

Validation of Image-Derived Input Function for Non-Invasive Kinetic Modeling of [18F]-Fluorodeprenyl-D2 in Neurological Diseases

Lukas Frontzkowski

Lukas.Frontzkowski@med.uni-muenchen.de

LMU Klinikum <https://orcid.org/0000-0001-9321-956X>

Nicolai Franzmeier

LMU: Ludwig-Maximilians-Universitat Munchen

Letizia Vogler

Klinikum rechts der Isar der Technischen Universitat Munchen

Thomas Saller

LMU Klinikum

Simon Lindner

LMU Klinikum

Marianthi Zeinaki

LMU Klinikum

Benjamin Kugelmann

LMU Klinikum

Artem Zatcepin

LMU Klinikum

Gloria Mueller

LMU Klinikum

Alexander Jäck

LMU Klinikum

Ilias Masouris

LMU Klinikum

Boris-Stephan Rauchmann

LMU Klinikum

Sowmitha Raju

LMU Klinikum

Nathalie Albert

LMU Klinikum

Lisa Tagnin

LMU Klinikum

David Vázquez García

Barcelonaβeta Brain Research Center: Barcelonabeta Brain Research Center

Gemma Salvadó

Barcelonaβeta Brain Research Center: Barcelonabeta Brain Research Center

Gérard Nisal Bischof

Lantheus Holdings Inc

Lena Kaiser

LMU Klinikum

Robert Perneczky

LMU Klinikum

Günter Höglinger

LMU Klinikum

Johannes Levin

LMU Klinikum

Sibylle Ziegler

MHH: Medizinische Hochschule Hannover

Adrian Jun Zounek

LMU Klinikum

Matthias Brendel

LMU Klinikum

Research Article

Keywords: [^{18}F]F-DED, MAO-B, image-derived input function, IDIF, Patlak graphical analysis, PET quantification

Posted Date: September 29th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10808549/v1>

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Abstract

Background.

[^{18}F]fluorodeprenyl-D2 ([^{18}F]F-DED) PET enables in vivo quantification of monoamine oxidase B (MAO-B) expression, a marker of reactive astrogliosis implicated in a range of neurodegenerative diseases. Full quantification of MAO-B expression with PET requires an arterial input function (AIF) derived from continuous blood sampling - an invasive procedure that limits clinical applicability. The aim of this study was to develop and validate a non-invasive, carotid image-derived input function (IDIF) extraction pipeline for [^{18}F]F-DED PET and to assess its agreement with the gold-standard AIF at the regional and voxel level. Eight subjects underwent 60-minute dynamic [^{18}F]F-DED PET/CT with concurrent arterial blood sampling and radiometabolite analysis. An IDIF was manually extracted from the internal carotid arteries and compared with the AIF. To improve the agreement of IDIF and AIF, a population-based, time-decaying peak-recovery correction was applied, and both input functions then received the same population-derived plasma-to-whole-blood and parent-fraction correction. Using the AIF, five kinetic models were ranked by region-level: one-tissue (1T2K), irreversible (2T3K) and reversible (2T4K) two-tissue compartment models, and Logan and Patlak graphical analyses. Total distribution volume (VT; 1T2K, 2T4K, Logan) and net influx rate constant (K_i ; 2T3K, Patlak) were estimated from both input functions, regionally and voxel-wise, and compared with the AIF.

Results.

The uncalibrated IDIF underestimated the arterial bolus peak by 78.1%, reduced to 18.2% after the population-based peak-recovery calibration was applied. The reversible 2T4K model best described regional tissue kinetics, not supporting purely irreversible trapping. After plasma- and metabolite-correction, IDIF- and AIF-derived regional VT and K_i agreed significantly for all five kinetic models ($R^2 = 0.53\text{--}0.77$, all $p < 0.05$), with Logan analysis yielding the most robust results across conditions ($R^2 = 0.62\text{--}0.73$). Voxel-wise VT maps preserved the AIF spatial pattern, differing only by a near-uniform positive offset (median + 60%).

Conclusions.

A carotid IDIF, corrected with population-derived plasma-to-whole-blood and parent-fraction curves and a time-decaying peak-recovery calibration, closely approximated the AIF for [^{18}F]F-DED PET. After calibration, all kinetic approaches agreed with the AIF reference, with Logan graphical analysis providing the most robust regional VT estimates across conditions.

Introduction

Monoamine oxidase B (MAO-B) is an outer mitochondrial membrane enzyme predominantly expressed in astrocytes and serotonergic neurons of the central nervous system¹. Elevated MAO-B expression has been consistently associated with reactive astrogliosis, a hallmark of neurodegenerative disorders including Alzheimer's disease, progressive supranuclear palsy, and amyotrophic lateral sclerosis²⁻⁴. Positron emission tomography (PET) with the irreversible MAO-B radioligand L-[¹¹C]-deprenyl-D2 has served as the reference standard for in vivo quantification of MAO-B availability for over two decades⁵. More recently, [¹⁸F]F-DED (¹⁸F-fluorodeprenyl) has been developed as a ¹⁸F-labelled analogue that retains the favourable kinetic properties of the ¹¹C-compound while offering the practical advantages of a longer physical half-life (110 min vs. 20 min), enabling distribution to centres without an on-site cyclotron⁶. However, gold-standard quantification of tracer binding requires a metabolite-corrected arterial plasma input function derived from continuous arterial blood sampling during the PET acquisition. This arterial input function (AIF) represents the gold standard for kinetic modelling but is associated with considerable methodological complexity, patient discomfort, radiation exposure to staff, and risk of vascular complications. These factors limit the clinical applicability of fully quantitative [¹⁸F]F-DED PET, particularly in elderly patient populations and in multi-centre trial settings where standardised arterial catheterisation is impractical. Reference tissue methods offer one alternative to arterial sampling, using a region devoid of specific binding (e.g. cerebellar grey matter) as a surrogate input function⁷. However, the validity of reference tissue approaches depends on the assumption that the reference region is free of on-target binding properties, a condition that may not hold for MAO-B, which is expressed in astrocytes throughout the brain, rendering reference tissue quantification as potentially biased⁸. Consequently, non-invasive quantification of [¹⁸F]F-DED binding remains an open challenge, as neither reference tissue methods nor simplified kinetic approaches can reliably substitute for the AIF. Image-derived input functions (IDIF) offer a non-invasive alternative by extracting the arterial blood curve directly from the dynamic PET images, typically from the internal carotid arteries within the field of view⁹. Several IDIF extraction strategies have been proposed, ranging from manual region-of-interest placement on late-frame anatomical images to automated approaches based on independent component analysis (ICA) or factor analysis of dynamic sequences¹⁰⁻¹². However, since carotid arteries are small structures relative to the spatial resolution of clinical PET scanners, the resulting IDIF is affected by partial volume effects (PVE) that attenuate the measured signal, particularly during the first-pass bolus peak^{10,13}. Population-based calibration strategies have been shown to effectively compensate for this PVE-induced bias, enabling accurate quantification of tracer uptake via kinetic modeling¹⁴. Several recent studies have demonstrated the feasibility of carotid IDIF extraction for brain PET tracers, including [¹⁸F]FDG, [¹⁸F]PI-2620 or [¹¹C]flumazenil, reporting good agreement between IDIF-derived and AIF-derived quantitative estimates after calibration^{9,15}. To our knowledge, no carotid IDIF-based quantification has been evaluated for [¹⁸F]F-DED.

Therefore, the aim of the present study was to develop and validate a non-invasive IDIF extraction and calibration pipeline for dynamic [¹⁸F]F-DED PET. Specifically, we sought to (i) establish a manual carotid IDIF extraction method operating in native PET space; (ii) evaluate a population-based, time-decaying

peak-recovery calibration to compensate for IDIF peak underestimation; (iii) identify the most appropriate kinetic model for [^{18}F]F-DED by comparing one-tissue (1T2K), irreversible two-tissue (2T3K) and reversible two-tissue (2T4K) compartment models together with Logan and Patlak graphical analyses; and (iv) assess the agreement between IDIF- and AIF-derived outcomes - total distribution volume (VT) and net influx rate constant (K_i) - at both the regional and voxel level.

Methods

Study population

Eight subjects were recruited from ongoing observational MAO-B imaging cohorts in neurodegenerative diseases at LMU Hospital. PET/CT imaging was performed at the Department of Nuclear Medicine. All participants underwent a 60-minute dynamic [^{18}F]F-DED PET/CT scan with concurrent continuous arterial blood sampling. This study was approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der LMU München, approval number 21–0721, approval date 28 Oct 2021) and radiation protection authorities (BfS: ZD 3-22464/2023-042-G).

PET data acquisition

[^{18}F]F-DED was synthesized as previously reported and administered via intravenous bolus injection (approximately 10 seconds) into the right arm¹⁶. Image acquisition was started simultaneously with tracer injection and continued for 60 minutes in dynamic list mode on a Siemens Biograph 64 TruePoint PET/CT scanner (Siemens Healthineers AG, Erlangen, Germany). Images were reconstructed iteratively using ordered subset expectation maximization (OSEM3D) with 4 iterations, 21 subsets, and a 336x336x109 matrix (1.02x1.02x2.03 mm³ voxel size). The reconstruction protocol used a sequence of 35 static frames with increasing durations to best capture the rapid distribution of the activity after injection: 12x5s; 6x10s; 3x20s; 7x60s; 4x300s; 3x600s. A 5 mm full width at half maximum (FWHM) Gaussian post-reconstruction filter was applied for image smoothing. Low-dose CT was acquired before the PET scan for attenuation correction.

PET processing

Dynamic [^{18}F]F-DED PET images were first motion-corrected using the motion correction tool Falconz and subsequently averaged to a 30–60 minute static window^{17,18}. The resulting mean PET image was then warped to Montreal Neurology Institute (MNI) space via the 30–60 minute summation image, using a custom in-house [^{18}F]F-DED MNI template, via a high-dimensional non-linear warping algorithm implemented in the Advanced Normalization Tools Software (ANTs) package¹⁹. Regional analyses were based on the Hammers anatomical atlas, which parcellates the brain into 95 regions in MNI space²⁰. Six

white matter and ventricular labels were excluded, leaving 89 cortical and subcortical grey matter regions used throughout this work²⁰.

Arterial input function (AIF)

Before PET acquisition, an arterial catheter connected to an Arcomed volumed μ VP7000 peristaltic infusion pump (Arcomed AG, Kloten, Switzerland) was inserted into the radial artery of the left arm (Fig. 1). Starting with tracer injection, blood was continuously withdrawn and pumped through the detector of a Swisstrace Twilite automated blood sampling system (Swisstrace GmbH, Menzingen, Switzerland). A variable flow rate protocol was used to balance temporal resolution with the sharp bolus peak of the blood activity: 0–6 min post-injection (p.i.): 300 ml/h; 7–12 min p.i.: 150 ml/h; 13–60 min p.i.: 20 ml/h. Blood counts were detected in 1-second intervals and converted to whole blood activity concentration while correcting for Fluorine-18 decay and branching ratio using the PMOD PSAMPLE software (PMOD Technologies, Zürich, Switzerland).

Six additional manual blood samples were drawn during the continuous sampling process at the timepoints $t_i = 4.5, 8, 15, 30, 45$, and 60 min p.i. to enable gamma counter activity measurements as well as metabolite correction. A systematic difference between the continuous AIF and the manual blood samples was observed and assumed to be caused by background radiation that leaked into the detector of the automatic blood sampler. Across the cohort, this background signal averaged 2.88 ± 1.24 kBq/mL over the 60-minute acquisition, demonstrating a relatively stable offset. Thus, an additive AIF correction was applied using the discrete blood samples. For each discrete sampling timepoint, the mean activity concentration of the raw AIF was calculated in a symmetric 60-second window that was centered at this timepoint to reduce noise. The difference between this value and the activity concentration from the discrete blood sample was then determined. The resulting six values were linearly interpolated to obtain a continuous time-dependent curve. Finally, background correction was applied by subtracting this curve from the AIF.

IDIF extraction and calibration

Carotid IDIFs were generated by manual extraction of the native carotid PET signal extracted over the 60-minute dynamic PET scan. In brief, two spherical regions of interests (ROIs) of 5 mm diameter, one positioned on each carotid artery, were delineated on the summed early PET frames using PMOD V3.407 (PMOD Technologies LLC, Bruker, Fällanden, Switzerland). Despite the careful placement of both ROIs, IDIFs remain affected by PVE and limited spatial resolution. Thus, additional IDIF calibration was performed based on the measured AIF. A population-based, peak-recovery calibration was applied to compensate for the time-varying net bias of PVE: underestimation is maximal during the narrow first-pass bolus peak and diminishes as the tissue activity becomes spatially smoother at later time points. A recovery coefficient (RC) was defined as the ratio of AIF-to-IDIF peak activity within the first 3 minutes

post-injection, and a population mean (RC_{pop}) was computed across all subjects. A smooth, time-decaying correction factor was then applied across the entire IDIF time-activity curve:

$$F(t) = 1 + (RC_{pop} - 1) \cdot \exp(-\lambda \cdot t),$$

where t denotes time in minutes. The decay constant $\lambda = 0.5 \text{ min}^{-1}$ was selected by minimising the mean whole-curve root-mean-squared error (RMSE) across a sweep of candidate values ($\lambda \in \{0.3, 0.5, 1.0, 1.5, 2.0, 3.0, 5.0\} \text{ min}^{-1}$). This two-parameter correction (RC_{pop}, λ) is entirely population-derived and can therefore be applied prospectively to new $[^{18}\text{F}]\text{F-DED}$ acquisitions.

Kinetic characterisation of $[^{18}\text{F}]\text{F-DED}$

To identify the most appropriate kinetic model for quantification of $[^{18}\text{F}]\text{F-DED}$, three compartment models were fitted to regional tissue TACs using the plasma-corrected AIF as input function: a one-tissue model with two rate constants (1T2K), an irreversible two-tissue model with three rate constants (2T3K), and a reversible two-tissue model with four rate constants (2T4K). Model fits were evaluated in two representative regions (putamen and frontal cortex) across all eight subjects. Model selection was based on the corrected Akaike information criterion (AICc), with the model yielding the lowest AICc designated as the best fit for each region-patient combination.

Regional and voxel-wise parametric imaging

Kinetic modelling was performed in two stages. First, all five modelling approaches were compared at the region level: the regional time-activity curves (TACs) of two representative regions - the putamen and a frontal composite region - were fitted with the AIF and the IDIF as input under each correction condition (i.e. raw, plasma-metabolite-corrected and peak-scaling), so that the IDIF- and AIF-derived outcomes could be compared directly. The three compartment models were solved by the basis-function (Alpert) method²¹, modelling the measured activity as

$$C(t) = (1 - vB) \cdot C_T(t) + vB \cdot C_{blood}(t),$$

where $C_T(t)$ is the tissue response, $C_{blood}(t)$ the whole-blood concentration, and vB the fractional cerebral blood volume (fixed at 0.05). For the 1T2K model $C_T(t) = K_1 \cdot C_p(t) \otimes e^{-(k_2 \cdot t)}$, with $C_p(t)$ the arterial plasma input and total distribution volume $VT = K_1/k_2$; the 2T3K and 2T4K models add a second tissue compartment, yielding the net influx rate constant K_i (2T3K) and VT (2T4K). The k_2 basis was logarithmically spaced (10^{-3} - 1 min^{-1}), and the parameters minimising the frame-weighted residual sum of squares were retained.

Logan and Patlak graphical analyses were additionally applied, estimating VT (Logan) and K_i (Patlak) as the slope of the respective linearised plot fitted to frames with mid-time $\geq t^* = 15 \text{ min}$ ^{22,23}.

Second, voxel-wise parametric maps were generated in MNI space for the two most robust models. Prior to fitting, the dynamic data were smoothed with an isotropic 3D Gaussian kernel (FWHM = 2.5 mm), and VT was clipped to [0, 30] mL·cm⁻³ to suppress noise-driven extremes (no per-voxel goodness-of-fit filter applied). AIF- and IDIF-derived maps were compared voxel-wise by percentage-difference maps, %Diff = $(VT_{IDIF} - VT_{AIF})/VT_{AIF} \times 100$, and regionally by averaging the parametric VT over 89 Hammers atlas regions (excluding white-matter and ventricular labels).

Statistical analysis

The population recovery coefficient (RC_{pop}) and decay constant (λ) of the peak-recovery calibration were derived from the full cohort, as the population mean across all eight subjects. Kinetic models were compared at the region level by the corrected Akaike information criterion (AICc), the lowest-AICc model being designated the best fit for each region-subject combination. Head-to-head agreement between each IDIF and the gold-standard AIF was quantified at the input-function level by the Pearson correlation coefficient (r), root-mean-squared error (RMSE, kBq/mL), area-under-the-curve ratio (AUC_{IDIF}/AUC_{AIF}), peak ratio ($IDIF_{peak}/AIF_{peak}$), and peak underestimation [$100 \times (AIF_{peak} - IDIF_{peak})/AIF_{peak}$]. Agreement between IDIF- and AIF-derived regional kinetic outcomes (VT and Ki) was assessed by linear regression across subjects, reporting the slope, coefficient of determination (R^2) and p-value; this was done both for the ROI-level model fits (**Table 3**) and for the region-averaged voxel-wise parametric maps. At the voxel level, percentage-difference maps were computed as %Diff = $(VT_{IDIF} - VT_{AIF})/VT_{AIF} \times 100$, and the mean $\pm$ SD, median and interquartile range (IQR) of the absolute percentage difference across all brain voxels reported. All analyses were implemented in Python (version 3.10) using NumPy, SciPy, NiBabel, nilearn and matplotlib.

Results

Study sample

Eight subjects (three female; mean age 59.8 ± 10.1 years, range 42–74) underwent dynamic [¹⁸F]F-DED PET/CT with concurrent arterial blood sampling. The cohort was clinically heterogeneous and comprised participants with Parkinson's disease ($n = 2$, one with subjective cognitive impairment), isolated REM sleep behaviour disorder ($n = 2$), multiple system atrophy ($n = 1$), essential tremor ($n = 1$), Alzheimer's disease with mild dementia ($n = 1$) and subjective cognitive impairment ($n = 1$). Diagnoses were established according to standard clinical criteria and supported, where available, by disease-relevant biomarkers, including amyloid and tau status (PET and/or CSF), dopamine transporter imaging (DaT-SPECT), cardiac ¹²³I-MIBG scintigraphy, [¹⁸F]FDG-PET, and serum neurofilament light chain (see **Table 1**). All participants provided written informed consent, and the study was approved by the local ethics committee.

Plasma and metabolite correction

Prior to kinetic modeling, both the continuous AIF and the IDIFs were corrected for plasma and parent fractions using the discrete manual blood samples (Fig. 2). After collecting the blood, the samples were centrifuged to separate the plasma, and the respective activity concentrations were measured using an automatic gamma counter (Hidex GmbH, Mainz, Germany). The plasma-to-whole-blood ratio was calculated for all available samples. Next, high-performance liquid chromatography (HPLC) was employed to determine the fraction of unmetabolized parent tracer and radiometabolites in the plasma samples. Here, three polar, presumably non-brain-penetrant radiometabolites were detected (**Supplementary Fig. 1**). To generate continuous correction curves across the entire scan duration, mono-exponential functions were fitted to the pooled discrete data: a decaying exponential with a non-zero plateau for the parent fraction, and a slowly decaying exponential for the plasma-to-whole-blood ratio, which remained approximately constant (~ 1.2) over the 60-minute acquisition. All AIFs and IDIFs were multiplied by these time-dependent population curves to obtain the metabolite-corrected arterial plasma input functions required for kinetic modelling.

Kinetic characterisation of [^{18}F]F-DED

Compartmental model comparison did not support a pure irreversible-trapping model for [^{18}F]F-DED. The reversible 2T4K model was preferred by the AICc under every input-function correction - in 5/8 subjects with the raw AIF, 6/8 with the individually corrected AIF and 7/8 with the population-corrected AIF - and achieved the lowest mean AICc in all three conditions with the irreversible 2T3K model favoured in the remaining subjects. This consistent preference for a two-tissue model containing a reversible compartment indicates a measurable, non-negligible reversible component in [^{18}F]F-DED kinetics. The improvement over the one-tissue (1T2K) model was nonetheless modest: although 1T2K was not selected by the AICc, it reproduced the dominant features of the regional TACs (Fig. 3). VT, which is well defined for both two-tissue configurations, was adopted as the primary outcome measure; given the voxel-level instability of the 2T4K VT, parametric maps were computed with the Logan graphical analysis, with 1T2K as a reversible alternative. Given the near-irreversible behaviour, an irreversible-trapping approximation - Patlak graphical analysis, which yields the net influx rate constant K_i - also represents a valid alternative for [^{18}F]F-DED quantification (**Supplementary Methods**).

Head-to-head Comparison of AIF and IDIF

Across all eight subjects, the extracted IDIF was strongly correlated with the AIF (mean $r = 0.89 \pm 0.07$; $R^2 = 0.79 \pm 0.12$), with a mean RMSE of 17.5 ± 3.1 kBq/mL (**Table 2**). However, the IDIF systematically underestimated the arterial bolus peak: the mean peak ratio ($\text{IDIF}_{\text{peak}}/\text{AIF}_{\text{peak}}$) was 0.22 ± 0.04 , corresponding to a mean peak underestimation of $78.1 \pm 4.0\%$. Cumulative tracer availability was less affected - the area-under-the-curve ratio ($\text{AUC}_{\text{IDIF}}/\text{AUC}_{\text{AIF}}$) was 0.47 ± 0.11 - indicating that the underestimation was concentrated in the narrow first-pass bolus and diminished at later, spatially smoother time points, consistent with the time-dependent nature of partial-volume effects (representative subject, Fig. 4).

IDIF calibration

The population-based, time-decaying peak-recovery calibration (recovery coefficient $RC_{pop} = 4.7 \pm 0.81$, decay constant $\lambda = 0.5 \text{ min}^{-1}$; see **Methods**) substantially improved agreement with the AIF (**Table 2**). The mean peak ratio increased from 0.22 ± 0.04 to 0.84 ± 0.17 , reducing the mean peak underestimation from $78.1 \pm 4.0\%$ to $15.9 \pm 6.3\%$. Whole-curve agreement likewise improved: mean r rose from 0.89 ± 0.07 to 0.93 ± 0.05 , R^2 from 0.79 ± 0.12 to 0.87 ± 0.08 , and RMSE fell by half, from 17.5 ± 3.1 to 8.7 ± 2.7 kBq/mL. The AUC ratio increased more modestly, from 0.47 ± 0.11 to 0.57 ± 0.13 , reflecting that the correction acts predominantly on the early bolus while leaving the later tail largely unchanged. The calibrated IDIF was used as the input function for all subsequent kinetic analyses.

ROI-level parametric mapping

Table 3 reports the agreement (R^2 and p) between IDIF- and AIF-derived regional outcomes for the five kinetic models, in the putamen and frontal cortex, under the three input conditions. Logan graphical analysis gave the most robust agreement: IDIF- and AIF-derived VT were significantly correlated in every condition and both regions ($R^2 = 0.62\text{--}0.73$, all $p \leq 0.02$), and Logan was the only approach that remained significant with uncorrected inputs (basal ganglia $R^2 = 0.69$, frontal $R^2 = 0.62$; Fig. 5A,D). The models that depend on the metabolite-corrected plasma input - the reversible 2T4K, irreversible 2T3K and Patlak analyses - showed weak, non-significant agreement when uncorrected (2T4K $R^2 = 0.35/0.33$, 2T3K $R^2 = 0.00$, Patlak $R^2 = 0.10/0.15$; all $p > 0.1$), but agreed strongly once the plasma- and metabolite-correction was applied (2T4K $R^2 = 0.71/0.77$, 2T3K $R^2 = 0.57/0.58$, Patlak $R^2 = 0.60/0.56$; all $p < 0.05$), the 2T4K model reaching the highest agreement of any model in this condition. The Patlak results are shown in **Supplementary Fig. 2**. The one-tissue 1T2K model already agreed well with uncorrected inputs ($R^2 = 0.66/0.61$) and remained significant after plasma correction ($R^2 = 0.62/0.53$, **Supplementary Fig. 3**). Thus, after plasma- and metabolite-correction all five models showed significant IDIF-AIF agreement ($R^2 = 0.53\text{--}0.77$, all $p < 0.05$). Adding the peak-recovery calibration preserved - and for Logan slightly improved - this agreement (Logan $R^2 = 0.73/0.67$; Fig. 5C,F), whereas for the other models the peak-scaled condition gave intermediate agreement that remained significant for 2T4K and 2T3K but became borderline for 1T2K and Patlak ($p \approx 0.05\text{--}0.07$). Overall, regional IDIF-derived outcomes tracked the arterial reference closely, with Logan VT resulting most stable across all input conditions.

Voxel-wise parametric mapping

Voxel-wise parametric VT maps were visually concordant between the AIF and the calibrated IDIF: the regional distribution of VT was preserved, while the voxel-wise difference map showed a near-uniform positive offset rather than a regional pattern, indicating that the IDIF reproduced the spatial pattern of VT while systematically overestimating its magnitude (Fig. 6). Consistently, the regional Logan VT values averaged from these parametric maps were strongly correlated between the IDIF and the AIF ($R^2 = 0.71$ uncorrected and 0.78 peak-scaled; Fig. 7A,B), with a regression slope above unity confirming the magnitude overestimation. At the voxel level, the percentage difference between IDIF- and AIF-derived

Logan VT was predominantly positive in both conditions, confirming this systematic overestimation; peak-recovery calibration reduced the median voxel-wise difference from + 86.1% (IQR 62.5-134.7) to + 69.6% (IQR 51.7–91.9) and markedly narrowed its spread, thereby bringing the voxel-wise VT closer to the arterial reference (Fig. 7C,D).

Discussion

The present study demonstrates the feasibility of non-invasive IDIF-based quantification of [^{18}F]F-DED PET for the assessment of MAO-B availability. Using a manual carotid IDIF extraction operating in native PET space, combined with a population-derived, time-decaying peak-recovery calibration, we show that IDIF-derived outcomes agree closely with the gold-standard arterial input function after calibration, with Logan graphical analysis providing the most robust agreement across all input conditions.

The carotid IDIF markedly underestimated the arterial bolus peak (78.1% uncalibrated), a more pronounced attenuation than typically reported for other ^{18}F -labelled tracers^{9,10,24}. This likely reflects the rapid first-pass kinetics of [^{18}F]F-DED combined with the limited spatial resolution of clinical PET relative to the carotid lumen diameter ($\sim 4\text{--}5\text{ mm}$). The underestimation was substantially reduced (to 18.2%) by the peak-recovery calibration. Notably, cumulative tracer exposure was far less affected than the peak (AUC ratio 0.47 uncalibrated), confirming that partial-volume effects (PVE) predominantly distort the early, rapidly changing phase of the time-activity curve, whereas the smoother later portion is well recovered.

Regional comparison of kinetic models did not support a purely irreversible-trapping model for [^{18}F]F-DED: the reversible two-tissue (2T4K) model was preferred by the AICc, indicating a measurable reversible component. This component was nonetheless small and weakly determined - k_4 was frequently poorly identifiable and the irreversible 2T3K model achieved comparable goodness-of-fit - so the tracer behaves as near-irreversible. This dual character of the radiotracer that is induced by deuteration is reflected in the choice of outcome measures: the total distribution volume (VT) is well defined for both two-tissue configurations, while the net influx rate constant (Ki) from Patlak analysis provides a valid irreversible approximation. Importantly, after plasma- and metabolite-correction, IDIF- and AIF-derived regional outcomes agreed significantly for all five modelling approaches, with Logan VT the most robust - significantly correlated with the AIF even for uncorrected inputs and stable across all conditions. Since the reversible VT is unstable at the voxel level, parametric maps were computed with the more stable Logan and 1T2K estimators, with Patlak Ki retained as an irreversible alternative (**Supplementary Methods**).

The peak-recovery calibration corrects the IDIF at the input-function level, before kinetic modelling, rather than rescaling the derived outcome. By applying a large correction at early time points - where PVE are most severe - and tapering to unity at later time points - where the TAC is spatially smooth - it restores the bolus peak while preserving the curve shape on which both compartmental and graphical analyses depend. This is reflected in the improved regional agreement and in a near-uniform, rather than region-

specific, residual difference. The two calibration parameters ($RC_{pop} = 4.71 \pm 0.81$, $\lambda = 0.5 \text{ min}^{-1}$) are entirely population-derived and can be applied prospectively without individual arterial sampling, a critical requirement for clinical translation. These findings align with previous IDIF validation studies for other brain PET tracers, which similarly showed that population-based calibration reduces PVE-induced bias to acceptable levels^{14,24,25}. However, the pronounced peak attenuation observed here underlines that, for tracers with very sharp bolus profiles, correction at the input-function level - rather than at the outcome level - may be essential to achieve meaningful agreement.

Voxel-wise parametric VT maps derived from the calibrated IDIF preserved the characteristic [^{18}F]F-DED binding pattern and showed a near-uniform positive offset relative to the AIF rather than a regional bias, indicating faithful reproduction of the spatial pattern with a systematic magnitude overestimation. Peak-recovery calibration reduced the median absolute voxel-wise difference (from 86.1% to 69.6%) and narrowed its distribution. Because this offset is near-constant across the brain, it is largely absorbed by a single scaling factor and is unlikely to affect group-level or longitudinal within-subject comparisons, where relative differences are of primary interest. Conversely, the dissociation in some regions between low bias and modest correlation - driven by the narrow dynamic range of the outcome and the small sample - highlights that R^2 alone is an incomplete measure of agreement in this context, and that low bias may be the more clinically relevant indicator.

Several limitations should be considered. First, the cohort is small ($n = 8$), and the population-derived calibration parameters were estimated from the same subjects; external validation of IDIF robustness in independent, larger cohorts is essential. However, the clinical heterogeneity of the sample allowed to challenge AIF vs. IDIF agreement by large variance of MAO-B expression in the studied brains. Second, the population metabolite and plasma-to-whole-blood correction curves were applied identically to the AIF and the IDIF, which ensures a fair comparison but does not capture the additional variability that individual metabolite profiles would introduce in practice. Third, the IDIF was extracted manually; although robust, this requires operator input and quality control, particularly in patients with carotid stenosis, calcification, or anomalous vascular anatomy. Fourth, the peak-recovery calibration parameters are expected to be scanner- and reconstruction-dependent; the values reported here apply specifically to the Siemens Biograph 64 TruePoint PET/CT scanner (Siemens Healthineers AG, Erlangen, Germany) used in this study and would need re-estimation for other platforms.

Conclusions

An IDIF extraction pipeline with population-derived peak-recovery calibration provides a viable non-invasive alternative to arterial blood sampling for [^{18}F]F-DED PET quantification. After calibration, all kinetic approaches agreed with the arterial reference, and Logan VT proved the most robust across conditions. Because the calibration parameters are derived entirely from the cohort and require no individual blood data, they can be applied prospectively for the same tracer-scanner combination, removing a major barrier to the clinical adoption of fully quantitative [^{18}F]F-DED PET in

neurodegenerative-disease research. Larger, multi-centre studies will be needed to refine these parameters and establish their generalisability across scanner platforms and patient populations.

Declarations

Ethics approval

This study was approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der LMU München, approval number 21–0721, approval date 28 Oct 2021) and radiation protection authorities (BfS: ZD 3-22464/2023-042-G).

Consent to participate

All study participants whose data are used in this study provided written informed consent.

Consent for publication

Written informed consent was obtained from the patient for publication of this study and accompanying images.

Competing Interests

AJZ is an employee of ITM Oncologics. GNB is a full-time employee of Lantheus Germany GmbH. MB is a member of the Neuroimaging Committee of the EANM. MB has received speaker honoraria from Roche, GE Healthcare, Iba, Miltenyi, and Life Molecular Imaging; has advised Life Molecular Imaging, MIAC, Cenos, and GE healthcare; and is currently on the advisory or imaging review boards of AC Immune and ZRO Imaging.

Funding

The project was funded by the Alzheimer's Drug Discovery Foundation (ADDF) and the Michael J Fox Foundation (MJFF-021137). MB was funded by the Deutsche Forschungsgemeinschaft (DFG) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy - ID 390857198), and within CRC1744 (Project-ID 548585053).

Authors' contributions

Concept and design: LF, NF, AJZ, MB; Acquisition, analysis, or interpretation of data: LF, LV, TS, TL, MZ, BK, AZ, GM, AJ, IM, BR, SR, NA, LT, DVG, GS, GNB, LK, RP, GH, JL, SZ, AJZ, MB; Critical revision of the manuscript for important intellectual content: LF, SL, DVG, GS, GNB, SZ, AJZ, MB; Drafting the

manuscript: LF, NF, AJZ, MB; Statistical analysis: LF, AJZ; Supervision: LF, AJZ, MB. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

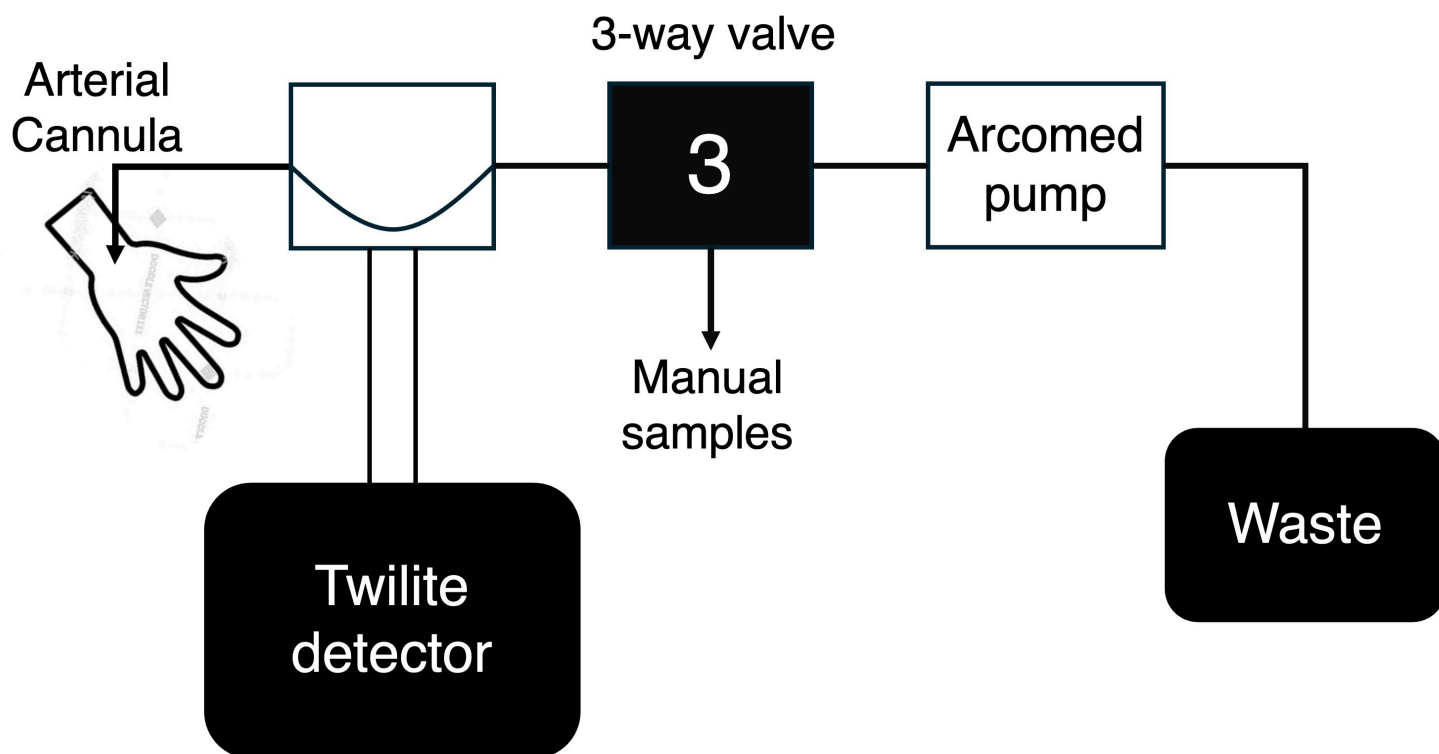


Figure 1

Arterial blood sampling setup. Blood is continuously withdrawn from the radial artery using a peristaltic pump. The blood flows through a coincidence detector for real-time measurement of whole-blood radioactivity. A 3-way valve located downstream of the detector facilitates the simultaneous collection of discrete manual blood samples.

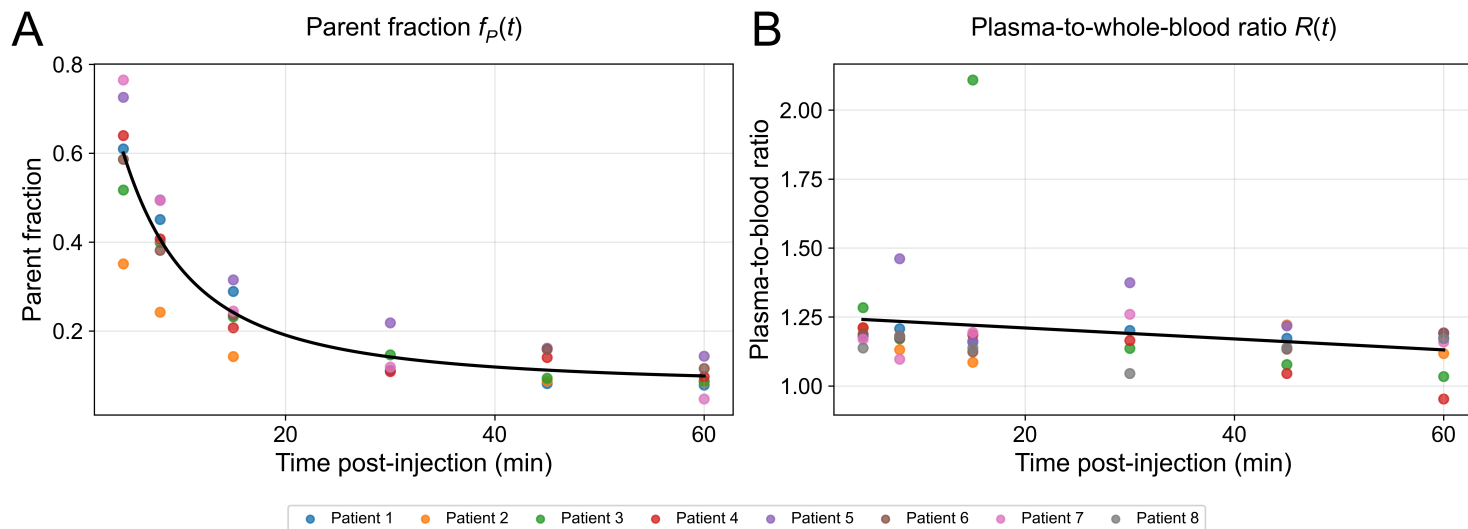


Figure 2

Population-derived metabolite and plasma correction curves applied to both the AIF and IDIF time-activity curves. Parent fraction $f(t)$, modelled as a mono-exponential decay to a plateau ($\lambda = 0.1331 \text{ min}^{-1}$, $C = 0.1106$), representing the fraction of total plasma radioactivity concentration attributable to the intact [^{18}F]F-DED parent compound. Plasma-to-whole-blood ratio $R(t)$, modelled as a slow exponential decay ($A = 1.2356$, $\lambda = 0.0015 \text{ min}^{-1}$), accounting for the differential distribution of tracer between plasma and cellular blood compartments. Time is expressed in minutes post-injection.

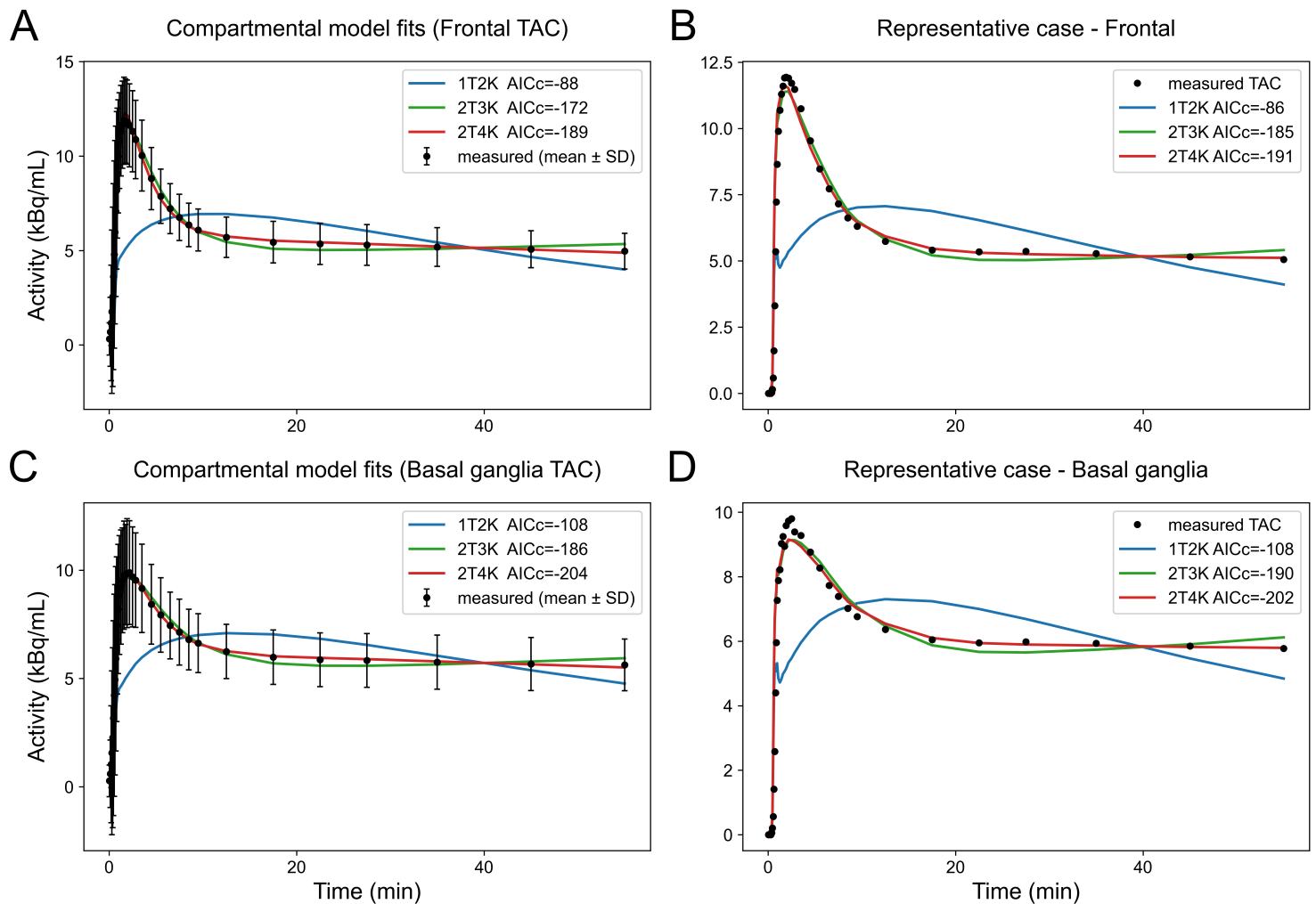


Figure 3

Compartmental model fits to regional time-activity curves (TACs). Measured TACs (black markers) and the corresponding one-tissue (1T2K, blue), irreversible two-tissue (2T3K, green) and reversible two-tissue (2T4K, red) compartment-model fits, using the population-corrected arterial input function. The left column shows the cohort-level result (mean $\pm$ SD across all eight subjects, with each model fitted per subject and averaged); the right column shows a representative single case. The top row corresponds to the frontal cortex and the bottom row to the basal ganglia. For the representative case, the corrected Akaike information criterion (AICc) are given in the legend; cohort panels report the mean AICc. Across both regions, the reversible 2T4K model most closely reproduced the measured kinetics - yielding the lowest AICc.

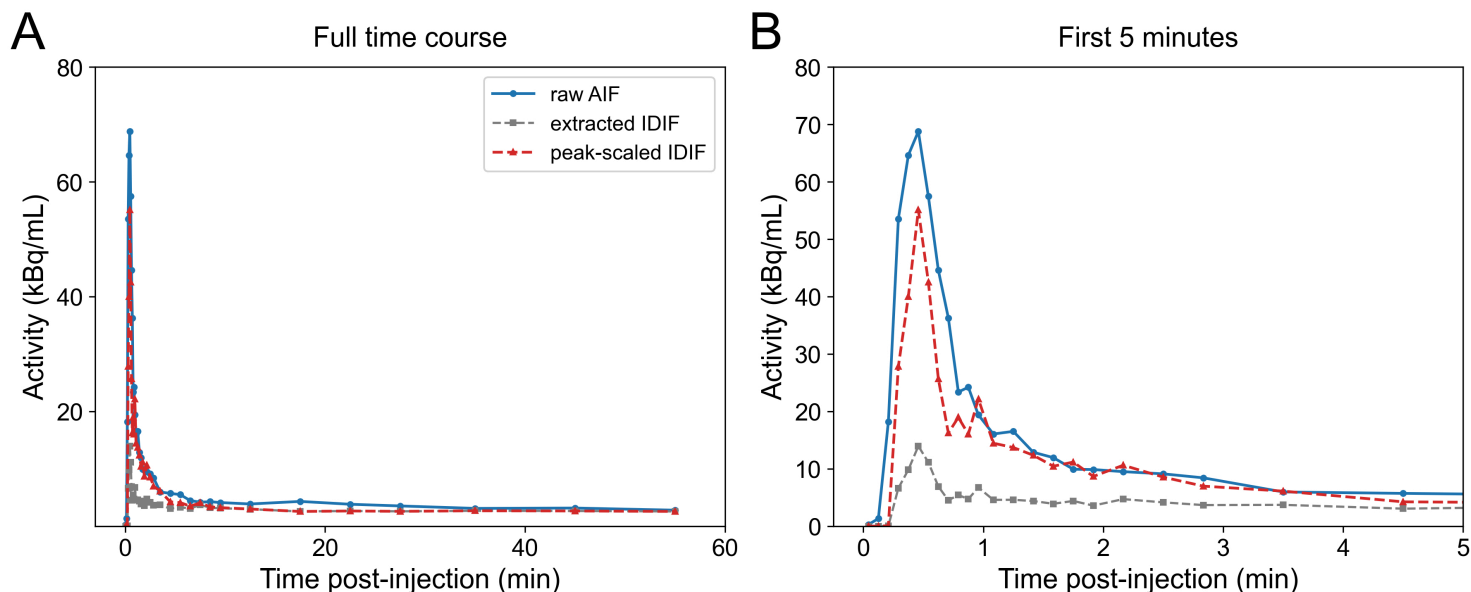


Figure 4

Head-to-head comparison of the arterial input function (AIF) and the carotid image-derived input function (IDIF) in a representative subject. Time-activity curves of the time-aligned raw AIF (blue), the uncalibrated extracted IDIF (grey) and the peak-scaled IDIF (red) over the full 60-minute acquisition (A) and the first 5 minutes (B). The continuous AIF was temporally aligned to the IDIF by matching bolus-peak times and frame-binned to the dynamic acquisition. The extracted IDIF closely tracks the AIF over the later, spatially smoother portion of the curve but severely underestimates the first-pass bolus peak owing to partial-volume effects; the population-based, time-decaying peak-recovery calibration restores the peak toward the arterial value while leaving the tail essentially unchanged. Activity concentrations are in kBq/mL.

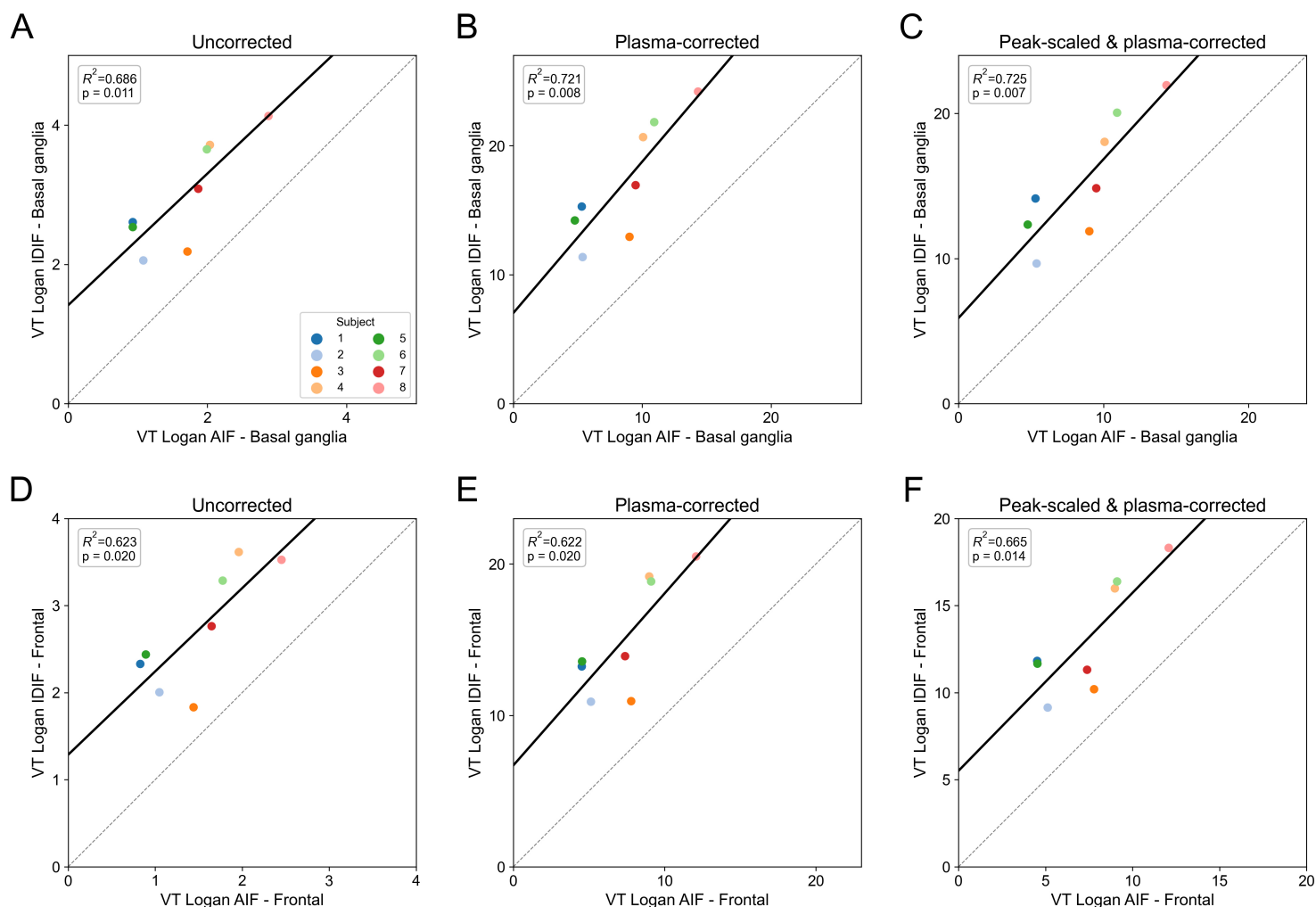


Figure 5

Region-level agreement between IDIF- and AIF-derived total distribution volume (VT) estimated by Logan graphical analysis. Each panel plots the regional VT obtained from the IDIF (y-axis) against the AIF reference (x-axis); each point is one subject and colours denote the eight subjects. Rows correspond to the two regions - basal ganglia (top, A-C) and frontal cortex (bottom, D-F) - and columns to the three input conditions: uncorrected (A, D), plasma- and metabolite-corrected (B, E), and peak-scaled plus plasma-corrected (C, F). For the uncorrected condition the IDIF and AIF are both unprocessed (raw), whereas the plasma-corrected and peak-scaled conditions use the plasma- and metabolite-corrected AIF as reference. The solid black line is the linear regression across subjects and the dashed line the line of identity; the coefficient of determination (R^2) and regression p-value are inset in each panel.

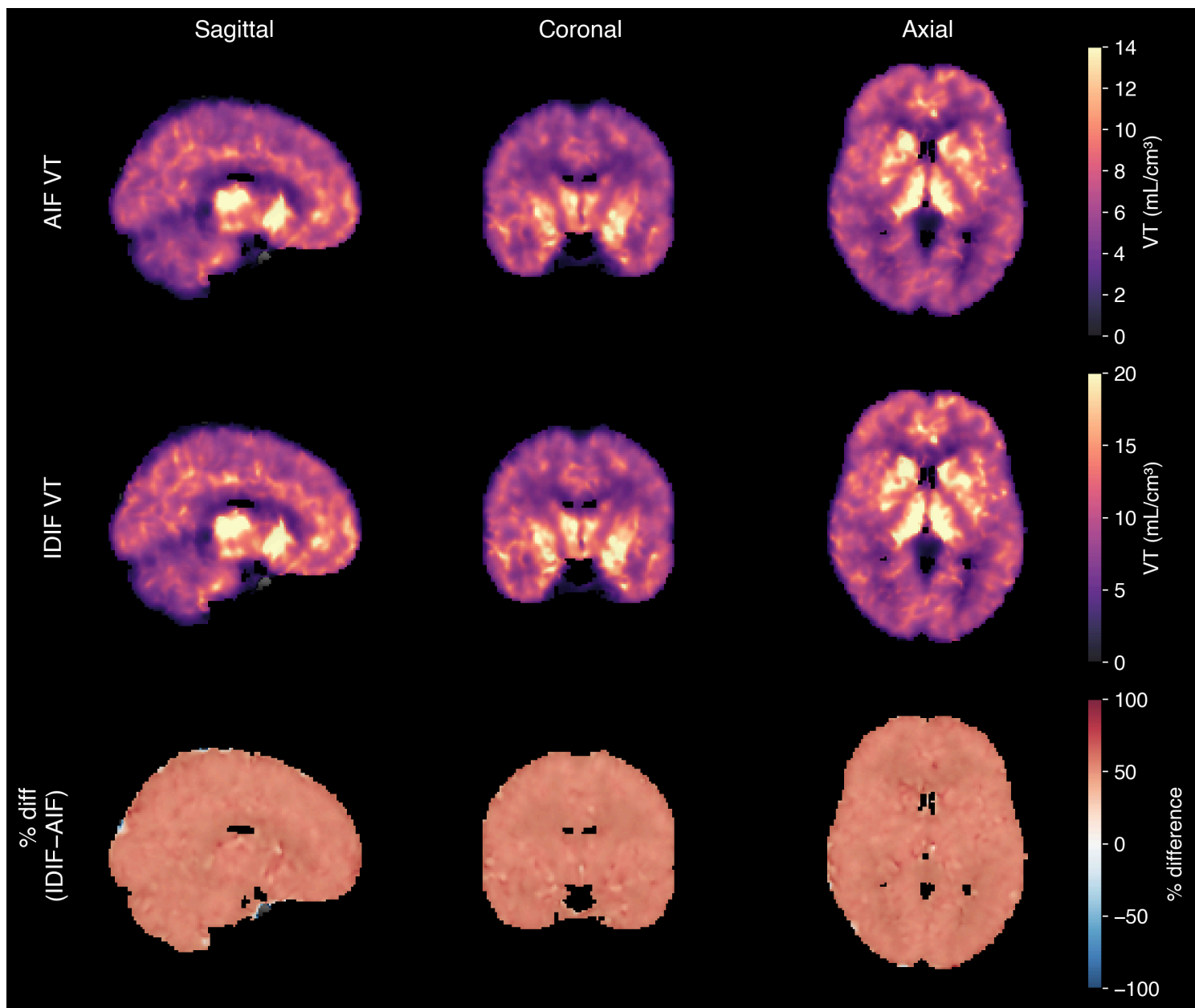


Figure 6

Voxel-wise comparison of Logan Plot derived total distribution volume (VT) based on the calibrated AIF and the calibrated IDIF. Parametric VT maps for a representative subject, shown as sagittal, coronal, and axial slices (columns). Top row: VT estimated with the plasma- and metabolite-corrected arterial input function (AIF). Middle row: VT estimated with the plasma-corrected, peak-scaled image-derived input function (IDIF). Bottom row: the voxel-wise percentage difference between the two, calculated as $(VT_{IDIF} - VT_{AIF}) / VT_{AIF} \times 100$. VT maps are displayed on a perceptually uniform scale (AIF, 0-14 mL/cm³; IDIF, 0-20 mL/cm³) and the difference map on a diverging red-blue scale ($\pm 100\%$), where red indicates higher VT from the IDIF. The spatial pattern of VT is closely preserved between the two input functions; the difference map shows a predominantly positive, spatially uniform offset, consistent with the near-constant regional overestimation observed at the ROI level.

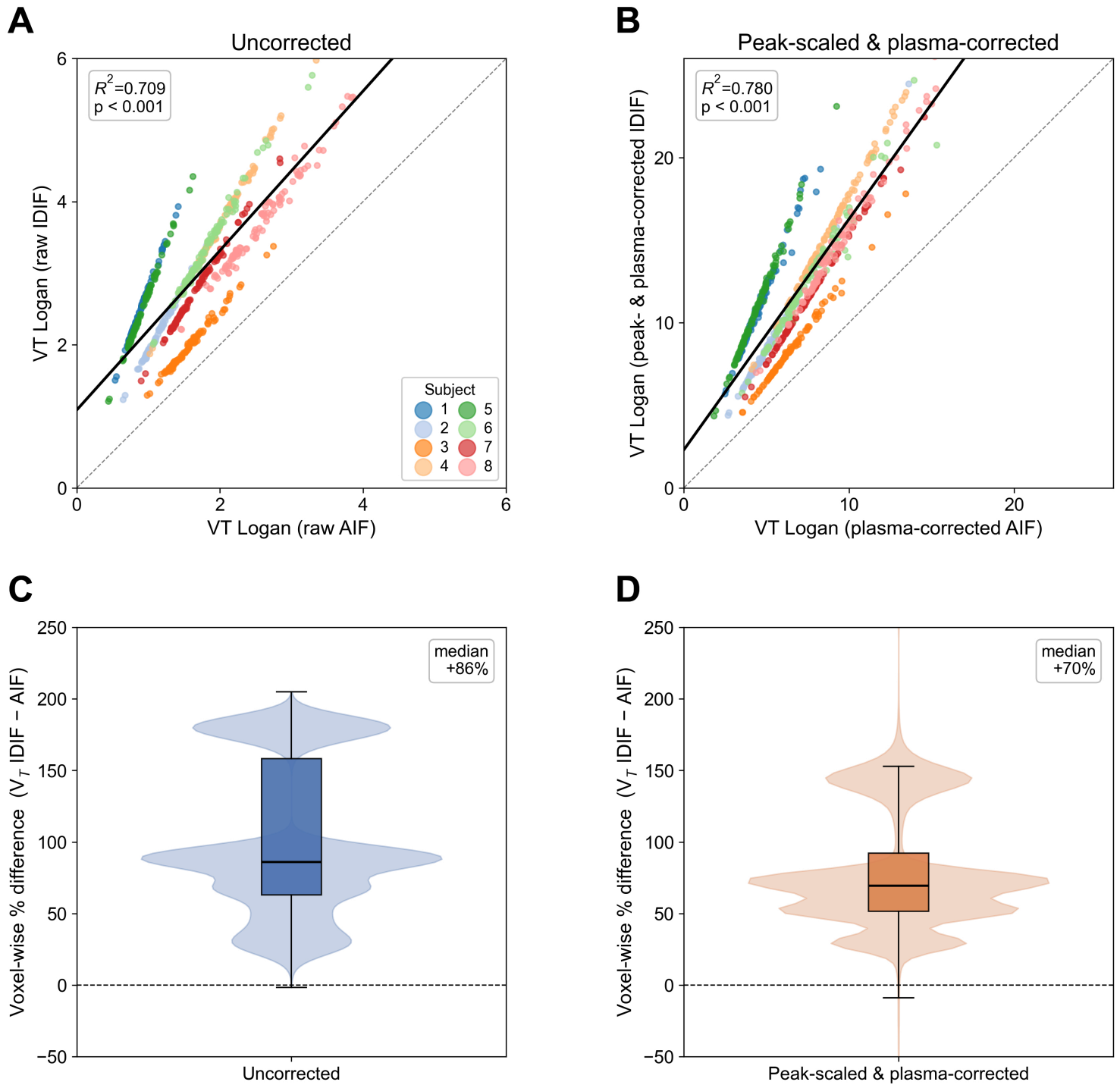


Figure 7

Agreement between IDIF- and AIF-derived Logan total distribution volume (VT) at the regional and voxel level. (A, B) Region-level agreement: the mean Logan VT of the 89 Hammers atlas regions derived from the IDIF (y-axis) plotted against the AIF reference (x-axis), for the uncorrected (A; raw IDIF versus raw AIF) and the peak-scaled plus plasma-corrected (B; against the plasma- and metabolite-corrected AIF) conditions. Each point is one region, colours denote the eight subjects; the solid black line is the linear regression across all region-subject pairs and the dashed line the line of identity, with the coefficient of determination (R^2) and p-value inset. (C, D) Voxel-wise agreement: distribution of the voxel-wise

percentage difference, $(VT_{IDIF} - VT_{AIF})/VT_{AIF} \times 100$, pooled across all brain voxels of the eight subjects, for the same uncorrected (C) and peak-scaled plus plasma-corrected (D) conditions; violin plots show the full distribution with an overlaid box (median), the dashed line marks zero (perfect agreement), and positive values indicate higher VT from the IDIF. Peak-recovery calibration shifted both the regional regression toward the line of identity and the voxel-wise difference distribution closer to zero.

Supplementary Files

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