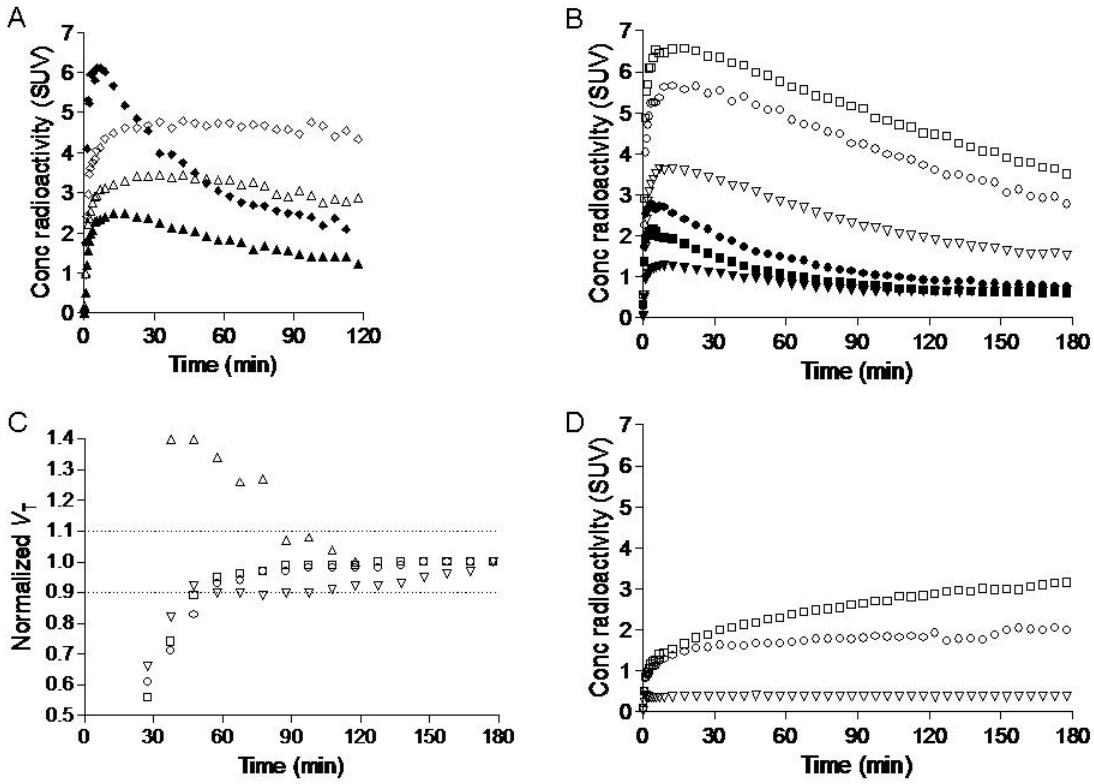
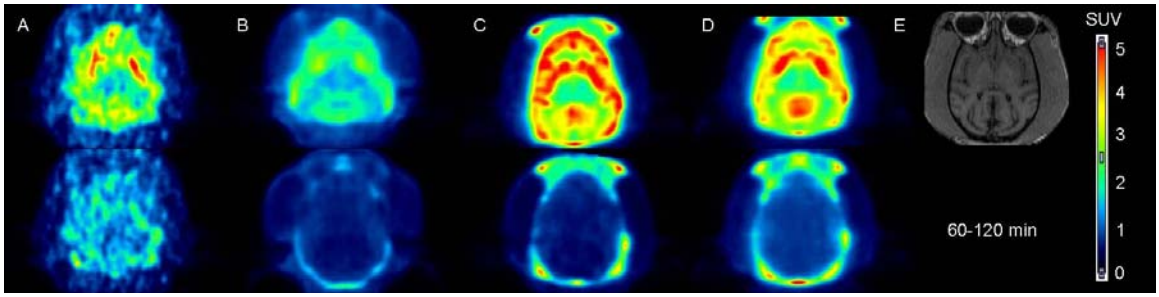


Supplemental Figure 1. ^{11}C-FMePPEP, ^{18}F-FEPEP, ^{18}F-FMPEP, or ^{18}F-FMPEP-d_2 in monkey. Time-activity curves were acquired under baseline conditions (open symbol) and 30 min after administration of rimonabant (3 mg/kg, i.v.; closed symbol). (A) ^{11}C-MePPEP (◇) is shown as a comparison to ^{11}C-FMePPEP (Δ), and (B) ^{18}F-FEPEP (∇), ^{18}F-FMPEP (□), and ^{18}F-FMPEP-d_2 (○) in monkey striatum. (C) Distribution volume (V_T) for ^{11}C-FMePPEP (Δ), ^{18}F-FEPEP (∇), ^{18}F-FMPEP (□), and ^{18}F-FMPEP-d_2 (○) was calculated using an unconstrained two-tissue compartment model with 0-30 or 0-180 min of data. (D) Radioactivity concentration in monkey bone was greatest in ^{18}F- FMPEP (□), followed by ^{18}F-FMPEP-d_2 (○) and ^{18}F-FEPEP (∇).



Supplemental Figure 2. ^{11}C-FMePPEP, ^{18}F-FEPEP, ^{18}F-FMPEP, or ^{18}F-FMPEP-d_2 in monkey brain. Axial PET images of monkey brain from 60 to 120 minutes after injection of (A) ^{11}C-FMePPEP and 120 to 180 after injection of (B) ^{18}F-FEPEP, (C) ^{18}F-FMPEP, and (D) ^{18}F-FMPEP-d_2 were averaged after baseline conditions (top row) and after pretreatment of rimonabant (3 mg/kg i.v.; bottom row). (E) A representative monkey MRI is provided for reference.

Supplemental Table 1. Distribution volume of several CB_1 selective radioligands in monkey brain

	V_T striatum			V_T pons		
Radioligand	Baseline	Blocked	Specific	Baseline	Blocked	Specific
^{11}C-MePPEP	24.3	2.9	88%	8.6	2.6	70%
^{11}C-FMePPEP	15.9	4.3	73%	6.5	3.5	46%
^{18}F-FEPEP	21.6	6.3	71%	25.0	13.2	47%
^{18}F-FMPEP	63.5	3.8	94%	37.1	8.0	78%
^{18}F-FMPEP-d_2	35.4	5.4	85%	20.1	8.5	58%

Supplemental Table 2. Kinetic rate constants and distribution volume (V_T) in 8 regions of brain from 9 subjects using 120 min of scanning data

	Rate Constant								V_T		
	K_1 (mL • cm^{-3} • min^{-1})		k_2 (min^{-1})		k_3 (min^{-1})		k_4 (min^{-1})		(mL • cm^{-3})		
Region		SE		SE		SE		SE		SE	Intersubject Variability
Prefrontal cortex	0.10 ± 0.03	2%	0.05 ± 0.02	14%	0.14 ± 0.03	11%	0.016 ± 0.004	5%	22.7 ± 6.4	2%	28%
Occipital cortex	0.11 ± 0.04	1%	0.05 ± 0.02	10%	0.11 ± 0.03	9%	0.020 ± 0.004	4%	14.3 ± 3.4	1%	24%
Hippocampus	0.08 ± 0.02	2%	0.06 ± 0.02	13%	0.12 ± 0.02	10%	0.010 ± 0.002	6%	17.4 ± 4.1	3%	24%
Putamen	0.12 ± 0.03	2%	0.04 ± 0.02	20%	0.13 ± 0.03	17%	0.017 ± 0.004	7%	24.3 ± 7.2	2%	29%
Thalamus	0.10 ± 0.03	3%	0.06 ± 0.02	16%	0.11 ± 0.02	15%	0.022 ± 0.004	6%	9.6 ± 2.5	2%	26%
Cerebellum	0.10 ± 0.03	2%	0.06 ± 0.02	10%	0.09 ± 0.03	9%	0.014 ± 0.002	5%	14.1 ± 3.0	2%	22%
Pons	0.09 ± 0.02	4%	0.06 ± 0.02	20%	0.09 ± 0.03	23%	0.027 ± 0.005	8%	6.0 ± 1.5	2%	25%
White matter	0.04 ± 0.01	7%	0.05 ± 0.01	50%	0.11 ± 0.03	43%	0.014 ± 0.004	20%	6.6 ± 1.9	8%	29%

Values of rate constants and V_T are mean ± SD. The identifiability of rate constants and V_T is inversely related to standard error (SE). The mean SE from 9 subjects is listed below each variable and is expressed as percent of the variable itself. Intersubject variability is the SD divided by the mean, and is expressed as percent.

Supplemental Table 3. Brain uptake and distribution volume (V_T) in regions of brain from 8 subjects using 120 min of data

	Brain Uptake$_{20-60}$				V_T			
Region	Test (SUV)	Retest (SUV)	Retest Variability	ICC	Test (mL • cm^{-3})	Retest (mL • cm^{-3})	Retest Variability	ICC
Prefrontal cortex	3.36 ± 0.57	2.92 ± 0.54	15%	0.56	22.9 ± 6.9 2%	21.5 ± 8.3 2%	16%	0.91
Occipital cortex	3.25 ± 0.55	2.83 ± 0.51	15%	0.54	14.2 ± 3.7 1%	13.4 ± 4.5 1%	13%	0.90
Hippocampus	2.46 ± 0.32	2.11 ± 0.33	16%	0.26	17.5 ± 4.4 3%	15.6 ± 5.2 3%	15%	0.86
Putamen	4.00 ± 0.57	3.42 ± 0.55	16%	0.37	24.3 ± 7.6 2%	22.7 ± 8.8 3%	17%	0.88
Thalamus	2.62 ± 0.39	2.22 ± 0.36	17%	0.30	9.5 ± 2.7 2%	8.7 ± 3.2 2%	15%	0.89
Cerebellum	2.83 ± 0.42	2.45 ± 0.43	15%	0.48	14.0 ± 3.2 2%	13.1 ± 4.0 3%	15%	0.85
Pons	2.10 ± 0.27	1.81 ± 0.25	15%	0.24	6.0 ± 1.6 2%	5.9 ± 1.7 7%	9%	0.94
White matter	1.20 ± 0.17	1.06 ± 0.15	13%	0.51	6.5 ± 2.1 8%	6.4 ± 2.1 12%	11%	0.88

Brain uptake is the mean concentration from 20 to 60 min after injection. Values of brain uptake and V_T are mean ± SD.

The identifiability of V_T is inversely related to standard error (SE). The mean SE from 8 subjects is listed below its V_T and is expressed as percent of the variable itself.

Retest variability is the absolute value of the difference between test and retest, divided by their mean, and is expressed as percent.

The intraclass correlation coefficient (ICC) is an analysis of variance comparing the differences within subjects against the differences between subjects. Values approaching 1 suggest that variability is due more to differences between individuals rather than variability of measurements.

Supplemental Table 4. Comparison of ^{11}C-MePPEP and ^{18}F-FMPEP-d_2

	^{11}C-MePPEP	^{18}F-FMPEP-d_2
Affinity*		
K_i (nM)	9.6 ± 0.1	9.6 ± 0.1
Brain uptake		
Peak in putamen (SUV)	3 - 4	3 - 4
% of peak after 2 hours	~80%	~70%
Intersubject variability	16%	14%
Retest variability	8%	16%
ICC	0.77	0.39
Distribution Volume		
V_T (mL • cm^{-3})	12 - 29	13 - 24
SE (%)	3 - 7	1 - 3
Intersubject variability	**> 50%**	**26%**
Retest variability	15%	14%
ICC	0.87	0.89
Plasma $AUC_{0-\infty}$		
Intersubject variability	**> 200%**	**13%**
Retest variability	**58%**	**16%**
ICC	**-0.02**	**0.80**

The data for ^{11}C-MePPEP derive from 17 healthy subjects, 8 of whom had retest scans (Terry et al., 2009). The data for ^{18}F-FMPEP-d_2 derive from 9 healthy subjects, 8 of whom had retest scans (current study).

* Unpublished data; measured in human cerebellum.

Four striking differences are in bold font. The intersubject variability of V_T and plasma AUC and the retest variability of plasma AUC of ^{11}C-MePPEP are much higher than those of ^{18}F-FMPEP-d_2. The ICC of plasma AUC for ^{11}C-MePPEP is poor.