Supplemental Information

Figure S1. 5-HT GPCRome and second messenger assays comparing LSD to 2-Br-LSD. *Related to Figures 1 and 2.*

(A) Concentration-response curves for 2-Br-LSD (blue) compared to LSD (red) and 5-HT (black) at each of the 5-HT receptor subtypes measuring indicated G protein subtype dissociation by BRET. Data represent mean and SEM from at least n=3 independent experiments performed in triplicate. Data were normalized to % 5-HT maximum stimulation, and parameter estimates are reported in Table S2. (B) Second messenger confirmatory assays measuring Gi/o-mediated cAMP inhibition (5-$HT_{1A/1B/1F}$ and $D_{2/4}$ receptors), Gq-mediated calcium flux (5-$HT_{2A/2B/2C}$) or Gs-mediated cAMP accumulation (5-HT_6 and 5-HT_{7a}). Data represent mean and SEM from at least n=3 independent experiments performed in triplicate. Data were normalized to either 5-HT maximum stimulation (for 5-HT receptors) or dopamine maximum stimulation for dopamine receptors.

Fig. S1

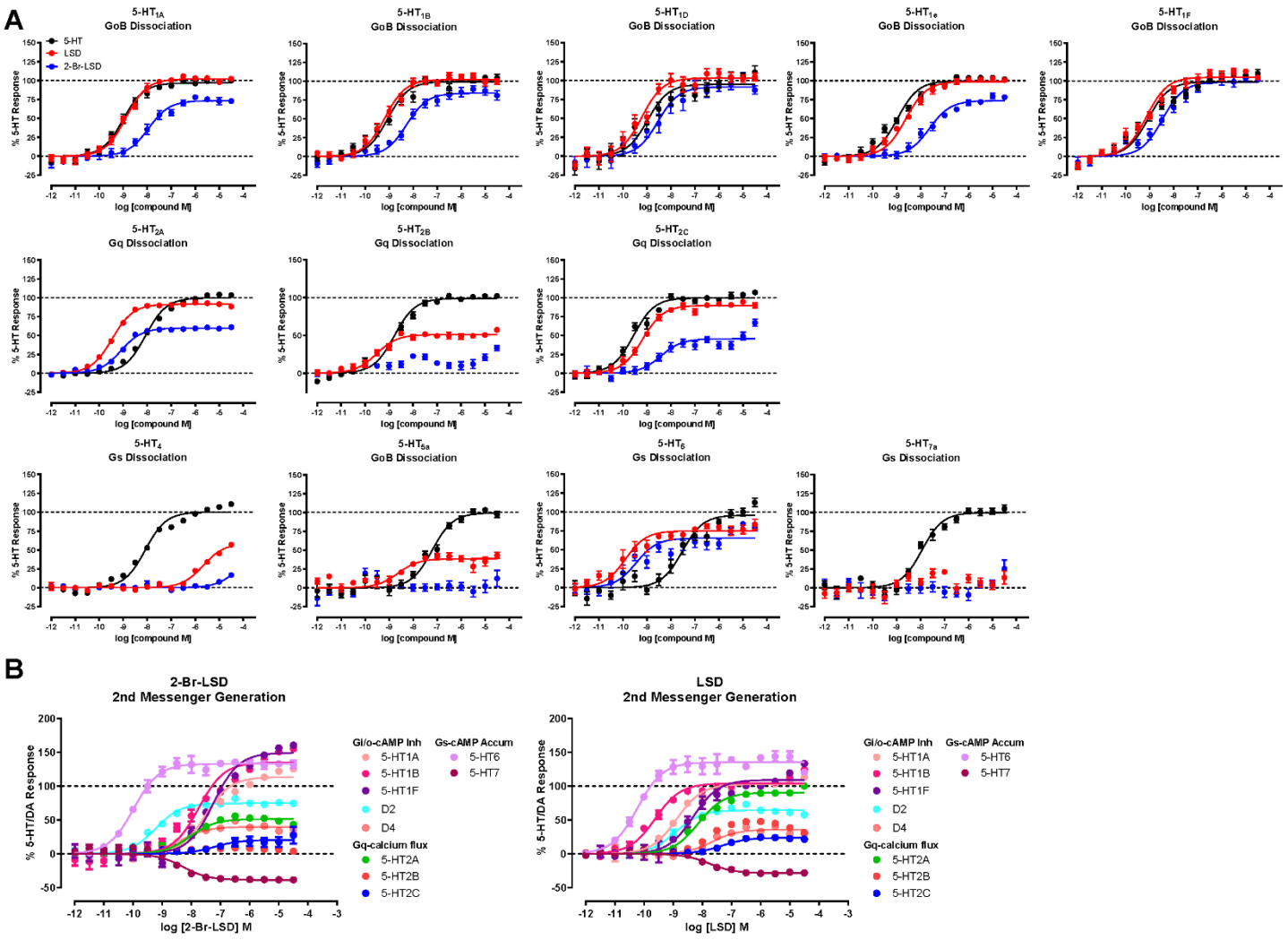
A
5-HT1A GoB Dissociation
5-HT1B GoB Dissociation
5-HT1D GoB Dissociation
5-HT1e GoB Dissociation
5-HT1F GoB Dissociation
5-HT2A Gq Dissociation
5-HT2B Gq Dissociation
5-HT2C Gq Dissociation
5-HT4 Gs Dissociation
5-HT6a GoB Dissociation
5-HT6 Gs Dissociation
5-HT7a Gs Dissociation
5-HT
LSD
2-Br-LSD
% 5-HT Response
log [compound M]
B
2-Br-LSD
2nd Messenger Generation
LSD
2nd Messenger Generation
% 5-HT/DA Response
log [2-Br-LSD] M
log [LSD] M
Gi/o-cAMP Inh
5-HT1A
5-HT1B
5-HT1F
D2
D4
Gs-cAMP Accum
5-HT6
5-HT7
Gq-calcium flux
5-HT2A
5-HT2B
5-HT2C

Figure S2. Amingeric GPCRome comparing LSD to 2-Br-LSD. *Related to Figure 1.*

Concentration-response curves for 2-Br-LSD (blue) compared to LSD (red) and specific positive control (black) tested in agonist mode at (A) dopamine receptor subtypes, (B) adrenergic α1 and α2 subtypes, (C) adrenergic β subtypes, (D) histamine subtypes, and (E) muscarinic acetylcholine subtypes. Each data set represents mean and SEM that is normalized to percent positive control response (DA dopamine, NE norepinephrine for α1, α2, and β1 subtypes, Epi/Epinephrine for β2 subtype, histamine for histamine subtypes, and pilocarpine for muscarinic subtypes Data represent mean and SEM from at least n=3 independent experiments performed in triplicate. Data were normalized to either percent maximum positive control stimulation.

Fig. S2

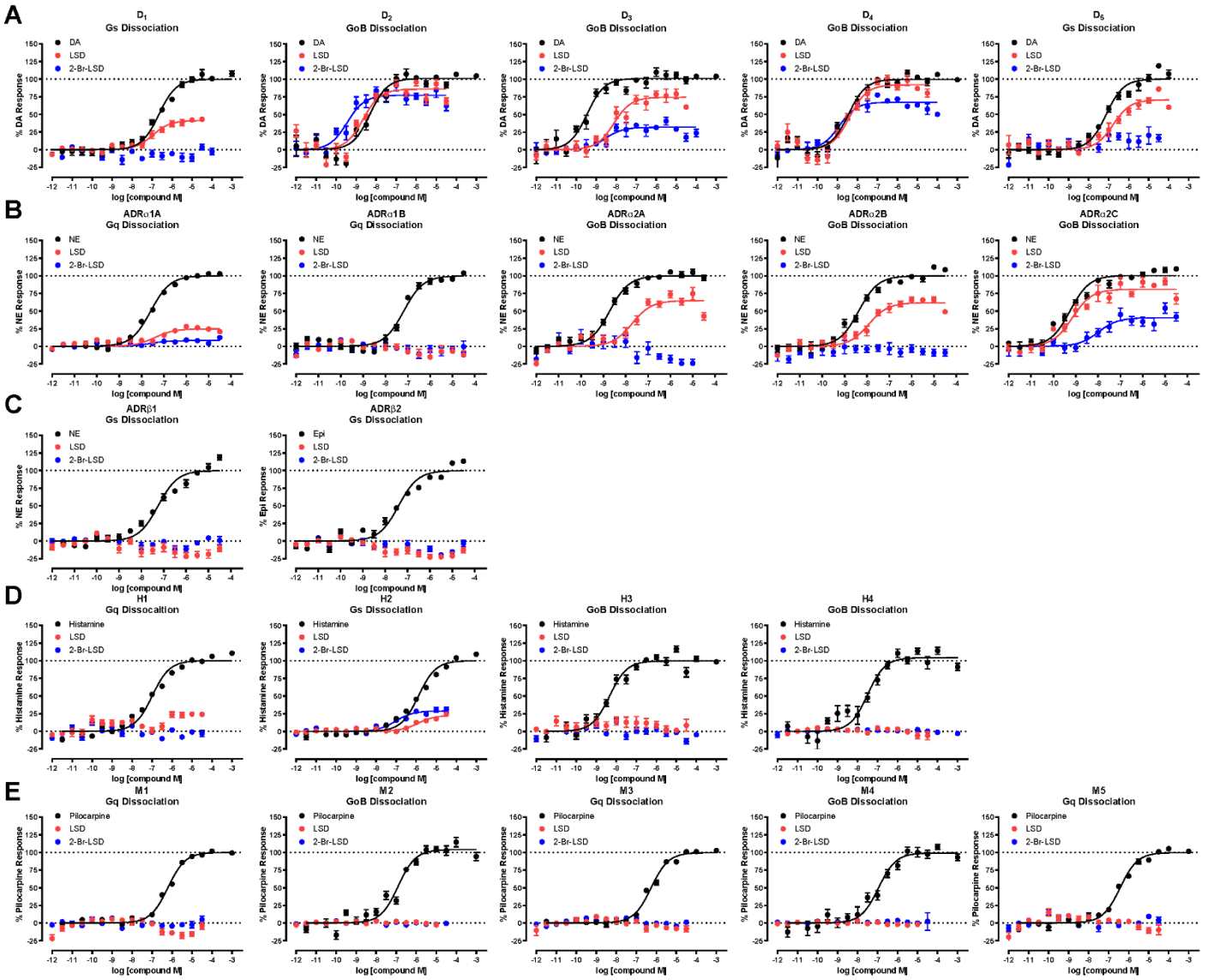
A
D1
Gs Dissociation
D2
Gob Dissociation
D3
Gob Dissociation
D4
Gob Dissociation
D5
Gs Dissociation
DA
LSD
2-Br-LSD
% DA Response
log [compound M]
B
ADRα1A
Gq Dissociation
ADRα1B
Gq Dissociation
ADRα2A
Gob Dissociation
ADRα2B
Gob Dissociation
ADRα2C
Gob Dissociation
NE
% NE Response
C
ADRβ1
Gs Dissociation
ADRβ2
Gs Dissociation
Epi
% Epi Reponse
D
H1
Gq Dissocaltion
H2
Gs Dissociation
H3
Gob Dissociation
H4
Gob Dissociation
Histamine
% Histamine Response
E
M1
Gq Dissociation
M2
Gob Dissociation
M3
Gq Dissociation
M4
Gob Dissociation
M5
Gq Dissociation
Pilocarpine
% Pilocarpine Response

Figure S3. 2-Br-LSD Brain and Plasma Pharmacokinetics and HTR blockade studies. *Related to Figure 2.*

(A) Brain concentration-time curves for 2-Br-LSD in female mice. Data are presented as group means ± SEM. 2-Br-LSD was injected at t = 0. (B) Plasma concentration-time curves for 2-Br-LSD in male mice. (C) Plasma concentration-time curves for 2-Br-LSD in female mice. (D) Pretreatment with the 5-HT_{1A} antagonist WAY-100,635 did not alter the effect of 2-Br-LSD on the head-twitch response (HTR). Mice were pretreated with vehicle or WAY-100,635 (1 mg/kg), vehicle or 2-Br-LSD (3 mg/kg) was injected 20 min later, and then HTR activity was recorded. Data are presented as group means ± SEM for the entire 30-minute test session. (E) Pretreatment with the $D_{2/3}$ antagonist *S*-(–)-raclopride did not alter the effect of 2-Br-LSD on the HTR. Mice were pretreated with vehicle or *S*-(–)-raclopride (1 mg/kg) vehicle or 2-Br-LSD (3 mg/kg) was injected 20 min later, and then HTR activity was recorded. Data are presented as group means ± SEM for the entire 30-minute test session. *p<0.05, significant difference between groups (Tukey's test). (F) Effect of pretreatment with the $D_{2/3}$ agonist (–)-quinpirole on the HTR induced by 2,5-dimethoxy-4-iodoamphetamine (DOI). Mice were pretreated with vehicle or (–)-quinpirole, DOI was injected 30 minutes later, and then HTR activity was recorded. Data are presented as group means ± SEM for the entire 30-minute test session. *p<0.05, significant difference between groups (Tukey's test).

Fig. S3

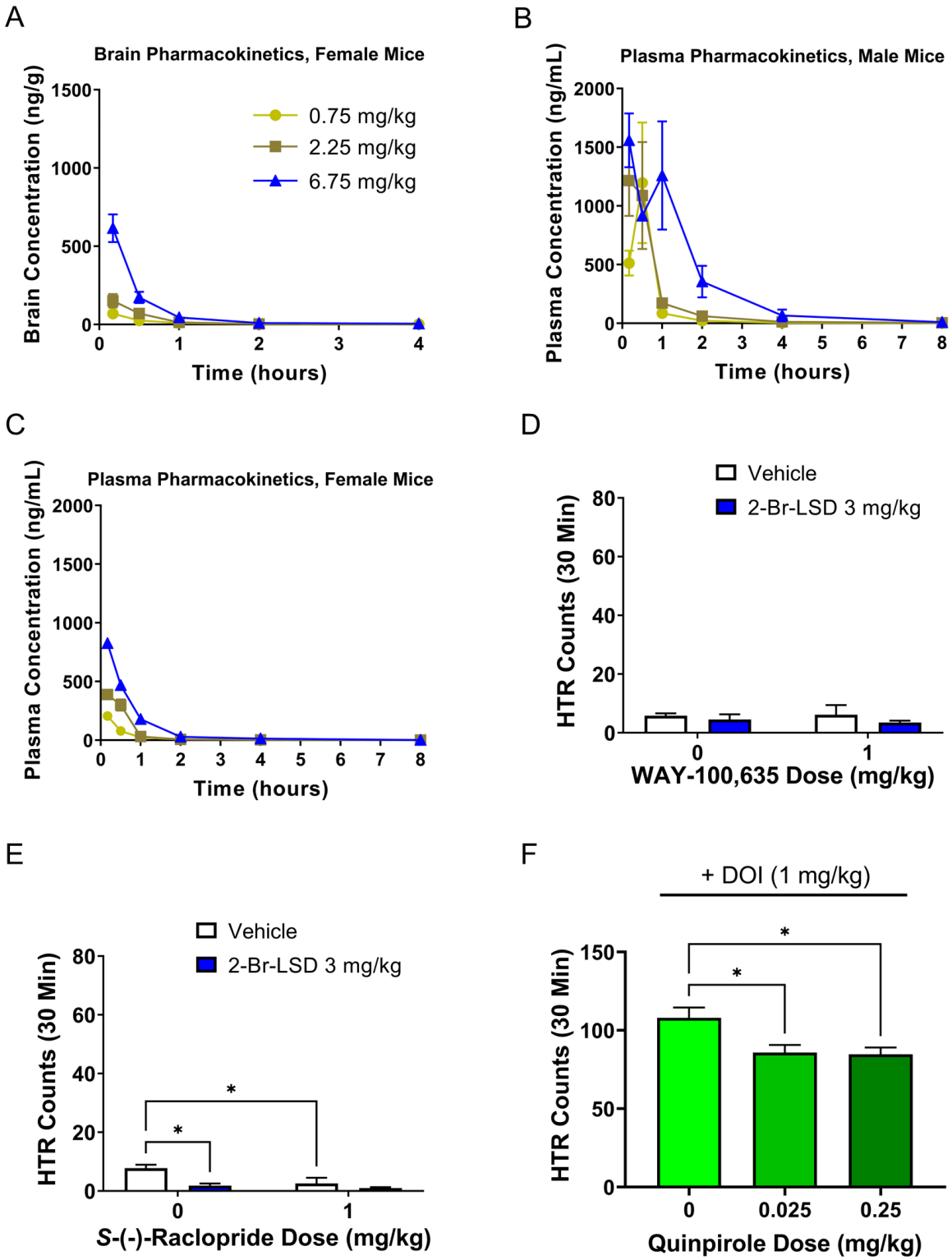
A
Brain Pharmacokinetics, Female Mice
Brain Concentration (ng/g)
1500
1000
500
0
0.75 mg/kg
2.25 mg/kg
6.75 mg/kg
0
1
2
3
4
Time (hours)
B
Plasma Pharmacokinetics, Male Mice
Plasma Concentration (ng/mL)
2000
1500
1000
500
0
0
1
2
3
4
5
6
7
8
Time (hours)
C
Plasma Pharmacokinetics, Female Mice
Plasma Concentration (ng/mL)
2000
1500
1000
500
0
0
1
2
3
4
5
6
7
8
Time (hours)
D
Vehicle
2-Br-LSD 3 mg/kg
HTR Counts (30 Min)
80
60
40
20
0
0
1
WAY-100,635 Dose (mg/kg)
E
Vehicle
2-Br-LSD 3 mg/kg
HTR Counts (30 Min)
80
60
40
20
0
*
*
0
1
S-(-)-Raclopride Dose (mg/kg)
F
+ DOI (1 mg/kg)
HTR Counts (30 Min)
150
100
50
0
*
*
0
0.025
0.25
Quinpirole Dose (mg/kg)

Figure S4. 2-Br-LSD 5-HT GPCRome G protein versus β-arrestin recruitment profiling. *Related to Figure 4.*

(A-K) Concentration-response curves for 2-Br-LSD comparing G protein dissociation (red) to β-arrestin2 recruitment (blue) at each of the 5-HT subtypes. All data represent mean and SEM from n=3 independent experiments performed in triplicate. Data were normalized to % 5-HT maximum stimulation, and parameter estimates are reported in Table S2.

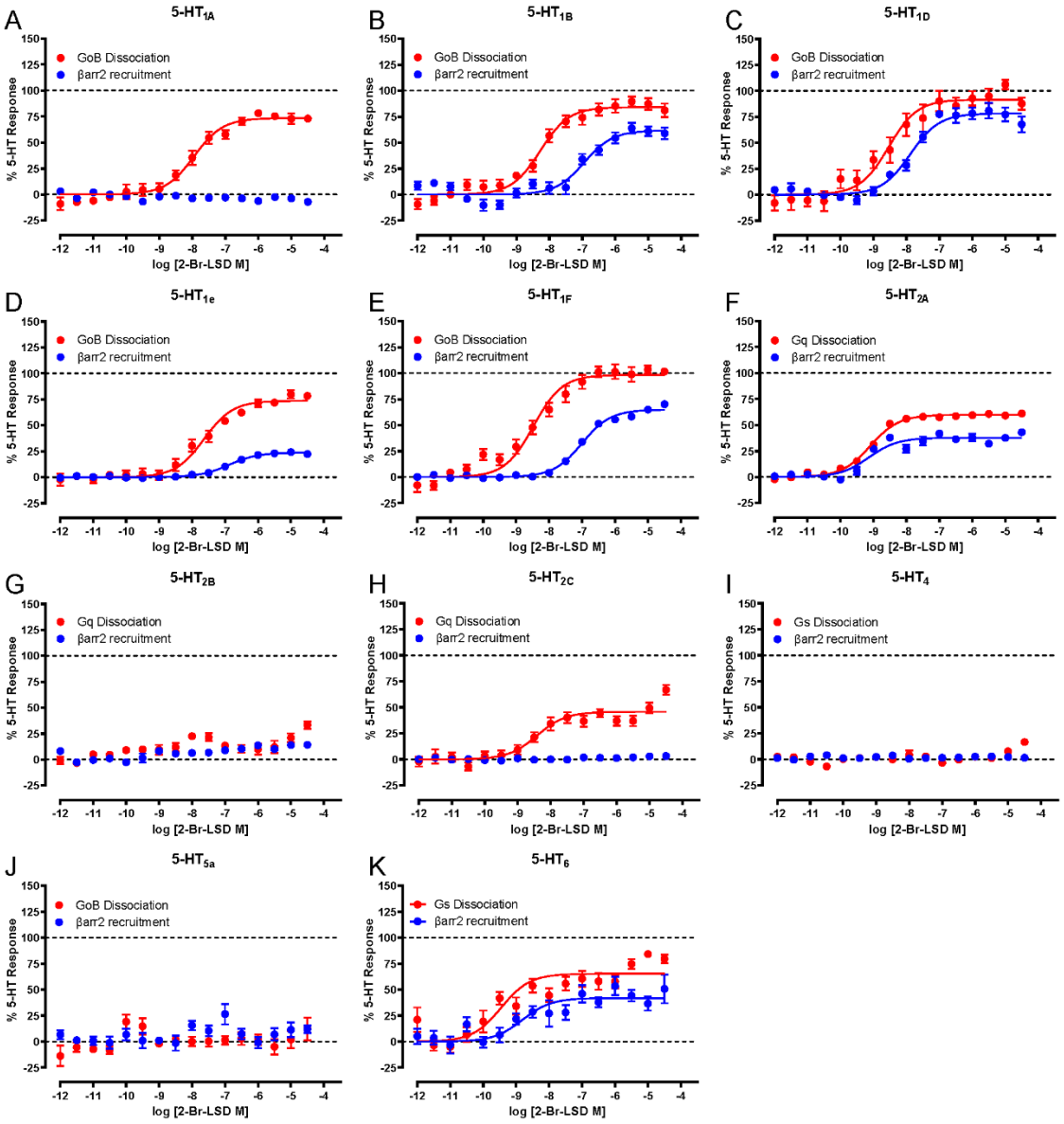

Figure S5. Neuron Viability and Open Field Activity. *Related to Figures 5 and 6.*

(A) Neuron viability was determined in rat cortical neurons in culture treated with five concentrations of 2-Br-LSD (0.001, 0.01, 0.1, 1, or 10 µM) or ketamine. The ratio of living to dead cells was measured at DIV 6; points represent the percentage of live cells (n=3). Horizontal lines represent the mean ± SEM. (B) and (C) Average heat maps of the location of female and male mice in the open field (from mice described in Fig. 6A-G). Mice had been treated with 2-Br-LSD at 3 different doses (IP, 0.3, 1 or 3 mg/kg) or vehicle 24 hrs prior (n=10-11/group/sex).

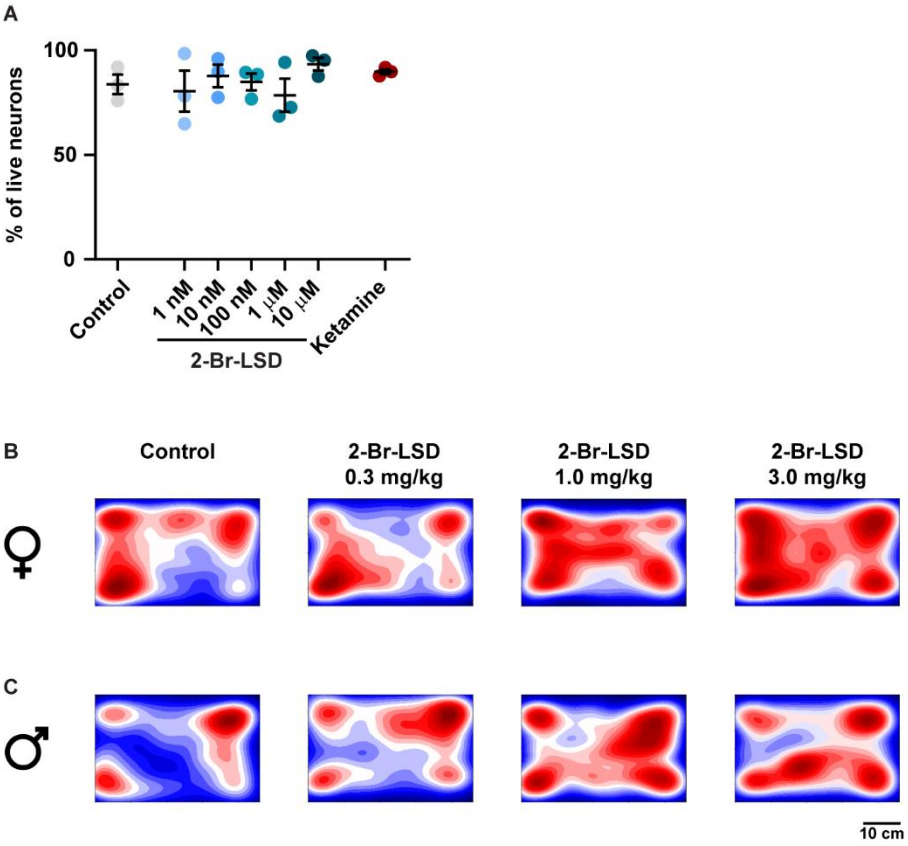

Figure S6. Center Exploration in Chronic Variable Stress and 2-Br-LSD 5-HT_{2A} blockade by Volinanserin. *Related to Figures 6 and 7.*

(A) and (B) Center exploration and grooming in chronically stressed female mice treated with one dose of 2-Br-LSD (3 mg/kg), four doses of 2-Br-LSD (1 mg/kg), or vehicle (as described in Fig. 6J-M). (A) The effect of 2-Br-LSD treatment on center exploration in the open field, 28 days post-treatment. Horizontal lines represent the mean ± SEM. (C) Volinanserin 5-HT_2 selectivity was measured by antagonism of 5-HT-stimuated Gq-mediated calcium flux at 5-HT_{2A} (green), 5-HT_{2B} (red), and 5-HT_{2C} (blue). The concentration of 5-HT used was 2 nM, and IC_{50} values of volinanserin are 2.1 nM, >10,000 nM, and 494 nM for 5-HT_{2A}, 5-HT_{2B}, and 5-$HT_{2C,}$ respectively. Data are normalized to percent 5-HT stimulation and represent mean and SEM from at least 3 independent experiments. (D) and (E) 5-HT (black), 2-Br-LSD (blue) and volinanserin blockade of 2-Br-LSD (red) as measured by (D) 5-HT_{2A} Gq dissociation (E) and 5-HT_{2A} β-arrestin2 recruitment. Volinanserin concentration used was 3 μM and was able to block 2-Br-LSD activity up to 10 μM. Data are normalized to percent 5-HT stimulation and represent mean and S.E.M from at least 3 independent experiments.

Fig. S6

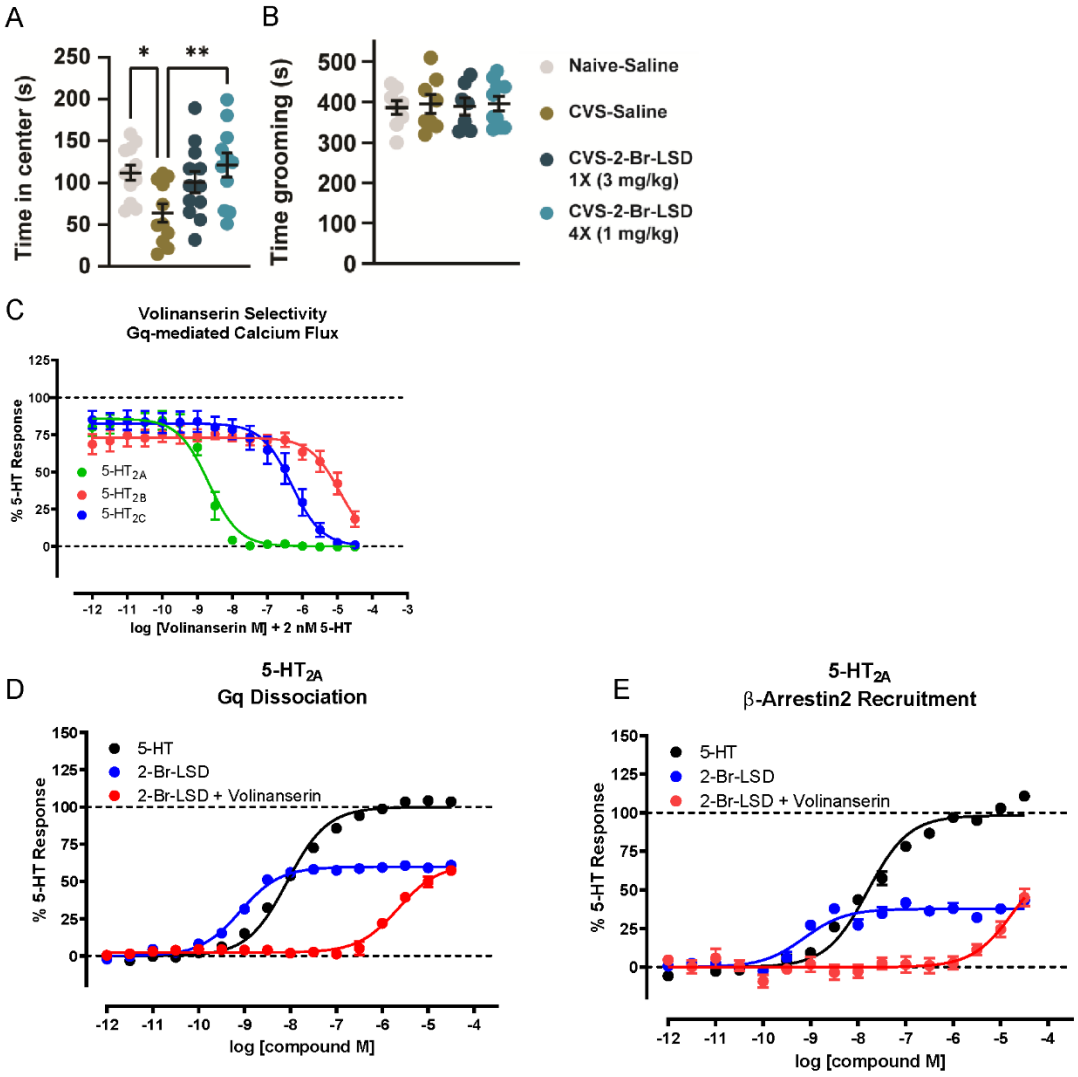
A
B
Time in center (s)
Time grooming (s)
Naive-Saline
CVS-Saline
CVS-2-Br-LSD 1X (3 mg/kg)
CVS-2-Br-LSD 4X (1 mg/kg)
C
Volinanserin Selectivity
Gq-mediated Calcium Flux
% 5-HT Response
5-HT2A
5-HT2B
5-HT2C
log [Volinanserin M] + 2 nM 5-HT
D
5-HT2A
Gq Dissociation
5-HT
2-Br-LSD
2-Br-LSD + Volinanserin
% 5-HT Response
log [compound M]
E
5-HT2A
β-Arrestin2 Recruitment
5-HT
2-Br-LSD
2-Br-LSD + Volinanserin
% 5-HT Response
log [compound M]

Table S1. GPCR Aminergic-ome BRET Assay Transfection Conditions

All aminergic GPCR-ome BRET assays utilized conditions and transfection ratios below. *Related to Figures 1-4.*

BRET Assay Transfection Conditions					
GPCR-G-protein		**G protein-dissociation ratio**	**β-Arrestin2 recruitment ratio**	**Drug Incubation Time (min)**	**Temp.**
Receptor	**Gα:β:γ**	**(Rec:Gα-Rluc8:β:GFP2-γ constructs)**	**(Rec:GFP-hβ-Arr2:GRK2)**	**G protein, β-Arr**	**˚Celsius**
5-HT_{1A}	GoB:β1:γ2	1:1:1:1	1:15:3	60, 60	37, 37
5-HT_{1B}	GoB:β1:γ2	1:1:1:1	1:15:3	60, 60	37, 37
5-HT_{1D}	GoB:β1:γ2	1:1:1:1	1:15:3	60, 60	37, 37
5-HT1e	GoB:β1:γ2	1:1:1:1	1:15:3	60, 60	37, 37
5-HT_{1F}	GoB:β1:γ2	1:1:1:1	1:15:3	60, 60	37, 37
5-HT_{2A}	Gq:β3:γ9	1:1:1:1	1:15:3	60, 60	37, 37
5-HT_{2B}	Gq:β3:γ9	1:1:1:1	1:15:0	60, 60	37, 37
5-HT_{2C}	Gq:β3:γ9	1:2:2:2	1:15:3	60, 60	37, 37
5-HT_{4}	Gs(short):β1:γ1	1:1:1:1	1:15:0	60, 60	37, 37
5-HT_{5a}	GoB:β1:γ2	1:1:1:1	1:15:3	60, 60	37, 37
5-HT_{6}	Gs(short):β1:γ1	1:1:1:1	1:15:0	60, 5	37, 37
5-HT_{7a}	Gs(short):β1:γ1	1:1:1:1	N.T.	60	37
D_1	Gs(short):β1:γ1	1:2:2:2	N.T.	60	37
D_2	GoB:β1:γ2	1:1:1:1	N.T.	60	37
D_3	GoB:β1:γ2	1:1:1:1	N.T.	60	37
D_4	GoB:β1:γ2	1:1:1:1	N.T.	60	37
D_5	Gs(short):β1:γ1	1:2:2:2	N.T.	60	37
$ADR\alpha_{1A}$	Gq:β3:γ9	1:2:2:2	N.T.	60	37
$ADR\alpha_{1B}$	Gq:β3:γ9	1:2:2:2	N.T.	60	37

$ADR\alpha_{2A}$	GoB:β1:γ2	1:1:1:1	N.T.	60	37
$ADR\alpha_{2B}$	GoB:β1:γ2	1:1:1:1	N.T.	60	37
$ADR\alpha_{2C}$	GoB:β1:γ2	1:1:1:1	N.T.	60	37
ADRβ1	Gs(short):β1:γ1	1:2:2:2	N.T.	60	37
ADRβ2	Gs(short):β1:γ1	1:2:2:2	N.T.	60	37
H1	Gq:β3:γ9	1:2:2:2	N.T.	60	37
H2	Gs(short):β1:γ1	1:2:2:2	N.T.	60	37
H3	GoB:β1:γ2	1:1:1:1	N.T.	60	37
H4	GoB:β1:γ2	1:1:1:1	N.T.	60	37
CHRM1	Gq:β3:γ9	1:2:2:2	N.T.	60	37
CHRM2	GoB:β1:γ2	1:1:1:1	N.T.	60	37
CHRM3	Gq:β3:γ9	1:2:2:2	N.T.	60	37
CHRM4	GoB:β1:γ2	1:1:1:1	N.T.	60	37
CHRM5	Gq:β3:γ9	1:2:2:2	N.T.	60	37

Table S2. Aminergic GPCRome Parameter Estimates for LSD and 2-Br-LSD All parameter estimates for Aminergic-ome and β-arrestin assays. All data represent mean and SEM from at least n=3 independent experiments. Positive controls used are 5-HT for 5-HT receptors, dopamine for dopamine receptors, norepinephrine for all adrenergic receptors except ADRβ2 where epinephrine was used, histamine for all histamine receptors, and pilocarpine for all muscarinic receptors. N.A. no activity; N.C. not calculated; N.D. not determined; N.T. not tested. *Related to Figures 1-4.*

	Positive Control					LSD					2-Br-LSD					2-Br-LSD Antagonist Mode		
Receptor	EC50, nM	pEC50	SEM	Emax	SEM	EC50, nM	pEC50	SEM	Emax	SEM	EC50, nM	pEC50	SEM	Emax	SEM	KB, nM	pKB	SEM
5-HT1A GoB	0.98	9.01	0.05	100.0	N.D.	1.31	8.88	0.05	102.2	1.5	11.3	7.95	0.08	73.4	2.0	N.T.		
5-HT1A βarr2	215	6.67	0.04	100.0	N.D.	187	6.73	0.06	67.7	1.7	N.A.					155	6.81	0.10
5-HT1B GoB	0.86	9.07	0.07	100.0	N.D.	0.66	9.18	0.06	102.2	1.8	5.28	8.28	0.08	84.1	2.2	N.T.		
5-HT1B βarr2	16.3	7.79	0.08	100.0	N.D.	15.3	7.82	0.07	95.4	2.4	114	6.94	0.11	61.7	2.7	N.T.		
5-HT1D GoB	1.07	8.97	0.11	100.0	N.D.	0.62	9.21	0.09	103.3	2.8	2.89	8.54	0.12	91.6	3.5	N.T.		
5-HT1D βarr2	2.41	8.62	0.07	100.0	N.D.	1.50	8.83	0.06	93.8	1.8	13.2	7.88	0.08	78.1	2.2	N.T.		
5-HT1e GoB	1.07	8.97	0.05	100.0	N.D.	2.38	8.62	0.05	98.9	1.4	23.2	7.63	0.07	73.6	2.0	N.T.		
5-HT1e βarr2	7.18	8.14	0.02	100.0	N.D.	28.9	7.54	0.02	99.7	0.7	131	6.88	0.05	23.6	0.5	152	6.28	0.02
5-HT1F GoB	0.84	9.08	0.07	100.0	N.D.	0.72	9.14	0.07	104.9	2.1	3.37	8.47	0.08	98.3	2.4	N.T.		
5-HT1F βarr2	14.7	7.83	0.03	100.0	N.D.	20.3	7.69	0.03	84.9	1.0	99.1	7.00	0.04	64.9	1.0	79.7	7.10	0.22
5-HT2A Gq	8.52	8.07	0.02	100.0	N.D.	0.35	9.46	0.02	91.5	0.6	0.81	9.09	0.04	59.8	0.7	0.18	9.75	0.11
5-HT2A βarr2	15.8	7.80	0.04	100.0	N.D.	0.82	9.09	0.05	84.6	1.2	0.73	9.14	0.10	37.7	1.1	0.07	10.18	0.22
5-HT2B Gq	1.66	8.78	0.04	100.0	N.D.	0.30	9.53	0.08	51.0	1.2	N.C.	N.C.	N.C.	<20%	N.C.	3.71	8.43	0.13
5-HT2B βarr2	3.26	8.49	0.04	100.0	N.D.	1.51	8.82	0.08	45.1	1.1	N.C.	N.C.	N.C.	<20%	N.C.	3.09	8.51	0.27
5-HT2C Gq	0.28	9.56	0.05	100.0	N.D.	0.66	9.18	0.05	89.8	1.4	3.85	8.41	0.14	45.8	2.1	1.53	8.82	0.22
5-HT2C βarr2	2.86	8.54	0.04	100.0	N.D.	3.92	8.41	0.05	35.0	0.5	N.A.					2.64	8.58	0.07
5-HT4 Gs	8.29	8.08	0.03	100.0	N.D.	>10,000	<5.00	N.C.	N.C.	N.C.	>10,000	<5.00	N.D.	N.D.	N.D.	>10,000	<5.00	N.D.
5-HT4 βarr2	28.5	7.55	0.03	100.0	N.D.	N.A.					N.A.					>10,000	<5.00	N.D.
5-HT5a GoB	61.5	7.21	0.07	100.0	N.D.	2.33	8.63	0.16	38.7	1.9	N.A.					4.14	8.38	0.14
5-HT5a βarr2	18.4	7.74	0.09	100.0	N.D.	1.30	8.89	0.15	64.5	2.8	N.D.	N.D.	N.D.	<20%	N.D.	1.07	8.97	0.33
5-HT6 Gs	29.9	7.52	0.10	100.0	N.D.	0.13	9.90	0.10	75.0	2.0	0.35	9.45	0.14	65.3	2.8	N.T.		
5-HT6 βarr2	91.4	7.04	0.11	100.0	N.D.	2.90	8.54	0.12	82.6	3.3	1.55	8.81	0.23	41.9	3.0	N.T.		
5-HT7a Gs	11.4	7.94	0.07	100.0	N.D.	1.74	8.76	0.69	11.1	2.3	N.A.					1.44	8.84	0.22
5-HT7a βarr2	N.T.																	
D1 Gs	295	6.53	0.05	100.0	N.D.	108	6.97	0.11	41.3	2.0	N.A.					33.0	7.48	0.54
D2 GoB	4.92	8.31	0.09	100.0	N.D.	2.17	8.66	0.10	86.0	2.8	0.35	9.45	0.12	77.4	2.72	N.D.		
D3 GoB	0.35	9.46	0.08	100.0	N.D.	7.57	8.12	0.12	74.5	3.0	2.84	8.55	0.19	31.8	1.94	7.13	8.15	0.28
D4 GoB	3.52	8.45	0.07	100.0	N.D.	4.03	8.40	0.10	91.9	2.8	1.22	8.91	0.09	67.3	1.76	N.D.		
D5 Gs	75.5	7.12	0.07	100.0	N.D.	166	6.78	0.11	70.7	3.4	N.D.	N.D.	N.D.	<20%	N.D.	25.1	7.60	1.02
ADR1A Gq	25.7	7.59	0.02	100.0	N.D.	38.5	7.42	0.12	24.8	1.1	N.D.	N.D.	N.D.	<20%	N.D.	56.9	7.25	0.23
ADRa1B Gq	65.6	7.18	0.05	100.0	N.D.	N.A.					N.A.					55.9	7.41	0.30
ADRa1D	N.T.																	
ADRa2A GoB	1.91	8.72	0.05	100.0	N.D.	19.4	7.71	0.12	64.7	2.7	N.A.					11.9	7.92	0.41
ADRa2B GoB	4.26	8.37	0.06	100.0	N.D.	11.8	7.93	0.10	61.8	2.1	N.A.					79.2	7.10	0.33
ADRa2C GoB	0.49	9.31	0.06	100.0	N.D.	0.56	9.25	0.11	80.2	3.9	10.4	8.0	0.21	40.5	2.97	16.0	7.80	0.93
ADRB1 Gs	55.8	7.25	0.06	100.0	N.D.	N.A.					N.A.					95.2	7.02	0.24
ADRB2 Gs	39.3	7.41	0.06	100.0	N.D.	N.A.					N.A.					17.6	7.75	0.19
H1 Gq	102	6.99	0.04	100.0	N.D.	N.D.	N.D.	N.D.	<20%	N.D.	N.A.					983	6.01	0.09
H2 Gs	1288	5.89	0.04	100.0	N.D.	3014	5.52	0.19	21.2	2.1	296	6.53	0.12	28.8	1.39	5188	5.29	0.39
H3 GoB	4.56	8.34	0.07	100.0	N.D.	N.A.					N.A.					N.D.		
H4 GoB	32.1	7.49	0.10	100.0	N.D.	N.A.					N.A.					N.D.		
CHRM1 Gq	619	6.21	0.04	100.0	N.D.	N.A.					N.A.					N.D.		
CHRM2 GoB	120	6.92	0.07	100.0	N.D.	N.A.					N.A.					N.D.		
CHRM3 Gq	551	6.41	0.04	100.0	N.D.	N.A.					N.A.					N.D.		
CHRM4 GoB	112	6.95	0.09	100.0	N.D.	N.A.					N.A.					N.D.		
CHRM5 Gq	374	6.43	0.04	100.0	N.D.	N.A.					N.A.					N.D.		

Table S3. GPCR Receptor Radioligand Binding Affinities

2-Br-LSD was evaluated by Eurofins Discovery, examining binding affinity in modes specified below. *Related to Figures 1 and 3.*

Receptor	Mode	radioligand	Ki (nM)
5-HT1A	agonist	8-OH-DPAT	9.3
5-HT1B	antagonist	GR125743	77
5-HT2A	agonist	DOI	2.2
5-HT2B	agonist	DOI	7
5-HT2C	agonist	DOI	19
5-HT7	agonist	LSD	3.81
α1A	antagonist	WB 4101	59
α2A	antagonist	yohimbine	10.3
α2B	antagonist	yohimbine	27
α2C	antagonist	yohimbine	27
β1	agonist	atenolol	110
β2	antagonist	ICI 118551	88
D1	antagonist	SCH 23390	25
D2	agonist	7-OH-DPAT	2.1

Table S4. Mouse Plasma Pharmacokinetic Data

2-Br-LSD was evaluated by Nucro-Technics according to their standard operating procedures. *Related to Figure 2.*

		Plasma				Brain			Brain/plasma ratio 0.17 h	Brain/plasma ratio 0.5 h
Dose (mg/kg)	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC (h*ng/mL)	$T_{1/2}$ (h)	C_{max} (ng/g)	T_{max} (h)	$T_{1/2}$ (h)		
0.75	M	1197.48	0.5	740	1.3	166.34	0.17	0.7	0.32	0.05
2.25	M	1215.83	0.2	1024	1.4	324.88	0.17	0.8	0.27	0.09
6.75	M	1558.74	0.2	2438	1.2	1139.87	0.17	1.0	0.73	0.37
0.75	F	206.49	0.2	117	0.9	69.78	0.17	1.3	0.34	0.32
2.25	F	389.35	0.2	270	2.6	152.02	0.17	0.4	0.39	0.85
6.75	F	826.06	0.2	626	1.7	615.76	0.17	0.8	0.75	0.37

Table S5. 2-Br-LSD Safety Pharmacological Screen

2-Br-LSD was evaluated by Eurofins Discovery in their SafetyScan, examining functional activity in modes specified below. *Related to Figure 3.*

Target Class	Target Name	Assay Name	Mode	Results type	μM	Reference Control
GPCR	Adenosine A2a Receptor	Calcium Flux	Agonist	EC50	>100	NECA
NHR	Androgen Receptor	NHR Nuclear Translocation	Agonist	EC50	>100	BMS-564929
GPCR	Arginine vasopressin receptor 1A	Calcium Flux	Agonist	EC50	>100	[Arg8]-Vasopressin
GPCR	Cholecystokinin A Receptor	Calcium Flux	Agonist	EC50	>100	(Tyr[SO3H]27)Cholecystokinin fragment 26-33 Amide
GPCR	Cholinergic Receptor Muscarinic 1	Calcium Flux	Agonist	EC50	>100	Acetylcholine chloride
GPCR	Cholinergic Receptor Muscarinic 2	cAMP	Agonist	EC50	>100	Acetylcholine chloride
GPCR	Cholinergic Receptor Muscarinic 3	Calcium Flux	Agonist	EC50	>100	Acetylcholine chloride
GPCR	Cannabinoid Receptor 1	cAMP	Agonist	EC50	>100	CP 55940
GPCR	Cannabinoid Receptor 2	cAMP	Agonist	EC50	>100	CP 55940
GPCR	Endothelin Receptor Type A	Calcium Flux	Agonist	EC50	>100	Endothelin 1
NHR	Glucocorticoid receptor	NHR Protein Inter-action	Agonist	EC50	>100	Dexamethasone
GPCR	Opioid Receptor Delta 1	cAMP	Agonist	EC50	>100	DADLE
GPCR	Opioid Receptor Kappa 1	cAMP	Agonist	EC50	>100	Dynorphin A (1-17)
GPCR	Opioid Receptor Mu 1	cAMP	Agonist	EC50	>100	DAMGO
GPCR	Adenosine A2a Receptor	Calcium Flux	Antagonist	IC50	>100	SCH 442416
NHR	Androgen Receptor	NHR Nuclear Translocation	Antagonist	IC50	>100	Geldanamycin
GPCR	Arginine vasopressin receptor 1A	Calcium Flux	Antagonist	IC50	>100	SR 49059
GPCR	Cholecystokinin A Receptor	Calcium Flux	Antagonist	IC50	>100	SR 27897
GPCR	Cholinergic Receptor Muscarinic 1	Calcium Flux	Antagonist	IC50	>100	Atropine
GPCR	Cholinergic Receptor Muscarinic 2	cAMP	Antagonist	IC50	>100	Atropine

GPCR	Cholinergic Receptor Muscarinic 3	Calcium Flux	Antagonist	IC50	>100	Atropine
GPCR	Cannabinoid Receptor 1	cAMP	Antagonist	IC50	>100	AM 251
GPCR	Cannabinoid Receptor 2	cAMP	Antagonist	IC50	>100	SR 144528
GPCR	Endothelin Receptor Type A	Calcium Flux	Antagonist	IC50	>100	BMS 182874
NHR	Glucocorticoid receptor	NHR Protein Inter-action	Antagonist	IC50	>100	Mifepristone
GPCR	Opioid Receptor Delta 1	cAMP	Antagonist	IC50	>100	Naltriben
GPCR	Opioid Receptor Kappa 1	cAMP	Antagonist	IC50	>100	nor-Binaltorphimine
GPCR	Opioid Receptor Mu 1	cAMP	Antagonist	IC50	>100	Naloxone
Ion Channel	L-type Cav1.2 calcium channel	Ion Channel	Blocker	IC50	66.71	Isradipine
Ion Channel	GABA A Receptor	Ion Channel	Blocker	IC50	>100	Picrotoxin
Ion Channel	hERG potassium ion channel	Ion Channel	Blocker	IC50	31.59	Astemizole
Ion Channel	5-HT Receptor 3A	Ion Channel	Blocker	IC50	45.44	Bemesetron
Ion Channel	KvLQT1 potassium channel	Ion Channel	Blocker	IC50	>100	XE 991
Ion Channel	Alpha-4 beta-2 nicotinic receptor	Ion Channel	Blocker	IC50	36.37	Dihydro-ß-erythroidine
Ion Channel	NAV1.5 voltage-gated sodium chan-nel	Ion Channel	Blocker	IC50	1.10	Lidocaine
Ion Channel	Glutamate ionotropic receptor NMDA type subunit 1	Ion Channel	Blocker	IC50	>100	(+)-MK 801 maleate
Transporter	Norepinephrine transporter (NET)	Transporter	Blocker	IC50	>100	Desipramine
Transporter	Dopamine transporter (DAT)	Transporter	Blocker	IC50	>100	GBR 12909
Transporter	Serotonin transporter (SERT)	Transporter	Blocker	IC50	>100	Clomipramine
Non-Kinase Enzymes	Acetylcholinesterase	Enzymatic	Inhibitor	IC50	8.36	Physostigmine
Non-Kinase Enzymes	Cytochrome C Oxidase 1 (COX1)	Enzymatic	Inhibitor	IC50	>100	Indomethacin
Non-Kinase Enzymes	Cytochrome C Oxidase 2 (COX2)	Enzymatic	Inhibitor	IC50	43.8	NS-398
Kinases	Insulin Receptor	Binding	Inhibitor	IC50	>100	BMS-754807

Kinases	Lymphocyte-specific protein tyrosine kinase	Binding	Inhibitor	IC50	>100	Gleevec
Non-Kinase Enzymes	Monoamine oxidase A	Enzymatic	Inhibitor	IC50	>100	Clorgyline
Non-Kinase Enzymes	Phosphodiesterase 3A	Enzymatic	Inhibitor	IC50	>100	Cilostamide
Non-Kinase Enzymes	cAMP-specific 3',5'-cyclic phos-phodiesterase 4D	Enzymatic	Inhibitor	IC50	54.6	Cilomilast
Kinases	Rho-associated coiled-coil kinase 1	Binding	Inhibitor	IC50	>100	Staurosporine
Kinases	Vascular endothelial growth factor receptor 2	Binding	Inhibitor	IC50	>100	SU-11248
Ion Channel	GABA A Receptor	Ion Channel	Opener	EC50	>100	GABA
Ion Channel	5-HT Receptor 3A	Ion Channel	Opener	EC50	>100	Serotonin Hydrochloride
Ion Channel	KvLQT1 potassium channel	Ion Channel	Opener	EC50	>100	ML-277
Ion Channel	Alpha-4 beta-2 nicotinic receptor	Ion Channel	Opener	EC50	>100	(-)-Nicotine
Ion Channel	Glutamate ionotropic receptor NMDA type subunit 1	Ion Channel	Opener	EC50	>100	L-Glutamic Acid

Table S6. 2-Br-LSD Safety Pharmacological Screen (Transporter Inhibition Assay)

2-Br-LSD was evaluated by Eurofins Discovery, examining transporter affinity in modes specified below. *Related to Figure 3.*

Target Name	% Inhibition of Control (10μM 2-Br-LSD)	IC50 (μM)*	Reference Compound
OCT2	75.6376	0.5	verapamil
P-gp	60.7608	7	verapamil
OATP1B3	41.1618	8.3	Rifampicin
OAT3	30.7252	6.7	Probenecid
OCT1	18.7826	>100	verapamil
MATE2-K	17.7685	na	verapamil
OATP1B1	14.2799	na	Rifampicin
BCRP	12.0292	na	KO143
MRP2	2.20263	na	MK571
OAT1	0.11207	na	Probenecid
BSEP	-2.07	na	Cyclosporine A
MATE1	-20.5	na	verapamil
Glycine (rat)	7	na	Sarcosine
VMAT2 (rat)	22	>100	Tetrabenazine