Supplemental Data

Corrections for Equilibrium Data

The initial awake studies were performed with tracer infusions with K_{bol} of 90 min, but this value was shown to not produce an optimal equilibrium. To correct these data, an SRTM-based correction algorithm was developed to determine correction factors in order to analyze all the awake data together. An anesthetized and an awake [^{11}C]flumazenil bolus scan were used to define the rate constant parameters used for the simulation. The SRTM model was used to estimate kinetic parameters from time-activity curves (TACs) in regions-of-interest (ROIs) for both awake and anesthetized studies, where the pons TAC was fitted with a sum of exponentials function and was used as the reference input. The estimated parameters were R_1 (R_1=K_1/K_1'), k_2, and k_2'. K_1 and K_1' (mL•cm^{-3}•min^{-1}) are the rate constants of tracer influx and k_2 (min^{-1}) and k_2' (min^{-1}) are the rate constants of tracer efflux in the ROI and reference tissue, respectively.

For the simulation, parameters R_1 and k_2' were fixed based on the mean value for the ROIs analyzed from the anesthetized and awake studies. Based on the range of BP_{ND} values from the anesthetized (0.49-4.31) and awake (0.64-5.32) studies, k_2 was varied to simulate bolus TACs from different ROIs with the SRTM model equation. $BP_{ND}{}^{true}$ was computed as

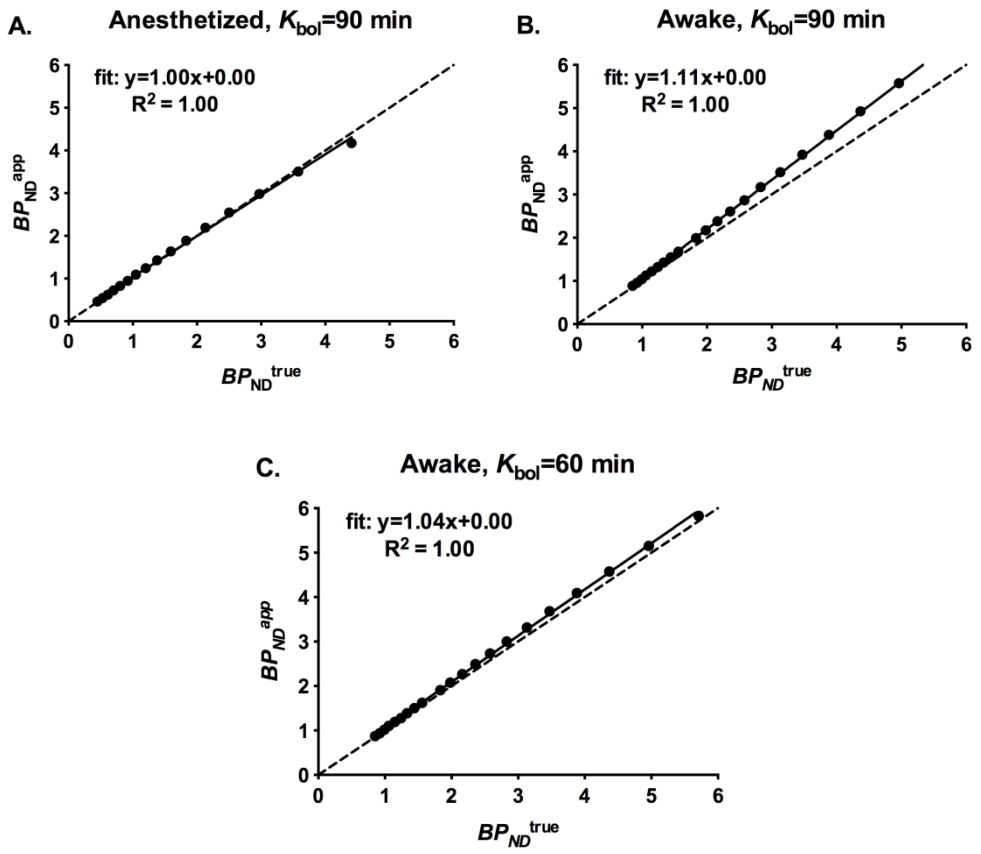
$$BP_{ND}{}^{true} = R_1 \frac{k_2'}{k_2} - 1. \qquad \text{Supplemental Eq. 1}$$

From the simulated bolus TACs, K_{bol} was chosen for the following cases to generate simulated B/I TACs: anesthetized with K_{bol}=90 min, awake with K_{bol}=90 min, and awake with K_{bol}=60 min. Using the simulated B/I TACs, equilibrium analysis was used to compute apparent BP_{ND} values ($BP_{ND}{}^{app}$) between 50-75 min as

$$BP_{ND}^{app} = \frac{C_{ROI}}{C_{REF}} - 1, \qquad \text{Supplemental Eq. 2}$$

where C_{ROI} and C_{REF} are the concentrations (Bq/mL) in the ROI and the pons reference region. BP_{ND}^{app} was plotted against BP_{ND}^{true}, and points were fitted with a linear regression where the slope was the correction factor (CF) for each case. The corrected BP_{ND} was computed as BP_{ND}^{app} /CF from parametric image analysis for each ROI in each case of awake B/I studies with K_{bol} = 90 min.

The correction factors (CF) for equilibrium analysis are shown for three cases in Supplemental Fig. 1 as determined by the slope of the regression between BP_{ND}^{true} and BP_{ND}^{app} values. For the anesthetized studies with K_{bol}=90min, the CF was 1.00, i.e., no correction for BP_{ND} was needed. For the awake studies with K_{bol}=90 min, CF for BP_{ND} was 1.11. For awake studies with K_{bol}=60 min, CF for BP_{ND} was 1.04. Thus, lowering K_{bol} for awake studies from 90 min to 60 min reduced the bias in BP_{ND} values from 11% to 4%.



Supplemental Figure 1. Correction factors for equilibrium analysis. BP_{ND}^{true} values were computed from bolus time-activity curves (TACs) simulated with SRTM. BP_{ND}^{app} was computed between 50-75 min with Supplemental Eq. 2 from simulated B/I curves for three cases: A) anesthetized studies with K_{bol}=90 min, B) awake studies with K_{bol}=90 min, and C) awake studies with K_{bol}=60 min. The slope of the regression line (solid) provided the correction factor for each case. The identity line (dashed) is shown for reference.