Supplementary Information

Table S1. Regional [^{18}F]FPEB V_T/f_p values and effect sizes

Region	Baseline V_T/f_p	Post-ketamine V_T/f_p	24hr post-ketamine V_T/f_p	Baseline vs. post-ketamine	Baseline vs. 24hr post-ketamine
				Cohen's d	Cohen's d
Frontal cx	484.3 (74.03)	434.8 (58.8)	464.81 (76.2)	0.80	0.23
Parietal cx	476.4 (84.3)	425.1 (65.8)	453.0 (76.6)	0.75	0.28
Temporal cx	544.9 (101.0)	492.6 (67.9)	518.0 (88.8)	0.69	0.30
Occipital cx	440.3 (80.1)	389.1 (47.3)	418.5 (68.8)	0.77	0.27
Cerebellum	201.7 (35.5)	180.5 (39.0)	195.8 (37.8)	0.71	0.18

Values are presented as mean (SD).

Table S2. Regional [^{18}F]FPEB V_T values and effect sizes

Region	Baseline V_T	Post-ketamine V_T	24hr post-ketamine V_T	Baseline vs. post-ketamine	Baseline vs. 24hr post-ketamine
				Cohen's d	Cohen's d
Frontal cx	20.3 (3.4)	19.9 (2.5)	21.5 (3.9)	0.11	0.34
Parietal cx	20.0 (3.7)	19.4 (2.1)	21.0 (3.4)	0.13	0.29
Temporal cx	22.8 (4.1)	22.5 (2.5)	23.9 (4.0)	0.07	0.29
Occipital cx	18.5 (3.7)	17.9 (2.7)	19.4 (3.7)	0.17	0.27
Cerebellum	8.4 (1.6)	8.2 (1.2)	9.0 (1.7)	0.12	0.37

Values are presented as mean (SD).

Table S3. Regional [^{11}C]ABP688 V_T values and effect sizes [previously collected data*]

Region	Baseline V_T	Post-ketamine V_T	24hr post-ketamine V_T	Baseline vs. post-ketamine	Baseline vs. 24hr post-ketamine
				Cohen's d	Cohen's d
Anterior cingulate cx	4.72 (1.09)	3.73 (1.19)	3.54 (1.04)	0.83	1.24
Medial cx	4.38 (1.02)	3.43 (1.02)	3.31 (1.06)	0.92	1.23
Orbital frontal cx	4.29 (0.96)	3.44 (1.06)	3.27 (0.91)	0.85	1.18
Parietal cx	4.17 (0.96)	3.24 (0.95)	3.22 (0.96)	0.92	1.11
Cerebellum	2.24 (0.37)	2.02 (0.56)	1.89 (0.49)	0.43	0.93

Values are presented as mean (SD).
*Data provided by Dr. Christine DeLorenzo, Stony Brook University.

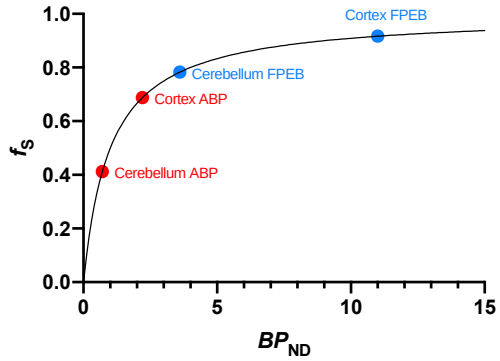
Explanation of ΔV_T/ $\Delta V_T/f_p$ in cerebellum

Due to a high fraction of specific binding in the cerebellum with [^{18}F]FPEB, ΔV_T is only expected to be marginally lower in the cerebellum than in high binding regions. In details, assuming that 1) the percent reduction of BP_{ND} due to ketamine, ΔBP_{ND}, was uniform in the brain, and that 2) the non-displaceable volume of distribution V_{ND} is unchanged, then indeed ΔV_T is expected to be regionally variant and equal to $\Delta BP_{ND}*f_S$, where f_S is the fraction of specific binding in each region: $f_S = BP_{ND}/(1+BP_{ND})$. f_S has a non-linear relationship with BP_{ND} and flattens out at high BP_{ND} values.

In our previous study [DeLorenzo, JCBFM, 2017, see supplemental data[1]], the non-displaceable volume of distribution V_{ND} of FPEB were estimated to be and 1.7 mL/cm^3, with a typical baseline V_T value of 7.9 mL/cm^3 in the cerebellum and ~20 mL/cm^3 in high binding regions. Thus, for [^{18}F]FPEB BP_{ND} is ~ 3.6 in the cerebellum and ~11 in high binding regions, and f_S is ~ 0.8 in the cerebellum and ~0.92 in high binding regions. The ΔV_T is only expected to be 14% lower in the cerebellum than in high binding regions. Thus, a 9% ketamine effect in high binding regions is expected to translate to an 8% ketamine effect in cerebellum. Thus, we cannot expect to reliably measure a lower ketamine effect in cerebellum with [^{18}F]FPEB.

For comparison, for [^{11}C]ABP688, V_{ND} was estimated to be 1.1 mL/cm^3 [DeLorenzo, JCBFM, 2017, see supplemental data[1]], with a typical baseline V_T of 1.9 mL/cm^3 in the cerebellum and ~3.5 mL/cm^3 in high binding regions. Thus, for [^{11}C]ABP688 BP_{ND} is ~0.73 in the cerebellum and ~2.2 in high binding regions, and f_S is ~0.42 in the cerebellum and ~0.69 in high binding regions. The ΔV_T is now expected to be 39% lower in the cerebellum than in high binding regions. Thus, a 20% ketamine effect in high binding regions is expected to translate to an 12% ketamine effect in cerebellum. In the previous ketamine [^{11}C]ABP688 study[2] the measured effects were 20% and 10% in cortex and cerebellum, respectively.

Thus, the relative results obtained with [^{18}F]FPEB and [^{11}C]ABP688 are consistent.



References

1. DeLorenzo C, Gallezot J-D, Gardus J, Yang J, Planeta B, Nabulsi N, et al. (2017): In vivo variation in same-day estimates of metabotropic glutamate receptor subtype 5 binding using [11C] ABP688 and [18F] FPEB. 37:2716-2727.
2. DeLorenzo C, DellaGioia N, Bloch M, Sanacora G, Nabulsi N, Abdallah C, et al. (2015): In vivo ketamine-induced changes in [11C] ABP688 binding to metabotropic glutamate receptor subtype 5. 77:266-275.