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An extended simplified reference tissue model for the quantification of dynamic PET with amphetamine challenge

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Background: **Equilibrium analysis to quantify dynamic positron emission tomography (PET) with bolus followed by continuous tracer infusion and acute amphetamine challenge assumes that all tissue kinetics attain steady states during pre- and post-challenge phases. Violations of this assumption may result in unreliable estimation of the amphetamine-induced percent change in the binding potential (ΔBP%).**
Method: **We derived an extended simplified reference tissue model (ESRTM) for modeling tracer kinetics in the pre- and post-challenge phases. Ninety-minute [^{11}C]raclopride PET studies with bolus injection followed by continuous tracer infusion were performed on 18 monkeys and 2 baboons. Forty minutes after the bolus injection, a single acute intravenous amphetamine administration was given of 2.0 mg/kg to monkeys and of 0.05, 0.1, 0.5, and 1.5 mg/kg to baboons. Computer simulations further evaluated and characterized the ESRTM.**
Results: **In monkey studies, the ΔBP% estimated by the ESRTM was 32 ± 11, whereas, the ΔBP% obtained using the equilibrium methods was 32% to 81% lower. In baboon studies, the ΔBP% values estimated with the ESRTM showed a linear relationship between the ΔBP% and the natural logarithm of amphetamine dose ($R^2 = 0.96$), where the ΔBP% = 10.67Ln(dose) + 33.79 (0.05 ≤ dose in mg/kg ≤ 1.5). At 1.5 mg/kg amphetamine, the ΔBP% estimates from equilibrium methods were 18% to 40% lower than those estimated by the ESRTM. Results showed that the nonsteady state of tracer kinetics produced an underestimation of the ΔBP% from the equilibrium analysis. The accuracy of the ΔBP% estimates from the equilibrium analysis was significantly improved by the ESRTM. The ΔBP% estimated by the ESRTM in the study was consistent with that from previous [^{11}C]raclopride PET with amphetamine challenge.**
Conclusion: **In conclusion, the ESRTM is a robust kinetic modeling approach and is proposed for the quantification of dynamic PET with acute amphetamine stimulation.**

Introduction

Positron emission tomography (PET) is a quantitative functional *in vivo* neuroimaging technique, which has being used to detect and measure amphetamine-induced cerebral dopamine release in both human and nonhuman primates (Kegeles and Mann, 1997; Laruelle, 2000). The basic and commonly used physiological parameter to quantify amphetamine challenge effects on the dopamine system is the percent change in tracer binding potential (BP) (Carson et al., 1997; Huang et al., 1986; Koeppe et al., 1991; Laruelle, 2000; Mintun et al., 1984; Wong et al., 1997). For the various PET experimental designs and data acquisition methods, tracer BP can be estimated by compartmental modeling with plasma input or reference tissue input (Gunn et al., 2001), graphical analysis (Logan et al., 1990, 1996), or equilibrium analysis (Carson, 2000; Carson et al., 1993; Farde et al., 1989; Lassen, 1992).

In dynamic PET studies with steady state designs, a radiolabeled tracer is administered by bolus followed by continuous infusion for tissue radioactivity to attain constant level, thus BP can be estimated by equilibrium analysis. A reference tissue-based concentration ratio (CR) method may be one of the simplest approaches for tracer kinetic equilibrium analysis in PET studies with steady state designs. The CR method is commonly used for the quantification of [^{11}C]raclopride dynamic PET studies with acute amphetamine challenges. The CR method assumes that the tracer kinetics attain steady states within pre- and post-amphetamine phases. In practical applications, the bolus-to-infusion ratio, and the time frames for pre- and post-amphetamine phases are usually fixed for all subjects based on prior knowledge of tracer kinetics, and simulations (Carson et al., 1993). Due to heterogeneity in inter- and intrasubject tissue kinetics, the fixed bolus-to-infusion ratio, and limited PET scan time for pre- and post-amphetamine phases may result in violations of the steady state assumption of the measured tracer kinetics (Carson et al., 1993, 1997; Houle et al., 1996). Using the CR method to quantify dynamic PET data that is not in steady state can result in systematic

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errors in the estimates of BP and amphetamine-induced changes in the BP. A procedure to determine steady state phases for optimal measurements of amphetamine-induced BP changes has been proposed (Watabe et al., 2000). However, the optimization is based on an empirical noise model for the specific application of [^{11}C] raclopride dynamic PET scans with acute amphetamine challenges. Estimating percent changes of BP as a function of selected "steady state" time frames from measured PET data is a straightforward ad hoc approach to determine steady state frames for the CR methods (Carson et al., 1997, 2001).

To minimize the bias and variation of estimates of the baseline BP resulting from the nonsteady state of tissue kinetics in pre-amphetamine phase, a CR with a simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) (SRTM-CR) for equilibrium analysis has been proposed (Watabe et al., 1998; Endres et al., 2002). For the SRTM-CR, the BPs in pre- and post-amphetamine challenge phases are estimated by CR with a steady state frame selected in the post-amphetamine phase. The baseline tissue tracer concentration in the post-stimulus phase (in the absence of amphetamine challenge) is extrapolated from the tissue concentration in pre-amphetamine phase by the SRTM model. However, the extrapolated baseline tissue kinetics may still not be able to attain steady states in post-amphetamine phase. In addition, the extrapolation may produce error propagation, especially when the measured baseline data have a high noise level. As in the CR method, violation of the steady state assumption in post-amphetamine phase tracer kinetics will have the same effects on the SRTM-CR method for BP estimation in the post-amphetamine phase.

In this study, we derive an extended simplified reference tissue model (ESRTM) for [^{11}C]raclopride dynamic PET scans with acute amphetamine challenges. ESRTM is a compartmental modeling approach using reference tissue input which does not have a steady state assumption for measured PET data. The objective of this study is to evaluate and characterize an ESRTM in nonhuman primate amphetamine challenge studies with [^{11}C]raclopride PET, and with computer simulations. For comparison purpose, the commonly used equilibrium analysis methods including CR and SRTM-CR were applied to the same data set as those used for evaluation of ESRTM.

Materials and methods

Definition of binding potential (BP)

The BP estimated by equilibrium analysis and ESRTM is defined as $BP=f_2B'_{max}/K_D=f_2k_{on}B'_{max}/k_{off}$, where f_2 is the free fraction of tracer in the free and nonspecific binding compartment, B'_{max} (nM) is the available receptor density for tracer binding, and K_D (nM) is the tracer equilibrium dissociation constant, k_{on} (1/nM/min) is the tracer–receptor association rate constant, and k_{off} (1/min) is the tracer dissociation rate constant from receptor (Huang et al., 1986; Mintun et al., 1984). In ligand-receptor dynamic PET studies with tracer of high specific activity, the $BP=k_3/k_4$, where the $k_3=f_2k_{on}B'_{max}$ is the rate of tracer specific binding, and $k_4=k_{off}$. The BP is also defined by tracer distribution volume as $BP=DV/DV_{F+NS}-1$, where DV and DV_{F+NS} are the total and free plus nonspecific tracer distribution volume (in mL/mL) in the tissue, respectively (Koeppe et al., 1991). In [^{11}C]raclopride PET studies, DV_{F+NS} is commonly estimated by the distribution volume in the cerebellum, the reference tissue devoid of tracer specific binding. The estimation of BP using PET with reference tissue input, such as the equilibrium analysis method, graphical analysis, and the SRTM kinetic modeling approach have been developed (Carson et al., 1993; Lammertsma and Hume, 1996, Logan et al., 1996).

Note that these simplified quantification methods with reference tissue input are derived from classical compartmental modeling theory (Farde et al., 1989; Huang et al., 1980, 1986; Koeppe et al., 1991; Laruelle et al., 2002; Mintun et al., 1984; Wong et al., 1984), and thus have the following fundamental assumptions: (1) The endogenous dopamine is in a steady state within the time of interest for tracer kinetic modeling and analysis. Dopamine receptor binding is in equilibrium condition, and the concentrations of dopamine and its receptors (D2/D3) are constants; (2) The concentrations of dopamine and tracer are homogenous in all compartments (free, nonspecific binding, and specific binding); and (3) The transports of tracer between compartments have first order kinetics. These assumptions are the basis for the application and quantification of ligand–receptor PET studies. In addition to the above assumptions, the following two equilibrium methods and the ESRTM model require more specific assumptions on the tracer kinetics as described below, respectively.

Equilibrium analysis: concentration ratio (CR) method

The CR method assumes that the steady states of tracer kinetics are attained within [$t0$ $T0$] for the pre-amphetamine phase and [$t1$ T] for the post-amphetamine phase. The tracer BP for the pre-amphetamine phase (BP0), and the post-amphetamine phase (BP1) are then estimated by CR as follows:

$$BP0 = \frac{C_T([t0\ T0])}{C_{REF}([t0\ T0])} - 1 \quad (1)$$

$$BP1 = \frac{C_T([t1\ T])}{C_{REF}([t1\ T])} - 1 \quad (2)$$

where $T0$ is amphetamine injection time, T is the PET scan end time, $C_T([t0\ T0])$ and $C_{REF}([t1\ T])$ are the target and reference tissue concentration on time frame [$t0$ $T0$] and [$t1$ T], respectively.

Equilibrium analysis: concentration ratio with the simplified reference tissue model (SRTM-CR)

The SRTM-CR method assumes that: (1) the target tissue kinetics follows the SRTM model in the pre-amphetamine phase [0 $T0$] (Lammertsma and Hume, 1996); (2) in the absence of an amphetamine stimulation, the target tissue kinetics follows a SRTM model in full study period [0 T], but the SRTM can be identified in [0 $T0$] and the tissue kinetics attain steady state in [$t1$ T]; and (3) the tissue tracer kinetic steady states are attained in [$t1$ T] with acute amphetamine challenge given at $T0$. Based on these assumptions, the baseline target tissue concentrations in the post-stimulation phase [$t1$ T] attain a steady state and can be predicted by the SRTM. So the BP0 can be estimated by Eq. (3)

$$BP0 = \frac{C_{Tbas}([t1\ T])}{C_{REF}([t1\ T])} - 1 \quad (3)$$

where C_{Tbas} is the model-predicted baseline target tissue concentration in the post-stimulation phase [$t1$ T]. For this method, the SRTM model parameters are first estimated by fitting the SRTM to the measured target tissue kinetics within the baseline phase [0 $T0$]. Then, the SRTM model with the fitted parameters, and with C_{REF} defined on [0 T] as input, is used to extrapolate the fitted tissue concentration over the post-stimulus phase to get C_{Tbas}. After computing C_{Tbas}, Eq. (3) is used to estimate BP0.

As the CR method, Eq. (2) is used to compute BP1 for SRTM-CR.

Extended simplified reference tissue model (ESRTM)

The essential tracer kinetics assumptions for ESRTM are: (1) the tracer kinetics follows the SRTM(R_1, k_2, BP) (Lammertsma and Hume, 1996) model for the pre- and post-amphetamine phases; (2) the amphetamine effects on R_1 (the target to reference tissue ratio of transport rate constant from blood to tissue) and k_2 (the efflux rate constant of target tissue from free and nonspecific binding to blood) are negligible; and (3) the time for amphetamine-induced changes in the BP from the pre-amphetamine phase (BP0) to the BP in the post-amphetamine phase (BP1) are negligibly short relative to PET data acquisition frame.

Thus, ESRTM is a four parameter (R_1, k_2, BP0, BP1) model that is a composite of two SRTM models: one for the baseline phase with parameters R_1, k_2, BP0, and the other for the post-amphetamine challenge phase with parameters R_1, k_2, and BP1. Based on the differential equation described for the SRTM (Zhou et al., 2003), the tracer kinetics described by the ESRTM are shown in Eqs. (4) (5).

$$\frac{dC_T(t)}{dt} = R_1\frac{dC_{REF}(t)}{dt} + k_2C_{REF}(t) - \frac{k_2}{1+BP0}C_T(t) \quad 0 \le t \le T0 \tag{4}$$

$$\frac{dC_T(t)}{dt} = R_1\frac{dC_{REF}(t)}{dt} + k_2C_{REF}(t) - \frac{k_2}{1+BP1}C_T(t) \quad T0 < t \le T \tag{5}$$

where the $C_T(t)$ and $C_{REF}(t)$ represent the tracer concentrations at time t for target and reference tissues, respectively. The analytical solutions of the above nonhomogeneous first order linear equations with initial conditions are given below (Walter, 1998, pp. 28).

$$C_T(t) = R_1C_{REF}(t) + (k_2 - R_1P_0)e^{-P_0t}\int_0^t C_{REF}(s)e^{P_0s}ds \quad 0 \le t \le T0 \tag{6}$$

$$C_T(t) = C_{T0}e^{-P_1(t-T0)} + R_1\left(C_{REF}(t) - C_{REFT0}e^{-P_1(t-T0)}\right) + (k_2 - R_1P_1)e^{-P_1t}\int_{T0}^t C_{REF}(s)e^{P_1s}ds \quad T0 < t \le T \tag{7}$$

where $C_T(0)=C_{REF}(0)=0$ are the initial conditions for Eq. (4) and $P_0=k_2/(1+BP0)$; $C_{T0}=C_T(T0)$ calculated from Eq (6), and $C_{REFT0}=C_{REF}(T0)$ are the initial conditions for Eq. (5), and $P_1=k_2/(1+BP1)$.

Monkey and baboon studies

Eighteen healthy male cynomologous monkeys (*Macaca fascicularis*) of body weight 6.5±1.2 kg (mean±SD, hereafter), and two male *Papio anubis* baboons (32.5±15.7 kg) were participated in [^{11}C]raclopride PET studies with amphetamine challenges. In each PET study, the animal was initially anesthetized intramuscularly with 8–10 mg/kg alfadolone and alfaxolone acetate (Saffan) (Arnolds Veterinary Products, Shropshire, U.K.). Two intravenous catheters were implanted for infusion of anesthesia and injection of radiotracer, respectively. Anesthesia was maintained throughout the study by a continuous intravenous infusion drip of 6–9 mg/kg/h alfadolone and alfaxolone acetate. The head motion was minimized using an individually fitted thermoplastic mask (Tru Scan Imaging, Annapolis, MD) attached to a head-holder. Ninety-minute dynamic PET studies were conducted for both monkeys and baboons using bolus followed by continuous tracer infusion with bolus to infusion ratio of K_{bol}=75 min (i.e., bolus dose equivalent to 46% of the total dose) (Carson et al., 1993). Forty minutes after the tracer bolus injection, amphetamine was administered intravenously over 2 min within the PET data acquisition frame [40 45] (see the following section). The 5 min frame [40 45] was classified as the baseline phase (Dewey et al., 1993). So the time frames [0 $T0$]=[0 45] and [$T0$ T]=[45 90] were used for the pre- and post-amphetamine phase. In the 18 monkey PET studies, [^{11}C]raclopride (26±2.2 mCi, specific activity 12.5±10.1 Ci/μmol (range 3.1 to 38.8 Ci/μmol) at time of injection) was delivered by bolus followed by continuous infusion over 90 min, with amphetamine injected at a fixed intravenous dose level of 2 mg/kg. In each of 2 baboon studies, four dynamic PET scans, corresponding to the four amphetamine intravenous dose levels of 0.05, 0.1, 0.5, and 1.5 mg/kg, were performed at 1 week intervals, and [^{11}C]raclopride (24.3±2.1 mCi, specific activity 8.2±2.3 Ci/μmol (n=8, range 4.5 to 11.4 Ci/μmol) at time of injection) was administered by bolus followed by continuous infusion through 90 min of PET scanning.

PET imaging, data acquisition, and analysis

PET scanning started at the beginning of the tracer administration. Each dynamic PET scan had 30 frames over 90 min (4×0.25, 4×0.5, 3×1, 2×2, 5×4, 12×5 min), and was performed on a GE Advance scanner in 3D mode. A 10-min ^{68}Ge transmission scan acquired in 2D mode was used for the attenuation correction of emission scans. Images (size 128×128, pixel size 2×2 mm, slice thickness 4.25 mm) were reconstructed using filtered back projection with a ramp filter resulting in spatial resolutions of about 4.5 mm full-width half-maximum at the center of the field of view. Images were decay corrected to the beginning of tracer administration and were expressed in microcuries per milliliter (μCi/mL). Regions of interest including cerebellum and striatum were drawn manually on the sum of dynamic PET images using MEDx (Medical Numerics, Inc., Sterling, VA). The tissue time activity curve (TAC) was obtained by applying regions of interest to all frames of the dynamic image data set. Note that the middle time points of frames are used to generate the tissue TAC in dynamic PET studies.

ESRTM was used for the analysis of measured [^{11}C]raclopride kinetics. The model parameters (R_1, k_2, BP0, BP1) were estimated by minimizing the weighted sum squares of errors given by $(C_T-Y)'W(C_T-Y)$, where $'$ is the matrix transpose operation, C_T is a

measured target tissue (striatum) time activity vector (30×1), Y is a vector determined by Eqs. (6) (7) with measured reference time activity curve C_{REF} as input and model parameters, W is a diagonal matrix (30×30) with positive diagonal element w_{ii}=(duration of ith frame of dynamic PET scanning). Corresponding to the time frames [0 $T0$]=[0 45] and [$T0$ T]=[45 90], the tissue TACs from frame 1 to 21 and TACs from frames 22 to 30 were used to determine pre- and post-amphetamine [^{11}C]raclopride kinetics. The Marquardt algorithm, a conventional nonlinear regression algorithm (Marquardt, 1963), was used for minimization. The percent change in BP was calculated using Eq. (8) after model fitting.

$$\Delta BP\% = 100\frac{BP0 - BP1}{BP0} \tag{8}$$

The equilibrium analysis methods, SRTM-CR and CR, were also applied to the TAC data sets obtained from the monkey and baboon studies for evaluation and comparison. As described in the Introduction, the steady state frame is a key variable for BP and ΔBP% estimation for both CR and SRTM-CR methods. To study how the selection of steady state frames affects the BP and the ΔBP% estimation, three time windows for the pre- and post-amphetamine phases were selected for CR approach, [$t0$ $T0$]= {[22 45], [26 45], [30 45]} and [$t1$ T]={[50 90], [60 90], [70 90]} (Breier et al., 1997; Carson et al., 1997). For SRTM-CR, three time windows {[50 90], [60 90], [70 90]} were used for the pre- and post-amphetamine steady state frames. The tissue concentration on the frame [T1 T2] (C([$T1$ $T2$])) in the Eqs. (1)–(3) for CR and SRTM-CR was calculated as

$$C([T1\ T2]) = \frac{\sum_{T1<t_i<T2} C(t_i)w_{ii}}{\sum_{T1<t_i<T2} w_{ii}} \tag{9}$$

where t_i is the mid time of ith frame of dynamic PET scanning, C (t_i) is the tissue concentration in the ith frame, [$T1$ $T2$]=[$t0$ $T0$] for pre-amphetamine phase, and [$T1$ $T2$]=[$t1$ T] for post-amphetamine phase, and w_{ii}, same as used for ESRTM fitting, is the duration of ith frame of dynamic PET scanning.

To evaluate the assumptions of the ESRTM on R_1 and k_2, and the stability of tracer kinetics in the pre-amphetamine phase, the estimates of R_1, k_2, and BP0 obtained by fitting ESRTM to the measured data in the pre-amphetamine phase only (frame [0 45]) were compared to those estimated by fitting the ESRTM to the measured PET data of full time course kinetics covering both the pre- and post-amphetamine phases (frame [0 90]). Note that the ESRTM is the same as SRTM if the study time is limited to the pre-amphetamine phase.

Computer simulation

The objectives of the computer simulation are: (1) to evaluate the tracer kinetic noise effects on the performance of CR, SRTM-CR, and ESRTM; and (2) to characterize how the tracer kinetic parameters such as tissue clearance rate k_2 and amphetamine dose level affect the tracer kinetics to attain steady states.

The ESRTM, as well as the CR and the SRTM-CR, were characterized by computer simulation. The ESRTM was used to simulate tissue kinetics. A typical cerebellar TAC from a monkey study was used for the input function. The model parameters listed in Table 1 were used for simulations. To evaluate the noise effects on the estimates from the ESRTM, the CR, and the SRTM-CR, Gaussian noise with zero mean and variance $\sigma_i^2=\alpha C_T(t_i)\exp(0.693t_i/\lambda)/\Delta t_i$ was added to the noise free TACs, where $C_T(t_i)$ is target tissue radioactivity at frame i, λ (=20.4 min) is the physical half life of the tracer, Δt_i is the length of the PET scanning interval of frame i, and t_i is the midtime of frame i. Three α values (0.01, 0.02, 0.03) were used to simulate three different noise levels, which we refer to as low, middle, and high noise levels. Based on the comparison of Akaike information criterion (Akaike, 1976, Carson et al., 1993, Turkheimer et al., 2003), the low and middle noise levels are used to simulate noise levels in monkey and baboon tissue TACs. Five hundred realizations for each noise level were obtained to evaluate the statistical properties of the estimates. We calculated variance, standard deviation, bias, and root mean square error. The percent bias (Bias%) and percent root mean square error (RMSE%) of each estimate are calculated as below:

Table 1
Parameter sets used for the computer simulations with an extended simplified reference tissue model (ESRTM)

Parameter	R_1	k_2	BP0	BP1
A	0.90	0.08	3.05	2.05
B	0.90	0.10	3.05	2.05
C	0.90	0.12	3.05	2.05
D	0.90	0.14	3.05	2.05
E	0.90	0.16	3.05	2.05
F	0.90	0.18	3.05	2.05

The parameter vector C ([0.90 0.12 3.05 2.05]) is the mean of the ESRTM model parameter estimates from 18 healthy male cynomologous monkey PET studies using bolus followed by continuous infusion delivery of [^{11}C] raclopride with acute administration of 2.0 mg/kg amphetamine at 40 min after the tracer bolus injection.

$$\text{Bias\%} = \frac{100}{p}\left(\sum_{i=1}^{N}\frac{(p_i - p)}{N}\right)$$

$$\text{RMSE\%} = \frac{100}{p}\left(\sqrt{\sum_{i=1}^{N}\frac{(p_i - p)^2}{N-1}}\right)$$

where p_i is the parameter estimated from the TACs with added noise, p is the "true" value listed in the Table 1, and N (=500) is the number of repeated realizations.

To evaluate the goodness of model fitting, the Akaike information criterion was calculated in monkey, baboon, and computer simulation studies. All parameter estimation methods including nonlinear regression for ESRTM were written in MATLAB (The MathWorks Inc.) and implemented on a Dell PWS650 workstation. Statistical software SAS (SAS Institute Inc.) was used for all statistical analysis.

Results

Monkey studies

The measured striatal TACs from the 18 monkey studies were well fitted by the ESRTM consistently. The percent coefficient of variation (=100 * standard deviation / mean) of the Akaike information criterion was as low as −8. Four typical TACs of the striatum

(open circle) and the cerebellum (reference tissue) (open square) from 4 monkey studies (A–D) are illustrated in Fig. 1. The solid lines are ESRTM fitting curves, and dashed lines are the curves extrapolated from fitted the pre-amphetamine striatal TAC by SRTM. When the extrapolated striatal curve continues increasing (Fig. 1A) then the steady state assumption results in an "undershoot" relative to the extrapolated curve. Conversely, when the extrapolated striatal curve continues decreasing then the steady state assumption produces an "overshoot" relative to the extrapolated curve (Fig. 1B). Both Figs. 1A and 1B demonstrate that the tracer kinetics in the baseline phase are not in steady state, thus the extrapolated curves show a discrepancy with an assumed steady state. Fig. 1C shows striatal TAC (open circle) and the extrapolated curve (dashed line) increase from 0 to the amphetamine injection, while in the post-amphetamine phase the measured striatal TAC decreases and the extrapolated striatal curve remains constant. The TACs in Fig. 1D represent optimal results with the striatal TAC attaining a constant level before amphetamine injection. Note that all the measured striatal TACs in Fig. 1 tend to decline by the end of the PET study, as was the case for almost all 18 monkey studies, which indicates that 50 min is not long enough for the striatal TAC to attain a steady state in the post-amphetamine phase. The estimates obtained by the ESRTM, the SRTM-CR, and the CR methods from the four monkey studies (Fig. 1) are listed in the Table 2. Note that the time frames for CR and SRTM-CR are [30 45; 70 90] and [70 90], respectively. The undershoot of the pre-amphetamine striatal TAC by CR (Fig. 1A) resulted in BP0 estimates 31% lower than those obtained from ESRTM. This underestimation in BP0 was reduced to 8% by SRTM-CR. Fig 1C is similar to Fig. 1A except that the extrapolated striatal TAC curves was in steady state. The BP0 estimated by CR was 24% lower than that estimated by ESRTM, and this underestimation was reduced by SRTM-CR to 5% in monkey C study. Striatal TACs of monkeys B and D approach constant levels within 30 to 45 min post-tracer injection, and the underestimation of BP0 by CR was less than 10%. The nonsteady state of striatal TACs in post-amphetamine phases in monkey B and D studies resulted in the BP1 estimates from the SRTM-CR or the CR about 11% higher than those from the ESRTM.

Table 2
The estimates from four healthy male cynomologous monkey [^{11}C]raclopride PET studies with bolus followed by continuous infusion of tracer delivery and acute administration of 2.0 mg/kg amphetamine at 40 min after the tracer bolus injection

Monkey ID	ESRTM					SRTM-CR[a]			CR[b]	
	R_1	k_2	BP0	BP1	ΔBP %	BP0	BP1	ΔBP %	BP0	ΔBP %
A	0.86	0.11	3.38	2.53	25	3.10	2.66	14.10	2.32	−15
B	0.95	0.16	2.77	2.01	28	2.86	2.25	21.30	2.70	17
C	0.82	0.11	2.51	1.67	34	2.38	1.85	22.60	1.91	3
D	0.89	0.13	3.16	1.80	43	2.96	1.99	32.60	2.83	30

[a] [70 90] was used for steady state frames for pre- and post-amphetamine phases.
[b] [30 45] and [70 90] were used for steady state frames for pre- and post-amphetamine phases, respectively. The BP1 estimated by CR is the same as that estimated by SRTM-CR.

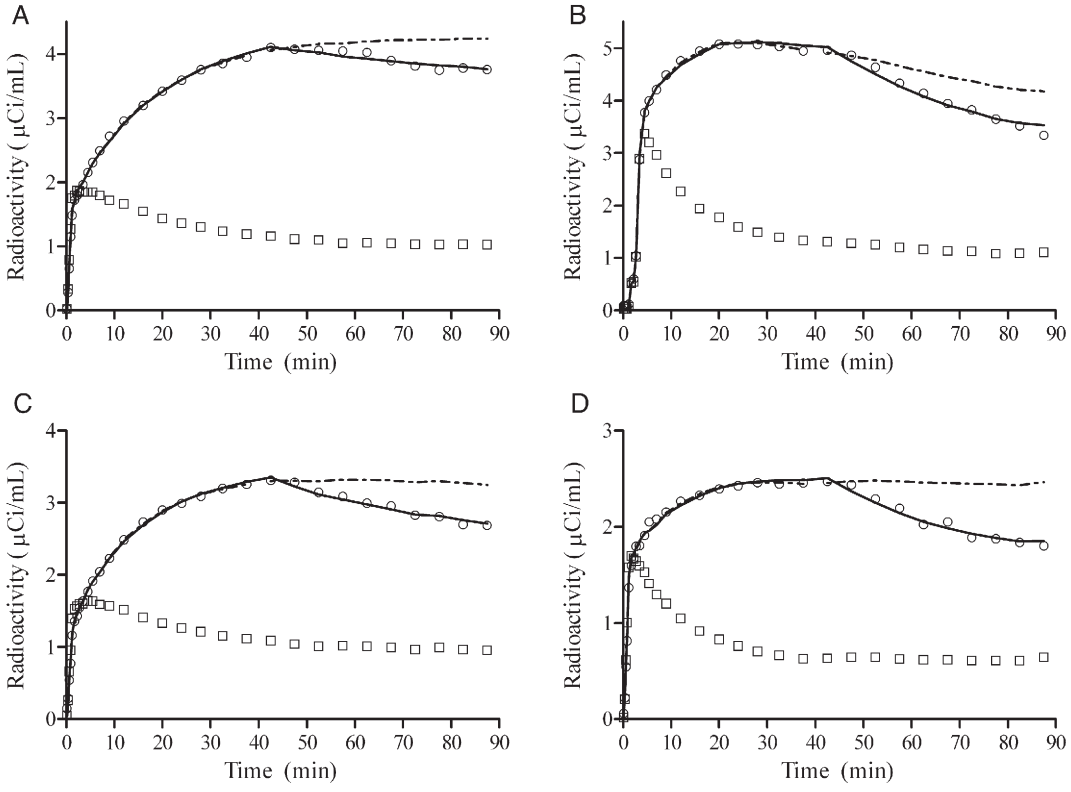

Fig. 1. Typical time activity curves (TACs) for the striatum (open circle), and the cerebellum (open square) measured from the [^{11}C]raclopride dynamic PET studies of four healthy male cynomologous monkeys with bolus followed by the continuous infusion of tracer delivery and an acute administration of 2.0 mg/kg amphetamine 40 min after the start of the scan. The fitting curves are from ESRTM (solid line) and the curves in dashed lines are extrapolated from the fitted pre-amphetamine striatal TACs using the SRTM.

In general, BP0 estimates obtained by CR were more sensitive to the selection of steady state frames than the BP0 estimates obtained by SRTM-CR. As demonstrated in Fig. 2A, the estimates of BP0 from CR increased from 2.22 to 2.43 as [$t0$ $T0$] changes from [22 45] to [30 45] ($p<0.0001$, paired t test). By contrast, for the SRTM-CR method, BP0 was almost constant (2.85 to 2.88) when the assumed steady state frame changes from [50 90] to [70 90]. The BP1 given by CR or SRTM-CR (both are same) decreased from 2.38 for [50 90] to 2.24 for [70 90] ($p<0.0001$, paired t test) (Fig. 2B). The variables of the selected steady state frames on BP0 and BP1 estimation for CR and SRTM-CR methods had significant effects on the ΔBP% estimation. The ΔBP% estimates from CR and SRTM-CR as a function of selected steady state frames in pre- and post-amphetamine phases are shown in Fig. 2C. On average, the ΔBP% estimates from the CR method increased from the lowest −9 for [22 45, 50 90] to the highest 6 for [30 45, 70 90]; and ΔBP% estimated by SRTM-CR increased from 16 for [50 90] to 22 for [70 90] ($p<0.0001$, paired t test). The ΔBP% estimated by the three methods was in the order of ΔBP%(CR) < ΔBP%(SRTM-CR) < ΔBP%(ESRTM).

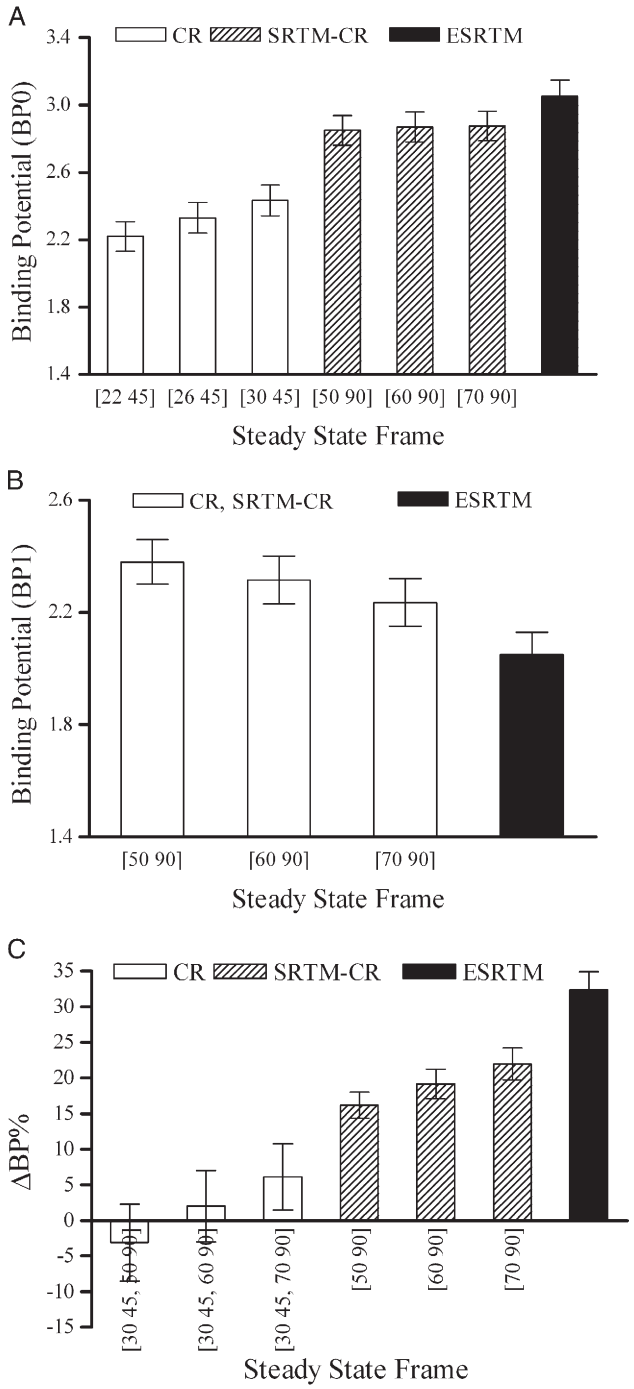

Fig. 2. The mean±standard error of the estimates of the BP0 (A), the BP1 (B), and the percent change in BP from BP0 (ΔBP%) (C) for the CR and the SRTM-CR methods. The BP0, BP1, and ΔBP% estimates from the CR and the SRTM-CR changed as a function of selected steady state frames. The estimates from the ESRTM were considered as reference. The PET studies were performed in the 18 healthy male cynomologous monkeys using bolus followed by a continuous infusion delivery of [^{11}C]raclopride with an acute administration of 2.0 mg/kg amphetamine 40 min after the start of the scan. The assumed steady state frame in minutes is shown in [ ] for CR and SRTM-CR methods.

The statistics of estimates from 18 monkey studies are listed in Table 3, where the steady state frames for the SRTM-CR and the CR are [70 90], and [30 45, 70 90], respectively. The BP0 estimated by the ESRTM was underestimated by (20±10)% and (6±5)% ($p<0.0001$, paired t test) by the CR and the SRTM-CR, respectively. The BP1 estimated by ESRTM was over-estimated by (9±5)% ($p<0.0001$, paired t test) by the SRTM-CR or the CR. The ΔBP% estimated by the ESRTM had the lowest percent coefficient of variation (=33). Compared to ESRTM, the under- and over-estimation of BP0 and BP1 for both the CR and the SRTM-CR resulted in lower estimation of ΔBP% by 81% and 32% for the CR and the SRTM-CR, respectively. The ΔBP% estimated by the CR was not statistically significantly different from zero ($p=0.20$).

The estimates of R_1, k_2, and BP0 from the ESRTM fitting on the full study period [0 T] were 0.90±0.08, 0.12±0.02, and 3.05±0.42 (Table 3), respectively. If the ESRTM fitting is constrained in the pre-amphetamine phase [0 $T0$], then, the estimates of R_1, k_2, and BP0 were 0.88±0.08, 0.13±0.02, and 2.82±0.36, respectively. Paired t test showed they were not significantly different ($p=0.44$, 0.29, 0.09 for R_1, k_2, BP0, respectively). In addition, there was no significant Pearson correlation (−0.04(0.88)) ($r(p)$, where the probability p for test correlation coefficient $r=0$) between the k_2 and BP0 estimates from the ESRTM. In contrast, the significant (0.62(0.007)) and insignificant correlations (0.23(0.36)) between the k_2 and BP0 estimates were found for the CR([30 45, 70 90]) and the SRTM-CR([70 90]), respectively. It was also consistently found that there was insignificant correlation (0.16(0.53)) between the k_2 and ΔBP% estimates from ESRTM. The correlations between the k_2 and ΔBP% estimates from the CR([30 45, 70 90]) and the SRTM-CR([70 90]) were significant (0.58(0.011)) and insignificant (0.40(0.10)), respectively.

Baboon studies

The ESRTM consistently provided good model fitting for all baboon studies. The percent coefficient of variation of Akaike information criterion was −4. The measured TACs of the striatum and the cerebellum with the fitted curves from the baboon A studies are demonstrated in Fig. 3. All striatal TACs attained a constant level prior to amphetamine injection. Panel A1 showed that the constant level of striatal TAC attained in the pre-amphetamine phase was continued in the post-amphetamine phase at the lowest dose level of 0.05 mg/kg. In the highest

Table 3
The statistics of estimates from 18 healthy male cynomologous monkey PET studies with bolus followed by continuous infusion delivery of [^{11}C]raclopride and acute administration of 2.0 mg/kg amphetamine 40 min after the start of PET scan

Statistics (n=18)	ESRTM					SRTM-CR[a]			CR[b]	
	R_1	k_2	BP0	BP1	ΔBP%	BP0	BP1	ΔBP%	BP0	ΔBP%
Mean	0.90	0.12	3.05	2.05	32	2.88	2.24	22	2.43	6
Median	0.89	0.12	3.05	2.05	32	2.92	2.26	22	2.50	7
SD	0.08	0.02	0.42	0.35	11	0.39	0.37	9.5	0.40	19
CV	9	18	14	17	33	14	17	43	16	317
Low 95% C.I.	0.86	0.11	2.84	1.88	27	2.68	2.05	17	2.24	−4
High 95% C.I.	0.94	0.13	3.26	2.23	38	3.07	2.43	27	2.63	16
Min	0.79	0.09	2.34	1.27	9	2.17	1.46	4	1.64	−27
Max	1.04	0.17	3.72	2.60	53	3.51	2.87	40	3.15	35

[a] [70 90] was used for the steady state frame for the pre- and post-amphetamine phases.
[b] [30 45] and [70 90] were used for steady state frames for the pre- and post-amphetamine phases, respectively. The BP1 estimated by CR is same as that estimated by the SRTM-CR.

amphetamine dose level of 1.5 mg/kg, the striatal TAC continued decreasing in the post- amphetamine phase (panel A4). In contrast to the highest dose levels, the tissue TACs in dose levels of 0.1 and 0.5 mg/kg were almost constant within [30 45] and [70 90] for the pre- and post-amphetamine phases, respectively (panels A2 and A3).

The effects of the selection of steady state frames on BP and ΔBP% estimates are consistent with the findings from the monkey studies. The estimates of BP0 from the SRTM-CR were robust to the selection of steady state frames over all dose levels. The estimates of BP0 from the SRTM-CR were 3.08±0.23, 3.07±0.23, and 3.05±0.23 (n=8) for [50 90], [60 90], and [70 90], respectively. In contrast, the estimates of BP0 obtained with the CR method increased from 2.78±0.26 to 2.94±0.28, as the steady state frames changed from [22 45] to [30 45]. Starting from dose 0.10 mg/kg, the estimates of BP1 from the CR or the SRTM-CR (equal to the BP1 estimates from the CR) decreased as steady state frames changed from [50 90] to [70 90]. The estimates of BP1 from

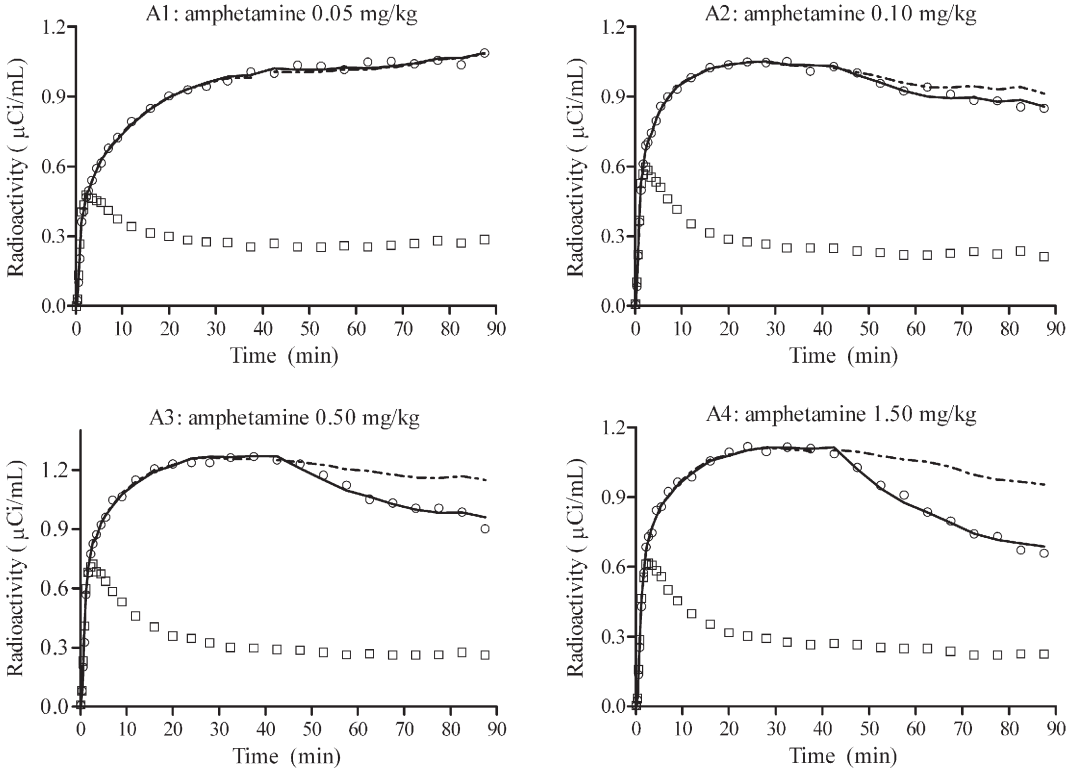

Fig. 3. The time activity curves (TACs) for the striatum (open circle), and the cerebellum (open square) measured from the [^{11}C]raclopride PET studies of a healthy male *Papio anubis* baboon with bolus followed by the continuous infusion of tracer delivery and the acute administration of amphetamine 40 min after the start of the scan. The fitting curves are from the ESRTM (solid line) and the curves in dashed lines are extrapolated from the fitted pre- amphetamine striatal TACs using the SRTM.

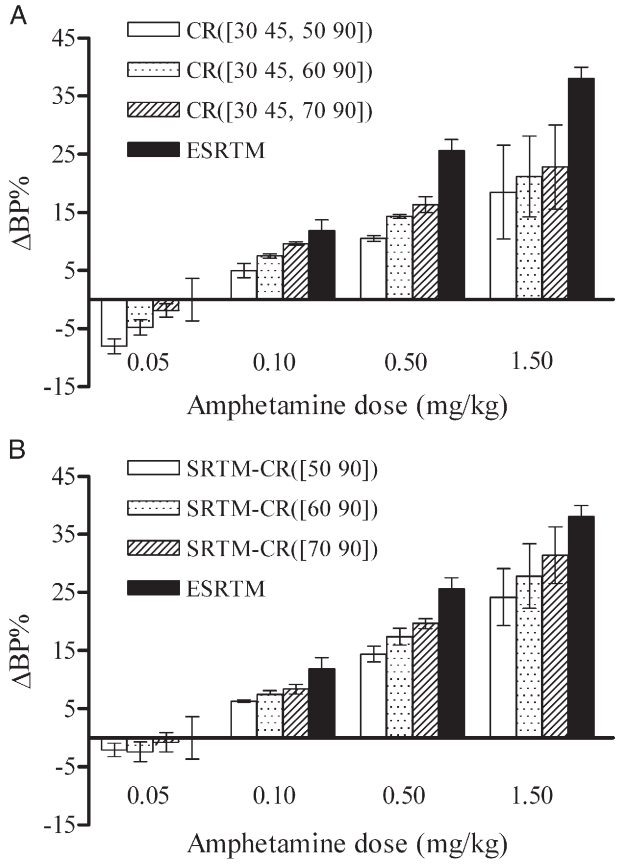

Fig. 4. The percent change in BP from BP0 (ΔBP%) (mean±standard error, $n=2$) estimated by the CR versus the ESRTM (A) and by the SRTM-CR versus the ESRTM (B) from baboon [^{11}C]raclopride PET studies using bolus followed by the continuous infusion of tracer delivery with the acute administration of amphetamine 40 min after the start of the scan.

the CR or the SRTM-CR for amphetamine dose levels (0.1, 0.5, and 1.5 mg/kg) were 2.68±0.32, 2.58±0.33, and 2.50±0.35 ($n=6$) for [50 90], [60 90], and [70 90]. The ΔBP% estimated by the CR (Fig. 4A) and the SRTM-CR (Fig. 4B) as functions of steady state frames were similar over the four dose levels and consistent with the monkey studies (Fig. 2C). Fig. 4 showed that the steady state frames [30 45, 70 90] for the CR and [70 90] for the SRTM-CR give the least underestimation of ΔBP% for dose levels ≥0.1 mg/kg among the selected steady state frames. It was also illustrated by Fig. 4 that the ΔBP% estimated by the three methods was in the order of ΔBP%(CR)<ΔBP%(SRTM-CR)<ΔBP%(ESRTM), and this was consistent with the results from monkey study (Fig. 2C).

The estimates of (R_1, k_2, BP0) from the ESRTM fitting in the pre-amphetamine phase [0 $T0$] and ESRTM fitting over the full PET study period [0 T] were (0.89±0.06, 0.17±0.03, 3.01±0.13) and (0.91±0.06, 0.17±0.03, 3.11±0.14) ($n=8$), respectively. Consistent with the findings from monkey study, there is no significant difference between the estimates from the two fitting process (paired t test, $p=0.67$, 0.68, and 0.16 for R_1, k_2, and BP0, respectively).

The estimates from the ESRTM, the SRTM-CR, and the CR for the baboon studies are listed in Table 4, where the selected steady state frames for the SRTM-CR and the CR are [70 90] and [30 45, 70 90], respectively. Compared to the ESRTM approach, the BP1 values estimated by the SRTM-CR or the CR were overestimated by 4% to 10%, respectively, as dose increased from 0.5 to 1.5 mg/kg. The ΔBP%s estimated from all three methods are about 0 with the lowest dose level 0.05 mg/kg. This means that the effects of the amphetamine-induced dopamine release on tracer kinetics are negligible at the amphetamine dose level 0.05 mg/kg, and steady states were attained in pre- and post-amphetamine phase. This is consistent with the Fig. 3 A1 which showed that the measured striatal radioactivity in the post-amphetamine phase was predicted very well by the SRTM model that was identified in the pre-amphetamine phase. At low dose level of 0.1 mg/kg, the ΔBP% estimates by three approaches were quite comparable and around 10. On average, the ΔBP% values estimated by the CR and the SRTM-CR at 1.5 mg/kg dose level were lower by 41% and 18%, respectively, as compared with the ESRTM. The linear relationships (Eqs. (9)–(11)) between the natural logarithm of amphetamine dose and the ΔBP%

Table 4
The estimates obtained from two baboon PET studies with bolus followed by continuous infusion of [^{11}C]raclopride and acute administration of amphetamine at 40 min after the tracer bolus injection

Baboon ID	Dose (mg/kg)	ESRTM					SRTM-CR[a]			CR[b]	
		R_1	k_2	BP0	BP1	ΔBP%	BP0	BP1	ΔBP%	BP0	ΔBP%
A	0.05	0.82	0.17	3.14	3.02	4	2.85	2.83	1	2.74	−3
	0.10	0.90	0.21	3.09	2.78	10	3.13	2.84	9	3.14	9
	0.50	0.92	0.17	3.39	2.45	28	3.36	2.67	21	3.24	18
	1.50	0.93	0.18	3.17	1.90	40	3.38	2.15	36	3.08	30
B	0.05	0.93	0.17	2.91	3.02	−4	2.82	2.89	−2	2.87	−1
	0.10	0.99	0.17	3.13	2.70	14	3.09	2.86	8	3.17	10
	0.50	0.92	0.14	3.09	2.36	24	3.01	2.44	19	2.88	15
	1.50	0.82	0.13	3.00	1.91	36	2.77	2.03	27	2.41	16
Mean (SD) of A and B	0.05	0.88 (0.08)	0.17 (0.00)	3.02 (0.16)	3.02 (0.00)	0 (5)	2.83 (0.02)	2.86 (0.04)	−1 (2)	2.81 (0.09)	−2 (2)
	0.10	0.95 (0.07)	0.19 (0.03)	3.11 (0.03)	2.74 (0.05)	12 (3)	3.11 (0.03)	2.85 (0.01)	8 (1)	3.15 (0.03)	10 (0)
	0.50	0.92 (0.00)	0.16 (0.02)	3.24 (0.21)	2.41 (0.07)	26 (3)	3.18 (0.24)	2.56 (0.16)	20 (1)	3.06 (0.26)	16 (2)
	1.50	0.88 (0.07)	0.16 (0.04)	3.08 (0.12)	1.91 (0.01)	38 (3)	3.07 (0.43)	2.09 (0.08)	31 (7)	2.74 (0.47)	23 (10)

Four levels of amphetamine doses (0.05, 0.1, 0.5, 1.5 mg/kg) were studied in each of the two baboons.

[a] [70 90] was used for the steady state frame for the pre- and post-amphetamine phases.

[b] [30 45] and [70 90] were used for the steady state frames for the pre- and post-amphetamine phases, respectively. The BP1 estimated by CR is the same as that estimated by SRTM-CR.

estimates were obtained for the ESRTM, the SRTM-CR, and the CR as below.

$$\Delta BP\%(ESRTM) = 10.67Ln(dose) + 33.79 \quad (9)$$

$$\Delta BP\%(SRTM\text{-}CR) = 9.00Ln(dose) + 27.23 \quad (10)$$

$$\Delta BP\%(CR) = 6.59Ln(dose) + 20.95 \quad (11)$$

where Ln is the natural logarithm function and the dose of amphetamine is in mg/kg of range $0.05 \leq dose \leq 1.5$. The R^2s, the goodness of linear fitting, for Eqs. (9)–(11) are 0.96, 0.94, and 0.79, respectively. There is a significant difference ($p=0.01$) in the regression intercept between Eq. (9)(33.79) and Eq. (10) (27.23), but there is no significant difference ($p=0.11$) in the regression slope between Eq. (9)(10.67) and Eq. (10)(9.00). The regression slop (6.59) and intercept (20.95) in the Eq. (11) were significantly lower then those in Eqs. (9) (10) ($p<0.04$).

Computer simulation

The simulated noise free TACs illustrated in Fig. 5 were of high variations in both magnitude and curve shape. Note that these variations were only resulted from the changes in k_2. This simulation visually shows that the BPs estimated by the CR or the SRTM-CR are unreliable if tissue kinetics are not in steady states. The bias of BP0, BP1, and ΔBP% estimated from the SRTM-CR and the CR as a function of k_2 is illustrated by Fig. 6. BP0 was underestimated at lower k_2 values e.g., $k_2<0.10$/min, and overestimated at higher k_2 values, e.g., $k_2 \geq 0.18$/min (Fig. 6A). Fig. 6A shows that the underestimation of BP0 for CR methods can be reduced significantly by the SRTM-CR in a low k_2 range (slow tissue kinetics, such as in monkey study), although the post-amphetamine phase [45 90] is not long enough for the extrapolated baseline tissue kinetics to attain steady states. The BP1 is always overestimated 10% to 20% by CR method (Fig. 6B). The value of ΔBP% is always underestimated and the underestimation is reduced linearly as k_2 increases, for all the selected steady state frames used in the studies (Fig. 6C). The least underestimation of ΔBP% for the SRTM-CR and the CR was obtained with the frames of [70 90] and [30 45, 70 90], respectively.

The percent root mean square error (RMSE%) of ΔBP% estimates as a function of noise level α from parameter vector C

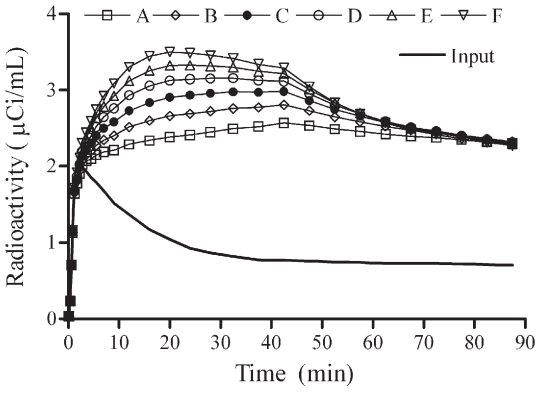

Fig. 5. The simulated noise free tissue time activity curves by the ESRTM model. The curves A to F correspond to parameter vectors A ([0.90 0.08 3.05 2.05]) to F ([0.90 0.18 3.05 2.05]) with step size 0.02 in k_2 only as listed in the Table 1.

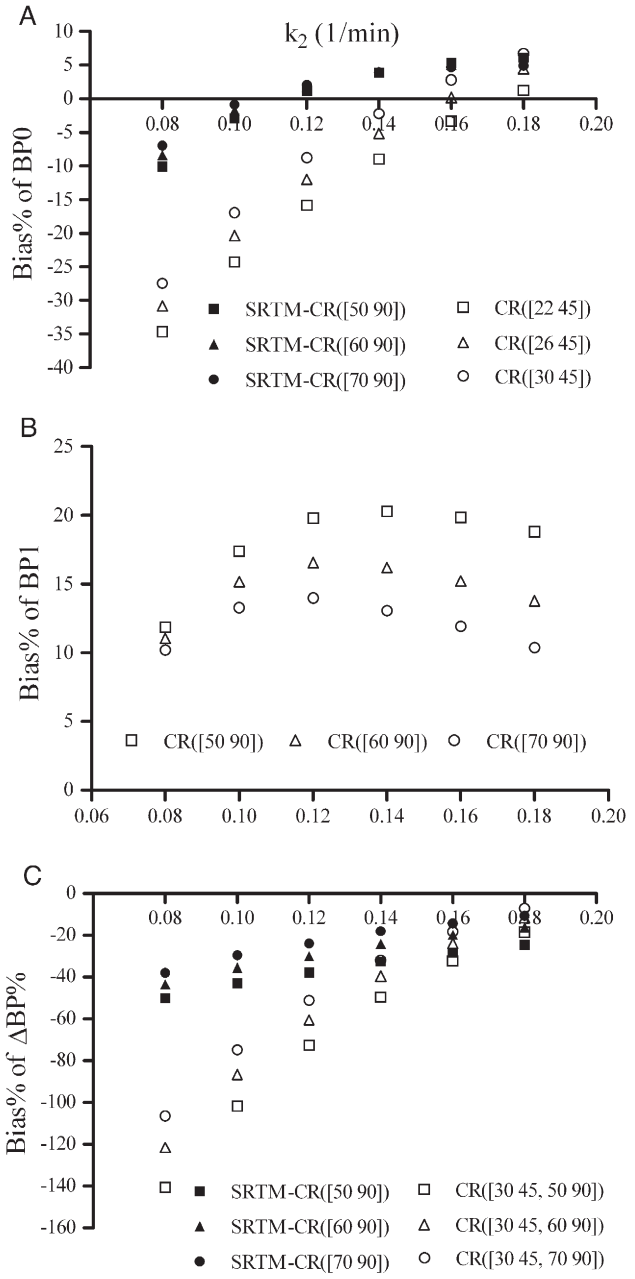

Fig. 6. The percent bias (Bias%) of BP0 (A), BP1 (B), and ΔBP% (C) as a function of k_2 (the tracer efflux rate from tissue) from simulation study for the CR([]) and the SRTM-CR([]) methods with the selected steady state frame [].

([R_1 k_2 BP0 BP1])=[0.90 0.12 3.05 2.05]) and vector F ([R_1 k_2 BP0 BP1]=[0.90 0.18 3.05 2.05]) are shown in Figs. 7A and B, respectively. There are linear relationships between RMSE% of ΔBP% and noise level α for the ESRTM, the SRTM-CR, and the CR. The ESRTM provides the most accurate estimates of ΔBP% at low and medium noise levels. The RMSE% of ΔBP% estimates is comparable among the ESRTM, the SRTM-CR, and the CR as $k_2=0.18$, especially for high noise level (Fig. 7B). Fig. 7 illustrates that the ESRTM is more sensitive to the noise level than SRTM-CR and CR approaches. This is because the RMSE of ΔBP% estimates from CR and SRTM-CR consist of a bias component,

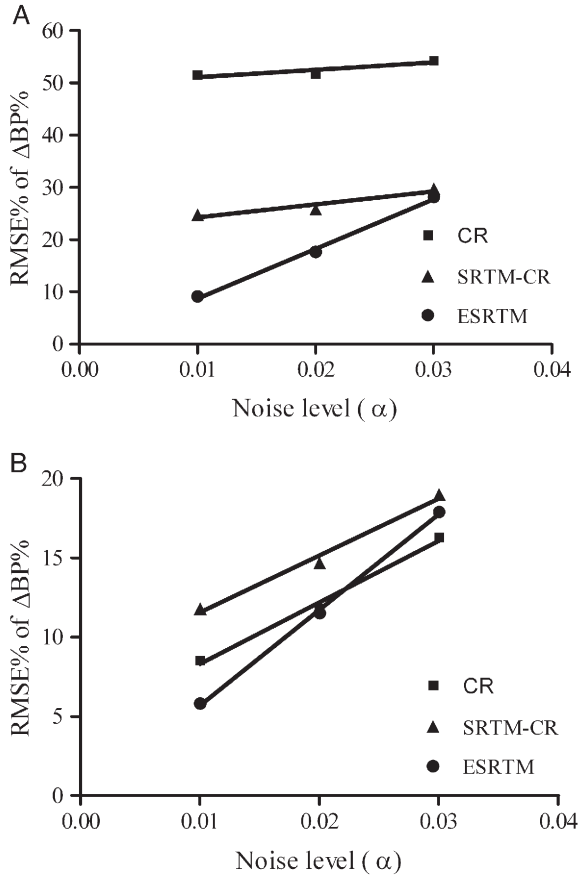

Fig. 7. The percent root mean square error (RMSE%) of ΔBP% (percent change in BP from BP0) from the simulations with the ESRTM and parameter vectors C ([0.90 0.12 3.05 2.05]) (A) and F ([0.90 0.18 3.05 2.05]) (B). The steady state frame for the CR and the SRTM-CR are [30, 45, 70 90] and [70 90], respectively.

which is constant across different noise levels, and the bias is significant for the low k_2 values (Fig. 7A).

Discussion

Comparison with previous studies

The effects of amphetamine challenge on the dopaminergic system have been studied extensively using PET with steady state and nonsteady state (tracer delivered by bolus only) experimental designs (Table 5). The BP0 estimated by dynamic PET using paired bolus only design and a 2-tissue 4-parameter compartmental model with arterial plasma input (Carson et al., 1997) was almost the same as that estimated by the ESRTM in the present study (3.12±0.56, n=5 versus 3.05±0.42, n=18). Using steady state design, the BP0 estimated by the CR([40 50]) (Carson et al., 2001; Marenco et al., 2004) is comparable to our BP0 estimates from the CR([30 45]) (2.51±0.05, n=3 and 2.45±0.06, n=3 versus 2.43±0.40, n=18). Using CR([40 60]), the BP0 estimates of 2.89±0.20 (n=6) reported in previous study (Carson et al., 2002) are close to our BP0 estimates (2.88±0.39, n=18) from the SRTM-CR method. By extending $t1$ to 90 or 100 min for steady state in the post-amphetamine phase, the ΔBP% estimates from the CR method are improved to as high as 27.9±5.5 and 30±3 (n=3) (Carson et al., 2001; Marenco et al., 2004). The comparable ΔBP% estimates of 32±11 (n=18) were obtained in our total 90 min study with the ESRTM method.

Note that different amphetamine dose levels have been used in the previous monkey PET studies. Amphetamine challenge at a dose level of 0.2 mg/kg in monkey resulted in about 10.5% reduction in BP on striatum (Breier et al., 1997). A 40% reduction in striatal BP was reported in monkey [^{11}C]raclopride PET with 2 mg/kg methamphetamine challenge (Doudet and Holden, 2003b). Their results are comparable to the results (ΔBP%=32±11) obtained in our monkey study of 2 mg/kg amphetamine dose level and those (ΔBP%=39±5) from another study listed in Table 5 of 0.4 mg/kg dose level (Carson et al., 1997, paired bolus only design). Combined, the "ceiling effect" observed in amphetamine challenge PET studies (BP reduction <50%) (Laruelle, 2000; Kortekaas et al., 2004), and results from our monkey studies, the 2 mg/kg amphetamine dose level is likely to achieve the maximal effect on [^{11}C]raclopride striatal binding.

As listed in Table 6, paired bolus [^{11}C]raclopride dynamic PET studies with arterial plasma input were commonly used in previous baboon amphetamine stimulation studies (Dewey et al., 1993; Drevets et al., 1999; Narendran et al., 2004; Price et al., 1998; van Berckel et al., 2005). The BP0 estimated by the ESRTM in the study is 3.11±0.14 (n=8) which is consistent with the reported BP0 estimates of the 3.20±0.19 (n=5) (Price et al., 1998) and 3.02±0.74 (3 baboons, 3 repeated measurements, n=9) (Narendran et al., 2004). Other reported BP0 estimates were 2.69±0.37 (n=4, four baboon studies, van Berckel et al., 2005), and 2.11±0.55 (n=3, three baboon studies, Dewey et al., 1993). Due to the limited number of subjects used in these studies, the differences in the BP0

Table 5
Reported binding potential values at baseline (BP0) and percent change in BP from BP0 (ΔBP%) in monkey dynamic PET studies with bolus only and bolus followed by continuous infusion of [^{11}C]raclopride and acute 0.4 mg/kg amphetamine stimulation

Dynamic PET design	Scan time (min)	Steady state frame		BP0 (mean±SD)	ΔBP% (mean±SD)	Sample size	References
		[$t0$ $T0$]	[$t1$ T]				
Continuous infusion	90	[25 40]	[65 90]	1.85±0.21	21.3±10.8	4	Breier et al., 1997
Continuous infusion	90	[30 40]	[60 90]	2.29±0.37	19±16	BP0, 7 ΔBP%, 5	Carson et al., 1997
Paired bolus only	60			3.12±0.56	39±5	BP0, 5 ΔBP%, 3	Carson et al., 1997
Continuous infusion	140	[40 50]	[100 140]	2.51±0.05	30±3	3	Carson et al., 2001
Continuous infusion	140	[40 60]	[90 140]	2.89±0.20	23±8	6	Carson et al., 2002
Continuous infusion	150	[40 50]	[80 150]	2.45±0.06	27.9±5.5	3	Marenco et al., 2004

Table 6
Reported percent change in binding potential (ΔBP%) from baboon [^{11}C] raclopride dynamic PET with paired (baseline versus amphetamine) bolus only tracer delivery and acute amphetamine administration at 5 min before tracer injection in the previous studies

References	Amphetamine dose (mg/kg)	ΔBP%	Sample size
Dewey et al., 1993	1.0	16	3
Price et al., 1998	0.6	26	3
	1.0	42	2
Narendran et al., 2004	0.3	24	3
	0.5	32	3
	1.0	44	3
Drevets et al., 1999	0.3	10[a]	4
	0.6	15[a]	4
	1.0	20[a]	4
van Berckel et al., 2005	0.5	28	4
Means of ΔBP% from	0.3	16[b]	7
above studies	0.5, 0.6	25[b]	10
	1.0	29[b]	9
Current baboon studies			
ESRTM	0.3	21[c]	2
	0.5	26	
	1.0	34[c]	
SRTM-CR	0.3	16[c]	2
	0.5	20	
	1.0	27[c]	
CR	0.3	13[c]	2
	0.5	16	
	1.0	21[c]	

The estimates of ΔBP% from the present baboon studies were included for comparison.
[a] The striatal ΔBP% is estimated by averaging sub tissues' ΔBP% weighted by corresponding volume.
[b] Averaged values are weighted by sample size.
[c] Interpolated from the dose response curves described by Eqs. (9)–(11) (see text).

estimates may be due to intersubject variability. As with BP0, the amphetamine-induced ΔBP% measurements in those studies show marked variability. For comparison, the dose responses obtained by linear regression fitting in Results (Eqs. (9)–(11)) are used to interpolate the ΔBP% at dose levels of 0.3 and 1.0 mg/kg. As demonstrated in Table 6, both the ESRTM and the SRTM-CR provide comparable dose response to the means of ΔBP% from previous studies at dose levels between 0.3 and 1.0 mg/kg.

Model assumptions and evaluation

It is necessary to be cautious in the interpretation of PET measurements of BP, especially for making inferences on the time profile of endogenous dopamine from the changes in BP. Strictly speaking, when it is assumed that BP is constant in a time interval, it is implicitly assumed that dopamine receptor occupancy is also constant in that time interval. In truth, endogenous dopamine may not be in a steady state after acute amphetamine challenge or cognitive activation. Thus, the ESTRM model, which assumes that dopamine goes from a baseline steady state to an activated steady state instantly after acute amphetamine challenge, may not be a physiologically accurate model and is not intended to be. For ESRTM, the physiological accuracy of the model is of secondary importance to the need for a robust estimate of the change in receptor binding. The effects of nonsteady state dopamine binding on BP measurements using PET have been well studied by computer simulations (Alpert et al., 2003; Endres and Carson, 1998; Morris et al., 1998; Yoder et al., 2004). It has been shown theoretically that, for a bolus tracer study with amphetamine challenge, the measured binding potential is equal to the time varying binding potential weighted by the free tracer concentration (Endres and Carson, 1998). As a balance between model complexity and accuracy of estimates, the steady state assumption on dopamine binding is commonly accepted in clinical PET with pharmacological challenge studies (Laruelle, 2000), and in neuroactivation studies where the steady state of endogenous dopamine during the activation period is questionable (Alpert et al., 2003; Endres et al., 2002; Koepp et al., 1998). To better interpret amphetamine-induced dopamine release from the changes in BP, validation studies with microdialysis have been carried out (Endres et al., 1997; Laruelle et al., 1997; Schiffer et al., 2005).

As demonstrated in the study, the violations in the assumptions on tracer kinetic can also result in variations in estimates of BP0 and amphetamine-induced ΔBP% among different analytical modeling approaches. The assumptions on the tracer kinetics for the CR, the SRTM-CR, and the ESRTM are different as described in Materials and methods. Results from the present study demonstrate that the accuracy of the estimates on amphetamine induced ΔBP% from the CR and the SRTM-CR with steady state assumption can be improved significantly by the ESRTM that does not employ steady state assumption on tracer kinetics. This was also confirmed by an ad hoc monkey [^{11}C]raclopride dynamic PET study without amphetamine challenge. As illustrated by Fig. 8, both the striatal and cerebellar tracer kinetics attained steady states as t>45 min, and the measured striatum TACs from 45 to 90 min was accurately predicted by the SRTM model fitted to the first 45 min. This was also confirmed in parameter space. The SRTM parameters of (R_1, k_2, and BP0) estimated by first 45 min model fitting were (0.79, 0.14, 3.08) that were almost identical to the estimates of (0.80, 0.13, 3.11) from 90 min SRTM fitting. However, the BP0 estimated by the CR ([30 45]) was 2.74, and it was underestimated 12%, as compared to the BP0 (=3.11)

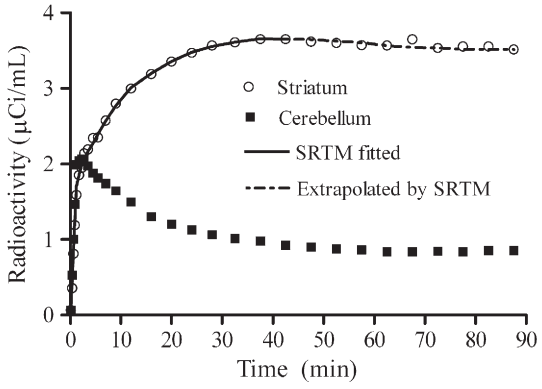

Fig. 8. The measured time activity curves (TACs) of striatum (open circle) and cerebellum (solid square) were obtained from a cynomologous monkey [^{11}C]raclopride dynamic PET study with bolus followed by continuous infusion of tracer delivery. Note that no amphetamine challenge was applied in the study. The curves in dashed lines are extrapolated from the fitted striatal TACs (solid line) in the time frame [0 45] (same as the pre-amphetamine phase) using the SRTM.

estimated from 90 min model fitting. The BP0 estimated by the SRTM-CR ([70 90]) was 3.15. The BP1 estimated by CR([70 90]) or SRTM-CR([70 90]) was 3.17. The estimates of ESRTM parameters (R_1, k_2, BP0 and BP1) from 90 min fitting were (0.79, 0.14, 3.03, and 3.13). The ΔBP% estimates from the control study (no amphetamine challenge) were −16, −1, and −3 for the CR, the SRTM-CR, and the ESRTM, respectively. Results from the study demonstrated it here again that the equilibrium analysis (SRTM-CR, CR) is equivalent to the ESRTM approach for BP estimation if the tracer kinetics is in steady state. In other words, the ESRTM is not biased, and the ESRTM is robust to the steady state assumption on the tracer kinetics for estimation of amphetamine-induced changes in BP. Mathematically, in "ideal situations", i.e. both striatal and cerebellar TACs are constants, the ESRTM, full kinetic modeling approach, becomes practically equivalent to the CR and the SRTM-CR approaches (see Eqs. (4) (5) under conditions of $dC_T/dt=0$ and $dC_{REF}/dt=0$). In other words, the longer for tissue tracer kinetics in baseline [$t0$ $T0$] and post-amphetamine phase [$t1$ T] to approach to steady states, the closer the BP0 and BP1 estimates between ESRTM and CR. This was illustrated by the results from previous studies listed in Table 5. To get reliable estimates of BP0 and ΔBP% from CR or SRTM-CR methods, the long steady state frame for pre- and post-amphetamine is necessary and obtained by extending study time in dynamic PET with single or paired bolus followed by continuous infusion tracer delivery (Carson et al., 2001, 2002; Doudet and Holden, 2003b; Martinez et al., 2003; Marenco et al., 2004).

In addition to the SRTM model assumptions on dopamine binding and tracer kinetics, the ESRTM assumes that (1) the rate constant R_1 and k_2 are not affect by amphetamine challenge; (2) the binding potential returned to a new constant level post-acute amphetamine challenge immediately, or the time for tracer BP to attain a new constant level is negligible as compared to the post-amphetamine study time and PET temporal resolution. These assumptions are both theoretically and practically acceptable. For example, the first assumption is used in a linear extension of the SRTM model for the quantification of single bolus only [^{11}C] raclopride dynamic PET studies with cognitive activation (Alpert et al., 2003). A generalized reference tissue model also includes the first assumption for the measurement of dopamine transporter occupancy using single [^{18}F]FECNT dynamic PET scan with a bolus injection of tracer followed by multi-injections of cocaine (Votaw et al., 2002). Note that R_1 and k_2 are not related to the tracer specific binding process, and K_1 (=blood flow * extraction ratio), the transport rate constant of tracer from vascular to brain tissue, of [^{11}C]raclopride is determined by passive diffusion process in above 0.17 mL/min/mL in monkey and baboon studies (Drevets et al., 1999; Endres et al., 1997). Therefore, the tissue K_1 is limited by extraction ratio and the effects of amphetamine-induced increases in cerebral blood flow on K_1 is expected to be reduced by passive diffusion process. Previous results showed that the amphetamine-induced change in K_1 was not significant (Drevets et al., 1999). Since R_1 is defined as K_1 ratio between target and reference tissue, the effects of amphetamine-induced cerebral blood flow increase on R_1 are expected to be negligible. The results from the present study are consistent with the basic assumptions made for the ESRTM. For example, there was no significant difference between the estimates of R_1, and k_2 from the first 45 min SRTM fitting and those from 90 min ESRTM fitting (see Results). In 18 monkey studies, the results from ESRTM showed that the Pearson correlation coefficient between R_1 and ΔBP%, was 0.28 ($p=0.26$), and the correlation coefficient between k_2 and ΔBP% was 0.16 ($p=0.53$), respectively. As a matter of fact, the assumption on the BPs in the ESRTM model is commonly used in the paired (control versus amphetamine challenge) bolus only [^{11}C]raclopride dynamic PET studies with acute amphetamine challenge (Carson et al., 1997; Drevets et al., 1999; Laruelle, 2000; Mach et al., 1997; Narendran et al., 2004; Oswald et al., 2005; Price et al., 1998; Slifstein et al., 2004; van Berckel et al., 2005; Yokoi et al., 2002). In these previous studies, bolus tracer injection was given 5 min post-acute amphetamine challenge in the stimulation scan, and the BP was estimated by conventional kinetic modeling, which was based on the assumption that the tracer BP is at a constant level after 5 min amphetamine injection. This assumption is also applied to the paired bolus only [^{11}C] raclopride dynamic PET studies with video game stimulation (Koepp et al., 1998). Although the BP during the behavioral task (video game) is questionable, the constant BP assumption is consistent with the measured tracer kinetics. The consistently good fitting results in the study suggest that the ESRTM model described the measured striatal tracer kinetics appropriately.

One common assumption for the CR, the SRTM-CR, the SRTM, and the ESRTM is that the radioactivity contributed from the intravascular space in both the reference and target tissues is negligible. This assumption can result in the underestimation in both BP0 and BP1, but its effect on the ΔBP% is quite negligible (Gunn et al., 2001; Lammertsma and Hume, 1996; Slifstein et al., 2004). Note that the violation of the steady state assumption on the tissue kinetics could also result from the blood component in the measured tissue radioactivity (Carson et al., 1993, 1997; Houle et al., 1996).

The homogeneity assumption on the measured tracer kinetics of region of interest was also made in the study. However, the amphetamine-induced decrease in BP varies in the caudate, the anterior and posterior putamen, and the ventral striatum (Drevets et al., 1999; Martinez et al., 2003). Thus, the BP0 and ΔBP% can be considered as spatially and temporally averaged estimates from dynamic PET data (Endres and Carson, 1998; Herholz and Patlak, 1987; Reimold et al., 2004, Yoder et al., 2004). Meaningful interpretations for amphetamine-induced BP reduction include blocking and displacement mechanism for agonists and antagonists, receptor internalization, and separation of tracer K_D and receptor B'_{max} from BP (Carson et al., 2002; Doudet and Holden, 2003a,b; Kortekaas et al., 2004; Laruelle, 2000). Using [^{11}C] raclopride dynamic PET with multi-tracer injection and acute amphetamine challenge, it was reported that there was a significant decrease in the apparent tracer affinity (=1/(apparent K_D)) and reduction in BP, but no significant change in the receptor density B'_{max} (Carson et al., 2002; Doudet and Holden, 2003a,b).

In summary, the ESRTM, the SRTM-CR, and the CR were evaluated by [^{11}C]raclopride dynamic PET with acute amphetamine challenge on 18 monkeys for the dose level of 2 mg/kg and 2 baboons for the dose levels of 0.05, 0.1, 0.5, and 1.5 mg/kg. Computer simulations characterized the three quantification methods. Both nonhuman primates and computer simulation studies showed that the underestimation of ΔBP% from the CR and the SRTM-CR resulted from the nonsteady state of tracer kinetics. The accuracy of the ΔBP% estimates from equilibrium analysis was significantly improved by the ESRTM. The results from the present study demonstrate that the ESRTM is a robust kinetic modeling approach and is proposed for quantification of dynamic PET with acute pharmacological challenge.

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