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Supplementary information

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A suite of engineered mice for interrogating psychedelic drug actions

In the format provided by the authors and unedited

SUPPLEMENTARY INFORMATION

Supplementary Results

Htr2a transcripts

The *Htr2a* transcript distribution displayed modest distinctions compared with HTR2A-EGFP-CT protein expression (Suppl. Fig. S4a). We also examined whether *Egfp*-tagged *Htr2a* transcripts were expressed normally in *Lamp5*-positive neurons (a marker for L2/3 and L5b), parvalbumin inhibitory interneurons, and *Cplx3*-positive neurons (a marker for L6b). *Htr2a-Egfp* transcripts were co-localized with *Lamp5* in L2/3 and L5b, as well as with the interneuron marker parvalbumin, and with *Cplx3* in L6b (Suppl. Fig. S4b). In the motor cortex, *Htr2a* transcripts were found in cortical layers L2/3, L5, and L6.

Thy1-GFP-M labels a neuronal population distinct from *Htr2a*$^{EGFP\text{-}CreERT2}$

Recently, Thy1-GFP-M mice have been used to quantify psychedelic-mediated spine formation and maintenance[1]. However, it is unknown to what extent Thy1-GFP$^+$ pyramidal neurons express HTR2A protein. To address this question, *Htr2a*$^{+/EGFP\text{-}CreERT2}$ x Ai9 animals were crossed with Thy1-GFP-M mice. Thy1-GFP$^+$ neurons did not co-localize with the L5a tdTomato+ cortical layer in the mPFC and somatosensory cortex areas (Suppl. Fig. S5). Quantification in the ACC/dPL region revealed very rare Thy1-GFP$^+$/tdTomato$^+$ double positive neurons (1.23 ± 1% from 445 neurons; n=3 animals) and Thy1-GFP were mainly observed in L5b/L6. This lack of a 1:1 HTR2A:Thy1-GFP co-localization implies that the study of psychedelic-induced plasticity in Thy1-GFP-M reporter mice likely reports spine formation and maintenance in non-HTR2A-expressing neurons.

The validation of Cre or CreERT2 recombinase:

We characterized the pattern of a Cre-dependent reporter (tdTomato here) to label HTR2A^{+} cells in various lines. For these experiments, the three lines (*Htr2a*^{Cre}, *Htr2a*$^{EGFP\text{-}CreERT2}$, and *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$) were crossed with transgenic reporter line (Ai9 mice) or were retro-orbitally injected with viral cargo (AAV.PHP.eB.FLEX.tdTomato virus) (Supplementary Fig. S6; Supplementary Table S7).

In the Ai9 groups (Supplementary Fig. S6a), the inducible CreERT2-driver line (*Htr2a*$^{EGFP\text{-}CreERT2}$) under tamoxifen temporal control reveals a pattern of tdTomato expression similar to HTR2A distribution. In the constitutive Cre-driver lines (Htr2a^{Cre} and Htr2a$^{A242S\text{-}EGFP\text{-}Cre}$), tdTomato expression showed widespread cortical labeling. This broad pattern likely reflects both ongoing postnatal Cre activity and transient HTR2A expression during embryonic development[2]. In these Cre lines, transient HTR2A expression early in development drives Cre recombinase production, resulting in permanent tdTomato labeling. Although HTR2A expressions may no longer be present in these cells in adulthood, the tdTomato signal persists, marking the historical expression pattern rather than the current receptor distribution. This result could be seen as a limitation for mapping adult receptor-expressing cells, whereas this constitutive Cre activity feature[3,4] makes these lines valuable for lineage tracing, enabling researchers to follow the developmental fate of cells that transiently (historically) expressed HTR2A. The temporal control of the inducible CreERT2 system also permits recombination for cell-fate mapping to be restricted to specific developmental windows or adult stages. This capacity expands its utility for studying both gene function and cell-lineage dynamics in a time-resolved manner.

Viral Cre-dependent reporters are commonly used for mapping and experimental

studies with Cre-driver lines. In the viral injection group (Suppl. Fig. S6b), tdTomato showed some differential expression compared with the HTR2A receptor patterns. Virally-mediated tdTomato expression was scattered in L5a, L5b, and L6 cortex, while Ai9-mediated inducible tdTomato was primarily localized in L5a and L6--and few in L5b in somatosensory cortex (Suppl. Fig. S6c). Despite similar distributions of HTR2A receptors in these three mouse lines, different Cre reporter approaches (viruses or mice) revealed dissimilar patterns of expression.

The difference in tdTomato labeling here arose not only from the Cre-driver lines themselves, but also from differences in: (1) **distinct Cre recombination timing** during development *versus* tamoxifen induction in adults; (2) **different Cre recombination efficiencies** (constitutive Cre *vs*. inducible CreERT2); (3) **reporter system**: transgenic reporter line Ai9 *vs*. AAV viral cargo reporter (4) **Reporter construct design** (promoter selection for specific cell types and reporter configuration): In one common design, a *loxP-STOP-loxP* cassette is placed upstream of a reporter gene in the sense orientation. Cre recombinase excises the STOP sequence, enabling transcription of the reporter (e.g. *loxP-STOP-loxP-tdTomato*). Alternatively, the FLEX system (also known as DIO, double-floxed inverted orientation) uses pairs of heterotypic lox sites (e.g., *loxP* and *lox2272*) to flank an inverted (antisense) reporter gene. Upon Cre-mediated recombination, the reporter is irreversibly flipped into the correct orientation for expression. This configuration provides tighter control with minimal background activity (e.g. *FLEX-tdTomato*, initially in the antisense orientation). (5) **viral transduction bias** (transduction efficiency and AAV tropism[5], as well as cell type/cortical layer-preferential AAV access); and (6) **reporter protein properties** (membrane *vs*. soluble proteins). Importantly, when utilizing

Cre/CrERT2 reporters to label HTR2A^{+} cells for HTR2A-mediated studies, it is essential to validate whether the reporter accurately reflects current HTR2A expression in the relevant cells.

References for Supplementary Information

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3. Taniguchi, H. et al. A resource of Cre driver lines for genetic targeting of GABAergic neurons in cerebral cortex. *Neuron*, **71**, 995–101(2011)
4. Gil-Sanz, C. et al, Lineage Tracing Using Cux2-Cre and Cux2-CreERT2 Mice. *Neuron*, **86**, 1091–1099 (2015)
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Supplementary Movies

Suppl. Movie S1: 3-D rendering of brain.

Suppl. Movie S2: Coronal view of brain.

Suppl. Movie S3: Horizontal view of brain.

Suppl. Movie S4: Sagittal view of brain.

Suppl. Movie S5: Subcellular distribution of the HTR2A-EGFP-CT fusion protein.

Suppl. Movie S6. Subcellular distribution of the HTR2A-A242S-EGFP-CT fusion proteins.

Suppl. Movies S1-S6. 3-D renderings of whole brain cleared tissues from *Htr2a*$^{+/EGFP\text{-}CreERT2}$ x Ai9 mice (Movies S1-S4) and subcellular distributions of HTR2A-EGFP-CT and HTR2A-A242S-EGFP-CT fusion proteins (Movies S5-S6). Movies S1-S4, *Htr2a*$^{+/EGFP\text{-}CreERT2}$ x Ai9 mice were treated with tamoxifen (100 mg/kg, i.p.) at p39-p42. Mice were perfused at 14 days later at p56 and then were submitted for tissue CLARITY (see Materials and Methods). The cleared whole-brains were scanned under a light-sheet microscope with a 3.6X objective. Whole-brains were stained with a GFP antibody. Signals with tdTomato (*red*) for HTR2A positive cells and GFP (*green*) for HTR2A-EGFP-CT fusion protein were captured. Three-dimensional (3D) renderings of brain are depicted (Movie S1), as coronal (Movie S2), horizontal (Movie S3), and sagittal views (Movie S4), respectively. **Movie S5** shows the subcellular distribution of HTR2A-EGFP-CT fusion protein. The video of Z-stack confocal images is from the insular cortex of *Htr2a*$^{EGFP\text{-}CreERT2/EGFP\text{-}CreERT2}$ mice. Experiments showed similar results from 3 animals. **Movie S6** depicts the subcellular distribution of HTR2A-A242S-EGFP-CT fusion proteins. The video shows Z-stack confocal images from the insular cortex of *Htr2a* $^{A242S\text{-}EGFP\text{-}}$

$^{Cre/A242S\text{-}EGFP\text{-}Cre}$ mice. Experiments showed similar results from 3 animals. The movies have been uploaded to an open-source website, A Mouse Imaging Server (AMIS, https://amis.docking.org/).

Suppl. Table S1. Whole brain distribution of HTR2A-EGFP-CT in *Htr2a*$^{EGFP\text{-}CreERT2}$ mice.

	Area	Sub-division	GFP density
Telencephalon			
	olfactory bulb	AON	**+++**
		PIR	**++**
		LOT	**++/++++**
	frontal pole	ACC	**++**
		PL	**++**
		MO	**++**
		VLO	**++**
		pAIC	**+++**
	medial prefrontal cortex	pgACC	**++**
		PL	**---**
		IL	**---**
	tenia tecta	TT	**++/+++**
	orbitofrontal cortex	MO	**++**
		VLO	**+++**
		LO	**+++**
		pAIC	**++++**
		DI	**++++**
	gustatory cortex	GUS	**++++**
	cingulate cortex	sCIN	**++**
		RSP	**---**
	motor cortex	M1	**++**
		M2	**++**
	somatosensory cortex	SSC	**+++**
	piriform cortex	PIR	**++**
	insular cortex		**+/++**
	claustrum	CL	**++/+++**
	endopiriform	END	**+**

auditory cortex	AUD	**++/+++**
entorhinal cortex	mENT	**---**
	/ENT	**+++/++++**
visual cortex	VIS	**++**
hippocampus	DG	**---**
	CA1d	**+**
	CA1v	**++**
	CA2d	**---**
	CA2v	**---**
	CA3d	**+**
	CA3v	**++++**
	CA4d	**---**
	CA4v	**+**
	SUBd	**---**
	SUBv	**---**
caudatoputamen (dorsal striatum)	CPs	**++++**
	CPm	**+/++**
nucleus accumbens	mNAc	**-/+**
	/NAc	**+++/++++**
olfactory tubercle	mTUO	**+++**
	/TUO	**++++**
diagonal band of Broca	hDBB	**---**
	vDBB	**---**
septum	LSN	**-/+**
	MSN	**---**
pallidum	GP	**---**
	VP	**---**
amygdala	LAN	**+++**
	BLN	**---**
	CeA	**-/+**
	MeA	**+++**
	BMN	**+**

		lPAC	**+/++**
	bed nucleus of stria terminalis		**---**
	preoptic area	mPOA	**---**
		/POA	**---**
Diencephalon			
	thalamus	RT	**---**
		VA/VL	**---**
		AV	**---**
		LDN	**+**
		APT	**+/++**
		RHM	**---**
		RE	**---**
		MD	**---**
		VM	**---**
		CM	**---**
		PF	**---**
		SUBT	**---**
		SPF	**+/++**
		MGN	**-/-**
		SGN	**-/+**
		LGN	**-/+**
	epithalamus	mHb	**-/+**
		/Hb	**+/++**
		PVT	**---**
	hypothalamus	AHA	**-/+**
		VMN	**+**
	mamillary bodies	DPMN	**---**
		VPMN	**---**
		LMN	**---**
		MMN	**++++**
		TMN	**++**
Mesencephalon			
	interpeduncular nucleus	IPN	**+**
	nucleus Darkschewitsch	ND	**+**

superior colliculus	SC	+
inferior colliculus	IPC	-/+
periaqueductal gray	PAG	-/+
dorsal raphe	DR	---

Rhombencephalon

pontine nucleus	BPN	+/++
	NRTP	+++/++++
parabrachial nucleus	/PBN	-/+
	mPBN	+
	K-F	+
Tegmental reticular nucleus		++
dorsal tegmental nucleus	DTN	++
superior olivary nucleus		-/+
inferior olivary nucleus	IO	+++/++++
motor trigeminal nucleus	V	+/++
nucleus gigantocellularis		-/+
medial vestibular nucleus	mVes	-/+
facial nucleus	VII	+/++
raphe magnus	RM	-/+
raphe obscurus		-/+
nucleus ambiguus	NA	+/++
dorsal motor nucleus of vagus	X	++

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Suppl. Table S2. Abbreviations for anatomical brain regions in HTR2A mice.

ACC	anterior cingulate cortex
AHA	anterior hypothalamic area
AON	anterior olfactory nucleus
APT	thalamic anterior pretectal nucleus
AUD	primary auditory cortex
AV	anteroventral thalamic nucleus
BLN	basolateral amygdala nucleus
BMN	basomedial amygdala nucleus
nrtp	basilar pontine nucleus
CA1d	dorsal hippocampus, CA1
CA1v	ventral (temporal) hippocampus, CA1
CA2d	dorsal hippocampus, CA2
CA2v	ventral (temporal) hippocampus, CA2
CA3d	dorsal hippocampus, CA3
CA3v	ventral (temporal) hippocampus, CA3
CA4d	dorsal hippocampus, CA4
CA4v	ventral (temporal) hippocampus, CA4
CeA	central amygdala nucleus
CERc	cerebellar cortex
CERdn	cerebellar deep nucleus
CIN	cingulate cortex
CL	claustrum

CM	thalamic central medial nucleus
CP	striatum (caudatoputamen)
CPm	striatum (caudatoputamen), matrix
CPs	striatum (caudatoputamen), striosome
DI	dysgranular cortex
DG	dentate gyrus
dHIP	dorsal hippocampus
dlPN	dorsolateral pontine nucleus
DR	dorsal raphe nucleus
DTN	dorsal tegmental nucleus
ENT	ectorhinal cortex
END	endopiriform cortex
FP	frontal pole
GP	globus pallidus
GUS	gustatory cortex
hDBB	diagonal band of Broca, horizontal limb
IC	insular cortex
IPC	inferior colliculus
IL	infralimbic cortex
IO	inferior olivary nucleus
IPN	interpeduncular nucleus
K-F	Kolliker-Fuse nucleus
/ENT	entorhinal cortex, lateral
LAN	lateral amygdala nucleus
LDN	thalamic laterodorsal nucleus
LGN	thalamic lateral geniculate nucleus

LHb	lateral habenula nucleus
LMN	lateral mammillary nucleus
/NAc	nucleus accumbens, lateral
LO	lateral orbital cortex
LOT	lateral olfactory tract
LSN	lateral septal nucleus
/PBN	parabrachial nucleus, lateral
/POA	preoptic area, lateral
/TUO	olfactory tubercle, lateral
M1	primary motor cortex
M2	secondary motor cortex
MeA	medium amygdala nucleus
mENT	entorhinal cortex, medial
MD	thalamic mediodorsal nucleus
MHb	medial habenula nucleus
MGN	thalamic medial geniculate nucleus
MMN	medial mammillary nucleus
mNAc	nucleus accumbens, medial
MO	medial orbital cortex
MOF	motor nucleus of the facial (VII)
MOT	motor nucleus of the trigeminal (V)
mPOA	preoptic area, medal
mPBN	parabracial nucleus, medial
MSN	medial septal nucleus
mTUO	olfactory tubercle, medial
mVES	medial vestibular nucleus

NA	nucleus ambiguus
NAc	nucleus accumbens
ND	nucleus Darkschewitsch
NRTP	nucleus reticularis tegmenti pontis
PAG	periaqueductal gray
pAIC	pregenual anterior insular cortex
pgACC	pregenual anterior cingulate cortex
PF	thalamic parafascicular nucleus
RE	thalamic reuniens nucleus
RHM	thalamic rhomboid nucleus
PIR	piriform cortex
PL	prelimbic cortex
PVT	thalamic paraventricular nucleus
RM	raphe magnus nucleus
RSP	retrospenial cortex
RT	thalamic reticular nucleus
sCIN	supracollosal cingulate cortex
SC	superior colliculus
SMC	somatomotor cortex
SPF	thalamic subparafascicular nucleus
SSC	somatosensory cortex
STN	subthalamic nucleus
SUBd	subiculum, dorsal hippocampus
SUBv	subiculum, ventral hippocampus
TMN	tuberomammillary nucleus
TRN	tegmental reticular nucleus of Bechterew

TT	tenia tecta
TUO	olfactory tubercle
V	motor trigeminal nucleus
VA/VL	thalamic ventral anterior/ventrolateral nucleus
vDBB	diagonal band of Broca, vertical limb
VIS	primary visual cortex
VLO	ventrolateral orbital cortex
VM	ventromedial thalamic nucleus
VMN	ventromedial nucleus
VP	ventral pallidum
VPN	ventral pontine nucleus
X	motor nucleus of vagus
ZI	zona incerta

Suppl. Table S3. Distribution of males and females by genotype and treatment in behavioral studies.

Treatment[a]	Mouse Line[b]	OF[C] Male	OF[c] Female	PPI[C] Male	PPI[c] Female
Veh	C57	5	4	10	5
	Htr2a$^{EGFP\text{-}CreERT2}$	4	6	6	8
	Htr2a$^{A242S\text{-}EGFP\text{-}Cre}$	7	3	5	4
	Htr2a^{Cre}	6	4	4	5
0.3 mg/kg LSD	C57	4	6	10	5
	Htr2a$^{EGFP\text{-}CreERT2}$	6	4	8	6
	Htr2a$^{A242S\text{-}EGFP\text{-}Cre}$	6	4	4	8
	Htr2a^{Cre}	6	4	4	4
1 mg/kg DOI	C57	5	4	10	5
	Htr2a$^{EGFP\text{-}CreERT2}$	6	4	9	6
	Htr2a$^{A242S\text{-}EGFP\text{-}Cre}$	6	4	9	6
	Htr2a^{Cre}	6	4	4	4
1 mg/kg Psilocin	C57	4	6	10	5
	Htr2a$^{EGFP\text{-}CreERT2}$	6	3	3	7
	Htr2a$^{A242S\text{-}EGFP\text{-}Cre}$	6	4	10	5
	Htr2a^{Cre}	6	4	4	3

[a]Veh, vehicle; LSD, lysergic acid diethylamide; DOI, 2,5-dimethoxy-4-iodoamphetamine.
[b]C57, C57BL/6J; *Htr2a*$^{EGFP\text{-}CreERT2}$, *Htr2a*$^{EGFP\text{-}CT\text{-}IRES\text{-}CreERT2/\ EGFP\text{-}CT\text{-}IRES\text{-}CreERT2}$; *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$, *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre/A242S\text{-}EGFP\text{-}Cre}$, *Htr2a*^{Cre}, *Htr2a*$^{Cre/Cre}$.
[c]OF, open field for testing locomotor, rearing, and stereotypical activities, as well as head twitch responses, grooming, and retrograde walking; PPI, prepulse inhibition with null and startle activities.

Suppl. Table S4. Statistical results.

Figure	Statistical Model[a]	Variable[b]	Degrees of Freedom	M-, F-, H-, t-, U-, or -W statistic	*p*-value	# Mice per Group
	Receptor Binding mRNA Down Reg					
Fig. 3a	t-test (unpaired) t-test (unpaired) (^{3}[H]ketanserin)	Gene (Kd) Gene (Bmax)	6 6	1.722 9.246	0.1359 <0.0001	4,4 4,4
Fig. 3b	1-way ANOVA (mRNA)	Gene	2,9	87.60	<0.001	4,4,4
	Tukey	C57 - +/ERT2			<0.001	
		C57 - ERT2/ERT2			<0.001	
		+/ERT2 - ERT2/ERT2			0.002	
Fig. 3c	2-way ANOVA (Down Reg)	Gene	1,21	24.09	<0.001	7,7, 5,6
	C57 – ERT2	Treat	1,21	27.11	<0.001	
		Gene x Treat	1,21	0.183	0.673	
	***Htr2a*^{ERT2} - C57**					
Fig. 4b	Levene's test	Sex, Gene, Treat	15,61	3.121	<0.001	5,4,5 4
	Mann-Whitney	Sex		693.000	0.632	4,6,4,6
	Levene's test	Gene, Treat	7,69	5.510	<0.001	4,6,6,6
	Kruskal-Wallis	GeneTreat	7	47.200	<0.001	6,4,4,3
	Bonferroni	ERT2 Veh – C57 Veh			0.191	
	(Post-Inj Loco)	ERT2 LSD – C57 LSD			0.190	
		ERT2 DOI – C57 DOI			0.018	
		ERT2 Psil – C57 Psil			0.826	
		ERT2 Veh – ERT2 LSD			0.008	
		ERT2 Veh – ERT2 DOI			<0.001	
		ERT2 Veh – ERT2 Psil			0.187	
		ERT2 LSD – ERT2 DOI			0.023	
		ERT2 LSD – ERT2 Psil			0.024	
		ERT2 DOI – ERT2 Psil			<0.001	
		C57 Veh – C57 LSD			0.009	
		C57 Veh – C57 DOI			<0.001	
		C57 Veh – C57 Psil			0.016	
		C57 LSD – C57 DOI			0.268	
		C57 LSD – C57 Psil			0.826	
		C57 DOI – C57 Psil			0.186	
Fig. 4c	Levene's test	Sex, Gene, Treat	15,61	4.886	<0.001	5,4,5 4
	Mann-Whitney	Sex		631.000	0.266	4,6,4,6
	Levene's test	Gene, Treat	7,69	5.244	<0.001	4,6,6,6
	Kruskal-Wallis	GeneTreat	7	35.602	<0.001	6,4,4,3
	Bonferroni	ERT2 Veh – C57 Veh			0.946	
	(Post-Inj Rear)	ERT2 LSD – C57 LSD			0.905	
		ERT2 DOI – C57 DOI			0.023	
		ERT2 Psil – C57 Psil			0.094	
		ERT2 Veh – ERT2 LSD			0.003	
		ERT2 Veh – ERT2 DOI			0.385	
		ERT2 Veh – ERT2 Psil			0.236	

		ERT2 LSD – ERT2 DOI			0.038	
		ERT2 LSD – ERT2 Psil			<0.001	
		ERT2 DOI – ERT2 Psil			0.042	
		C57 Veh – C57 LSD			0.007	
		C57 Veh – C57 DOI			0.003	
		C57 Veh – C57 Psil			0.676	
		C57 LSD – C57 DOI			0.708	
		C57 LSD – C57 Psil			0.020	
		C57 DOI – C57 Psil			0.008	
Fig. 4d	Levene's test	Sex, Gene, Treat	15,61	1.147	0.337	5,4,5 4
	3-Way` ANOVA	Sex	1,61	0.878	0.353	4,6,4,6
	(Post-Inj Stereo)	Gene	1,61	0.991	0.324	4,6,6,6
		Treat	3,61	8.225	<0.001	6,4,4,3
		Sex x Gene	1,61	0.658	0.421	
		Sex x Treat	3,61	0.513	0.675	
		Gene x Treat	3,61	1.008	0.395	
		Sex x Gene x Treat	3,61	0.299	0.826	
	Bonferroni	Veh - LSD			0.003	
		Veh - DOI			0.051	
		Veh - Psil			1.000	
		LSD-DOI			1.000	
		LSD-Psil			<0.001	
		DOI-Psil			0.014	
Fig. 4e	Levene's test	Sex, Gene, Treat	15,61	4.563	<0.001	5,4,5 4
	Mann-Whitney	Sex		665.000	0.444	4,6,4,6
	Levene's test	Gene, Treat	7,69	6.382	<0.001	4,6,6,6
	Kruskal-Wallis	GeneTreat	7	54.657	<0.001	6,4,4,3
	Bonferroni	ERT2 Veh – C57 Veh			1.000	
	(HTR)	ERT2 LSD – C57 LSD			0.745	
		ERT2 DOI – C57 DOI			0.064	
		ERT2 Psil – C57 Psil			0.161	
		ERT2 Veh – ERT2 LSD			<0.001	
		ERT2 Veh – ERT2 DOI			<0.001	
		ERT2 Veh – ERT2 Psil			0.051	
		ERT2 LSD – ERT2 DOI			0.562	
		ERT2 LSD – ERT2 Psil			0.038	
		ERT2 DOI – ERT2 Psil			0.130	
		C57 Veh – C57 LSD			<0.001	
		C57 Veh – C57 DOI			<0.001	
		C57 Veh – C57 Psil			<0.001	
		C57 LSD – C57 DOI			0.332	
		C57 LSD – C57 Psil			0.308	
		C57 DOI – C57 Psil			0.050	
Fig. 4f	Mauchly's test	PPI (within subjects)	2	0.836	<0.001	10,10,10,10
	Box's test	PPI (within subjects)	84,45 00.44 5	162.027	0.002	5,5,5,5
	Levene's test	4 dB	15,97	2.520	0.003	6,8,9,3
	Levene's test	8 dB	15,97	3.349	<0.001	8,6,6,7
	Levene's test	12 dB	15,97	2.155	0.013	
	Greenhouse-Geisser corrections	PPI	1.719, 166.7 15	305.552	<0.001	

	Within Subjects	PPI x Sex	1.719, 166.715	0.877	0.404	
	(PPI)	PPI x Gene	1.719, 166.715	20.435	<0.001	
		PPI x Treat	5.156, 166.715	3.826	0.002	
		PPI x Sex x Gene	1.719, 166.715	1.568	0.214	
		PPI x Sex x Treat	5.156, 166.715	1.124	0.350	
		PPI x Gene x Treat	5.156, 166.715	1.409	0.222	
		PPI x Sex x Gene x Treat	5.156, 166.715	2.163	0.059	
	Between Subjects	Sex	1,97	3.568	0.062	
		Gene	1,97	31.586	<0.001	
		Treat	3,97	21.135	<0.001	
		Sex x Gene	1,97	3.154	0.079	
		Sex x Treat	3,97	0.850	0.470	
		Gene x Treat	3,97	0.507	0.679	
		Sex x Gene x Treat	3,97	2.152	0.099	
	Bonferroni	Veh - LSD			<0.001	
		Veh - DOI			<0.001	
		Veh - Psil			<0.001	
	Electrophysiology					
Fig. 5c	t-test (paired) (Firing Freq)	Treat	8	2.790	0.024	4♂,5♀
	t-test (one-sample) (Firing Freq)	% Baseline (DOI)	8	5.102	0.0009	
Fig. 5e	Mauchly's test (Firing Freq)	Treat	2	0.145	<0.001	4♂,5♀
	RMANOVA Greenhouse-Geisser corrections	Treat	1.113, 8.903	67.637	<0.001	
	Bonferroni	Baseline – M100907			<0.001	
	(Firing Freq)	Baseline – M100907+DOI			<0.001	
		M100907 – M100907+DOI			0.151	
Fig. 5f	t-test (one-sample) (Firing Freq)	% Baseline (M100907)	8	11.59	<0.0001	
Fig. 5g	t-test (one-sample) (Firing Freq)	% Baseline (M100907+DOI)	8	3.355	0.010	
	mRNA, Kd, Bmax					

Ext. Data Fig. 4d	Levene's test (mRNA)	Gene	3,12	1.226	0.343	4,4,4,4
	1-Way ANOVA	Gene	3,12	53.624	<0.001	
	Tukey	C57 – ERT2			<0.001	
		C57 – A242S			<0.001	
		C57 - Cre			0.001	
		ERT2 – A242S			0.204	
		ERT2 - Cre			0.004	
		A242S - Cre			<0.001	
Ext. Data Fig. 4e	Levene's test (Kd)	Gene	3,15	0.761	0.533	4,4,5,6
	1-Way ANOVA	Gene	3,15	1.159	0.338	
Ext. Data Fig. 4f	Levene's test (Bmax)	Gene	3,15	0.455	0.717	4,4,5,6
	1-Way ANOVA	Gene	3,15	27.521	<0.001	
	Tukey	C57 – ERT2			<0.001	
		C57 – A242S			<0.001	
		C57 - Cre			<0.001	
		ERT2 – A242S			0.992	
		ERT2 - Cre			0.168	
		A242S - Cre			0.219	
	***Htr2a*^{A242S} - C57**					
Ext. Data Fig. 7b	Levene's test	Sex, Gene, Treat	15,62	2.926	0.002	5,4,5 4
	Mann-Whitney	Sex		909.000	0.116	4,6,4,6
	Levene's test	Gene, Treat	7,70	3.797	0.002	7,6,6,6
	Kruskal-Wallis	GeneTreat	7	48.670	<0.001	3,4,4,4
	(Post-Inj Loco)	A242S Veh - C57 Veh			0.158	
		A242S LSD - C57 LSD			0.119	
		A242S DOI - C57 DOI			0.006	
		A242S Psil - C57 Psil			0.287	
		A242S Veh - A242S LSD			0.006	
		A242S Veh - A242S DOI			<0.001	
		A242S Veh - A242S Psil			0.053	
		A242S LSD - A242S DOI			0.029	
		A242S LSD - A242S Psil			0.418	
		A242S DOI - A242S Psil			0.003	
		C57 Veh - C57 LSD			0.010	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			0.024	
		C57 LSD - C57 DOI			0.372	
		C57 LSD - C57 Psil			0.752	
		C57 DOI - C57 Psil			0.236	
Ext. Data Fig. 7c	Levene's test	Sex, Gene, Treat	15,62	3.937	<0.001	5,4,5 4
	Mann-Whitney	Sex		802.500	0.615	4,6,4,6
	Levene's test	Gene, Treat	7,70	3.200	0.005	7,6,6,6
	Kruskal-Wallis	GeneTreat	7	36.187	<0.001	3,4,4,4
	(Post-Inj Rear)	A242S Veh – C57 Veh			0.696	

		A242S LSD – C57 LSD			0.191	
		A242S DOI – C57 DOI			0.603	
		A242S Psil – C57 Psil			0.231	
		A242S Veh - A242S LSD			0.329	
		A242S Veh - A242S DOI			<0.001	
		A242S Veh - A242S Psil			0.271	
		A242S LSD - A242S DOI			0.018	
		A242S LSD - A242S Psil			0.038	
		A242S DOI - A242S Psil			<0.001	
		C57 Veh - C57 LSD			0.009	
		C57 Veh - C57 DOI			0.002	
		C57 Veh - C57 Psil			0.627	
		C57 LSD - C57 DOI			0.608	
		C57 LSD - C57 Psil			0.029	
		C57 DOI - C57 Psil			0.008	
Ext. Data Fig. 7d	Levene's test	Sex, Gene, Treat	15,62	0.937	0.530	5,4,5 4
	3-Way ANOVA	Sex	1,62	2.094	0.153	4,6,4,6
	(Post-Inj Stereo)	Gene	1,62	0.115	0.736	7,6,6,6
		Treat	3,62	5.512	0.002	3,4,4,4
		Sex x Gene	1,62	0.244	0.623	
		Sex x Treat	3,62	0.151	0.929	
		Gene x Treat	3,62	2.189	0.098	
		Sex x Gene x Treat	3,62	0.254	0.858	
	Bonferroni	Veh-LSD			0.944	
		Veh - DOI			0.006	
		Veh - Psil			0.008	
		LSD – DOI			0.233	
		LSD – Psil			0.923	
		DOI - Psil			0.005	
Ext. Data Fig. 7e	Levene's test	Sex, Gene, Treat	15,62	3.782	<0.001	5,4,5 4
	Mann-Whitney	Sex		861.500	0.273	4,6,4,6
	Levene's test	Gene, Treat	7,70	6.381	<0.001	7,6,6,6
	Kruskal-Wallis	GeneTreat	7	50.221	<0.001	3,4,4,4
	(HTR)	A242S Veh - C57 Veh			0.612	
		A242S LSD - C57 LSD			0.590	
		A242S DOI - C57 DOI			0.031	
		A242S Psil - C57 Psil			0.152	
		A242S Veh - A242S LSD			0.002	
		A242S Veh - A242S DOI			0.005	
		A242S Veh - A242S Psil			<0.001	
		A242S LSD - A242S DOI			0.707	
		A242S LSD - A242S Psil			0.265	
		A242S DOI - A242S Psil			0.136	
		C57 Veh - C57 LSD			<0.001	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			0.001	
		C57 LSD - C57 DOI			0.204	
		C57 LSD - C57 Psil			0.393	
		C57 DOI - C57 Psil			0.036	

Ext. Data Fig. 7f	Mauchly's test	PPI (within subjects)	2	0.897	0.006	10,10,10,10
	Box's test	PPI (within subjects)	90,3181.123	210.264	<0.001	5,5,5,5
	Levene's test	4 dB	15,95	2.589	0.003	5,4,9,10
	Levene's test	8 dB	15,95	2.778	0.001	4,8,6,5
	Levene's test	12 dB	15,95	1.915	0.031	
	(PPI) Greenhouse-Geisser corrections	PPI	1.813, 172.267	177.974	<0.001	
	Within Subjects	PPI x Sex	1.813, 172.267	1.323	0.268	
		PPI x Gene	1.813, 172.267	2.428	0.097	
		PPI x Treat	5.440, 172.267	1.858	0.098	
		PPI x Sex x Gene	1.813, 172.267	1.127	0.322	
		PPI x Sex x Treat	5.440, 172.267	1.567	0.166	
		PPI x Gene x Treat	5.440, 172.267	3.742	0.002	
		PPI x Sex x Gene x Treat	5.440, 172.267	0.705	0.633	
	Between Subjects	Sex	1,95	5.125	0.026	
		Gene	1,95	11.858	<0.001	
		Treat	3,95	16.929	<0.001	
		Sex xGene	1,95	2.013	0.159	
		Sex x Treat	3,95	1.498	0.220	
		Gene x Treat	3,95	1.426	0.240	
		Sex x Gene x Treat	3,95	3.006	0.034	
	Bonferroni	♂ A242S Veh - ♀ A242S Veh			0.028	
		♂ A242S LSD - ♀ A242S LSD			0.048	
		⚷ A242S DOI - ♀ A242S DOI			0.759	
		♂ A242S Psil - ♀ A242S Psil			0.152	
		♂ C57 Veh - ♀ C57 Veh			0.052	
		♂ C57 LSD - ♀ C57 LSD			0.115	
		♂ C57 DOI - ♀ C57 DOI			0.122	
		♂ C57 Psil - ♀ C57 Psil			0.760	
		♂ A242S Veh – ♂ C57 Veh			0.001	
		♂ A242S LSD – ♂ C57 LSD			0.352	

		♂ A242S DOI – ♂ C57 DOI			0.219	
		♂ A242S Psil – ♂ C57 Psil			0.028	
		♀ A242S Veh – ♀ C57 Veh			0.249	
		♀ A242S LSD – ♀ C57 LSD			0.113	
		♀ A242S DOI – ♀ C57 DOI			0.838	
		♀ A242S Psil – ♀ C57 Psil			0.012	
		♂ A242S Veh - ♂ A242S LSD			<0.001	
		♂ A242S Veh - ♂ A242S DOI			<0.001	
		♂ A242S Veh - ♂ A242S Psil			0.005	
		♂ A242S LSD - ♂ A242S DOI			1.000	
		♂ A242S LSD - ♂ A242S Psil			0.686	
		♂ A242S DOI - ♂ A242S Psil			0.155	
		♀ A242S Veh - ♀ A242S LSD			1.000	
		♀ A242S Veh - ♀ A242S DOI			0.297	
		♀ A242S Veh - ♀ A242S Psil			1.000	
		♀ A242S LSD - ♀ A242S DOI			0.201	
		♀ A242S LSD - ♀ A242S Psil			1.000	
		♀ A242S DOI - ♀ A242S Psil			0.042	
		♂ C57 Veh – ♂ C57 LSD			0.003	
		♂ C57 Veh – ♂ C57 DOI			0.001	
		♂ C57 Veh – ♂ C57 Psil			0.090	
		♂ C57 LSD – ♂ C57 DOI			1.000	
		♂ C57 LSD – ♂ C57 Psil			1.000	
		♂ C57 DOI – ♂ C57 Psil			1.000	
		♀ C57 Veh – ♀ C57 LSD			0.031	
		♀ C57 Veh – ♀ C57 DOI			0.017	
		♀ C57 Veh – ♀ C57 Psil			0.012	
		♀ C57 LSD – ♀ C57 DOI			1.000	
		♀ C57 LSD – ♀ C57 Psil			1.000	
		♀ C57 DOI – ♀ C57 Psil			1.000	
	Down Regulation					
Ext. Data Fig. 8a	2-way ANOVA	Gene	1,24	3.297	<0.0819	7,7,7,7
	C57 – A242S	Treat	1,24	20.12	0.0002	
		Gene x Treat	1,24	0.8471	0.3665	
Ext. Data Fig. 10a	2-way ANOVA	Gene	1,18	16.929	<0.001	7,7,4,4
	C57 – Cre	Treat	1,18	18.398	<0.001	
		Gene x Treat	1,18	0.147	0.706	

	***Htr2a*^{Cre} - C57**					
Ext. Data Fig. 9b	Levene's test	Sex, Gene, Treat	15,62	6.016	<0.001	5,4,5 4
	Mann-Whitney	Sex		972.000	0.030	4,6,4,6
	Kruskal-Wallis	SexGeneTreat	15	60.917	<0.001	6,6,6,6
	Bonferroni	♂ Htr2a Veh - ♀ Htr2a Veh			0.824	4,4,4,4
	(Post-Inj Loco)	♂ Htr2a LSD - ♀ Htr2a LSD			0.353	
		♂ Htr2a DOI - ♀ Htr2a DOI			0.085	
		♂ Htr2a Psil - ♀ Htr2a Psil			0.955	
		♂ C57 Veh - ♀ C57 Veh			0.534	
		♂ C57 LSD - ♀ C57 LSD			0.914	
		♂ C57 DOI - ♀ C57 DOI			0.757	
		♂ C57 Psil - ♀ C57 Psil			0.945	
		♂ Htr2a Veh - ♂ C57 Veh			0.160	
		♂ Htr2a LSD - ♂ C57 LSD			0.008	
		♂ Htr2a DOI - ♂ C57 DOI			0.002	
		♂ Htr2a Psil - ♂ C57 Psil			0.002	
		♀ Htr2a Veh - ♀ C57 Veh			0.112	
		♀ Htr2a LSD - ♀ C57 LSD			0.102	
		♀ Htr2a DOI - ♀ C57 DOI			0.170	
		♀ Htr2a Psil - ♀ C57 Psil			0.002	
		♂ Htr2a Veh - ♂ Htr2a LSD			0.637	
		♂ Htr2a Veh - ♂ Htr2a DOI			0.601	
		♂ Htr2a Veh - ♂ Htr2a Psil			0.779	
		♂ Htr2a LSD - ♂ Htr2a DOI			0.959	
		♂ Htr2a LSD - ♂ Htr2a Psil			0.452	
		♂ Htr2a DOI - ♂ Htr2a Psil			0.422	
		♀ Htr2a Veh - ♀ Htr2a LSD			0.303	
		♀ Htr2a Veh - ♀ Htr2a DOI			0.073	
		♀ Htr2a Veh - ♀ Htr2a Psil			0.629	
		♀ Htr2a LSD - ♀ Htr2a DOI			0.445	
		♀ Htr2a LSD - ♀ Htr2a Psil			0.130	
		♀ Htr2a DOI - ♀ Htr2a Psil			0.023	
		♂ C57 Veh - ♂ C57 LSD			0.088	
		♂ C57 Veh - ♂ C57 DOI			0.036	
		♂ C57 Veh - ♂ C57 Psil			0.127	
		♂ C57 LSD - ♂ C57 DOI			0.790	
		♂ C57 LSD - ♂ C57 Psil			0.864	
		♂ C57 DOI - ♂ C57 Psil			0.655	
		♀ C57 Veh - ♀ C57 LSD			0.308	
		♀ C57 Veh - ♀ C57 DOI			0.115	
		♀ C57 Veh - ♀ C57 Psil			0.383	
		♀ C57 LSD - ♀ C57 DOI			0.480	
		♀ C57 LSD - ♀ C57 Psil			0.868	
		♀ C57 DOI - ♀ C57 Psil			0.393	
Ext. Data Fig. 9c	Levene's test	Sex, Gene, Treat	15,62	11.282	<0.001	5,4,5 4
	Mann-Whitney	Sex		832.000	0.446	4,6,4,6
	Levene's test	Gene, Treat	7,70	11.787	<0.001	6,6,6,6
	Kruskal-Wallis	GeneTreat	7	58.593	<0.001	4,4,4,4
	Bonferroni	Htr2a Veh - C57 Veh			<0.001	
	(Post-Inj Rear)	Htr2a LSD - C57 LSD			<0.001	

		Htr2a DOI - C57 DOI			<0.001	
		Htr2a Psil - C57 Psil			0.003	
		Htr2a Veh – Htr2a LSD			0.321	
		Htr2a Veh – Htr2a DOI			0.741	
		Htr2a Veh – Htr2a Psil			0.424	
		Htr2a LSD – Htr2a DOI			0.509	
		Htr2a LSD – Htr2a Psil			0.073	
		Htr2a DOI – Htr2a Psil			0.259	
		C57 Veh – C57 LSD			0.208	
		C57 Veh – C57 DOI			0.126	
		C57 Veh – C57 Psil			0.953	
		C57 LSD – C57 DOI			0.757	
		C57 LSD – C57 Psil			0.217	
		C57 DOI – C57 Psil			0.131	
Ext. Data Fig. 9d	Levene's test	Sex, Gene, Treat	15,62	3.680	<0.001	5,4,5 4
	Mann-Whitney	Sex		930.000	0.081	4,6,4,6
	Levene's test	Gene, Treat	7,70	6.662	<0.001	6,6,6,6
	Kruskal-Wallis	GeneTreat	7	60.528	<0.001	4,4,4,4
	Bonferroni	Htr2a Veh - C57 Veh			<0.001	
	(Post-Inj Stereo)	Htr2a LSD - C57 LSD			0.002	
		Htr2a DOI - C57 DOI			<0.001	
		Htr2a Psil - C57 Psil			<0.001	
		Htr2a Veh – Htr2a LSD			0.110	
		Htr2a Veh – Htr2a DOI			0.380	
		Htr2a Veh – Htr2a Psil			0.693	
		Htr2a LSD – Htr2a DOI			0.471	
		Htr2a LSD – Htr2a Psil			0.046	
		Htr2a DOI – Htr2a Psil			0.203	
		C57 Veh – C57 LSD			0.241	
		C57 Veh – C57 DOI			0.270	
		C57 Veh – C57 Psil			0.743	
		C57 LSD – C57 DOI			0.967	
		C57 LSD – C57 Psil			0.385	
		C57 DOI – C57 Psil			0.422	
Fig. 9e	Levene's test	Sex, Gene, Treat	15,62	4.479	<0.001	5,4,5 4
	Mann-Whitney	Sex		762.500	0.948	4,6,4,6
	Levene's test	Gene, Treat	7,70	6.283	<0.001	6,6,6,6
	Kruskal-Wallis	GeneTreat	7	64.307	<0.001	4,4,4,4
	Bonferroni	Htr2a Veh - C57 Veh			0.655	
	(HTR)	Htr2a LSD - C57 LSD			0.035	
		Htr2a DOI - C57 DOI			0.007	
		Htr2a Psil - C57 Psil			0.015	
		Htr2a Veh - Htr2a LSD			0.001	
		Htr2a Veh - Htr2a DOI			<0.001	
		Htr2a Veh - Htr2a Psil			0.039	
		Htr2a LSD – Htr2a DOI			0.976	
		Htr2a LSD – Htr2a Psil			0.219	
		Htr2a DOI – Htr2a Psil			0.208	
		C57 Veh - C57 LSD			<0.001	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			<0.001	
		C57 LSD – C57 DOI			0.515	

		C57 LSD – C57 Psil			0.361	
		C57 DOI – C57 Psil			0.124	
Ext. Data Fig. 9f	Mauchly's test	PPI (within subjects)	2	0.911	0.030	10,10,10,10
	Box's test	PPI (within subjects)	84,20 82.61 5	177.524	0.008	5,5,5,5
	Levene's test	4 dB	15,76	2.352	0.008	4,4,4,4
	Levene's test	8 dB	15,76	2.307	0.009	5,4,4,3
	Levene's test	12 dB	15,76	2.269	0.011	
	(PPI) Greenhouse-Geisser corrections	PPI	1.837, 139.5 76	199.537	<0.001	
	Within Subjects	PPI x Sex	1.837, 139.5 76	0.301	0.722	
		PPI x Gene	1.837, 139.5 76	7.840	<0.001	
		PPI x Treat	5.510, 139.5 76	2.982	0.011	
		PPI x Sex x Gene	1.837, 139.5 76	0.115	0.876	
		PPI x Sex x Treat	5.510, 139.5 76	3.125	0.008	
		PPI x Gene x Treat	5.510, 139.5 76	1.770	0.116	
		PPI x Sex x Gene x Treat	5.510, 139.5 76	1.001	0.424	
	Between Subjects	Sex	1,76	0.400	0.529	
		Gene	1,76	88.042	<0.001	
		Treat	3,76	10.851	<0.001	
		Sex x Gene	1,76	11.973	<0.001	
		Sex x Treat	3,76	0.962	0.415	
		Gene x Treat	3,76	3.073	0.033	
		Sex x Gene x Treat	3,76	1.220	0.308	
	Bonferroni	♂ Htr2a - ♂ C57			<0.001	
	(Sex x Gene)	♀ Htr2a - ♀ C57			<0.001	
		Htr2a ♂ - Htr2a ♀			0.079	
		C57 ♂ - C57 ♀			0.001	
	(Gene x Treat)	Htr2a Veh – C57 Veh			0.012	
		Htr2a LSD – C57 LSD			<0.001	
		Htr2a DOI – C57 DOI			<0.001	
		Htr2a Psil – C57 Psil			<0.001	
		Htr2a Veh – Htr2a LSD			0.680	
		Htr2a Veh – Htr2a DOI			1.000	
		Htr2a Veh – Htr2a Psil			0.205	

		Htr2a LSD – Htr2a DOI			1.000	
		Htr2a LSD – Htr2a Psil			1.000	
		Htr2a DOI – Htr2a Psil			1.000	
		C57 Veh - C56 LSD			<0.001	
		C57 Veh - C56 DOI			<0.001	
		C57 Veh - C56 Psil			<0.001	
		C57 LSD – C57 DOI			1.000	
		C57 LSD – C57 Psil			1.000	
		C57 DOI – C57 Psil			1.000	
	Chemogenetic Study					
Ext. Data Fig. 10b	Unpaired t-test	Treat	17	2.160	0.045	9,10
	Basal Motor Activities					
Suppl. Fig. S1a	Levene's test (ERT2-C57)	Sex, Gene, Treat	15,61	1.202	0.295	5,4,5 4
	3-Way ANOVA	Sex	1,61	3.655	0.061	4,6,4,6
	(Baseline Loco)	Gene	1,61	10.398	0.002	4,6,6,6
		Treat	3,61	0.170	0.916	6,4,4,3
		Sex x Gene	1,61	0.695	0.408	
		Sex x Treat	3,61	0.368	0.776	
		Gene x Treat	3,61	1.434	0.242	
		Sex x Gene x Treat	3,61	0.822	0.487	
Suppl. Fig S1b	Levene's test (ERT2-C57)	Sex, Gene, Treat	15,61	1.351	0.201	5,4,5 4
	3-Way ANOVA	Sex	1,61	4.164	0.046	4,6,4,6
	(Baseline Rear)	Gene	1,61	14.526	<0.001	4,6,6,6
		Treat	3,61	0.627	0.600	6,4,4,3
		Sex x Gene	1,61	3.921	0.052	
		Sex x Treat	3,61	2.597	0.060	
		Gene x Treat	3,61	0.200	0.896	
		Sex x Gene x Treat	3,61	4.489	0.007	
	Bonferroni	♂ ERT2 Veh - ♀ ERT2 Veh			0.004	
		♂ ERT2 LSD - ♀ ERT2 LSD			0.480	
		♂ ERT2 DOI - ♀ ERT2 DOI			0.500	
		♂ ERT2 Psil - ♀ ERT2 Psil			0.009	
		♂ C57 Veh - ♀ C57 Veh			0.974	
		♂ C57 LSD - ♀ C57 LSD			0.019	
		♂ C57 DOI - ♀ C57 DOI			0.027	
		♂ C57 Psil - ♀ C57 Psil			0.315	
		♂ ERT2 Veh - ♂ C57 Veh			0.003	
		♂ ERT2 LSD - ♂ C57 LSD			0.522	
		♂ ERT2 DOI - ♂ C57 DOI			0.674	
		♂ ERT2 Psil - ♂ C57 Psil			0.389	
		♀ ERT2 Veh - ♀ C57 Veh			0.762	
		♀ ERT2 LSD - ♀ C57 LSD			0.023	
		♀ ERT2 DOI - ♀ C57 DOI			0.019	
		♀ ERT2 Psil - ♀ C57 Psil			0.006	
		♂ ERT2 Veh - ♂ ERT2 LSD			1.000	

		♂ ERT2 Veh - ♂ ERT2 DOI			0.127	
		♂ ERT2 Veh - ♂ ERT2 Psil			0.001	
		♂ ERT2 LSD - ♂ ERT2 DOI			1.000	
		♂ ERT2 LSD - ♂ ERT2 Psil			0.027	
		♂ ERT2 DOI - ♂ ERT2 Psil			0.524	
		♀ ERT2 Veh - ♀ ERT2 LSD			1.000	
		♀ ERT2 Veh - ♀ ERT2 DOI			1.000	
		♀ ERT2 Veh - ♀ ERT2 Psil			0.420	
		♀ ERT2 LSD - ♀ ERT2 DOI			1.000	
		♀ ERT2 LSD - ♀ ERT2 Psil			1.000	
		♀ ERT2 DOI - ♀ ERT2 Psil			1.000	
		♂ C57 Veh - ♂ C57 LSD			1.000	
		♂ C57 Veh - ♂ C57 DOI			1.000	
		♂ C57 Veh - ♂ C57 Psil			1.000	
		♂ C57 LSD - ♂ C57 DOI			1.000	
		♂ C57 LSD - ♂ C57 Psil			1.000	
		♂ C57 DOI - ♂ C57 Psil			1.000	
		♀ C57 Veh - ♀ C57 LSD			1.000	
		♀ C57 Veh - ♀ C57 DOI			1.000	
		♀ C57 Veh - ♀ C57 Psil			1.000	
		♀ C57 LSD - ♀ C57 DOI			1.000	
		♀ C57 LSD - ♀ C57 Psil			1.000	
		♀ C57 DOI - ♀ C57 Psil			1.000	
Suppl. Fig. S1c	Levene's test (ERT2-C57)	Sex, Gene, Treat	15,61	2.106	0.021	5,4,5 4
	Mann-Whitney	Sex		831.500	0.351	4,6,4,6
	Levene's test	Gene, Treat	7,69	0.803	0.588	4,6,6,6
	2-Way ANOVA	Gene	1,69	44.086	<0.001	6,4,4,3
	(Baseline Stereo)	Treat	3,69	1.340	0.268	
		Gene x Treat	3,69	1.866	0.143	
Suppl. Fig. S1d	Levene's test (A242S-C57)	Sex, Gene, Treat	15,62	1.231	0.274	5,4,5 4
	3-Way ANOVA	Sex	1,62	0.594	0.444	4,6,4,6
	(Baseline Loco)	Gene	1,62	0.014	0.907	7,6,6,6
		Treat	3,62	0.345	0.793	3,4,4,4
		Sex x Gene	1,62	5.513	0.022	
		Sex x Treat	3,62	0.356	0.785	
		Gene x Treat	3,62	0.754	0.524	
		Sex x Gene x Treat	3,62	0.601	0.617	
	Bonferroni	♂ C57 - ♀ C57			0.031	
		♂ A242S - ♀ A242S			0.269	
		♂ A242S - ♂ C57			0.100	
		♀ A242S - ♀ C57			0.103	
Suppl. Fig. S1e	Levene's test (A242S-C57)	Sex, Gene, Treat	15,62	2.438	0.007	5,4,5 4
	Mann-Whitney	Sex		468.500	0.004	4,6,4,6
	Kruskal-Wallis	Treat	3	1.104	0.776	7,6,6,6
	Levene's test	Sex, Gene	3,74	2.469	0.069	3,4,4,4
	2-Way ANOVA	Sex	1,74	9.121	0.003	
	(Baseline Rear)	Gene	1,74	7.039	0.010	
		Sex x Gene	1,74	0.349	0.556	

Suppl. Fig. S1f	Levene's test (A242S-C57)	Sex, Gene, Treat	15,62	1.522	0.125	5,4,5 4
	3-Way ANOVA	Sex	1,62	0.040	0.843	4,6,4,6
	(Baseline Stereo)	Gene	1,62	7.445	0.008	7,6,6,6
		Treat	3,62	1.256	0.297	3,4,4,4
		Sex x Gene	1,62	0.717	0.400	
		Sex x Treat	3,62	0.221	0.881	
		Gene x Treat	3,62	0.526	0.666	
		Sex x Gene x Treat	3,62	0.970	0.412	
Suppl.. Fig. S1g	Levene's test (Cre-C57)	Sex, Gene, Treat	15,62	1.489	0.138	5,4,5 4
	3-Way ANOVA	Sex	1,62	8.894	0.004	4,6,4,6
	(Baseline Loco)	Gene	1,62	28.121	<0.001	6,6,6,6
		Treat	3,62	2.369	0.079	4,4,4,4
		Sex x Gene	1,62	0.010	0.922	
		Sex x Treat	3,62	0.242	0.867	
		Gene x Treat	3,62	0.968	0.413	
		Sex x Gene x Treat	3,62	0.214	0.886	
Suppl. Fig. S1h	Levene's test (C57-Cre)	Sex, Gene, Treat	15,62	3.078	<0.001	5,4,5 4
	Mann-Whitney	Sex		634.500	0.223	4,6,4,6
	Levene's test	Sex, Gene	7,70	1.974	0.071	6,6,6,6
	2-way ANOVA	Gene	1,70	33.167	<0.001	4,4,4,4
	(Baseline Rear)	Treat	3,70	0.262	0.853	
		Gene x Treat	3,70	0.279	0.840	
Suppl. Fig. S1i	Levene's test (Cre-C57)	Sex, Gene, Treat	15,62	2.479	0.006	5,4,5 4
	Mann-Whitney	Sex		912.500	0.117	4,6,4,6
	Levene's test	Gene, Treat	7,70	2.197	0.045	6,6,6,6
	Kruskal-Wallis	GeneTreat	7	39.326	<0.001	4,4,4,4
	Bonferroni	Htr2a Veh - C57 Veh			0.050	
	(Baseline Stereo)	Htr2a LSD - C57 LSD			<0.001	
		Htr2a DOI - C57 DOI			0.084	
		Htr2a Psil - C57 Psil			<0.001	
		Htr2a Veh – Htr2a LSD			0.114	
		Htr2a Veh – Htr2a DOI			0.615	
		Htr2a Veh – Htr2a Psil			0.364	
		Htr2a LSD – Htr2a DOI			0.282	
		Htr2a LSD – Htr2a Psil			0.502	
		Htr2a DOI – Htr2a Psil			0.686	
		C57 Veh – C57 LSD			0.551	
		C57 Veh – C57 DOI			0.483	
		C57 Veh – C57 Psil			0.444	
		C57 LSD – C57 DOI			0.188	
		C57 LSD – C57 Psil			0.863	
		C57 DOI – C57 Psil			0.138	
	Grooming, Retro. Walking					

Suppl. Fig. S2a	Levene's test (ERT2-C57)	Sex, Gene, Treat	15,61	3.304	<0.001	5,4,5 4
	Mann-Whitney	Sex		941.000	0.040	4,6,4,6
	Kruskal-Wallis	SexGeneTreat	15	49.123	<0.001	4,6,6,6
	(Grooming)	♂ ERT2 Veh - ♀ ERT2 Veh			0.595	6,4,4,3
		♂ ERT2 LSD - ♀ ERT2 LSD			0.083	
		♂ ERT2 DOI - ♀ ERT2 DOI			1.000	
		♂ ERT2 Psil - ♀ ERT2 Psil			0.673	
		♂ C57 Veh - ♀ C57 Veh			0.046	
		♂ C57 LSD - ♀ C57 LSD			0.716	
		♂ C57 DOI - ♀ C57 DOI			0.592	
		♂ C57 Psil - ♀ C57 Psil			0.548	
		♂ ERT2 Veh - ♂ C57 Veh			0.093	
		♂ ERT2 LSD - ♂ C57 LSD			0.069	
		♂ ERT2 DOI - ♂ C57 DOI			0.023	
		♂ ERT2 Psil - ♂ C57 Psil			0.844	
		♀ ERT2 Veh - ♀ C57 Veh			0.840	
		♀ ERT2 LSD - ♀ C57 LSD			0.653	
		♀ ERT2 DOI - ♀ C57 DOI			0.150	
		♀ ERT2 Psil - ♀ C57 Psil			0.251	
		♂ ERT2 Veh - ♂ ERT2 LSD			0.533	
		♂ ERT2 Veh - ♂ ERT2 DOI			0.406	
		♂ ERT2 Veh - ♂ ERT2 Psil			0.050	
		♂ ERT2 LSD - ♂ ERT2 DOI			0.816	
		♂ ERT2 LSD - ♂ ERT2 Psil			0.134	
		♂ ERT2 DOI - ♂ ERT2 Psil			0.206	
		♀ ERT2 Veh - ♀ ERT2 LSD			0.564	
		♀ ERT2 Veh - ♀ ERT2 DOI			0.173	
		♀ ERT2 Veh - ♀ ERT2 Psil			0.007	
		♀ ERT2 LSD - ♀ ERT2 DOI			0.077	
		♀ ERT2 LSD - ♀ ERT2 Psil			0.003	
		♀ ERT2 DOI - ♀ ERT2 Psil			0.178	
		♂ C57 Veh - ♂ C57 LSD			0.005	
		♂ C57 Veh - ♂ C57 DOI			0.002	
		♂ C57 Veh - ♂ C57 Psil			0.984	
		♂ C57 LSD - ♂ C57 DOI			0.981	
		♂ C57 LSD - ♂ C57 Psil			0.007	
		♂ C57 DOI - ♂ C57 Psil			0.003	
		♀ C57 Veh - ♀ C57 LSD			0.219	
		♀ C57 Veh - ♀ C57 DOI			0.704	
		♀ C57 Veh - ♀ C57 Psil			0.135	
		♀ C57 LSD - ♀ C57 DOI			0.416	
		♀ C57 LSD - ♀ C57 Psil			0.002	
		♀ C57 DOI - ♀ C57 Psil			0.056	
Suppl. Fig. S2b	Levene's test (ERT2-C57)	Sex, Gene, Treat	15,61	1.968	0.033	5,4,5 4
	Mann-Whitney	Sex		755.500	0.874	4,6,4,6
	Levene's test	Gene, Treat	7,69	3.389	0.004	4,6,6,6
	Kruskal-Wallis	GeneTreat	7	48.918	<0.001	6,4,4,3
	Bonferroni	ERT2 Veh – C57 Veh			0.413	
	(Retro Walking)	ERT2 LSD – C57 LSD			0.752	
		ERT2 DOI – C57 DOI			0.916	

		ERT2 Psil – C57 Psil			0.249	
		ERT2 Veh – ERT2 LSD			<0.001	
		ERT2 Veh – ERT2 DOI			<0.001	
		ERT2 Veh – ERT2 Psil			0.442	
		ERT2 LSD - ERT2 DOI			0.673	
		ERT2 LSD - ERT2 Psil			0.013	
		ERT2 DOI - ERT2 Psil			0.004	
		C57 Veh – C57 LSD			<0.001	
		C57 Veh – C57 DOI			<0.001	
		C57 Veh – C57 Psil			0.006	
		C57 LSD - C57 DOI			0.605	
		C57 LSD - C57 Psil			0.091	
		C57 DOI - C57 Psil			0.031	
Suppl. Fig. S2c	Levene's test (A242S-C57)	Sex, Gene, Treat	15,62	3.728	<0.001	5,4,5 4
	Mann-Whitney	Sex		924.000	0.085	4,6,4,6
	Levene's test	Gene, Treat	7,70	2.876	0.011	7,6,6,6
	Kruskal-Wallis	GeneTreat	7	48.265	<0.001	3,4,4,4
	(Grooming)	A242S Veh - C57 Veh			0.015	
		A242S LSD - C57 LSD			<0.001	
		A242S DOI - C57 DOI			<0.001	
		A242S Psil - C57 Psil			0.601	
		A242S Veh - A242S LSD			<0.001	
		A242S Veh - A242S DOI			<0.001	
		A242S Veh - A242S Psil			0.003	
		A242S LSD - A242S DOI			0.805	
		A242S LSD - A242S Psil			0.309	
		A242S DOI - A242S Psil			0.441	
		C57 Veh - C57 LSD			0.003	
		C57 Veh - C57 DOI			0.013	
		C57 Veh - C57 Psil			0.359	
		C57 LSD - C57 DOI			0.686	
		C57 LSD - C57 Psil			<0.001	
		C57 DOI - C57 Psil			<0.001	
Suppl. Fig. S2d	Levene's test (A242S-C57)	Sex, Gene, Treat	15,62	2.759	0.003	5,4,5 4
	Mann-Whitney	Sex		879.000	0.200	4,6,4,6
	Levene's test	Gene, Treat	7,70	7.351	<0.001	7,6,6,6
	Kruskal-Wallis	GeneTreat	7	40.052	<0.001	3,4,4,4
	(Retro Walking)	A242S Veh - C57 Veh			0.117	
		A242S LSD - C57 LSD			0.002	
		A242S DOI - C57 DOI			0.043	
		A242S Psil - C57 Psil			0.360	
		A242S Veh – A242 LSD			0.762	
		A242S Veh – A242 DOI			0.112	
		A242S Veh – A242 Psil			0.480	
		A242S LSD - A242S DOI			0.198	
		A242S LSD - A242S Psil			0.687	
		A242S DOI - A242S Psil			0.376	
		C57 Veh - C57 LSD			<0.001	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			0.002	

		C57 LSD - C57 DOI			0.751	
		C57 LSD - C57 Psil			0.084	
		C57 DOI - C57 Psil			0.046	
Suppl. Fig. S2e	Levene's test (Cre-C57)	Sex, Gene, Treat	15,62	4.479	0.005	5,4,5 4
	Mann-Whitney	Sex		762.500	0.071	4,6,4,6
	Levene's test	Gene, Treat	7,70	6.283	0.079	6,6,6,6
	2-way ANOVA	Gene	1,70	6.942	0.010	4,4,4,4
	(Grooming)	Treat	3,70	9.488	<0.001	
		Gene x Treat	3,70	8.687	<0.001	
	Bonferroni	Htr2a Veh - C57 Veh			0.473	
		Htr2a LSD - C57 LSD			<0.001	
		Htr2a DOI - C57 DOI			0.005	
		Htr2a Psil - C57 Psil			0.126	
		Htr2a Veh - Htr2a LSD			1.000	
		Htr2a Veh - Htr2a DOI			1.000	
		Htr2a Veh - Htr2a Psil			1.000	
		Htr2a LSD – Htr2a DOI			1.000	
		Htr2a LSD – Htr2a Psil			1.000	
		Htr2a DOI – Htr2a Psil			1.000	
		C57 Veh - C57 LSD			<0.001	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			1.000	
		C57 LSD – C57 DOI			1.000	
		C57 LSD – C57 Psil			<0.001	
		C57 DOI – C57 Psil			<0.001	
Suppl. Fig. S2f	Levene's test (Cre-C57)	Sex, Gene, Treat	15,62	5.085	<0.001	5,4,5 4
	Mann-Whitney	Sex		833.500	0.406	4,6,4,6
	Levene's test	Gene, Treat	7,70	10.732	<0.001	6,6,6,6
	Kruskal-Wallis	GeneTreat	7	66.014	<0.001	4,4,4,4
	Bonferroni	Htr2a Veh - C57 Veh			0.152	
	(Retro Walking)	Htr2a LSD - C57 LSD			<0.001	
		Htr2a DOI - C57 DOI			<0.001	
		Htr2a Psil - C57 Psil			<0.001	
		Htr2a Veh - Htr2a LSD			1.000	
		Htr2a Veh - Htr2a DOI			1.000	
		Htr2a Veh - Htr2a Psil			0.928	
		Htr2a LSD – Htr2a DOI			1.000	
		Htr2a LSD – Htr2a Psil			0.928	
		Htr2a DOI – Htr2a Psil			0.928	
		C57 Veh - C57 LSD			0.002	
		C57 Veh - C57 DOI			0.001	
		C57 Veh - C57 Psil			0.036	
		C57 LSD – C57 DOI			0.840	
		C57 LSD – C57 Psil			0.291	
		C57 DOI – C57 Psil			0.219	
	Null & Startle Activities					
Suppl. Fig. S3a	Levene's test (ERT2-C57)	Sex, Gene, Treat	15,97	4,177	<0.001	10,10,10,10

	Mann-Whitney	Sex		1342.000	0.223	5,5,5,5
	Levene's test	Gene, Treat	7,105	6.614	<0.001	6,8,9,3
	Kruskal-Wallis	GeneTreat	7	72.229	<0.001	8,6,6,7
	Bonferroni	ERT2 Veh - C57 Veh			0.084	
	(Null Activity)	ERT2 LSD - C57 LSD			0.001	
		ERT2 DOI - C57 DOI			0.052	
		ERT2 Psil - C57 Psil			0.034	
		ERT2 Veh - ERT2 LSD			<0.001	
		ERT2 Veh - ERT2 DOI			<0.001	
		ERT2 Veh - ERT2 Psil			0.052	
		ERT2 LSD - ERT2 DOI			0.343	
		ERT2 LSD - ERT2 Psil			0.121	
		ERT2 DOI - ERT2 Psil			0.015	
		C57 Veh - C57 LSD			0.016	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			0.112	
		C57 LSD - C57 DOI			0.019	
		C57 LSD - C57 Psil			0.417	
		C57 DOI - C57 Psil			0.002	
Suppl. Fig. S3b	Levene's test (ERT2-C57)	Sex, Gene, Treat	15,97	2.273	0.009	10,10,10,10
	Mann-Whitney	Sex		1279.000	0.113	5,5,5,5
	Levene's test	Gene, Treat	7,105	3.596	0.002	6,8,9,3
	Kruskal-Wallis	GeneTreat	7	61.619	<0.001	8,6,6,7
	Bonferroni	ERT2 Veh - C57 Veh			<0.001	
	(Startle Activity)	ERT2 LSD - C57 LSD			<0.001	
		ERT2 DOI - C57 DOI			0.361	
		ERT2 Psil - C57 Psil			<0.001	
		ERT2 Veh - ERT2 LSD			0.135	
		ERT2 Veh - ERT2 DOI			0.007	
		ERT2 Veh - ERT2 Psil			0.544	
		ERT2 LSD - ERT2 DOI			<0.001	
		ERT2 LSD - ERT2 Psil			0.049	
		ERT2 DOI - ERT2 Psil			0.069	
		C57 Veh – C57 LSD			0.121	
		C57 Veh – C57 DOI			0.841	
		C57 Veh – C57 Psil			0.120	
		C57 LSD - C57 DOI			0.080	
		C57 LSD - C57 Psil			0.002	
		C57 DOI - C57 Psil			0.176	
Suppl. Fig. S3c	Levene's test (A242S-C57)	Sex, Gene, Treat	15,95	4.278	<0.001	10,10,10,10
	Mann-Whitney	Sex		1330.000	0.424	5,5,5,5
	Levene's test	Gene, Treat	7,103	5.899	<0.001	5,4,9,10
	Kruskal-Wallis	GeneTreat	7	63.927	<0.001	4,8,6,5
	Bonferroni	A242S Veh - C57 Veh			0.120	
	(Null Activity)	A242S LSD - C57 LSD			0.005	
		A242S DOI - C57 DOI			0.061	
		A242S Psil - C57 Psil			0.011	
		A242S Veh - A242S LSD			0.003	
		A242S Veh - A242S DOI			<0.001	
		A242S Veh - A242S Psil			0.042	

		A242S LSD – A242S DOI			0.271	
		A242S LSD - A242S Psil			0.263	
		A242S DOI - A242S Psil			0.019	
		C57 Veh - C57 LSD			0.018	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			0.112	
		C57 LSD - C57 DOI			0.024	
		C57 LSD - C57 Psil			0.442	
		C57 DOI - C57 Psil			0.002	
Suppl. Fig. S3d	Levene's test (A242S-C57)	Sex, Gene, Treat	15,95	2.835	<0.001	10,10,10,10
	Mann-Whitney	Sex		1100.000	0.028	5,5,5,5
	Kruskal-Wallis	SexGeneTreat	15	45.733	<0.001	5,4,9,10
	Bonferroni	♂ A242S Veh - ♀ A242S Veh			0.081	4,8,6,5
	(Startle Activity)	♂ A242S LSD - ♀ A242S LSD			0.060	
		♂ A242S DOI - ♀ A242S DOI			0.093	
		♂ A242S Psil - ♀ A242S Psil			0.042	
		♂ C57 Veh - ♀ C57 Veh			0.540	
		♂ C57 LSD - ♀ C57 LSD			0.654	
		♂ C57 DOI - ♀ C57 DOI			0.590	
		♂ C57 Psil - ♀ C57 Psil			0.968	
		♂ A242S Veh – ♂ C57 Veh			<0.001	
		♂ A242S LSD – ♂ C57 LSD			0.177	
		♂ A242S DOI – ♂ C57 DOI			0.512	
		♂ A242S Psil – ♂ C57 Psil			0.070	
		♀ A242S Veh – ♀ C57 Veh			0.599	
		♀ A242S LSD – ♀ C57 LSD			0.292	
		♀ A242S DOI – ♀ C57 DOI			0.633	
		♀ A242S Psil – ♀ C57 Psil			0.003	
		♂ A242S Veh - ♂ A242S LSD			0.005	
		♂ A242S Veh - ♂ A242S DOI			<0.001	
		♂ A242S Veh - ♂ A242S Psil			0.003	
		♂ A242S LSD - ♂ A242S DOI			0.502	
		♂ A242S LSD - ♂ A242S Psil			0.667	
		♂ A242S DOI - ♂ A242S Psil			0.152	
		♀ A242S Veh - ♀ A242S LSD			0.466	
		♀ A242S Veh - ♀ A242S DOI			0.727	
		♀ A242S Veh - ♀ A242S Psil			0.325	
		♀ A242S LSD - ♀ A242S DOI			0.213	

		♀ A242S LSD - ♀ A242S Psil			0.708	
		♀ A242S DOI - ♀ A242S Psil			0.144	
		♂ C57 Veh - ♂ C57 LSD			0.081	
		♂ C57 Veh - ♂ C57 DOI			0.786	
		♂ C57 Veh - ♂ C57 Psil			0.199	
		♂ C57 LSD - ♂ C57 DOI			0.044	
		♂ C57 LSD - ♂ C57 Psil			0.002	
		♂ C57 DOI - ♂ C57 Psil			0.310	
		♀ C57 Veh - ♀ C57 LSD			0.753	
		♀ C57 Veh - ♀ C57 DOI			0.798	
		♀ C57 Veh - ♀ C57 Psil			0.160	
		♀ C57 LSD - ♀ C57 DOI			0.569	
		♀ C57 LSD - ♀ C57 Psil			0.086	
		♀ C57 DOI - ♀ C57 Psil			0.250	
Suppl. Fig. S3e	Levene's test (Cre-C57)	Sex, Gene, Treat	15,76	2.811	0.002	10,10,10,10
	Mann-Whitney	Sex		882.000	0.313	5,5,5,5
	Levene's test	Gene, Treat	7,84	3.950	<0.001	4,4,4,4
	Kruskal-Wallis	GeneTreat	7	51.533	<0.001	5,4,4,3
	(Null Activity)	Htr2a Veh - C57 Veh			0.004	
		Htr2a LSD - C57 LSD			0.055	
		Htr2a DOI - C57 DOI			0.103	
		Htr2a Psil - C57 Psil			0.208	
		Htr2a Veh - Htr2a LSD			0.236	
		Htr2a Veh - Htr2a DOI			0.005	
		Htr2a Veh - Htr2a Psil			0.993	
		Htr2a LSD – Htr2a DOI			0.116	
		Htr2a LSD - Htr2a Psil			0.262	
		Htr2a DOI - Htr2a Psil			0.008	
		C57 Veh - C57 LSD			0.010	
		C57 Veh - C57 DOI			<0.001	
		C57 Veh - C57 Psil			0.085	
		C57 LSD - C57 DOI			0.012	
		C57 LSD - C57 Psil			0.383	
		C57 DOI - C57 Psil			<0.001	
Suppl. Fig. S3f	Levene's test (Cre-C57)	Sex, Gene, Treat	15,76	3.656	<0.001	10,10,10,10
	Mann-Whitney	Sex		850.000	0.206	5,5,5,5
	Levene's test	Gene, Treat	7,84	6.302	<0.001	4,4,4,4
	Kruskal-Wallis	GeneTreat	7	65.936	<0.001	5,4,4,3
	(Startle Activity)	Htr2a Veh - C57 Veh			<0.001	
		Htr2a LSD - C57 LSD			0.001	
		Htr2a DOI - C57 DOI			<0.001	
		Htr2a Psil - C57 Psil			<0.001	
		Htr2a Veh - Htr2a LSD			0.758	
		Htr2a Veh - Htr2a DOI			0.447	
		Htr2a Veh - Htr2a Psil			0.687	
		Htr2a LSD – Htr2a DOI			0.299	
		Htr2a LSD - Htr2a Psil			0.495	
		Htr2a DOI - Htr2a Psil			0.748	

		C57 Veh - C57 LSD			0.203	
		C57 Veh - C57 DOI			0.758	
		C57 Veh - C57 Psi			0.151	
		C57 LSD - C57 DOI			0.114	
		C57 LSD - C57 Psil			0.007	
		C57 DOI - C57 Psil			0.259	
	Intrinsic Membrane Properties (WT & ERT2))					
Suppl, Fig. S6	Welch t-test Cm(pF)	Gene	28.83	0.053	0.959	15,16
	Welch t-test (membrane capacitance)	Gene	21.06	0.517	0.610	15,16
	Welch t-test Tau (ms)	Gene	23.21	1.189	0.247	15,16
	Welch t-test (membrane potential)	Gene	28.96	0.633	0.532	15,16
	***Htr1a* & *Htr2c* mRNAs**					
Suppl. Fig. S7a	1-way ANOVA (*Htr1a* mRNA)	Gene	3,12	0.000	1.000	4,4,4,4
Suppl. Fig. S7b	1-way ANOVA (*Htr2c* mRNA)	Gene	3,12	0.125	0.9435	4,4,4,4

[a]Abbreviations: Down Reg, down regulation of receptor; Post-Inj, post-injection (31-120 min in open field); Loco, locomotion; Rear, Rearing; Stereo, stereotypy; HTR, head twitch response; PPI, prepulse inhibition; Retro Walking, retrograde walking; Firing Freq, firing frequency; Kd, dissociation constant; Bmax, maximal binding of a ligand; C57, C57BL/6J; ERT2, *Htr2a*$^{EGFP\text{-}CreERT/EGFP\text{-}CreERT}$; A242S, *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$, Cre, *Htr2a*^{Cre} mice.

[b]Abbreviations: Kd, dissociation constant; Bmax, maximal binding of a ligand; gene, genotype; Treat, treatment (vehicle, LSD, DOI, Psil), Veh, vehicle, LSD, lysergic acid diethylamide; DOI, 2,5-dimethoxy-4-iodoamphetamine; Psil, psilocin; ♂, male; ♀, female; *Htr2a*^{ERT2} - C57, comparison of *Htr2a*$^{EGFP\text{-}CreERT2}$ and C57BL/6J mice; *Htr2a*^{A242S} – C57, comparison of *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$ and C57BL/6J mice; *Htr2a* – C57, comparison of *Htr2a*^{Cre} and C57BL/6J mice; PPI, prepulse inhibition, dB, decibel; Treat comparisons: Veh-Veh, LSD–LSD, DOI–DOI, Psil–Psil, LSD–DOI, LSD-Psil, DOI-Psil; Bmax, maximum specific binding; and Kd, equilibrium dissociation constant for ligand binding; +/ERT2, heterozygous *Htr2a*$^{EGFP\text{-}CreERT2}$ mice; +/+, ERT2/ERT2, 242/242, Cre/Cre, refer respectively to homozygous wild-type (C57), *Htr2a*$^{EGFP\text{-}CreERT}$, *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$, *Htr2a*^{Cre} mice; M100907, MDL100,907 a HTR2A antagonist; DOI-eYFP, control for chemogenetics study; and DOI-hM3Dq, chemogenetic actuator.

[c]Numbers of groups of mice.

Suppl. Table S5. Intrinsic membrane properties and baseline firing in mPFC neurons from C57BL6/J and *Htr2*$^{EGFP\text{-}CreERT2}$ mice.

	Membrane Capacitance Cm (pF)	Membrane Resistance Rm(MΩ)	Time Constant Tau (μs)	Membrane Potential Vm (mV)	Baseline Firing (Hz)
C57 (*Htr2a*$^{+/+}$) n = 10-15	114.4± 7.0	148.4±30.9	2146±250	-63.34±1.33	1.3 ± 0.3
Htr2a$^{EGFP\text{-}CreERT2}$ n = 9-16	109.1± 8.5	210.2±38.2	1723±171	-62.25±1.18	1.6 ± 0.3

Suppl. Table S6. Summary of sex, genotype, and treatment effects on behaviors of C57, *Htr2a*$^{\text{EGFP-CreERT2/EGFP-CreERT2}}$, *Htr2a*$^{\text{A242S-EGFP-Cre/A242S-EGFP-Cre}}$, and *Htr2a*$^{\text{Cre/Cre}}$ mice.

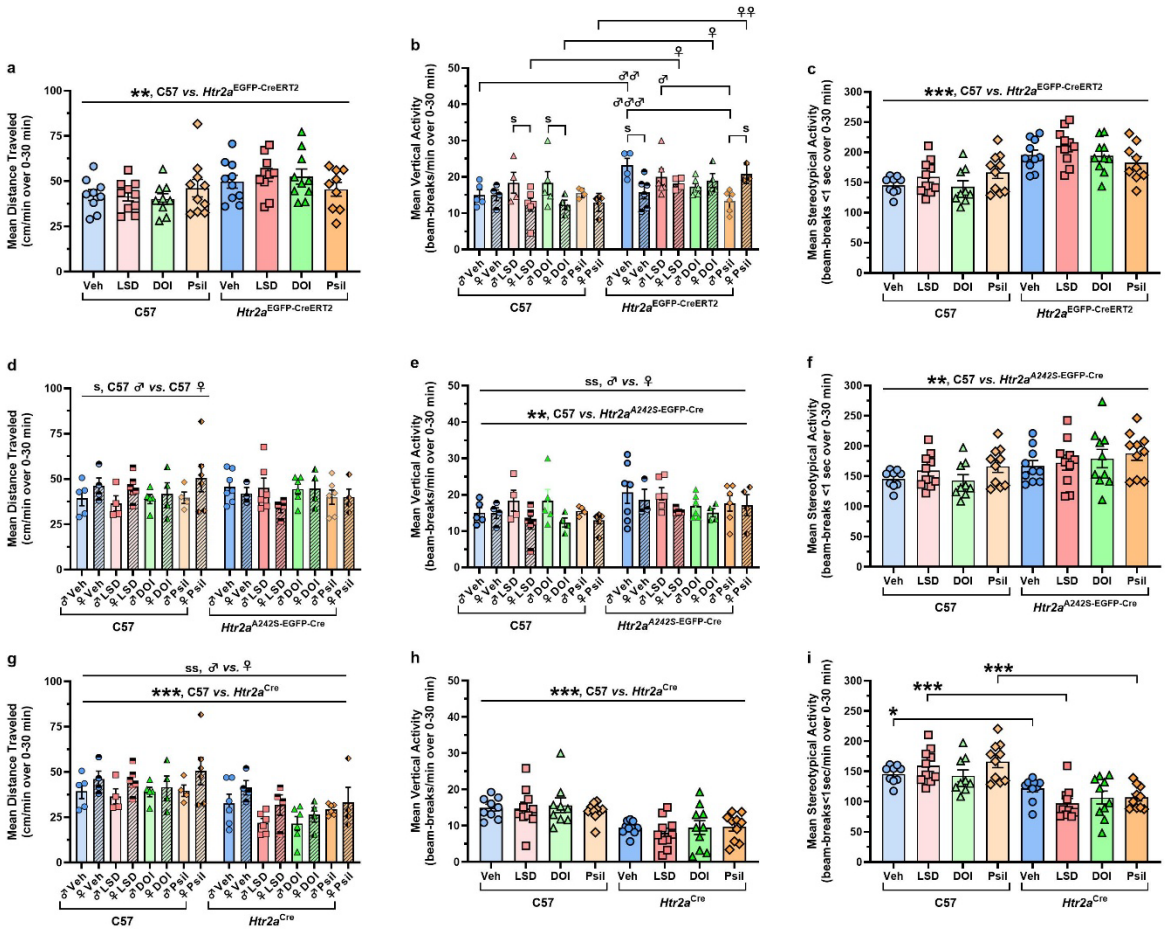
Test[a]	C57 *vs.* ERT2[b]	ERT2[b]	C57 *vs.* 242[b]	242[b]	C57 *vs.* Cre[b]	Cre[b]
Basal Loco	C57<ERT2	C57<ERT2	♂C57<♀C57		Cre<C57 ♂<♀	Cre<C57 ♂<♀
Basal Rear	Veh:♂C57<♂ERT2 LSD,DOI,Psil:♀C57<♀ERT2 LSD,DOI:♀<♂	Veh:♂C57<♂ERT2 LSD,DOI,Psil:♀C57<♀ERT2 Veh:♀<♂ Psil:♂<♀ ♂ Psil<♂Veh,LSD	C57<242 ♀<♂	C57<242 ♀<♂	Cre<C57	Cre<C57
Basal Stereo	C57<ERT2	C57<ERT2	C57<242	C57<242	Veh,LSD,Psil:Cre<C57	Veh,LSD,Psil:Cre<C57
Stim Loco	DOI:C57<ERT2 Veh<LSD,DOI,Psil	DOI:C57<ERT2 Veh,Psil<LSD,DOI LSD<DOI	DOI:C57<242 Veh<LSD,DOI,Psil	DOI:C57<242 Veh<LSD,DOI LSD,Psil<DOI	LSD,DOI,Psil:♂Cre<♂C57 Psil:♀Cre<♀C57 ♂Veh<♂DOI	LSD,DOI,Psil:♂Cre<♂C57 Psil:♀Cre<♀C57 ♀Psil<♀DOI
Stim Rear	DOI:ERT2<C57 Veh,Psil<LSD,DOI	DOI:ERT2<C57 Veh,DOI,Psil<LSD Psil<DOI	Veh,Psil<LSD,DOI Psil<DOI	Veh<DOI LSD<DOI Psil<LSD,DOI	Veh,LSD,DOI,Psil:Cre<C57	Veh,LSD,DOI,Psil:Cre<C57
Stim Stereo	Veh<LSD Psil<LSD,DOI	Veh<LSD Psil<LSD,DOI	Veh<DOI,Psil Psil<DOI	Veh<DOI,Psil Psil<DOI	Veh,LSD,DOI,Psil:Cre<C57	Veh,LSD,DOI,Psil:Cre<C57 Psil<LSD
HTR	Veh<LSD,DOI,Psil	Veh<LSD,DOI Veh<Psil (p=0.051)	DOI:242<C57 Veh<LSD,DOI,Psil Psil<DOI	DOI:242<C57 Veh<LSD,DOI,Psil	LSD,DOI,Psil:Cre<C57 Veh<LSD,DOI,Psil	LSD,DOI,Psil:Cre<C57 Veh<LSD,DOI,Psil
Groom	DOI:♂ERT2<♂C57 Veh:♂<♀ ♂Veh<♂LSD,DOI ♂Psil<♂DOI ♂♀Psil<♂♀LSD	DOI:♂ERT2<♂C57 ♀Psil<♀Veh,LSD	Veh:C57<242 LSD,DOI:242<C57 Veh,Psil<LSD,DOI	Veh:C57<242 LSD,DOI:242<C57 LSD,DOI,Psil<Veh	LSD,DOI:Cre<C57 Veh,Psil<LSD,DOI	LSD,DOI:Cre<C57
Retro Walk	Veh<LSD,DOI,Psil Psil<DOI	Veh,Psil<LSD,DOI	LSD,DOI:242<C57 Veh<LSD,DOI,Psil Psil<DOI	LSD,DOI:242<C57	LSD,DOI,Psil:Cre<C57 Veh<LSD,DOI,Psil	LSD,DOI,Psil:Cre<C57
PPI	C57<ERT2 LSD,DOI,Psil<Veh	C57<ERT2 LSD,DOI,Psil<Veh	Veh,Psil:♂C57<♂242 Psil:♀C57<♀242 ♂LSD,DOI<♂Veh ♀LSD,DOI,Psil<♀Veh	Veh,Psil:♂C57<♂242 Psil:♀C57<♀242 Veh,LSD:♂<♀ ♂LSD,DOI,Psil<♂Veh ♀LSD<♀Psil	♂♀C57<♂♀Cre ♂C57<♀C57 Veh,LSD,DOI,Psil:C57<Cre LSD,DOI,Psil<Veh	♂♀C57<♂♀Cre ♂C57<♀C57 Veh,LSD,DOI,Psil:C57<Cre
Null	LSD,Psil:C57<ERT2 Veh<LSD,DOI Psil<DOI	LSD,Psil:C57<ERT2 Veh<LSD,DOI Psil<DOI	LSD,Psil:C57<242 Veh<LSD,DOI LSD,Psil<DOI	LSD,Psil:C57<242 Veh<LSD,DOI,Psil Psil<DOI	Veh:C57<Cre Veh<LSD,DOI LSD,Psil<DOI	Veh:C57<Cre Veh,Psil<DOI
Startle	Veh,LSD,Psil:ERT2<C57 LSD<Psil	Veh,LSD,Psil:ERT2<C57 Veh<DOI LSD<DOI,Psil	Veh:♂242<♂C57 Psil:♀242<♀C57 Psil:♀<♂ ♂LSD<♂DOI.Psil	Veh:♂242<♂C57 Psil:♀242<♀C57 Psil:♀<♂ ♂Veh<♂LSD,DOI,Psil	Veh,LSD,DOI,Psil:Cre<C57 LSD<Psil	Veh,LSD,DOI,Psil:Cre<C57

[a]Loco, locomotion; Rear, Rearing; Stereo, Stereotypy; HTR, head twitch response; groom, grooming; retro walk, retrograde walking; and PPI, prepulse inhibition.
[b]C57, C57BL/6J; ERT2, *Htr2a*$^{\text{EGFP-CT-IRES-CreERT2}}$; 242, *Htr2a*$^{\text{A242S-EGFP-CT-IRES-Cre}}$; Cre, *Htr2a*$^{\text{IRES-Cre}}$, Veh, vehicle; LSD, lysergic acid diethylamide; DOI, 2,5-dimethoxy-4-iodoamphetamine; Psil, psilocin; ♂, male; ♀, female.

Suppl. Table S7. Comparison of Cre- and CreERT2 lines.

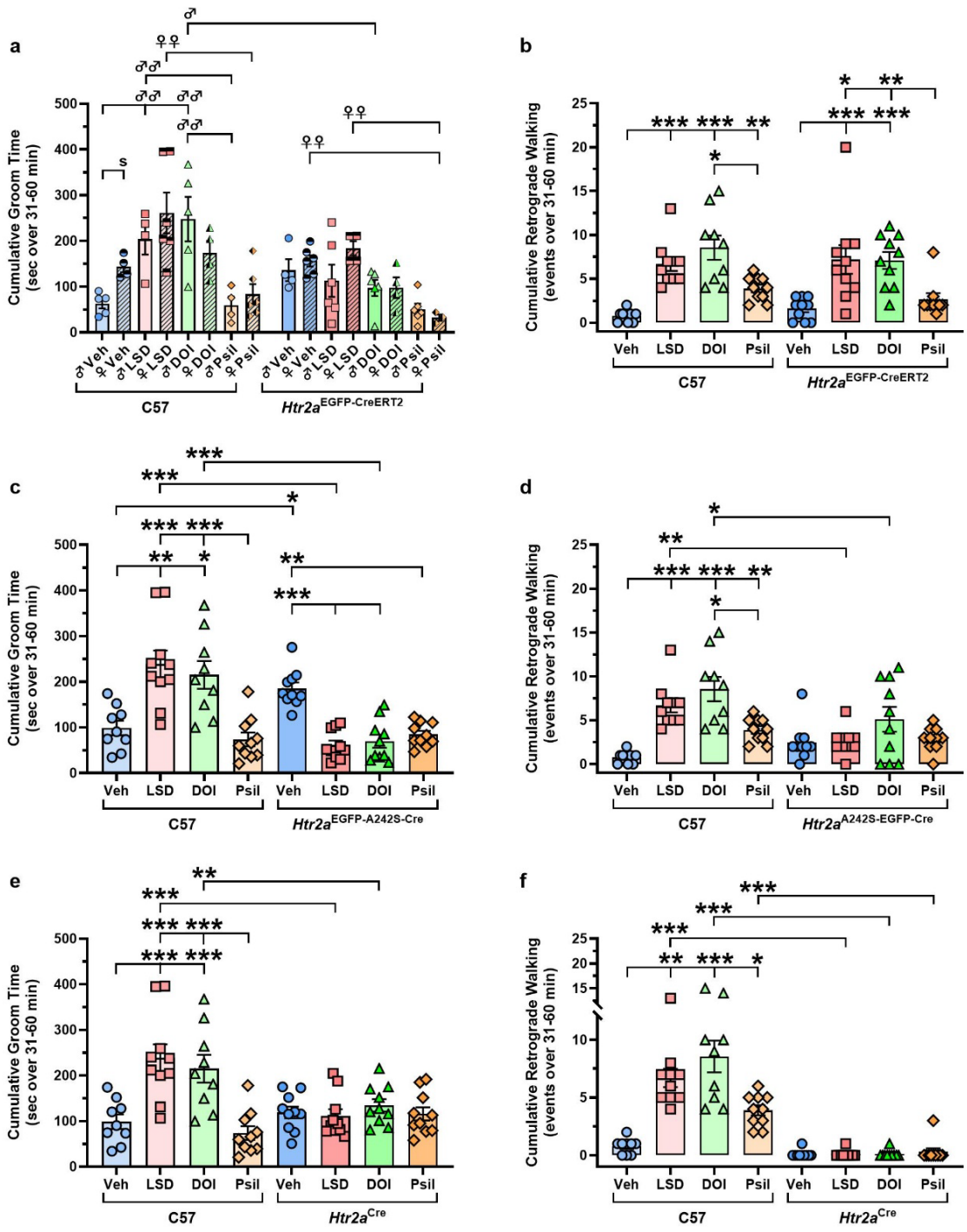
Cre driver	**Cre[a]**		**CreERT2[b]**	
Enzyme activity	Constitutive		Inducible by tamoxifen (TAM) nuclear translocation	
Cre spatial control	Promoter-dependent		Promoter-dependent	
Cre temporal control	No		Yes by TAM	
Cre-dependent reporter	*Transgenic (Ai9)*	*Virus (PHP.eB.FLEX-tdTomato)*	*Transgenic (Ai9)*	*Virus (PHP.eB.FLEX-tdTomato)*
(Cre-loxP recombination): temporal control	No	Yes by viral reporter	Yes by TAM	Yes by TAM + viral reporter
Recombination efficiency	higher		Variable by TAM (dose/ injection times/incubation time)	
Reporter (tdT) labeling	Developmental or adult expression	Region- and time-limited by injection site/time	distribution by TAM induction	Region- and time-limited by TAM and injection site/time
specificity to HTR2A pattern	Poor specificity (Reporter marks both transient and adult HTR2A+ cells)	Moderate to good depending on virus	good	Moderate to good depending on virus
Notes	1. Robust Cre efficiency 2. Useful for lineage tracing 3. Not differentiate developmental and adult HTR2A+ cells	1. Viral injection control 2. Varies by AAV tropism/transfection efficiency/incubation time	1. Variable by TAM 2. Good for HTR2A+ labeling at any age	1. Control by TAM (but less efficient recombination) 2. Control by virus (AAV tropism/ transfection efficiency/incubation time)

[a]Cre lines (*Htr2a*^{Cre} and *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$); [b]CreERT2 line (*Htr2a*$^{EGFP\text{-}CreERT2}$).



Suppl. Fig. S1. Baseline locomotor, rearing, and stereotypical activities of C57, *Htr2a*$^{\text{EGFP-CreERT2/EGFP-CreERT2}}$, *Htr2a*$^{\text{A242S-EGFP-Cre/A242S-EGFP-Cre}}$, and *Htr2a*$^{\text{Cre/Cre}}$ mice. Adult male and female C57 and *Htr2a* knock-in mice were placed into the open field for 30 min to collect baseline motor activities. Note, to reduce mouse numbers results from the same C57 mice are presented in each panel for comparisons to the transgenics. **a-c**, Comparisons of baseline locomotion, rearing, and stereotypy in C57 and *Htr2a*$^{\text{EGFP-CreERT2/EGFP-CreERT2}}$ mice. **d-f**, Respective baseline locomotor, rearing, and stereotypical activities in C57 and *Htr2a*$^{\text{A242S-EGFP-Cre/A242S-EGFP-Cre}}$ mice. **g-l**, Baseline locomotor, rearing, and stereotypical comparisons between C57 and *Htr2a*$^{\text{Cre/Cre}}$ mice. In panels a-c, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57

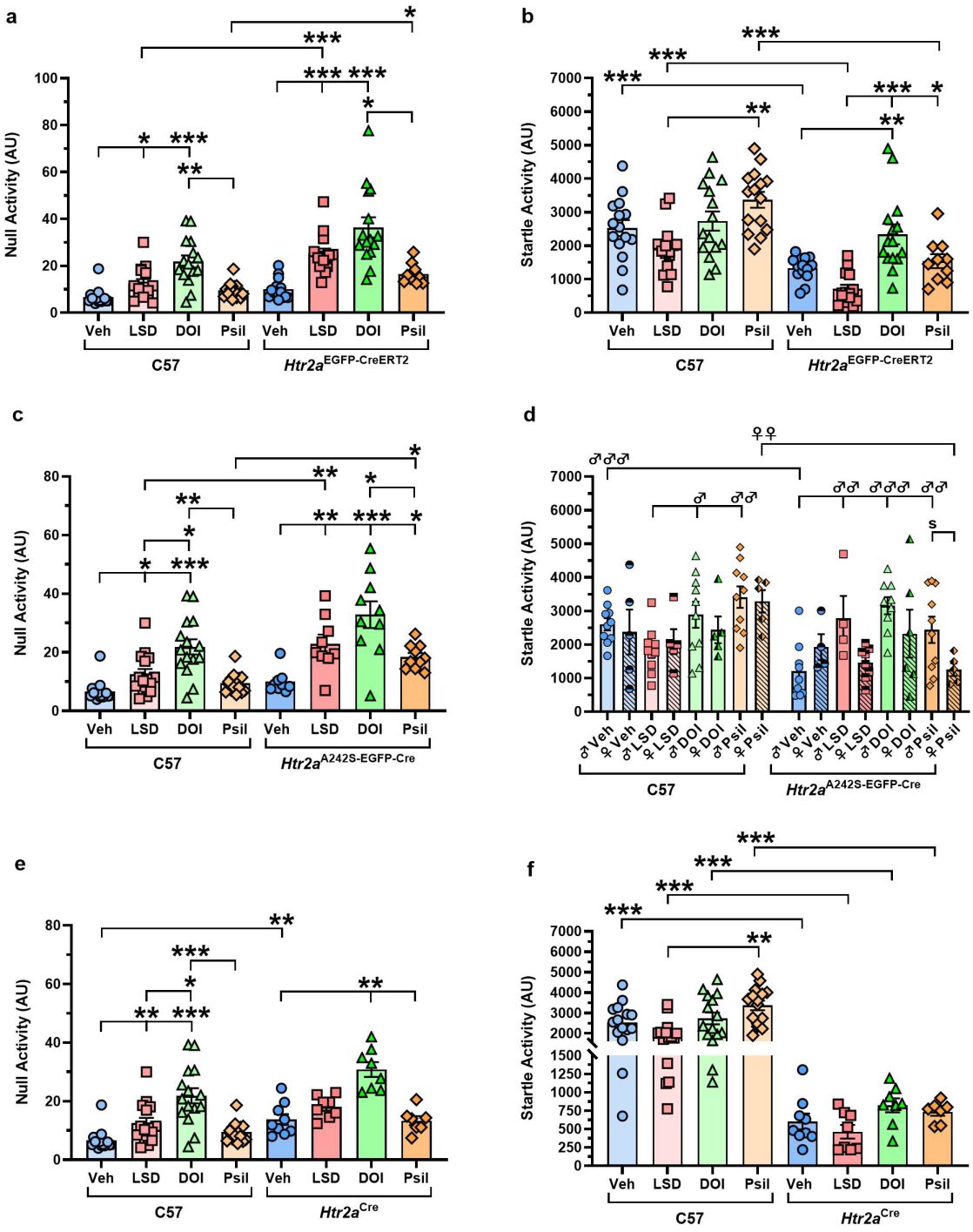
males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*$^{EGFP\text{-}CreERT2}$ males – 4, 6, 6, 6; *Htr2a*$^{EGFP\text{-}CreERT2}$ females – 6, 4, 4, 3. In panels d-f, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$ males – 7, 6, 6, 6; *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$ females – 3, 4, 4, 4. In panels g-i, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*^{Cre} males – 6, 6, 6, 6; *Htr2a*^{Cre} females – 4, 4, 4, 4. All data are presented as means ±SEMs; data in panels a, b, d, f, and g were analyzed by three-way ANOVA, and panels c, e, h, and I by Mann-Whitney and Kruskal-Wallis, the latter were followed with Bonferroni tests; $^{s}p<0.05$, $^{ss}p<0.01$, male *vs.* female; ♂$p<0.05$, ♂♂$p<0.01$, ♂♂♂$p<0.001$, between genotypes or between/among treatments within males; ♀$p<0.05$, ♀♀$p<0.01$, , between genotypes or between/among treatments within females; all other significant effects are presented as *$p<0.05$, **$p<0.01$, ***$p<0.001$, between and within genotypes and treatment as indicated in each comparison. The numbers of mice according to genotype, sex, and treatment, as well as the statistics are presented in respective Supplementary Tables S3 and S4.



Suppl. Fig. S2. Pharmacological effects of psychedelics (LSD, DOI, and Psilocin) on grooming and retrograde walking in C57, *Htr2a*$^{EGFP\text{-}CreERT2/EGFP\text{-}CreERT2}$, *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre/A242S\text{-}EGFP\text{-}Cre}$, and *Htr2a*$^{Cre/Cre}$ mice. Adult male and female C57 and *Htr2a* knock-

in mice were placed into the open field for baseline motor activities (30 min), administered the vehicle or different psychedelics, and returned to the open field for 90 min (31-120 min). Grooming and retrograde walking were evaluated over the first 30-min post administration. Note, to reduce mouse numbers results from the same C57 mice are presented in each panel for comparisons to the transgenics. **a-b,** Effects of 0.3 mg/kg LSD, 1 mg/kg DOI, and 1 mg/kg psilocin on grooming (a) and retrograde walking (b) in C57 (*Htr2a*$^{+/+}$) and *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre/A242\text{-}EGFP\text{-}Cre}$ mice. **c-d,** Psychedelic effects on grooming (c) and retrograde walking (d) in C57 and *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre/A242S\text{-}EGFP\text{-}Cre}$ mice. **e-f**, Effects of psychedelics on grooming (e) and retrograde walking (f) in C57 and *Htr2a*$^{Cre/Cre}$ mice. In panels a-b, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*$^{EGFP\text{-}CreERT2}$ males – 4, 6, 6, 6; *Htr2a*$^{EGFP\text{-}CreERT2}$ females – 6, 4, 4, 3. In panels c-d, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$ males – 7, 6, 6, 6; *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre}$ females – 3, 4, 4, 4. In panels e-f, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*^{Cre} males – 6, 6, 6, 6; *Htr2a*^{Cre} females – 4, 4, 4, 4. All data are presented as means ±SEMs; the data were analyzed by Mann-Whitney U and Kruskal-Wallis, the latter followed with Bonferroni tests; $^{s}p<0.05$; male *vs.* female; $^{♂}p<0.05$, $^{♂♂}p<0.01$, between genotypes or between/among treatments within males; $^{♀♀}p<0.01$, between genotypes or between/among treatments within females; all other significant effects are presented as $*p<0.05$, $**p<0.01$, $***p<0.001$, between and within genotypes and treatments as indicated in each comparison. The numbers of mice according to genotype, sex, and

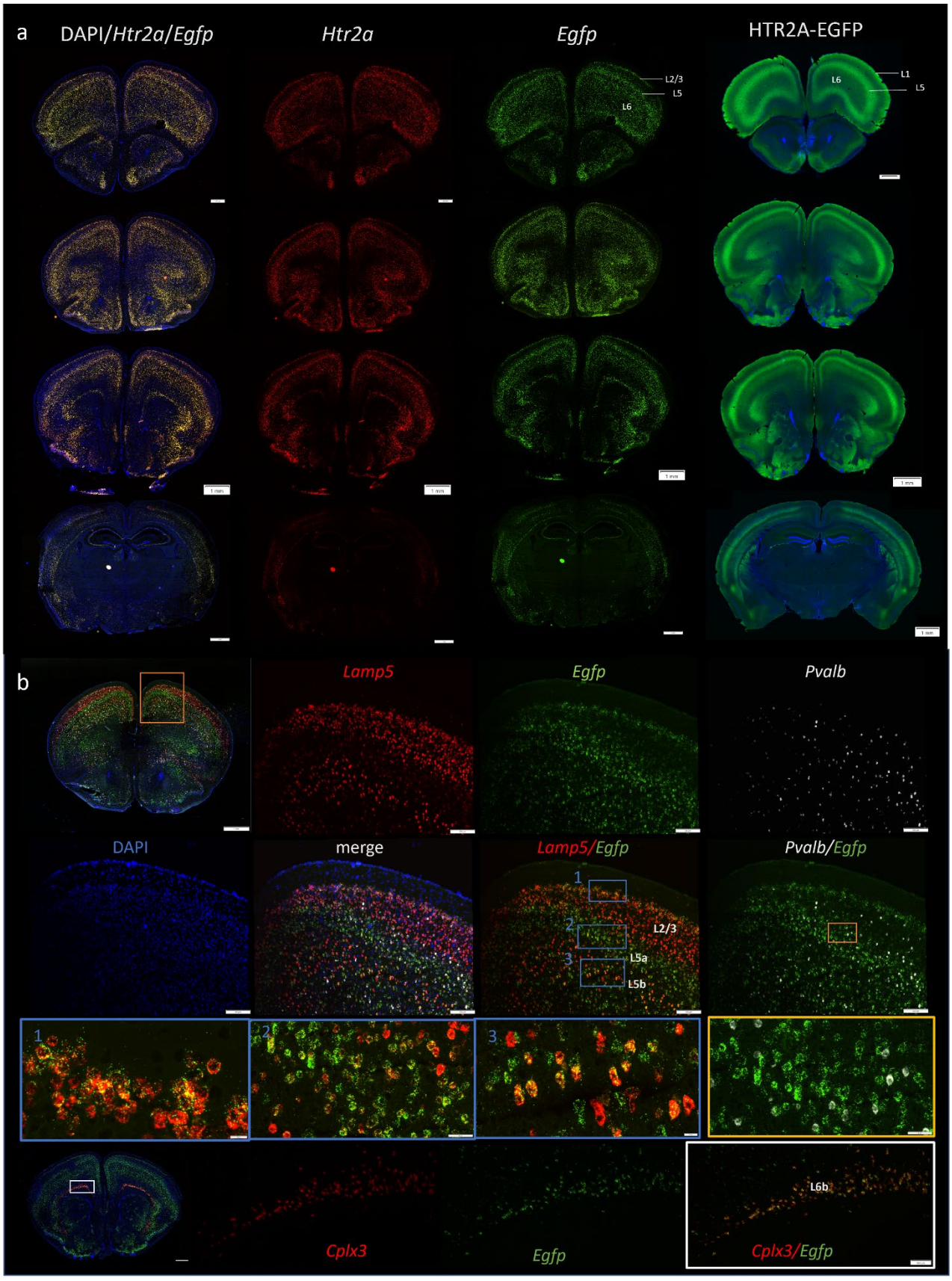
treatment, as well as the statistics are presented in respective Supplementary Tables S3 and S4.



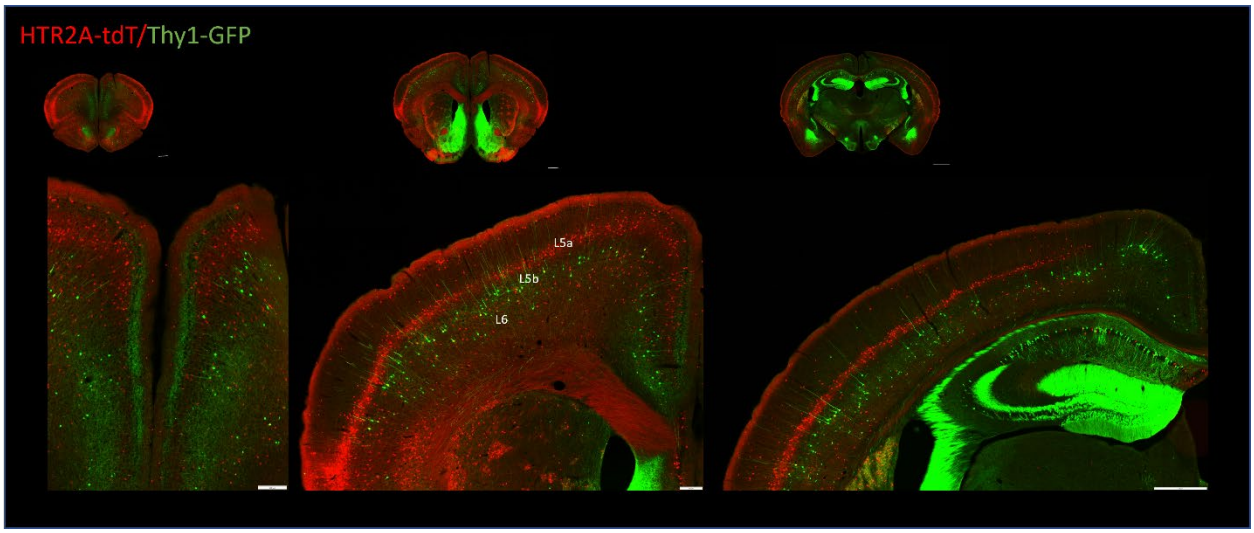
Suppl. Fig. S3. Pharmacological effects of psychedelics (LSD, DOI, and Psilocin) on null and startle activities in prepulse inhibition with C57, *Htr2a*$^{EGFP\text{-}CreERT2/EGFP\text{-}CreERT2}$, *Htr2a*$^{A242S\text{-}EGFP\text{-}Cre/A242S\text{-}EGFP\text{-}Cre}$, and *Htr2a*$^{Cre/Cre}$ mice. These null and startle

activities data are companions to the prepulse inhibition results in Figure 4, Extended Data Figure 7, and Extended Data Figure 9, respectively. Adult male and female C57 and *Htr2a* knock-in mice were injected with the Veh, 0.3 mg/kg LSD, 1 mg/kg DOI, or 1 mg/kg Psil and tested 30 min in prepulse inhibition. Note, to reduce mouse numbers results from the same C57 mice are presented in each panel for comparisons to the transgenics. **a-b,** Effects of LSD, DOI, and psilocin on null (a) and startle activity (b) in C57 (*Htr2a*$^{+/+}$) and *Htr2a*$^{\text{A242S-EGFP-Cre/A242-EGFP-Cre}}$ mice. **c-d,** Psychedelic effects on null (c) and startle activities (d) in C57 and *Htr2a*$^{\text{A242S-EGFP-Cre/A242S-EGFP-Cre}}$ mice. **e-f**, Effects of psychedelics on null (e) and startle activities (f) in C57 and *Htr2a*$^{\text{Cre/Cre}}$ mice. In panels a-b, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*$^{\text{EGFP-CreERT2}}$ males – 4, 6, 6, 6; *Htr2a*$^{\text{EGFP-CreERT2}}$ females – 6, 4, 4, 3. In panels c-d, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*$^{\text{A242S-EGFP-Cre}}$ males – 7, 6, 6, 6; *Htr2a*$^{\text{A242S-EGFP-Cre}}$ females – 3, 4, 4, 4. In panels e-f, the numbers of mice by genotype, sex, and treatment (Veh, LSD, DOI, Psil) are: C57 males – 5, 4, 5, 4; C57 females – 4, 6, 4, 6; *Htr2a*$^{\text{Cre}}$ males – 6, 6, 6, 6; *Htr2a*$^{\text{Cre}}$ females – 4, 4, 4, 4. All data are presented as means ±SEMs; the data were analyzed by Mann-Whitney U and Kruskal-Wallis, the latter followed with Bonferroni tests; $^{s}p<0.05$; male *vs.* female; $^{♂}p<0.05$, $^{♂♂}p<0.01$, $^{♂♂♂}p<0.001$ between genotypes or between/among treatments within males; $^{♀♀}p<0.01$, between genotypes or between/among treatments within females; all other significant effects are presented as $*p<0.05$, $**p<0.01$, $***p<0.001$, between and within genotypes and treatment as indicated in each comparison. The numbers of mice

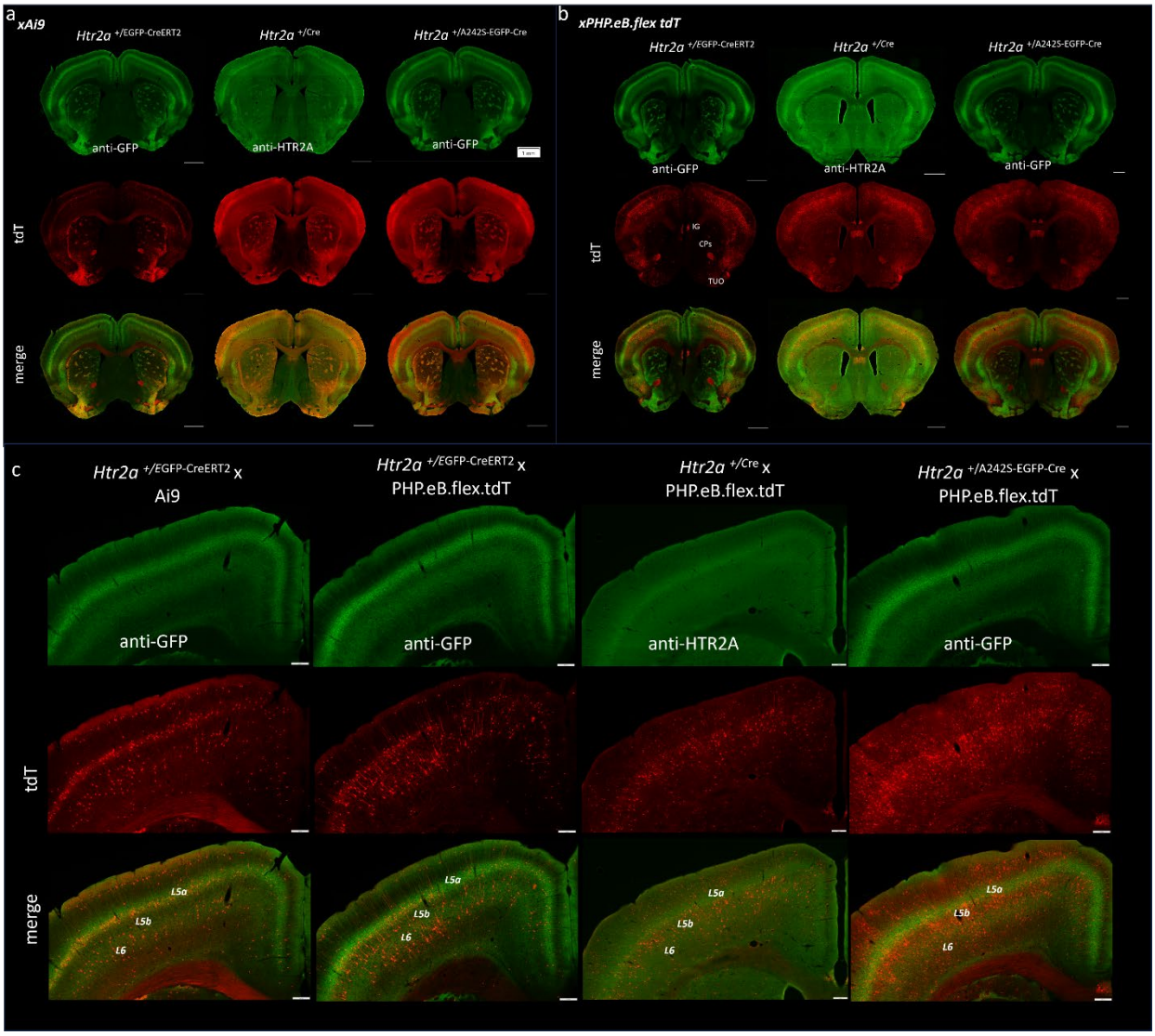
according to genotype, sex, and treatment, as well as the statistics are presented in respective Supplementary Tables S3 and S4.


a
DAPI/Htr2a/Egfp
Htr2a
Egfp
HTR2A-EGFP
L2/3
L5
L6
L1
L6
L5
b
Lamp5
Egfp
Pvalb
DAPI
merge
Lamp5/Egfp
Pvalb/Egfp
1
2
3
L2/3
L5a
L5b
Cplx3
Egfp
L6b
Cplx3/Egfp

Suppl. Fig. S4. *Htr2a* mRNA distribution. **a**, RNAscope was used to detect *Htr2a* and *Egfp* transcripts in *Htr2a*$^{EGFP\text{-}CreERT2/EGFP\text{-}CreERT2}$ mice. Brain sections were stained also with an anti-GFP antibody to detect the HTR2A-EGFP-CT fusion protein. Experiments were conducted with 4 animals containing similar results. Images were taken under a 10X objective using an Olympus VS120 slide-scanner (scale bar 1 mm). **b**, In the motor cortex, *Egfp* transcripts were co-localized with *Lamp5* in L2/3 and L5b, and with *parvalbumin (Pvalb)*-positive interneurons. *Cplx3* as a L6b marker showed its co-localization with *Egfp* transcripts. Images were taken under 10X objective with an Olympus VS120 slide-scanner and under a 20X objective with an Olympus FV3000RS confocal microscope. Experiments were conducted with 3 animals achieving similar results.

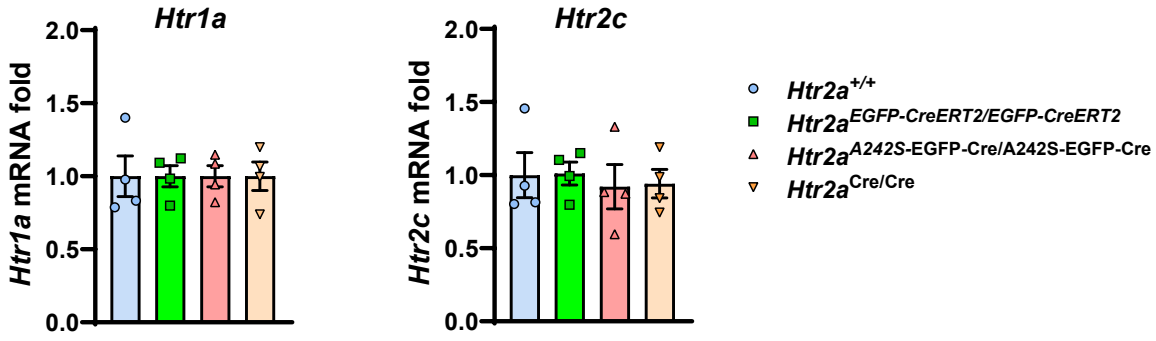


Suppl. Fig. S5. The distribution of HTR2A-containing neurons and Thy1-expressing neurons. Since HTR2A-EGFP-CT fluorescence is very dim without antibody amplification, it was difficult to directly detect. Thus, in this experiment we used tdTomato to label HTR2A-containing neurons and Thy1-GFP to observe their distribution in the cerebral cortex. *Htr2a*$^{+/EGFP\text{-}CreERT2}$ x Ai9 x *Thy1*$^{+/GFP}$ mice were treated with tamoxifen (100 mg/kg for 4 days) to induce tdTomato expression. Images were captured using an Olympus slide-scanner with 10X objective. The experiments were conducted on 3 brains with similar results.



Suppl. Fig. S6. Comparison of different Cre-dependent reporters (Ai9 mice *vs*. PHP.eB.FLEX.tdT AAV virus) among the three *Htr2a* Cre/CreERT2-driver lines. Mice were perfused and then stained with anti-HTR2A for *Htr2a*$^{+/Cre}$ mice or with anti-GFP for *Htr2a*$^{+/EGFP\text{-}CreERT2}$ and *Htr2a*$^{+/A242S\text{-}EGFP\text{-}Cre}$ mice. Images were captured in two channels for tdTomato (*red*) and anti-HTR2A or anti-GFP (*green*) signals using an Olympus slide-scanner with a 10X objective. (CPs: striosome, TUO: olfactory tubercle, IG: induseum griseum). **a**, The distribution patterns of the Cre-dependent tdTomato reporter from *Htr2a*$^{+/EGFP\text{-}CreERT2}$ x Ai9, *Htr2a*$^{+/Cre}$ x Ai9, and *Htr2a*$^{+/A242S\text{-}EGFP\text{-}Cre}$ x Ai9 mice. **b**,

Htr2a$^{+/EGFP\text{-}CreERT2}$, *Htr2a*$^{+/Cre}$, and *Htr2a*$^{+/A242S\text{-}EGFP\text{-}Cre}$ mice that were retro-orbitally injected with PHP.eB.FLEX.tdTomato virus. **c**, Comparisons of tdTomato patterns in the somatosensory cortex from *Htr2a*$^{+/EGFP\text{-}CreERT2}$ x Ai9, *Htr2a*$^{+/EGFP\text{-}CreERT2}$ x PHP.eB.FLEX.tdT, *Htr2a*$^{+/Cre}$ x PHP.eB.FLEX.tdT, and *Htr2a*$^{+/A242S\text{-}EGFP\text{-}Cre}$ x PHP.eB.FLEX.tdT mice. The experiments were conducted with 3-4 brains from each group with similar results.



Suppl. Fig. S7. *Htr1a* and *Htr2c* mRNA levels in cerebral cortex from C57 and different genotypes of HTR2A knock-in mice. Real-time qPCR was used to determine the *Htr1a* and *Htr2c* mRNA levels from whole cerebral cortex from *Htr2a*$^{+/+}$ (C57), *Htr2a*$^{Cre/Cre}$, *Htr2a*$^{EGFP-CreERT2/EGFP-CreERT2}$, and *Htr2a*$^{A242S-EGFP-Cre/A242S-EGFP-Cre}$ mice. Data are shown as means ±SEMs, the statistics are presented in Suppl. Table S4; n=4 samples/genotype; the data were analyzed by one-way ANOVA. The statistics are presented in Suppl. Table S4.