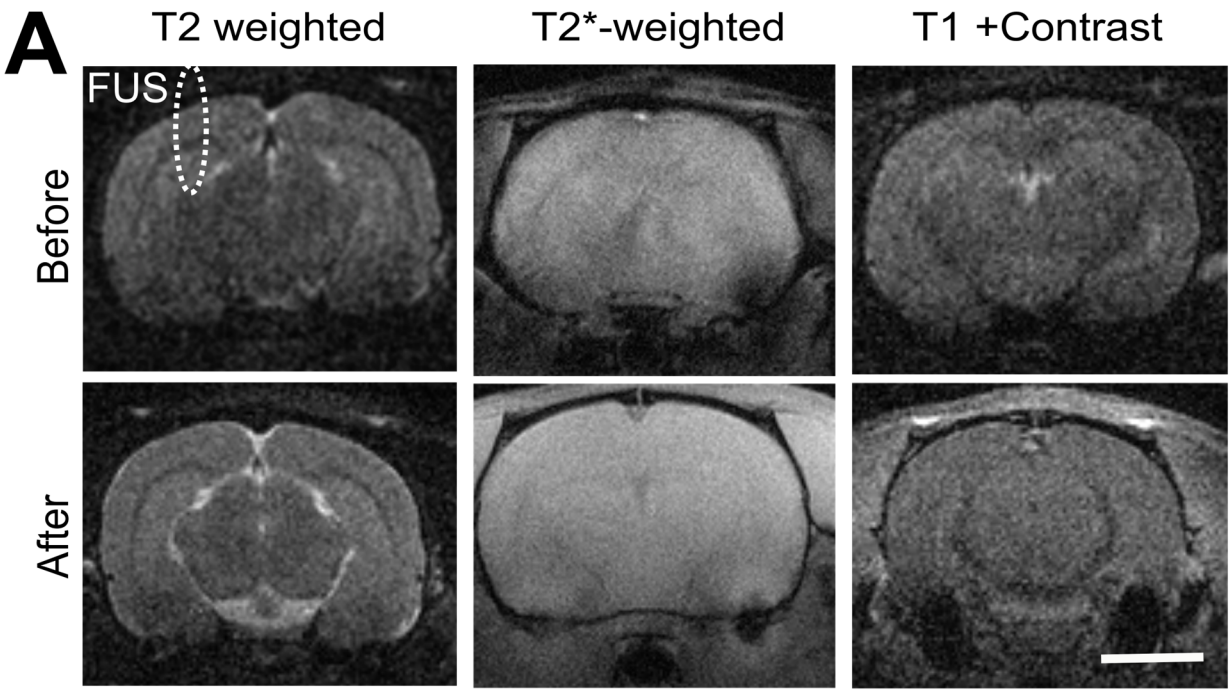
SUPPLEMENTAL DATA



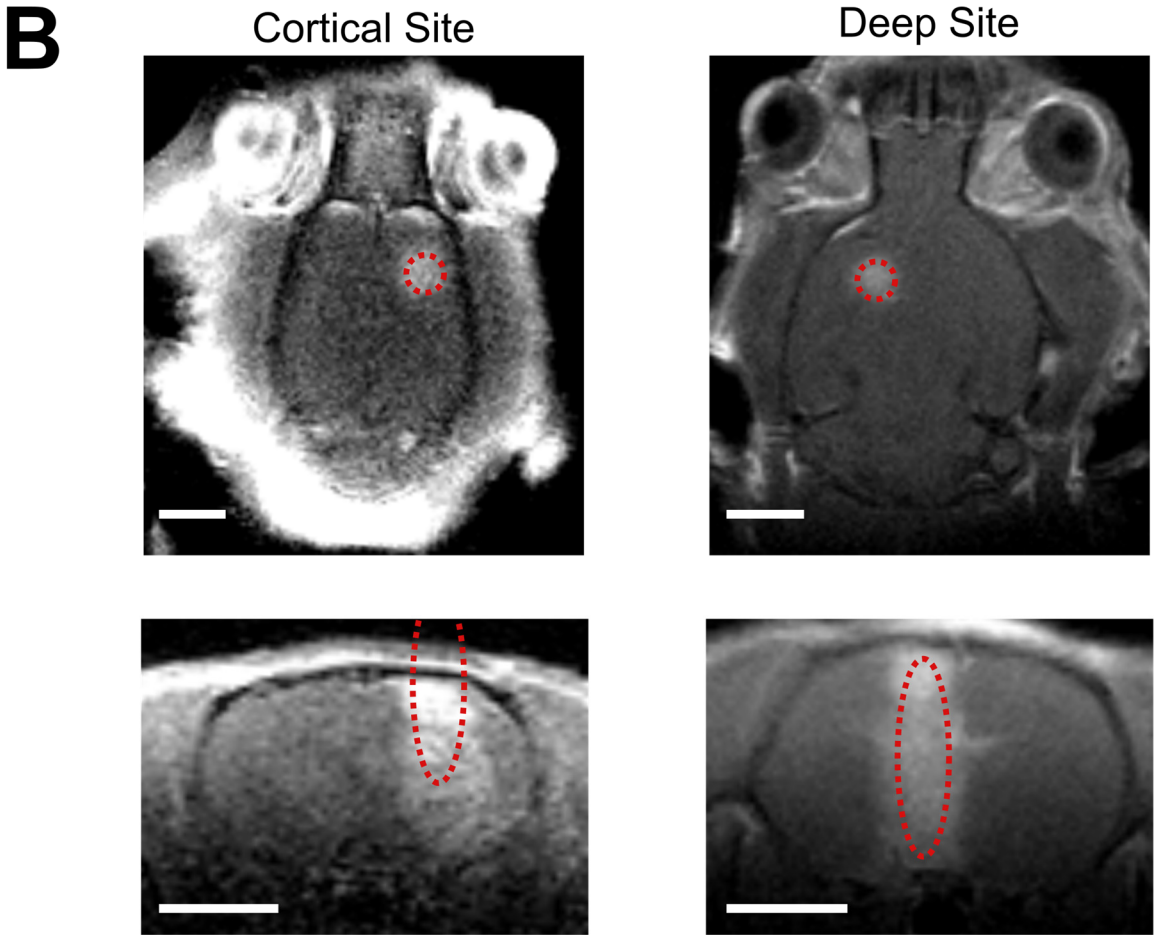


Fig. S1: Representative MRI evaluation of the effects of ultrasonic drug uncaging on the brain parenchyma. Related to Figures 1, 4, and 5.

(A) No effects such as edema (which would be bright on T2-weighted MRI, left), hemorrhage (which would be dark on T2*-weighted MRI, middle), or blood-brain barrier disruption (which would be bright on post-contrast T1-weigthed MRI, right) were noted in the parenchyma by MRI with and without contrast when comparing before (top) and after (bottom) focused ultrasound (FUS; 60 x 100 ms bursts at 1 Hz burst frequency with 1.8 MPa peak in situ pressure) application to a single focus in visual cortex (dashed ellipse, top left: expected sonication focus full-width at half-maximum) after intravenous administration of propofol-loaded nanoparticles (bolus of 1 mg/kg encapsulated propofol). Scale bar: 5 mm. **(B)** To visualize the maximal *in vivo* sonication field in the rat and provide a positive control for the analysis in **A**, we performed microbubble-mediated blood-brain barrier disruption with a sonication pressure ~3 times the estimated threshold for this effect (0.4 MPa with 10 ms pulses delivered every second for 5 minutes) (McDannold et al., 2013). Depicted are representative post-contrast T1-weighted 3T MRI images for each target used for PET experiments. It is estimated that areas exposed to sonication of at least ~0.12 MPa = 30% of maximum would appear bright on these images (McDannold et al., 2013). This is supported by the extent of gadolinium uptake beyond the sonication FWHM (red dashed ellipse). Scale bars: 5 mm

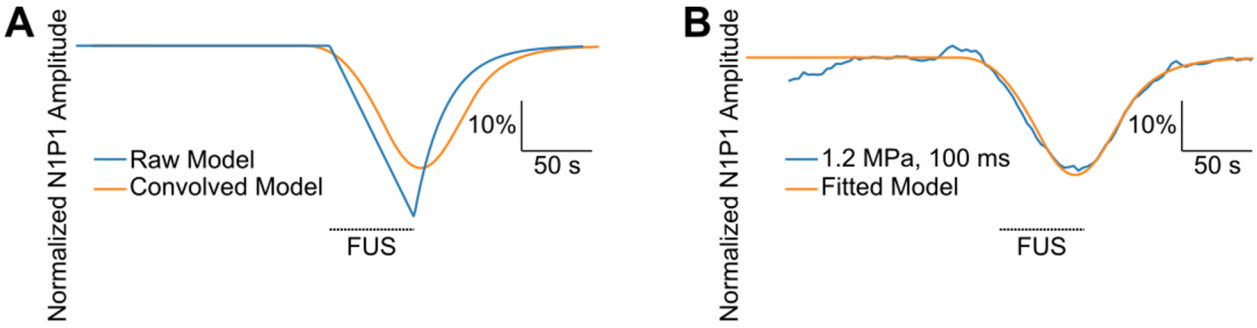


Fig. S2: Modeling of anesthesia of visual evoked potentials (VEPs) with ultrasonic propofol uncaging. Related to Figure 2.

(A) In the raw model, before sonication, the VEP is assumed to be unchanging from its normalized baseline value. Upon sonication, the VEP amplitude decreases linearly during sonication as a first-order approximation of the net effect of uncaged propofol supply, redistribution, and metabolism. After sonication stops, the VEP N1P1 amplitude recovers back to its baseline with exponential decay. In the convolved model, we convolve with a Gaussian kernel that matches the kernel used to compute our N1P1 amplitude from the raw data. Depicted here is the model with the same parameters fit for our propofol nanoparticles when exposed to 1.2 MPa peak negative pressure and a burst length of 100 ms. The dashed bar is the time for which sonication (FUS) is applied. **(B)** Comparison of our fitted model with the N1P1 amplitudes recorded during ultrasonic propofol uncaging with 1.2 MPa peak negative pressure and 100 ms burst length (N=6). Here, root mean square error is 2.16% (in the units of normalized N1P1 amplitude) and model R^2 is 90.2%.

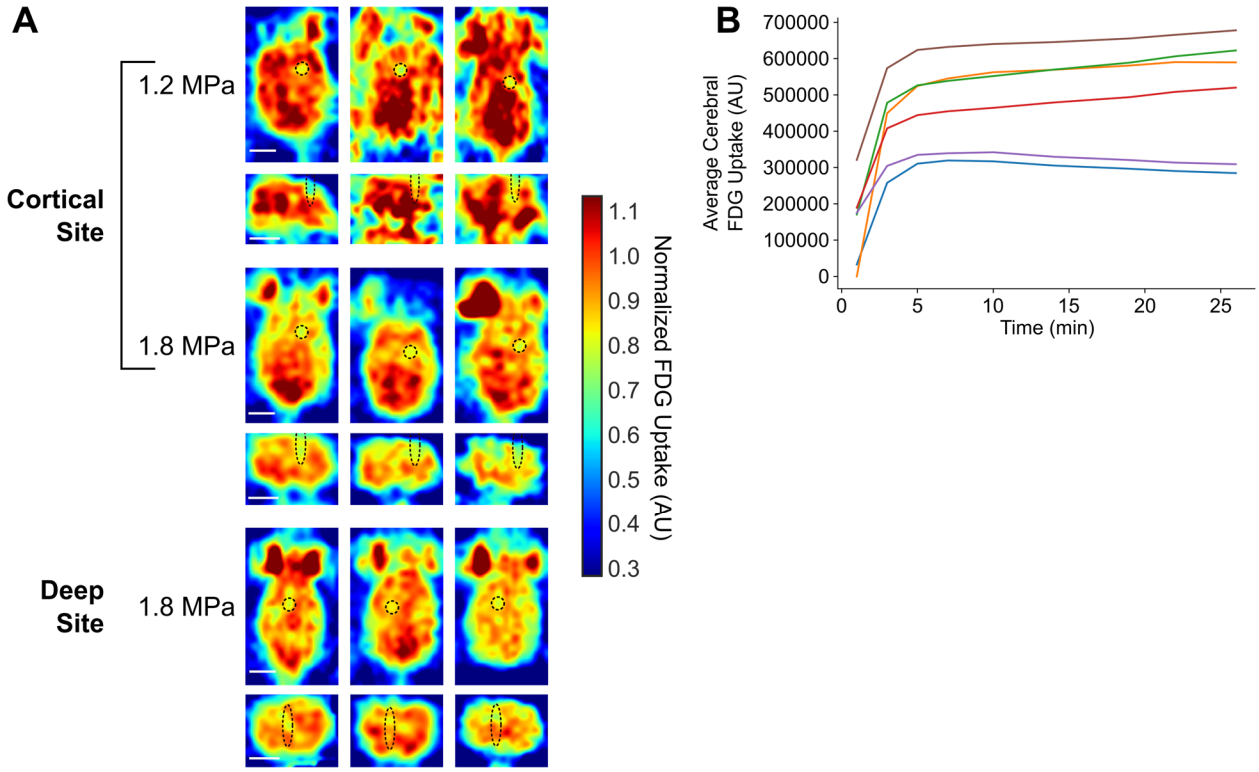


Fig S3: Reproducibility of neuromodulation induced by ultrasonic drug uncaging and diversity of FDG uptake profiles between animals. Related to Figures 3 and 4.

(A) Representative examples for individual animal PET images during ultrasonic propofol uncaging directed to the target indicated by the black dashed ellipses. Images are normalized by uptake of the contralateral region from the target. Note that the first column is repeated from **Figs. 3 and 4**. Scale bars: 5 mm. **(B)** Average FDG uptake in the cerebrum for each of the six animals in the 1.2 MPa cortical sonication cohort with propofol-loaded nanoparticles demonstrating the variability of uptake across animals, as expected given that FDG uptake is dependent on factors like depth of anesthesia, animal body weight, and resting glucose level.

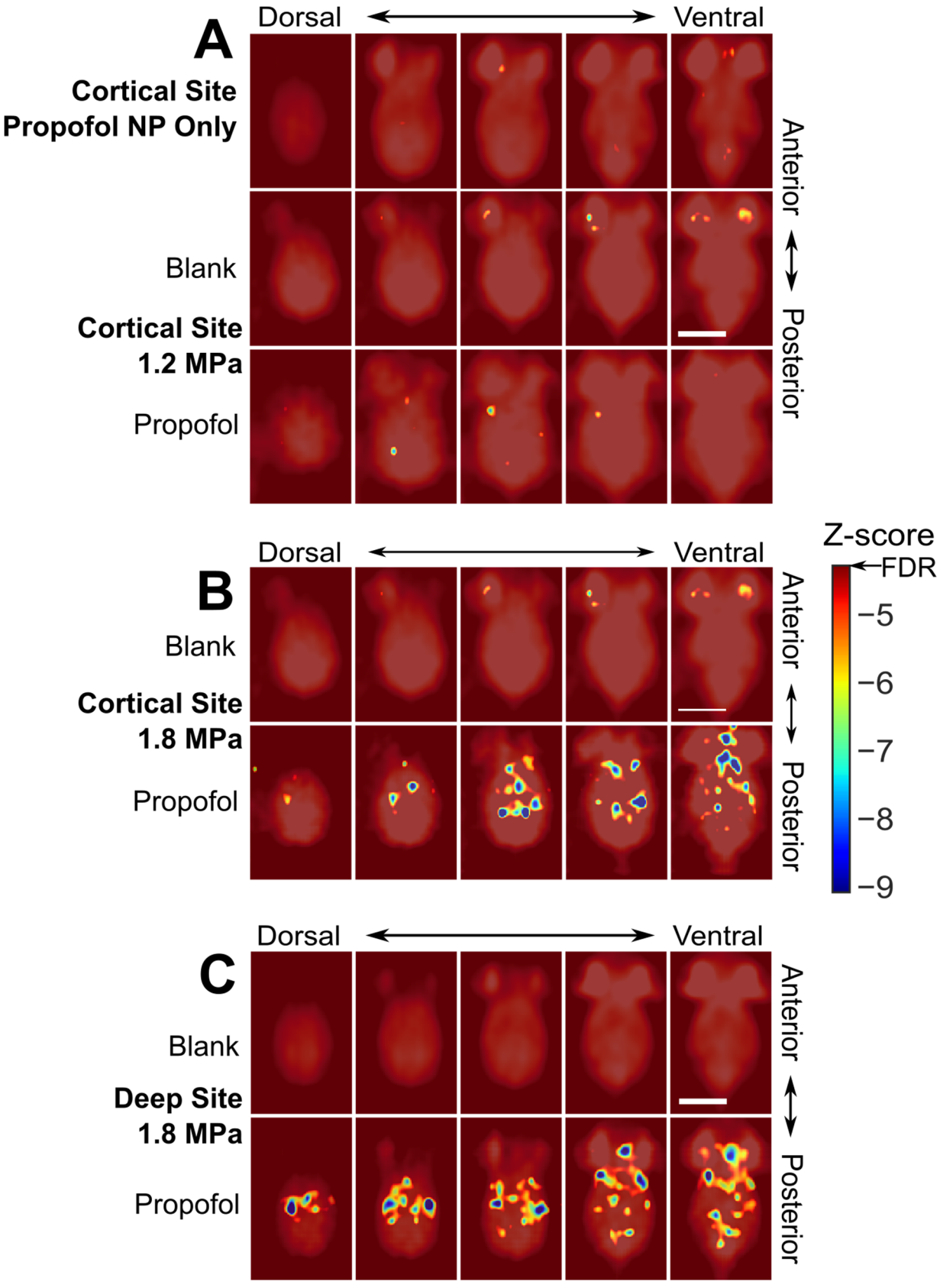

A
Cortical Site
Propofol NP Only
Blank
Cortical Site
1.2 MPa
Propofol
Dorsal
Ventral
Anterior
Posterior
B
Blank
Cortical Site
1.8 MPa
Propofol
Dorsal
Ventral
Anterior
Posterior
Z-score
FDR
−5
−6
−7
−8
−9
C
Blank
Deep Site
1.8 MPa
Propofol
Dorsal
Ventral
Anterior
Posterior

Fig. S4: Unlabeled statistical parametric maps. Related to Figures 4 and 5.

(A) Statistical parametric maps from data generated after nanoparticle administration with no sonication (top), or with sonicating at the cortical target with a peak negative pressure of 1.2 MPa, with blank (middle) or propofol-loaded (bottom) nanoparticles. Note that the anterior paired structures outside the brain are the Harderian glands. Changes in these glands represent the noise floor of this technique. **(B)** Statistical parametric maps generated from sonicating at the cortical target with a peak negative pressure of 1.8 MPa. Note that the top row is repeated from **A**. **(C)** Statistical parametric maps generated from sonicating at the deep site with a peak negative pressure of 1.8 MPa, with blank (top) or propofol-loaded (bottom) nanoparticles. Scale bars: 5 mm.

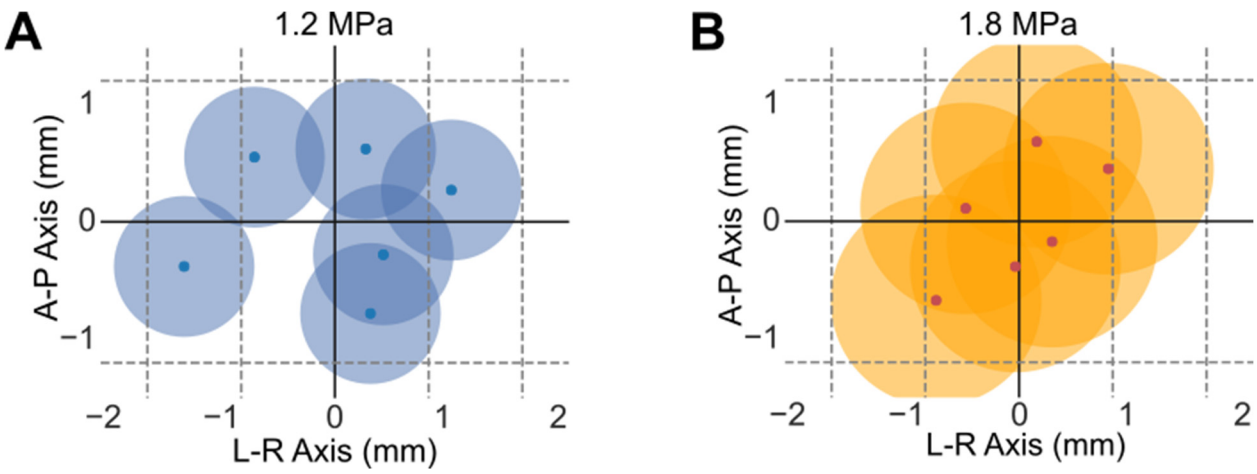


Fig. S5: Overlap of sonication sites following whole-brain coregistration. Related to Figures 4 and S4.

(A) Relative coordinates of the point with minimal FDG uptake at the primary sonication target (for cortical sonication at 1.2 MPa) in the transverse plane, as identified by tricubic interpolation, following the whole-brain registration procedure used for **Fig. S4A**, bottom. Points are centered around the mean of all interpolated coordinates. Grid lines represent the non-interpolated voxel dimensions (not necessarily the exact voxel boundary locations), solid dots represent the sonicated target coordinate for each animal in the cohort, and the larger shaded circles represent the FWHM size of the anesthesia effect (from Fig. 3F). **(B)** Relative placement of coordinates for the 1.8 MPa cortical sonication condition following the whole-brain coregistration completed for **Fig. S4B**, bottom. All conventions are the same as in **A**.

Drug	Sonication Site	Peak Negative Pressure (MPa)	Burst Length (ms)	Number of experiments	RMSE
Propofol	V1	0.8	50	6	2.71%
		1.2	10	4	3.70%
			50	9	1.83%
			100	6	2.16%
		1.8	50	5	5.20%
	V1 (First)	1.2	50	4	3.20%
	M1			5	1.82%
	V1 (Second)			4	3.07%
	LGN			7	2.69%
Blank	V1			7	3.06%

Table S1: Errors for modeling anesthesia of visually evoked potentials (VEPs). Related to Figure 2.

Root mean square error of fitted model for computing VEP effect sizes and recovery times under different conditions as shown in **Fig. 2**.

Protocol	Sonication Site	Caudal from Bregma (mm)	Lateral of Midline (mm)	Depth from Bregma (mm)
VEP	V1	-6.5	3.5	-2
	M1	-2	1.5	-2
	LGN	-4	3.5	-5
PET	Cortical	-2	2	-2
	Deep	-3	1.2	-5

Table S2. Stereotactic coordinates of sonication sites. Related to STAR Methods and Figures 2, 3, and 4.