Supplemental Information

Neurochemical Characterization of 5-HT_{2A}R Partial Agonists with Simultaneous PET-MRI

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phMRI Data Processing

Gamma fits were conducted for each NHP on a case-by-case basis using open-source imaging software developed at the Martinos Center for Biomedical Imaging, Massachusetts General Hospital (https://www.nitrc.org/projects/jip). Specifically, pre-processed fMRI signals were visualized to determine the effective τ values; time from the drug-injection to peak signal changes. The α were determined iteratively in order to maximize fit shape and correspondence to the observed signals. For psilocybin and lisuride, this was performed by fitting the first peak signal change (γ_1), followed by the second peak signal change (γ_2), where the final signal model is a linear combination of both functions. Because 25CN-NBOH only had one major peak change induced by drug injection corresponding to increased CBV, this is noted solely as γ_2 for consistency. After successful fitting, absolute signal values were normalized as percentages relative to the pre-drug signal and by removal of signal drift. CBV profiles shown in **Figure 3** and **Figure S5** are the result of this processing averaged between respective drug groups and doses.

	Baseline	**Psilocybin**			**Lisuride**	**25CN-NBOH**
	No Drug	30μg/kg	60μg/kg	90μg/kg	5μg/kg	30μg/kg
NHP1	**XX**	**X**	**X**	**X**	**X**	**XX**
NHP2	**XX**	**X**	**X**	**X**	**X**	**X**
NHP3			**X**			

Table S1: Summary of PET/MRI experimental conditions for each NHP dataset. **X**: PET and MRI; **X**: PET only; **X**: MRI only.

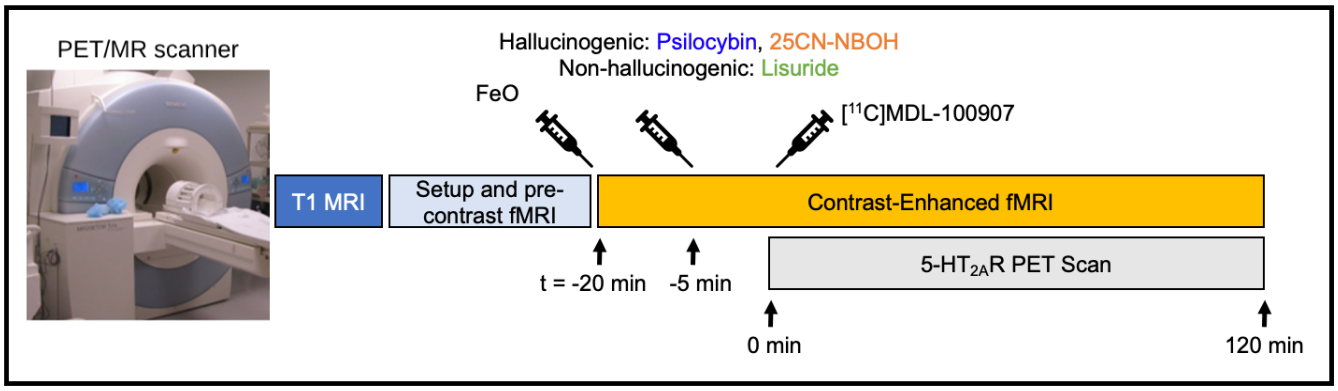

Figure S1: Experimental schematic of the PET/MR scanner and imaging protocol. T1: anatomical images used in neuroimaging registrations to brain templates. FeO: Iron oxide particles (MION) used to enhance fMRI signals.

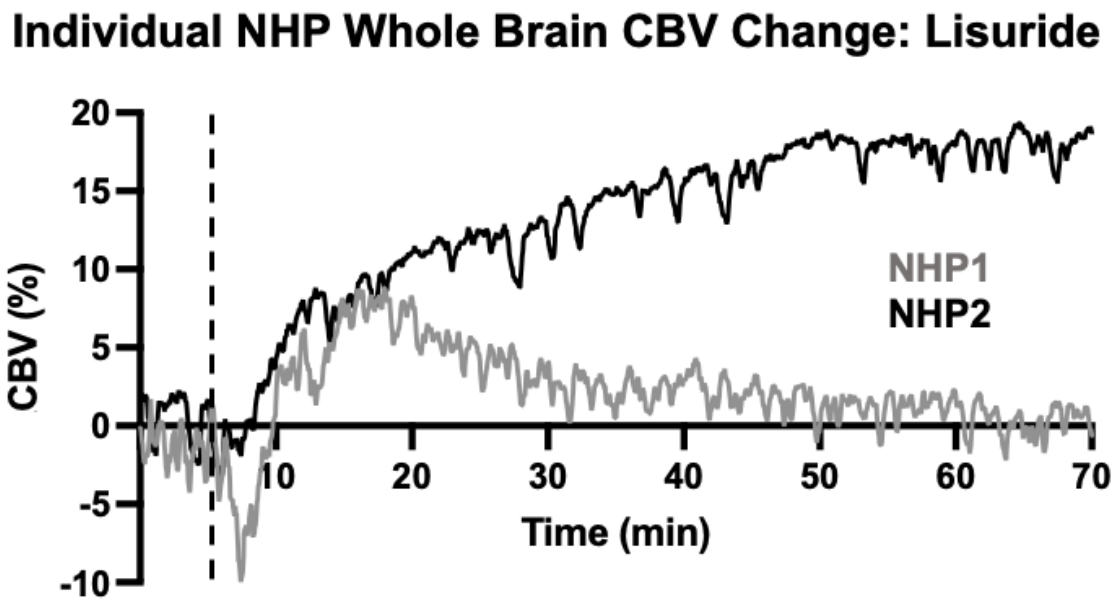

Figure S2: Individual NHP CBV profiles of the whole brain from the two lisuride scans, highlighting different patterns beyond acute lisuride injection between the NHP.

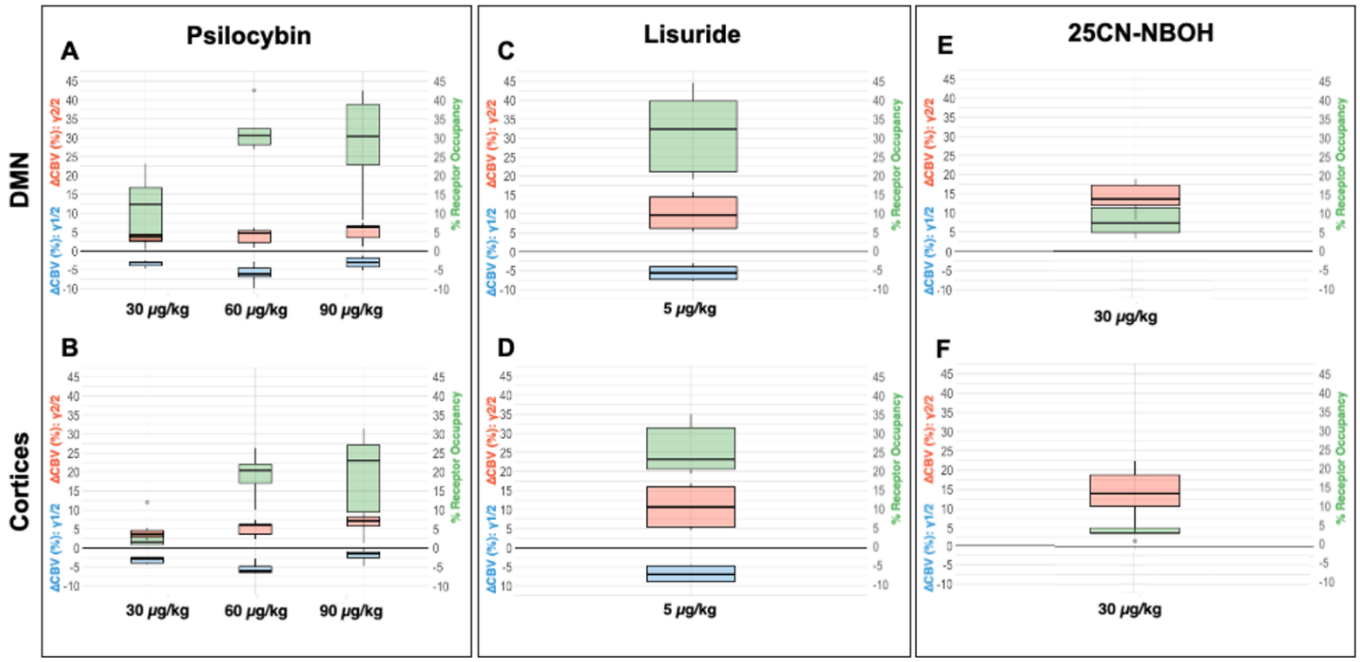

Figure S3: Occupancy (green) and DCBV (%) changes from γ_1 (blue) and γ_2 (red) for Psilocybin (A, B), Lisuride (C, D), and 25CN-NBOH (E, F). DMN (top row) is combined values across the ACC, PCC, and Precuneus. Cortices (bottom row) are combined values across Motor, Occipital, and Sensory cortices. Occupancy values below 0% were omitted. After thresholding in the Cortices, total datapoints for Psilocybin 30, 90μg/kg and Lisuride are N=6 for both CBV and *%O*; total datapoints for psilocybin 60μg/kg for *%O* are N=6, for CBV N=9; total datapoints for 25CN-NBOH are N=9 for CBV, N=6 for *%O*. After thresholding in the DMN, all total datapoints were the same as Cortices, with the exception of 25CN-NBOH N=3 for *%O.*

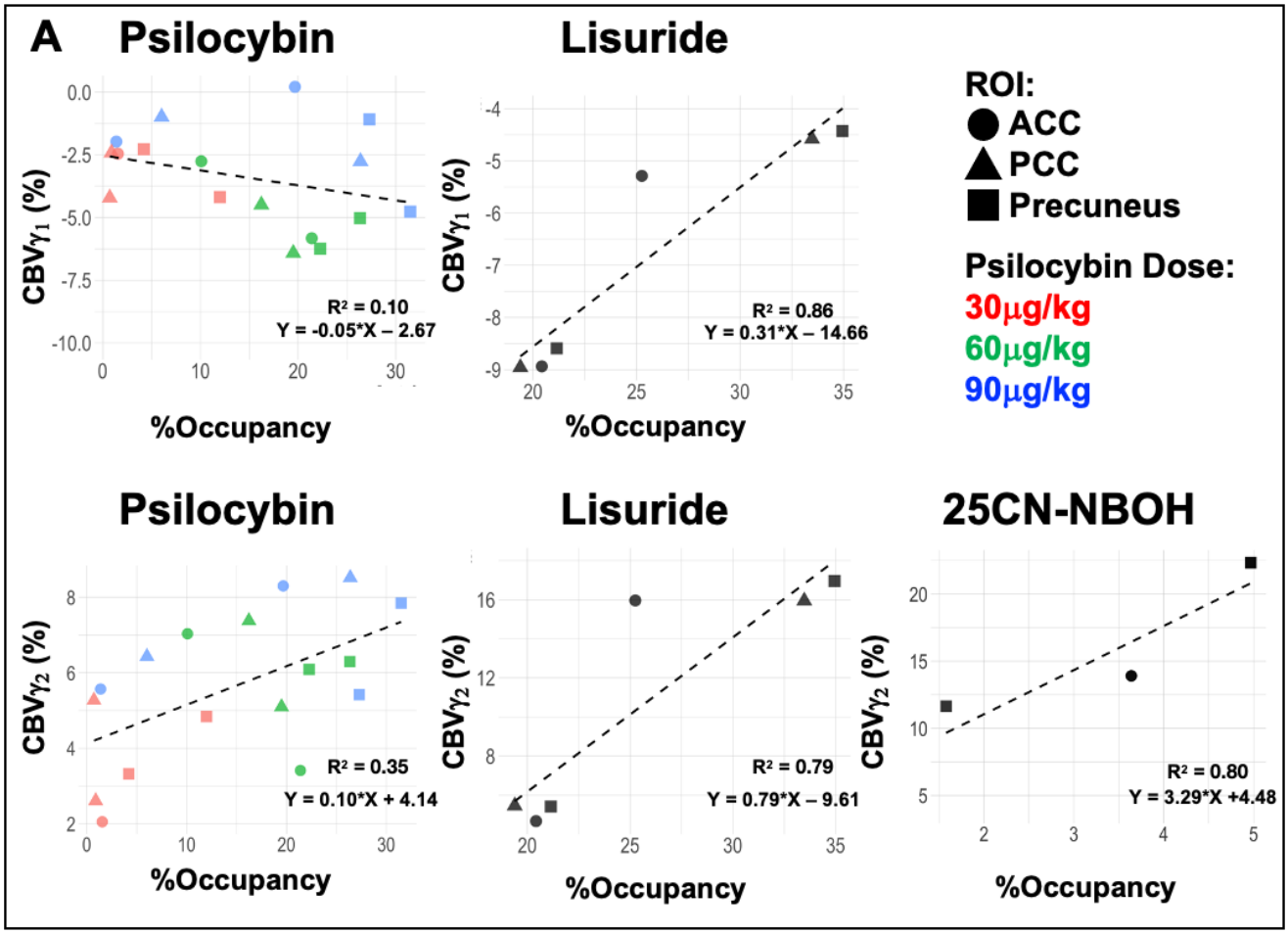

Figure S4: Assessment for trends between receptor occupancy (%) and CBV (%) changes for γ_1 and γ_2 in DMN regions. Datapoints with occupancies below 0% were excluded. Total number of datapoints: Psilocybin N=17; Lisuride N=6; 25CN-NBOH N=3

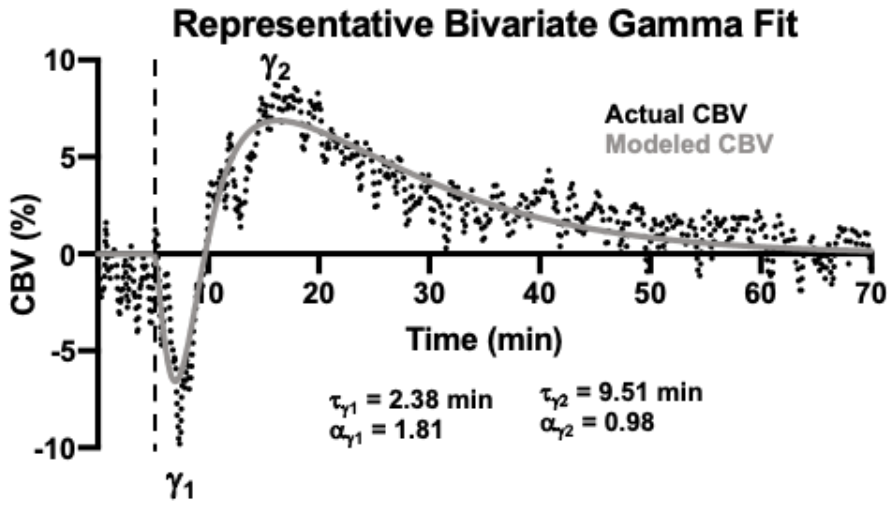

Figure S5: Representative model fit of an NHP with biphasic temporal CBV profile (black dots) and γ_1, γ_2 fits (grey line) for NHP1. Fits were performed on the raw fMRI signal, converted to percent difference relative to pre-injection signal, and detrended. τ and α represent time to peak change and shape for each function, respectively Conversion to relative changes in CBV based on previously used conversion methods (see MRI, phMRI Data Reconstruction and Processing in the main text). Dashed line represents the point of drug injection.

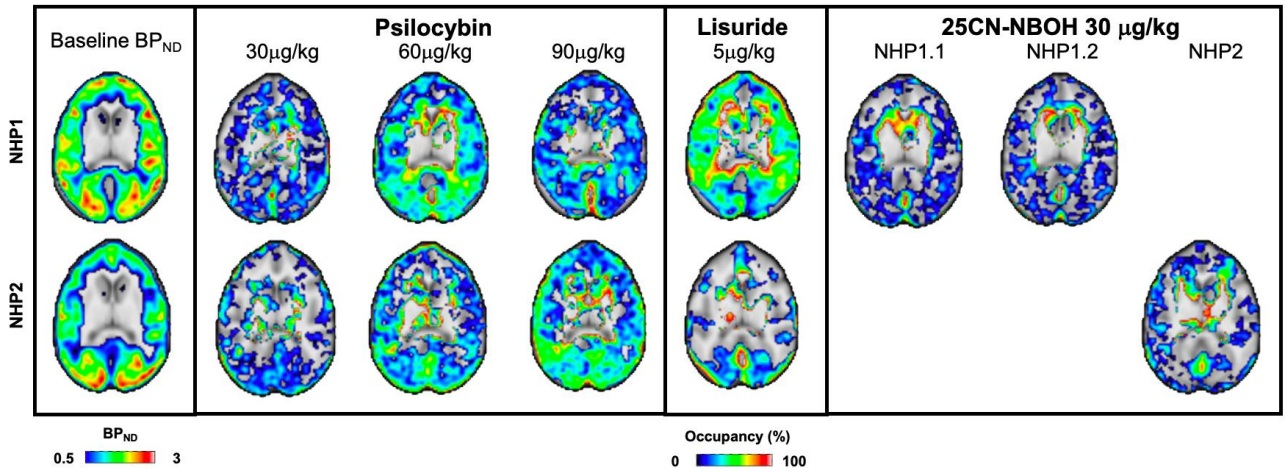

Figure S6: Occupancy maps derived for individual NHP to indicate sensitivity from across animals for each drug challenge scan. In the 25CN-NBOH group, NHP1.1 and NHP1.2 correspond to the drug challenge scan 1 and scan 2, respectively, that NHP1 underwent.

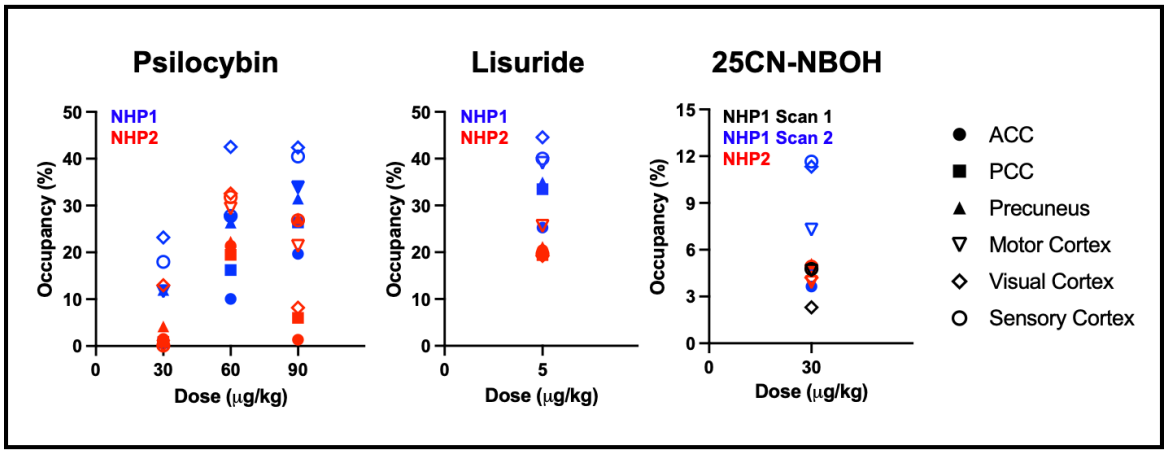

Figure S7: Occupancy maps derived for individual NHP to indicate sensitivity from across animals for each drug challenge scan. In the 25CN-NBOH group, NHP1.1 and NHP1.2 correspond to the drug challenge scan 1 and scan 2, respectively, that NHP1 underwent.

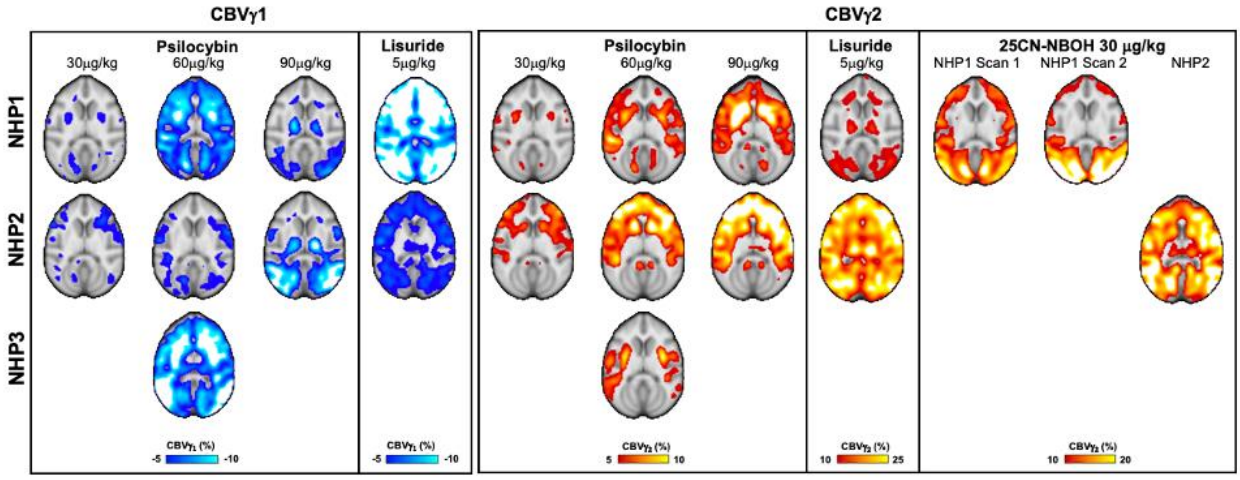

Figure S8: CBV maps derived for individual NHP to indicate sensitivity from across animals for each drug challenge scan. In the 25CN-NBOH group, NHP1.1 and NHP1.2 correspond to the drug challenge scan 1 and scan 2, respectively, that NHP1 underwent. NHP3 is not included in Figure 2 as it did not have a paired PET scan but is included for here for transparency.

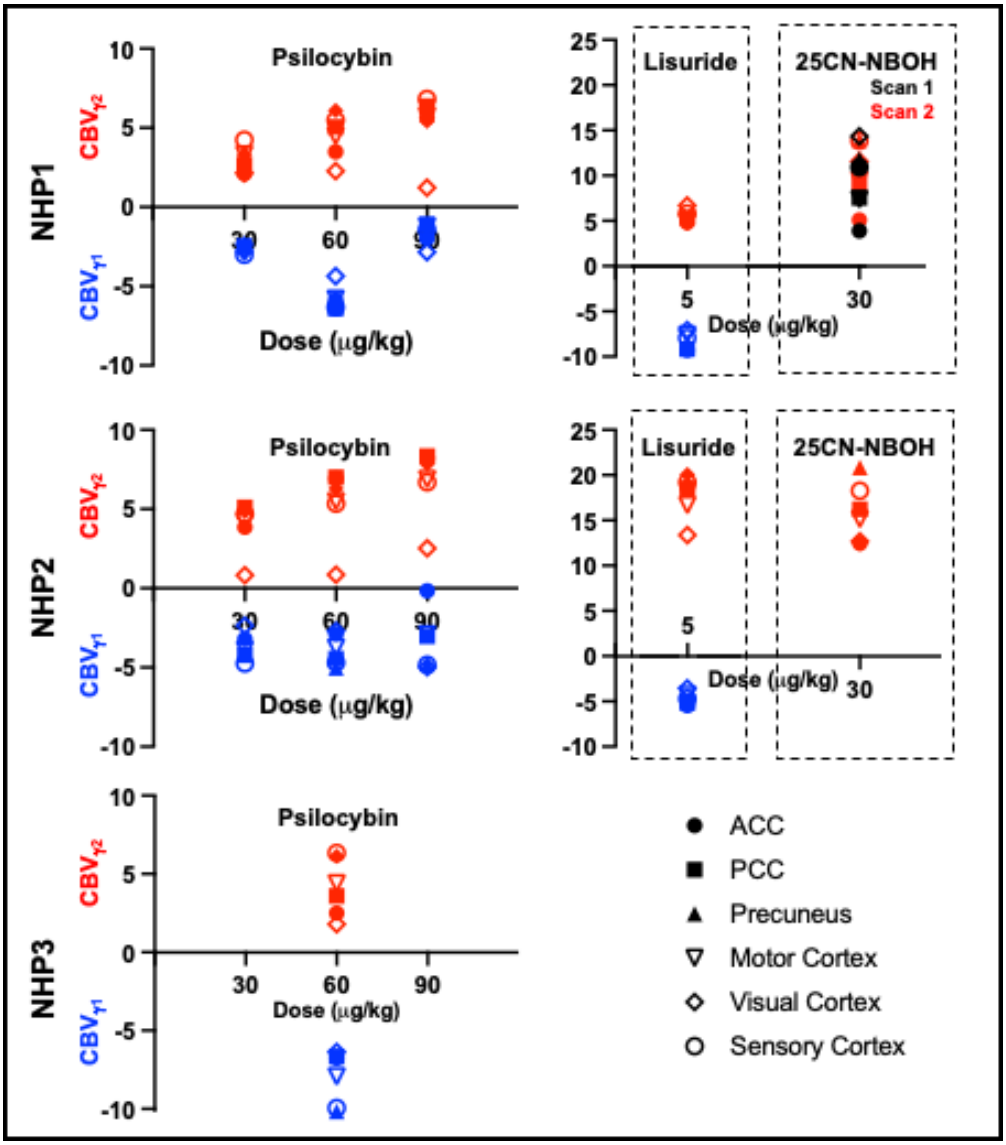

Figure S9: ROI-specific derived CBV derived for individual NHP to indicate sensitivity from across animals for each drug challenge scan. In the 25CN-NBOH group, NHP1.1 and NHP1.2 correspond to the drug challenge scan 1 and scan 2, respectively, that NHP1 underwent. NHP3 is not included in Figure 2 as it did not have a paired PET scan but is included for here for transparency.