonisation was carried out between the two datasets, the transfer learning procedure enabled effective adaptation despite differences in acquisition protocols, injected dose, reconstruction parameters and cohort characteristics. Importantly, the spatiotemporal image encoder (M1), which captures image- and scanner-dependent features, was transferred without retraining, whereas the blood-informed modules (M2 and M3) required only minimal fine-tuning. Of note, the framework was optimised to achieve robust performance on Dataset 1 and to subsequently enable transfer to Dataset 2, rather than to operate as a single model independently optimised for each dataset.

In the current implementation, the metabolite-correction module (M3) refines the uncorrected plasma curve estimated by M2 from the latent image representation. This configuration was chosen to directly assess whether ASTRA in NN-dPET mode could match the performance when corrected blood is known (NN-unBlood). However, it necessarily restricts M3 to information present in the estimated uncorrected signal. As a result, it may not fully exploit the spatial and temporal cues embedded in the latent representation that are potentially relevant for metabolite dynamics. Future work will investigate providing M3 with the latent representation from M1, to evaluate whether direct access

to the complete latent information can enhance metabolite-correction accuracy.

When interpreting these results, several limitations should be acknowledged. First, the present study focused on the TSPO tracer $[^{11}\text{C}]\text{PBR28}$. However, ASTRA is tracer-agnostic and could in principle be applied to other radiotracers with suitable temporal properties. Future work should evaluate its performance across tracers with diverse metabolic profiles and kinetic complexities, and investigate the feasibility of partial acquisitions to enable shorter scan protocols. Second, transfer-learning to new datasets required partial retraining with blood-derived labels. Achieving calibration-free deployment will require domain adaptation or unsupervised strategies that can adapt to new acquisition protocols and populations without explicit blood data. Third, the current system outputs only the metabolite-corrected plasma curve; some kinetic models would benefit from concurrent estimation of the uncorrected whole-blood curve. Fourth, the three modules were trained independently. While this simplifies optimisation and allows individual component validation, it may prevent globally optimal representations from emerging; end-to-end training could reduce error propagation across the pipeline. Additionally, although ASTRA in both NN-dPET and NN-unBlood modes consistently outperformed state-of-the-art IDIF methods, further benchmarking against similar AI-based approaches, should they become openly available, and across more diverse datasets will be important to confirm generalisability. It is also worth noting that while evaluated across two scanners and heterogeneous protocols, a larger multi-site benchmark will be required to fully establish scanner independence and broader applicability. These findings therefore highlight feasibility but also underscore the need for continued development to improve robustness and generalisability. In particular, future work will require validation in larger multi-centre cohorts, evaluation across additional tracers and kinetic regimes, and the development of self-adaptive strategies to support deployment across new sites. Finally, patient data were analysed collectively without stratification by diagnosis; subgroup-specific modelling may further improve accuracy and robustness.

By enabling quantitative PET imaging without arterial sampling, ASTRA could accelerate translational radiotracer research, extend quantitative PET to new clinical settings, and support precision molecular imaging. Predicting subject-specific AIFs directly from dynamic image data provides a foundation for scalable, generalisable and clinically actionable PET quantification.

Outlook

The ability to estimate metabolite-corrected input functions directly from dynamic PET images has long represented a barrier to the broader adoption of fully quantitative PET imaging. By making a step toward overcoming the need for arterial blood sampling, ASTRA points to more practical and scalable approaches for quantifying tracer kinetics in both research and clinical contexts. With further advances, this direction could open new opportunities for deploying experimental radiotracers in larger-scale studies, early-phase clinical trials, and eventually routine diagnostic workflows, particularly in settings where arterial sampling is impractical or contraindicated.

The present evaluation across independent datasets with different scanners and acquisition protocols indicates that blood-free modelling can extend beyond single-site settings, opening new possibilities for broader multi-centre PET applications. In neurology and

psychiatry, where PET tracers are increasingly used to investigate neuroinflammation, blood-free quantification could accelerate biomarker development, aid in patient stratification, and provide more accessible tools for monitoring treatment response. Comparable benefits may also extend to other domains where dynamic PET is applied, such as oncology, cardiology, and immunology, helping to lower barriers to quantitative adoption and improving reproducibility across sites.

Methods

Dataset Description

Four datasets comprising a total of 179 dynamic $[^{11}\text{C}]\text{PBR28}$ PET scans were analysed in this study. Datasets 1 ($n=90$; patients = 24, controls = 66) and 2 ($n=52$; patients = 42, controls = 10) were used for model training, tuning, and transfer learning. Dataset 3 ($n=32$; patients = 21, controls = 11) served as a held-out test set. Dataset 2 included 13 re-scans. Dataset 3 was curated from a previously published cohort²⁶, after excluding subjects overlapping with Dataset 2 and incomplete dynamic scans. Finally, Dataset 4 consisted of 5 TSPO-blocking scans from schizophrenia subjects who underwent pharmacological TSPO blockade XBD173³⁰. Baseline scans for these subjects are present in Dataset 1.

All datasets included both High Affinity Binder (HAB) and Mixed Affinity Binder (MAB) genotypes to ensure exposure to genotype-related variability in $[^{11}\text{C}]\text{PBR28}$ signal^{28,29}. The patient cohort comprised multiple diagnostic subgroups; for the purposes of this study they were analysed collectively as a single “patient” group. Full details of the specific patient characteristics in each dataset are provided in Supplementary Table 1.

Data Acquisition

Dataset 1 (King’s College London, UK): Dynamic $[^{11}\text{C}]\text{PBR28}$ PET/CT scans were acquired on a Siemens Biograph TruePoint PET/CT scanner (transaxial FOV: 60.5 cm; axial FOV: 16.2 cm). Each scan lasted 90 minutes with an average injected dose of 330 MBq. Data were binned into 26 dynamic frames and reconstructed using filtered back projection with 5 mm Gaussian smoothing. Reconstructed PET volumes had dimensions of $128 \times 128 \times 82$ per frame (26 in total), with voxel dimension of $2.051 \times 2.051 \times 2$ mm. Arterial blood sampling included continuous whole-blood activity for the first 15 minutes and discrete samples up to 90 minutes for plasma activity and metabolite correction. Blood sample centrifugation, radioactivity counting, and metabolite correction with High Performance Liquid Chromatography (HPLC) were performed to quantify the plasma parent radiotracer activity.

Dataset 2 (Martinos Center for Biomedical Imaging, US): Scans were acquired on a Siemens Biograph mMR PET/MR scanner (transaxial FOV: 59.4 cm; axial FOV: 25.8 cm). Each scan lasted 90 minutes with an average injected dose of 524 MBq. Data were binned into 28 dynamic frames and reconstructed using ordered subset expectation maximisation (OSEM)³⁴ with 4 iterations, 21 subsets, 3 mm FWHM Gaussian smoothing. Reconstructed PET volumes had dimensions of $344 \times 344 \times 127$ per frame, with voxel sizes of $2.09 \times 2.09 \times 2.03$ mm. Attenuation correction was performed using T1-weighted MR images³⁵. Arterial blood samples were collected at 5, 10, 20, 30, 50, 70, and 90 minutes.

Blood samples centrifugation, activity counting and metabolite correction (either by HyperSep C18 solid-phase extraction cartridge for 16 subjects, or HPLC for the remaining 36 subjects) was performed to derive the corrected plasma tracer concentration¹⁴.

Dataset 3 (Martinos Center for Biomedical Imaging, US): Scans were acquired using the same scanner and imaging protocol as Dataset 2, but without arterial blood sampling. No ground-truth blood data were available for this cohort, which was used exclusively as a fully held-out blind test set. Dynamic images had the same spatial resolution and frame structure as Dataset 2.

Dataset 4 (King’s College London, UK): Scans were acquired using the same PET/CT scanner and imaging protocol as Dataset 1. It comprises dynamic [¹¹C]PBR28 PET scans from five subjects with schizophrenia, who underwent pharmacological TSPO blockade with XBD173 prior to the scan.

All pipelines included a motion-correction step for the dynamic PET data, implemented according to each site’s established research protocols^{14,36}.

Ethics Statement

All study procedures were conducted in accordance with the Declaration of Helsinki and were approved by the relevant institutional review boards and local research ethics committees. All participants provided written informed consent prior to participation.

Data Preprocessing

All dynamic PET images, uncorrected blood curves, and metabolite-corrected plasma curves were converted to Standardised Uptake Value (SUV) units for consistency across datasets. Time Activity Curves (TACs) were extracted from predefined ROIs covering the whole brain. To harmonise data across acquisition protocols, images from the Dataset 2 were spatially smoothed using a 6 mm FWHM Gaussian kernel and temporally resampled to match the frame timing of Dataset 1 (26 frames). TACs were then extracted from predefined whole-brain ROIs. For Dataset 1, 94 ROIs were defined using MIAKAT^{TM14}. For Datasets 2 and 3, 69 ROIs were defined using the Harvard–Oxford atlas³⁷. In Dataset 3, additional regions including grey matter, white matter, thalamus, anterior cingulate cortex, posterior cingulate cortex, primary somatosensory cortex, and pituitary gland, were included based on regions previously reported to show TSPO increases in KOA patients²⁶.

Network Input Preparation

For network input, all PET volumes were standardised for intensity and zero-padded to a uniform cubic shape to allow consistent 3D patch extraction, while clinical covariates were harmonised to a unified coding scheme (health status 0/1, sex 0/1, TSPO genotype 1/2), tracer and scanner type treated as categorical variables, and continuous variables (age, injected dose, body weight) z-scored, with all processed variables provided as conditioning inputs to the model’s FiLM layers (see Supplementary Methods for details).

399 The ASTRA architecture comprises three modular components. In the first module
 400 (M1), the dynamic PET sequence is compressed into a low-dimensional spatiotemporal
 401 representation. In the second module (M2), this representation is used to estimate a
 402 subject-specific, uncorrected plasma input function. In the final module (M3), this plasma
 403 curve undergoes metabolite correction to produce the final input function for kinetic
 404 modelling. Full architectural hyperparameters, including patch size, convolutional filter
 405 dimensions, transformer configurations, are provided in Supplementary Table 2.

406 **Module 1 (M1) – Dimensionality reduction:** M1 encodes dynamic PET volumes
 407 into a compact latent representation using a ST-pAE. Each 4D scan is partitioned
 408 into overlapping spatio-temporal patches, which are processed independently through
 409 a multi-stage 3D convolutional encoder with progressive space-to-depth downsampling
 410 (latent size 128 per patch). FiLM layers integrate subject-level metadata (e.g., age, sex,
 411 genotype, scanner type) at multiple encoding and decoding stages to adapt feature scal-
 412 ing to acquisition and biological context. The decoder mirrors the architecture design
 413 of the encoder using depth-to-space upsampling to reconstruct the original spatial struc-
 414 ture, encouraging latent embeddings to retain spatio-temporal information relevant for
 415 downstream modelling.

416 **Module 2 (M2) – Signal extraction:** The temporally ordered latent sequence from
 417 M1 is passed through local temporal convolutional layers to capture short-range dynam-
 418 ics, followed by a transformer encoder stack to model long-range temporal dependencies.
 419 Multi-head self-attention enables global contextual integration across all time frames,
 420 while FiLM conditioning within each transformer block modulates temporal features ac-
 421 cording to subject-specific covariates. The final transformer output is projected via a
 422 Multi-Layer Perceptron (MLP) to estimate the uncorrected plasma input function.

423 **Module 3 (M3) – Metabolite correction:** M3 transforms the M2-predicted un-
 424 corrected plasma curve into a metabolite-corrected AIF using a transformer architec-
 425 ture. FiLM conditioning is applied at every transformer block to adjust predictions for
 426 subject-level differences. The model outputs a Gaussian distribution at each time point,
 427 parameterised by a learnable mean and standard deviation.

428 In addition to its role within the end-to-end ASTRA pipeline, M3 can also operate in-
 429 dependently for post-hoc metabolite correction of externally estimated input functions,
 430 such as uncorrected plasma curves (NN-unBlood mode).

431 *Regularisation strategy*

432 Across the different modules, training is guided by a composite objective that combines
 433 reconstruction terms with auxiliary regularisation components to promote stability and
 434 physically plausible outputs. All models employ FiLM commitment regularisation, which
 435 ensures feature modulation without strictly constraining their values.

436 For modules operating directly on spatial or temporal signals, an additional curvature-
 437 based regularisation term is applied in the form of a mean squared error on the Laplacian

of the predicted output, computed relative to the corresponding target. This term encourages the preservation of fine-scale structure by penalising discrepancies in second-order derivatives, thereby promoting smooth reconstructions.

Where applicable, further latent-space regularisation is used to stabilise intermediate representations, including decorrelation penalties that reduce redundancy across embedding dimensions. Rather than fixing the relative importance of individual loss components, all regularisation terms are weighted using learnable uncertainty parameters, following the approach of³⁸. This allows the model to adaptively balance competing objectives based on the observed variability during training. All loss terms are normalised by frame length, ensuring that longer sequences receive proportionally stronger regularisation.

Model Training, Cross-Validation, and Transfer Learning

Model development and evaluation were conducted in multiple stages, integrating hyperparameter optimisation, cross-validation, transfer learning, and targeted generalisation analyses.

Hyperparameter tuning and cross-validation on Dataset 1. Dataset 1 was partitioned into 10 subject-level folds of equal size. One fold was reserved exclusively for hyperparameter tuning, including optimisation of the learning rate, latent dimensionality, and network depth (see Supplementary Tables 2 and 3), while the remaining nine folds were used for cross-validation. Hyperparameters selected during the tuning phase were fixed for all subsequent experiments. Cross-validation was performed by iteratively holding out one fold as the test set and training on the remaining folds, enabling assessment of model stability and within-dataset generalisation. Aggregate performance metrics were computed across all cross-validation runs (Supplementary Tables 4 and 5).

Transfer learning and cross-validation on Dataset 2. Dataset 2 was partitioned into 11 subject-level folds, comprising ten folds with five subjects and one fold with two subjects. One fold of five subjects was held out to assess transfer learning performance, while the remaining folds were used for cross-validation. Transfer learning was performed using the model pretrained on Dataset 1, with module M1 kept frozen and modules M2 and M3 initialised from the pretrained weights and fine-tuned for a fixed number of epochs (see Software and computing hardware settings section). Subjects with multiple or follow-up visits were always assigned to the same fold to prevent data leakage.

Fold construction and subject stratification. For all cross-validation and transfer-learning procedures, folds were constructed at the subject level using silhouette-based clustering on clinical and acquisition metadata to ensure balanced and diverse fold composition. Subjects with multiple or follow-up visits were consistently assigned to a single fold, ensuring that no subject contributed data to both training and evaluation sets.

Held-out evaluation on Dataset 3. The final model, trained on Dataset 1 and adapted via transfer learning on Dataset 2, was evaluated on Dataset 3 without any additional training or fine-tuning. Dataset 3 therefore served as a fully independent, blind test set for assessing out-of-distribution generalisation.

Blocking analysis on Dataset 4.

To evaluate model generalisation under pharmacological TSPO blockade with XBD173, ASTRA in NN-dPET mode was tested on $n = 10$ scans, comprising five paired baseline and post-blocking scans from five subjects with schizophrenia. The baseline scans for these subjects were already included in Dataset 1. Models were trained on Dataset 1 excluding these five subjects and evaluated on the held-out baseline–blocking scan pairs. This represents a challenging generalisation scenario, as TSPO blockade induces marked alterations in tracer kinetics and plasma input functions. Statistical analyses were conducted at two complementary levels. First, within-subject comparisons across ROIs were performed using two-sided paired t-tests to evaluate blockade effects. Second, V_T values were averaged across ROIs for each subject, and two-sided paired t-tests were applied at the group level ($n = 5$). Given the exploratory design and small sample size, no correction for multiple comparisons was applied.

Signal Evaluation and Kinetic Modelling

To benchmark ASTRA-derived input functions, four classes of metabolite-corrected plasma input curves were evaluated: (1) NN-dPET, corresponding to the output of the full ASTRA pipeline (modules M1–M3); (2) NN-unBlood, corresponding to the output of the final ASTRA module (M3) when applied to ground-truth uncorrected plasma curves; (3) p-metcorIDIF, obtained by applying a population-based metabolite correction to image-derived input functions and representing a lower-bound reference for NN-dPET; and (4) p-metcorBLOOD, obtained by applying the same population-based metabolite correction to ground-truth uncorrected plasma curves and representing a lower-bound reference for NN-unBlood. All approaches were compared against gold-standard arterial blood data when available. Pseudo-code for NN-dPET and NN-unBlood is provided in the Supplementary Materials (Algorithms 1 and 2).

For ASTRA-based methods, the model predicts a Gaussian distribution at each time point, characterised by a mean and standard deviation. For quantitative analyses (e.g., V_T and microparameter estimation), 32 representative samples were drawn at each time point from the Gaussian distributions defined by the predicted mean and standard deviation. The sample mean across these realisations was used as the representative input function, while the associated variance was retained as an indicator of prediction reliability.

The IDIF was computed as described in Supplementary materials.

Kinetic Modelling and V_T Estimation: For all input function types (IDIF-corrected, NN-unBlood, dPET), regional volume of distribution (V_T) was estimated using the Logan graphical method²⁵. To further characterise performance, full kinetic modelling was also conducted using a 2T4K, with a 1T1K reduced model implemented for comparison¹⁴. See Supplementary Materials for additional information.

Quantitative evaluation and statistical analyses: For each model configuration, V_T was estimated across all available regional TACs. In datasets with arterial blood data (Datasets 1 and 2), agreement between predicted and measured V_T values was assessed using the coefficient of determination (R^2) and Bland–Altman analysis across all regions.

For Dataset 3, which lacked ground-truth blood data, clinical validity was assessed by comparing V_T s and DVRs (ratio metric) estimates between patients and healthy controls

across selected ROIs that correspond to regions showing SUVR elevations in previously published semi-quantitative (SUVR) clinical analyses of this cohort²⁶. Group differences in diagnostic group were evaluated using a general linear model (GLM) with age, BMI, and TSPO genotype included as covariates, in accordance with the statistical approach used in the original SUVR analyses.

Error metrics: To quantify prediction accuracy, Mean Absolute Error (MAE), RMSE, coefficient of determination (R^2), and CCC were computed between predicted and true V_T values. For each cross-validation fold, metrics were calculated by pooling all regional V_T estimates across subjects and ROIs, and subsequently aggregated across folds for each model configuration. Kinetic microparameters were summarised across subjects using the median and median absolute deviation (MAD), and agreement with blood-derived estimates was assessed using Pearson’s correlation coefficient and CCC.

In addition, to assess the relationship between predictive uncertainty and actual error, subject-wise RMSE values were computed between predicted and arterial blood curves for both the early uptake (“Peak”) and post-peak (“Tail”) phases. Error analyses were performed both in absolute units and after normalisation by a subject-specific signal scale, defined as the mean value of the true blood curve over the central 25–75% portion of the corresponding phase. In each case, prediction errors were related to the corresponding predicted uncertainty (σ), with mean trends and inter-subject variability summarised across quantile bins ($n=4$) of predicted uncertainty.

Software and computing hardware settings

ASTRA was implemented in Python 3.10.12 using TensorFlow 2.15.0.post1 and Keras 2.15.0 as the high-level API. Supporting libraries included NumPy 1.26.4, Pandas 2.2.3, and scikit-learn 1.6.1. The framework was developed and tested on Linux. Training was performed across workstations equipped with GPUs supporting CUDA 11.8 and cuDNN 8.6. During training, peak GPU memory usage reached approximately 22.7 GB. Each module (M1, M2, M3) was trained independently for memory efficiency. For Dataset 1, the total number of training epochs was 13k for M1, 5k for M2, and 30k for M3. For Dataset 2, transfer learning was applied without retraining M1; M2 was fine-tuned for 2k epochs and M3 for 5 epochs.

Author contributions

L.B. and A.C.W. conceived the study and designed the computational framework. A.C.W. implemented the core codebase, and L.B. completed and refined the implementation. L.B. performed the statistical analyses, evaluated the results, and drafted the manuscript. L.Ba. and L.M. contributed to kinetic modelling analyses. Z.A. and M.K. contributed to data acquisition. O.H., T.R.M., M.A.N., V.M., and C.P. contributed to data acquisition and funding. C.C. and M.L.L. provided expertise and oversight for data quality control. A.M., N.T., M.F., M.I., M.V., E.G., and F.E.T. contributed to interpretation of the findings. J.G. and M.L.L. contributed to funding. M.L.L. oversaw all stages of the study and provided scientific guidance. All authors contributed to manuscript revision and approved the final version.

Reporting summary

Further information is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data supporting the findings of this study will be made available from the owning institutions upon reasonable request and subject to institutional approval.

Code availability

The code supporting the findings of this study will be made available from the corresponding author upon reasonable request.

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Competing interests

The authors declare no competing interests.

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