Supplementary Materials and Methods

The reference tissue model

If the reference tissue includes a vascular component and tissue with irreversible FDG uptake, it can be described by a common irreversible two-tissue compartment model including vascular space (Fig 1).

$$\begin{aligned} C_R(t) &= v_t C_P(t) + (1-v_R)K_R \int_0^t dt' C_P(t') \\ &\quad + (1-v_R)K_{1R}\left(1-\frac{K_R}{K_{1R}}\right)\int_0^t dt' C_P(t') e^{-\frac{K_{1R}}{\lambda_R}\left(\frac{1}{1-K_R/K_{1R}}\right)(t-t')} \end{aligned} \tag{1}$$

Eq. (1) expresses the time course of radioactivity concentration in the reference tissue ($C_R(t)$) as a function of the tracer input ($C_P(t)$, plasma radioactivity concentration), the fraction of blood volume in the reference tissue (v_R), the unidirectional transport rate constant from blood to tissue (K_{1R}), the partition coefficient ($\lambda_R = K_{1R}/k_{2R}$), and the net FDG influx rate constant ($K_R = K_{1R}k_{3R}/(k_{2R}+k_{3R})$) with k_{2R} being the rate constant for transport from tissue to blood and k_{3R} the phosphorylation rate constant (see Fig 1). $v_t = v_R\Phi_t$ with Φ_t multiplied by $C_P(t)$ providing the whole blood radioactivity concentration ($C_B(t) = \Phi_t C_P(t)$).

For constant v_t Eq. (1) can be transformed into the following inhomogeneous second order differential equation for $C_P(t)$ with constant coefficients:

$$\begin{aligned} v_t \frac{d^2}{dt^2}C_P(t) &+ \left(v_t \frac{K_{1R}}{\lambda_R}\frac{1}{1-\frac{K_R}{K_{1R}}} + (1-v_R)K_{1R}\right)\frac{d}{dt}C_P(t) \\ &+ (1-v_R)\frac{K_{1R}}{\lambda_R}\frac{K_R}{1-\frac{K_R}{K_{1R}}}C_P(t) \\ &= \frac{K_{1R}}{\lambda_R}\frac{1}{1-\frac{K_R}{K_{1R}}}\frac{d}{dt}C_R(t) + \frac{d^2}{dt^2}C_R(t). \end{aligned} \tag{2}$$

Taking into account the initial conditions $C_P(0) = 0$ and $\frac{d}{dt}C_P(0) = 0$ the solution can be calculated by first solving the homogeneous equation and then constructing a particular solution from the homogeneous solution by variation of the constants to obtain:

$$\begin{aligned} C_P(t) &= \frac{1}{v_t}C_R(t) + \chi_+ \int_0^t dt' C_R(t') e^{-\sigma_+(t-t')} \\ &\quad + \chi_- \int_0^t dt' C_R(t') e^{-\sigma_-(t-t')} \end{aligned} \tag{3}$$

with

$$\begin{aligned} \sigma_\pm &= \frac{1}{2}\left(\frac{K_{1R}}{\lambda_R}\frac{1}{1-K_R/K_{1R}} + \frac{1-v_R}{v_t}K_{1R}\right) \\ &\pm \sqrt{\frac{1}{4}\left(\frac{K_{1R}}{\lambda_R}\frac{1}{1-K_R/K_{1R}} + \frac{1-v_R}{v_t}K_{1R}\right)^2 - \frac{1-v_R}{v_t}\frac{K_{1R}}{\lambda_R}\frac{K_R}{1-K_R/K_{1R}}} \end{aligned} \tag{4}$$

$$\chi_\pm = \pm\frac{1}{v_t}\frac{\sigma_\pm^2 - \frac{K_{1R}}{\lambda_R}\frac{1}{1-K_R/K_{1R}}\sigma_\pm}{\sigma_- - \sigma_+}. \tag{5}$$

Eq. (3) is only a solution for Eq. (1) and Eq. (2) for $v_t = v_R\Phi_t$ being constant in time. However, Φ_t is time dependent. Huang et al. determined a functional expression in mouse blood, which we use here: $\Phi_t = 1/(1.09 + 0.39\exp\{-0.072t\})$, with t the time after bolus injection in minutes (*1*). In order to calculate $C_P(t)$ taking into account the time dependence of the ratio of whole blood to plasma radioactivity concentration (Φ_t), the solution can be derived using sufficiently small time intervals during which Φ_t can be assumed to be constant and Eq. (3) is the correct solution. Therefore we first re-write Eq. (3) in the following way:

$$\begin{aligned} F(t_0 + \Delta t) &= C_P(t_0 + \Delta t) - \frac{1}{v_t}C_R(t_0 + \Delta t) \\ &= \chi_+ \int_{t_0}^{t_0+\Delta t} dt' C_R(t') e^{-\sigma_+(t_0+\Delta t - t')} \end{aligned} \tag{6}$$

$$+\chi_- \int_{t_0}^{t_0+\Delta t} dt' C_R(t') e^{-\sigma_-(t_0+\Delta t-t')}$$
$$+e^{-\sigma_+(\Delta t)} G_+(t_0)$$
$$+e^{-\sigma_-(\Delta t)} G_-(t_0).$$

The integral expressions on the right-hand side contain only contributions from time $t \geq t_0$. All contributions from $t \leq t_0$ are summarized in the functions $G_\pm(t_0)$, which are explicitly given by:

$$G_\pm(t_0) = \chi_\pm \int_0^{t_0} dt' C_R(t') e^{-\sigma_\pm(t_0-t')}. \quad (7)$$

Analogous to Eq. (6), the temporal derivative of $F(t)$ is given by:

$$\begin{aligned} F'(t_0+\Delta t) \;=\; & (\chi_+ + \chi_-) C_R(t_0+\Delta t) \quad (8) \\ & -\sigma_+\chi_+ \int_{t_0}^{t_0+\Delta t} dt' C_R(t') e^{-\sigma_+(t_0+\Delta t-t')} \\ & -\sigma_-\chi_- \int_{t_0}^{t_0+\Delta t} dt' C_R(t') e^{-\sigma_-(t_0+\Delta t-t')} \\ & -\sigma_+ e^{-\sigma_+(\Delta t)} G_+(t_0) \\ & -\sigma_- e^{-\sigma_-(\Delta t)} G_-(t_0). \end{aligned}$$

Taking Eq. (3) and Eq. (7) $G_\pm(t_0)$ can be expressed in terms of $F(t_0)$ and $F'(t_0)$ as

$$G_\pm(t_0) = \pm \frac{1}{\sigma_- - \sigma_+} (\sigma_\mp F(t_0) - F'(t_0) - (\chi_+ - \chi_-) C_R(t_0)). \quad (9)$$

$C_P(t)$ can then be calculated in the following way:

1. Starting point: $t_0 = 0$.
2. Determine Δt such that $\frac{\Phi_{t_0+\Delta t}}{\Phi_{t_0}} = acc$, where acc is the desired accuracy. (Here we used $acc = 1.001$).

3. Calculate $\sigma_\pm$ and $\chi_\pm$ with $v_t = v_R \Phi_{t_0}$ using Eq. (4) and Eq. (5).
4. Calculate $F(t_0 + \Delta t)$ and $F'(t_0 + \Delta t)$ using Eq. (6) and Eq. (8) (Note that $G_\pm(0) = 0$ (Eq. (7))).
5. Calculate $G_\pm(t_0 + \Delta t)$ using Eq. (9).
6. Set t_0 to $t_0 + \Delta t$ and continue with step 2. Repeat the whole procedure until time t is reached.
7. $C_P(t)$ is then given by $C_P(t) = F(t) + C_R(t)/v_t$.
8. Whole blood radioactivity concentration is then given by $C_B(t) = \Phi_t C_P(t)$.

If the kinetic parameters of the reference tissue $(v_R, K_{1R}, \lambda_R, K_R)$ are known, the tracer input function and whole blood radioactivity concentration can be calculated from the reference tissue time activity curve (TAC) using the procedure introduced above.

The 2-compartment model with 4 rate constants

FDG kinetics in cerebral tissue can be described by a two-compartment model with four rate constants (K_1, k_2, k_3, k_4) and the fractional blood volume (v_B) (*2*)

$$\begin{aligned} C_T(t) &= v_B C_B(t) \\ &+ (1 - v_B)\left(A_- \int_0^t dt' C_P(t') e^{-r_-(t-t')} - A_+ \int_0^t dt' C_P(t') e^{-r_+(t-t')}\right) \end{aligned} \tag{10}$$

with

$$\begin{aligned} r_\pm &= \frac{k_2 + k_3 + k_4}{2} \pm \frac{1}{2}\sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4} \\ A_\pm &= \frac{K_1}{r_+ - r_-}(k_3 + k_4 - r_\pm). \end{aligned}$$

Reversible reference tissue

Given that the kinetic rate constants are known, the input function can also be derived from a reversible reference tissue ($k_{4R} \neq 0$). The radioactivity concentration in the reference tissue is then given by Eq. (10). Solving for $C_P(t)$ the solution is the same as Eq. (3) but with different parameters:

$$\begin{aligned}\sigma_\pm &= \frac{1}{2}\left((1-v_B)(A_- - A_+) + \frac{1}{v_t}(r_+ - r_-)\right) \\ &\pm\sqrt{\begin{array}{c}\frac{1}{4}\left((1-v_B)(A_- - A_+) + \frac{1}{v_t}(r_+ - r_-)\right)^2 \\ -r_+r_- + (1-v_B)(A_+r_- - A_-r_+)\end{array}}\end{aligned} \tag{11}$$

$$\chi_\pm = \pm\frac{(\sigma_\pm - r_+)(\sigma_\pm - r_-)}{\sigma_- - \sigma_+}. \tag{12}$$

Again this solution is only valid for constant v_t. The full solution can be derived following the same procedure as for the irreversible tissue but with $\sigma_\pm$ and $\chi_\pm$ in step 3 calculated from Eq. (11) and Eq. (12).

Parameters for variable lumped constant

Hasselbalch and colleagues have determined the values $L_1 = 1.48$ and $L_3/L_2 = 0.26$ in humans (*3*, *4*). In their work they compare L_1 with the values of this parameter for rats reported in literature and come to the conclusion that there is no species difference (*3*). Also their value of $L_3 = 0.38$ agrees well with the value of 0.37 obtained in rats by Cunningham and Cremer (*5*). L_2 is assumed to be equal to L_1 (which is equivalent to the assumption that $K_{1,glc}/k_{2,glc} = K_1/k_2$). For the calculations presented here we used the values determined by Hasselbalch et al. (*3*, *4*).

References

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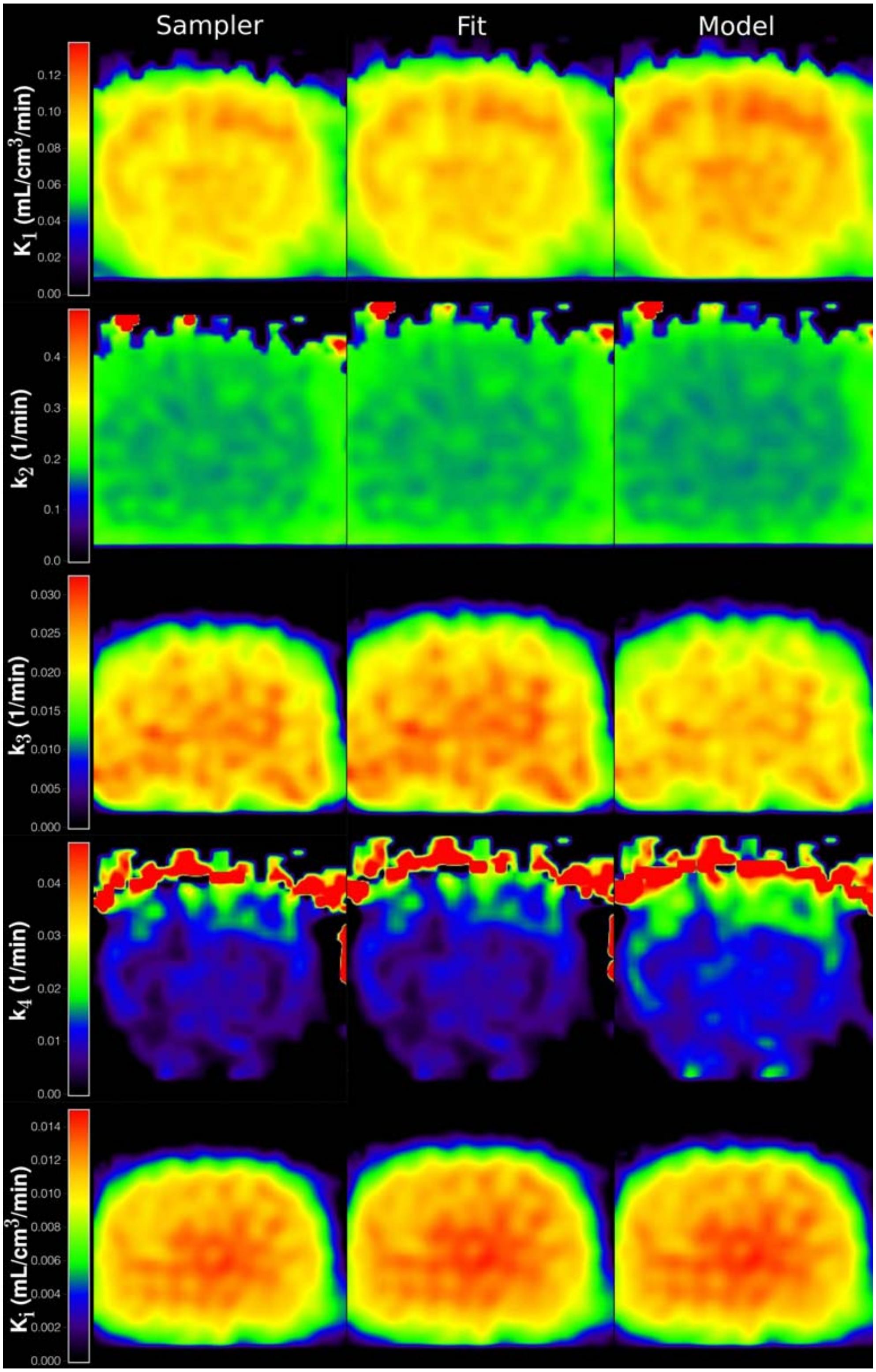
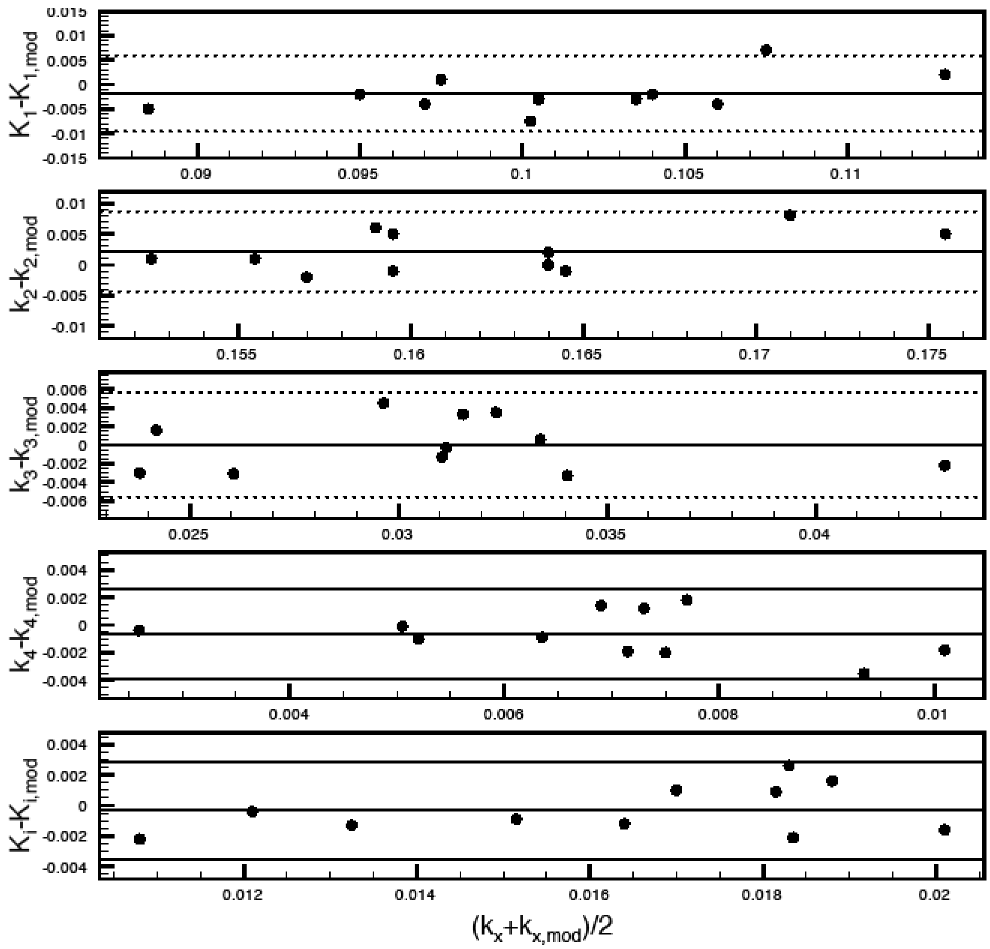
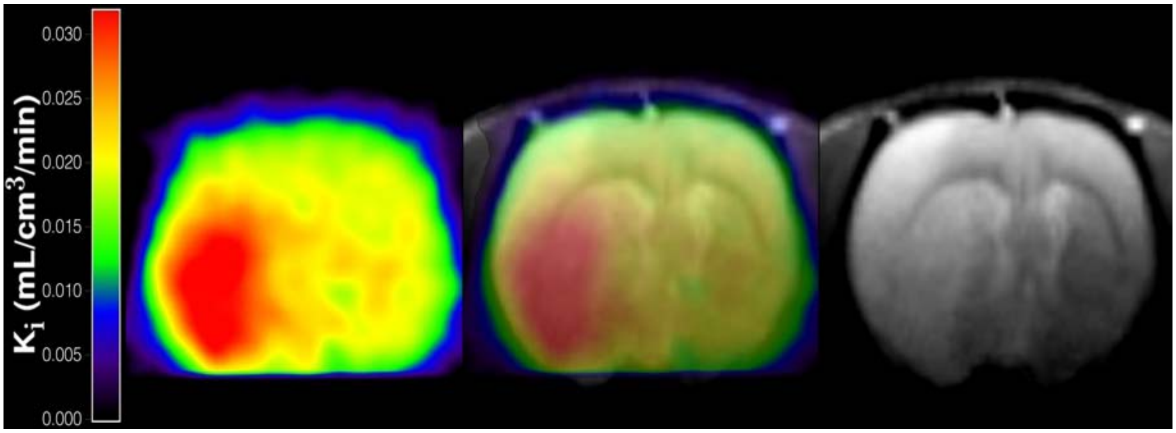


SUPPLEMENTAL FIGURE 1 Parametric images resulting from kinetic modeling using the sampled input function (IF, 1st row), the reference TAC with individually fitted reference parameters (Fit, 2nd row), and the reference TAC with average reference kinetic parameters (Mod, last row)



SUPPLEMENTAL FIGURE 2 Bland-Altman plots of the whole brain kinetic parameters calculated with the reference tissue model with fixed reference kinetic parameters (*mod*) and parameters calculated with the measured input function from blood sampling. Solid lines indicate the mean difference and dashed lines indicate the mean ±1.96 times the standard deviation of the difference. In the label of the *x*-axis: *x* is a replacement character for 1,2,3,4,*i* depending on the parameter plotted. K_1 and K_i are in ml/cm^3/min, k_2, k_3, k_4 in 1/min.



SUPPLEMENTAL FIGURE 3 T2 weighted MRI performed on a 4.7 T BioSpect system (Bruker BioSpin, Ettlingen, Germany) 24 hours after induction of ischemia (right), parametric image of the net influx rate constant K_i one hour after induction of ischemia (left), and fused images (middle). Images were co-registered using the VINCI software (see reference (15) in main manuscript).