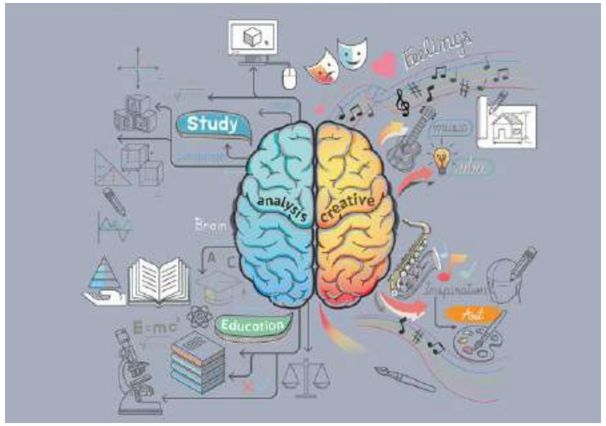
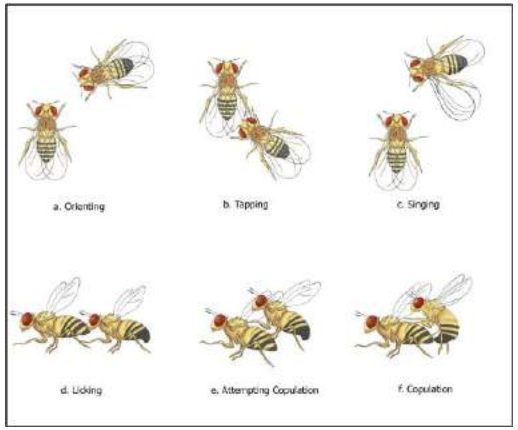
Contribution of the serotonergic system in model animals

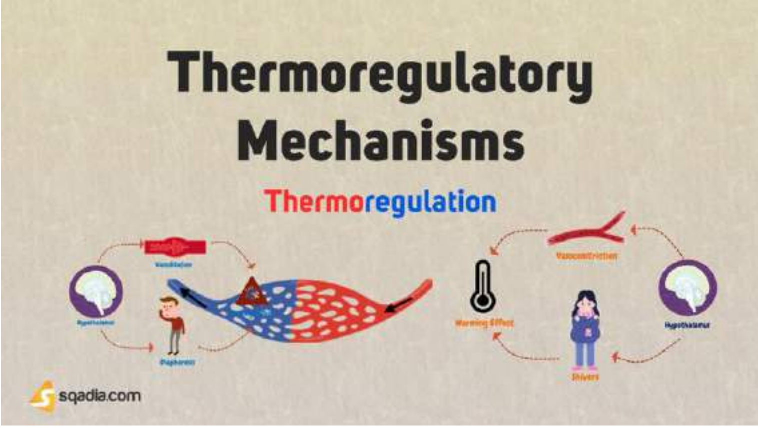
姜思梅　张兆琨　李子奇

2024.06.27

Biogenic Amines (BA)







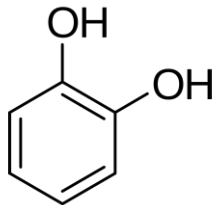
What is biogenic amines？

- Biogenic amines are nitrogenous organic bases of low molecular weight with biological functions in animals, plants, microorganisms and humans.
- Their formation is the result of the breakdown of free amino acids by amino acid decarboxylase.

Classification（chemical structure）：

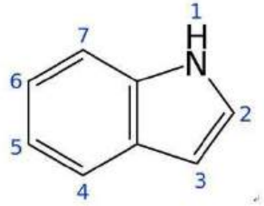
- Catecholamines 儿茶酚胺

多巴胺、去甲肾上腺素、肾上腺素



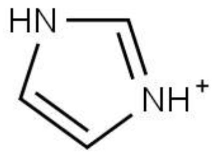
- Indolethylamines 吲哚胺

5-羟色胺



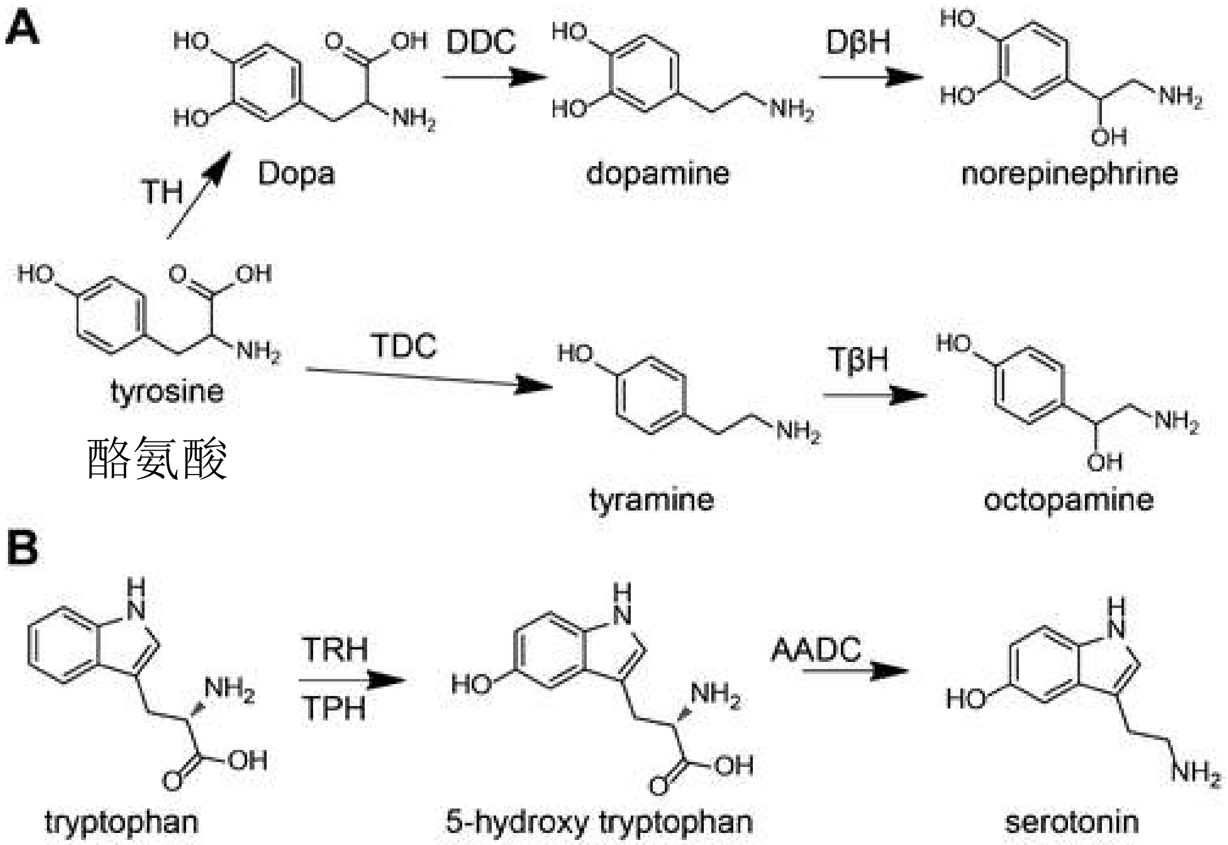
- Imidazoleethylamines 咪唑胺

组胺



Biosynthetic pathway of biogenic amines

dopamine、octopamine、tyramine、serotonin、histamine



色胺酸

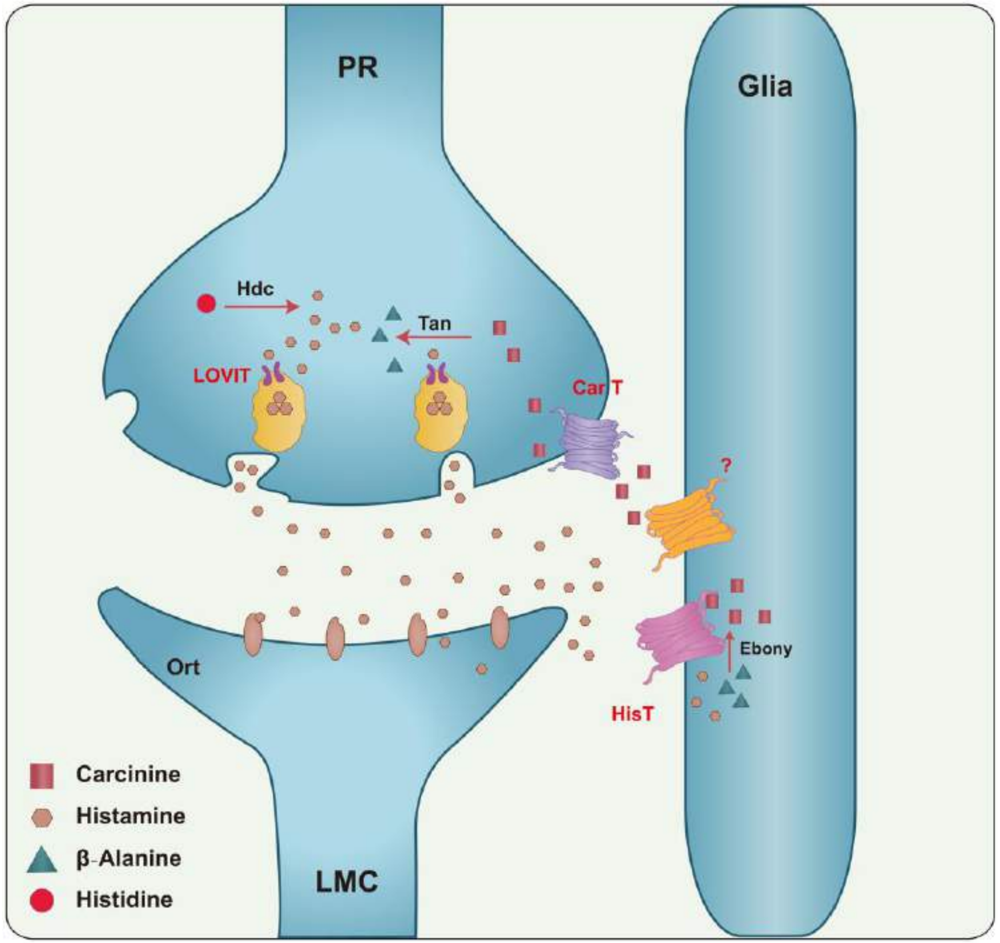
5-羟色胺酸

Monoamine	Gene name	*Drosophila melanogaster*	*Caenorhabditis elegans*
Dopamine	Tyrosine hydroxylase (TH)	*pale*	*cat-2*
	Tetrahydrobiopterin (BH_4)	*Punch*	—
	Aromatic amino acid decarboxylase (AADC)	*Ddc*	*bas-1*
	Vesicular monoamine transporter (VMAT)	*Vmat*	*cat-1*
	Catecholamines up	*Catsup*	—
	Dopamine Transporter (DAT)	*Fumin*	*dat-1*
Serotonin	Tryptophan hydroxylase (TPH)	*Trh*	*tph-1*
	DDC, also known as AADC	*Ddc*	*bas-1*
	Serotonin Transporter	*SERT*	*mod-5*
Tyramine	Tyrosine decarboxylase (TDC)	*Tdc*	*tdc-1*
Octopamine	Tyramine β -hydroxylase	*Tbh*	*tbh-1*
Histamine	Histidine decarboxylase	*Hdc*	—
	Histidine transporter	*Tadr*	—
	Putative synaptic vesicular transporter	*lovit*	—
	Carcinine Transporter	*CarT*	—
	N-β-alanyl dopamine synthase	*ebony*	—
	β-alanyl histamine hydrolase	*tan*	—

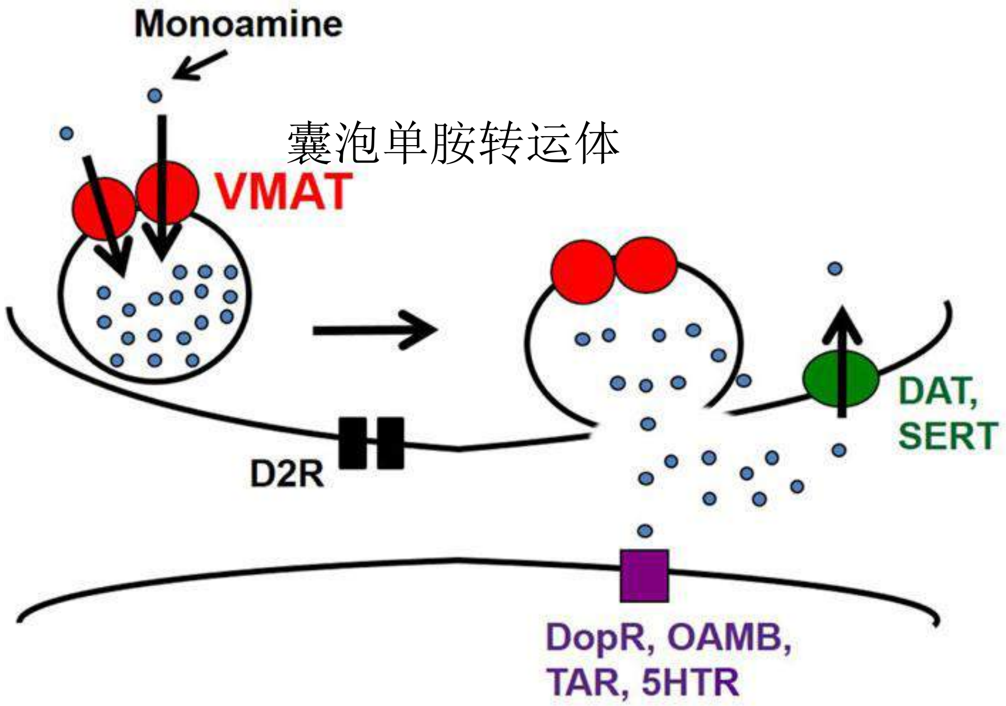
Huang J, et al. *ACS Symp Ser*. 2017

Rosikon KD, et al. *Front Physiol*. 2023

Synaptic release in a monoaminergic neuron

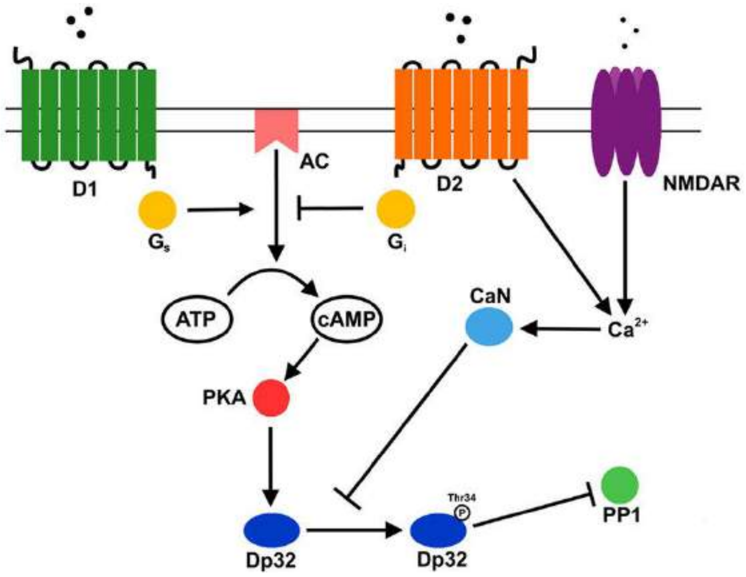


Xie J, et al. *Sci Adv*. 2022



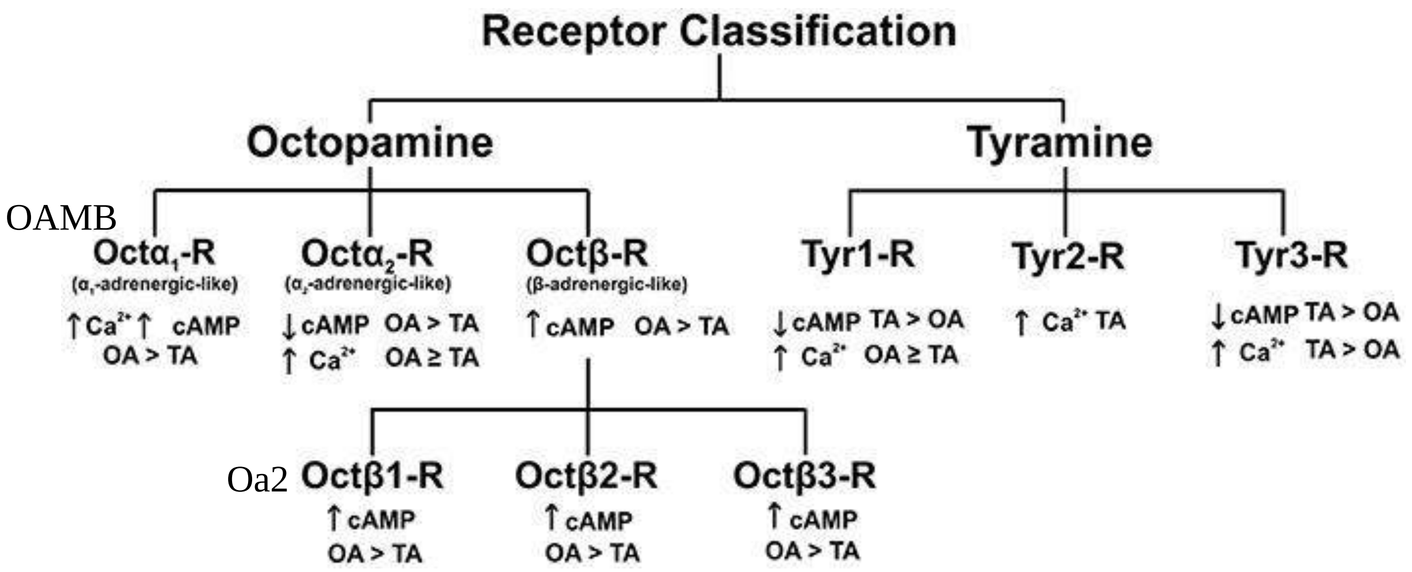
Rosikon KD, et al. *Front Physiol*. 2023

Classification of biogenic amine receptors in *Drosophila*



dopamine receptor

Avanes A, et al. *Biochem Pharmacol*. 2019



octopamine and tyramine receptor

Hana S, et al. *Front Physiol*. 2017

HA receptor { HisCl1, Ort }

Contribution of the serotonergic system in model animals

1、A brief introduction of the serotonergic system in *Drosophila*

— 姜思梅

2、The regulation of different behaviors by serotonin in *Drosophila*

— 张兆琨

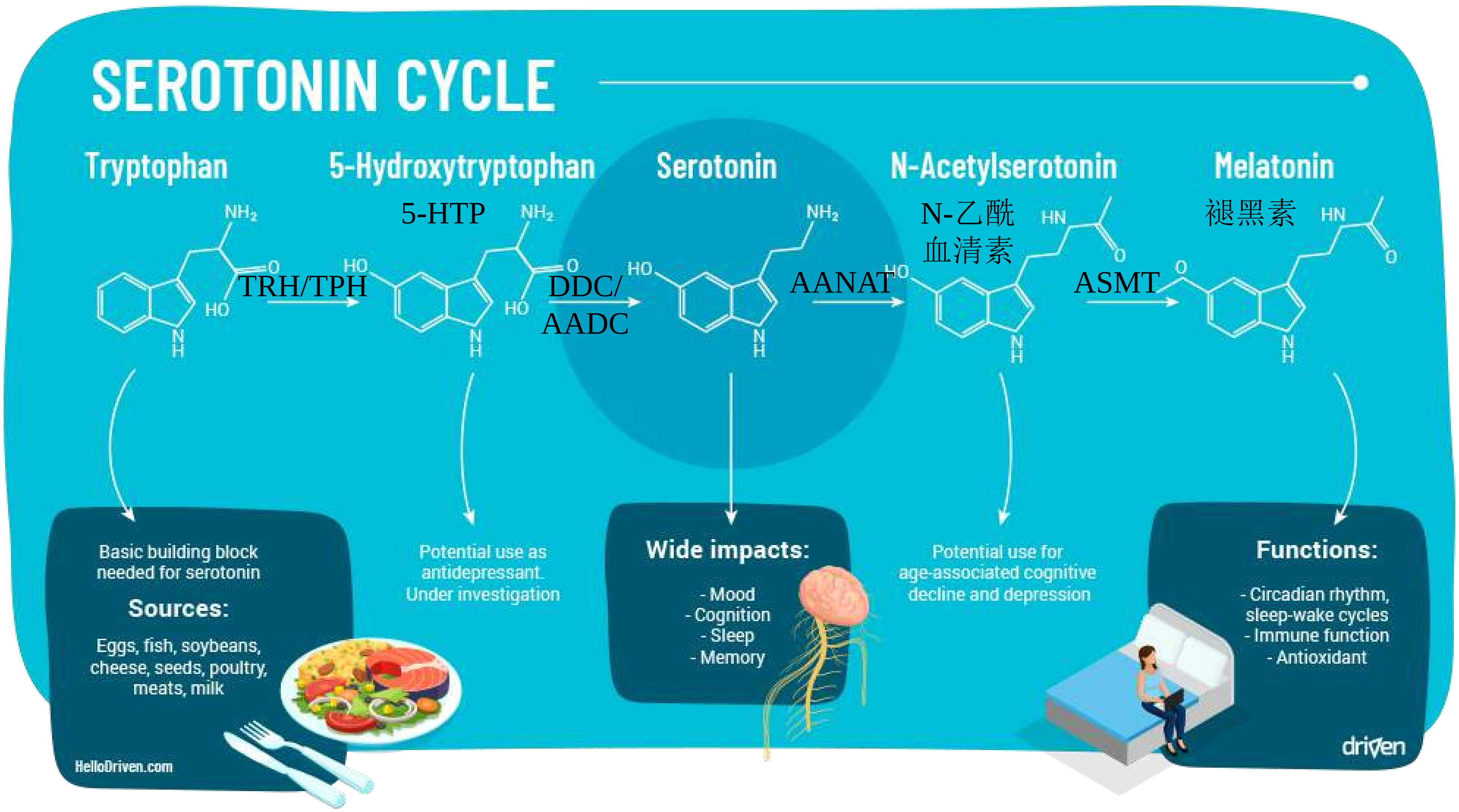
3、Serotonin and disease treatment in animal models

— 李子奇

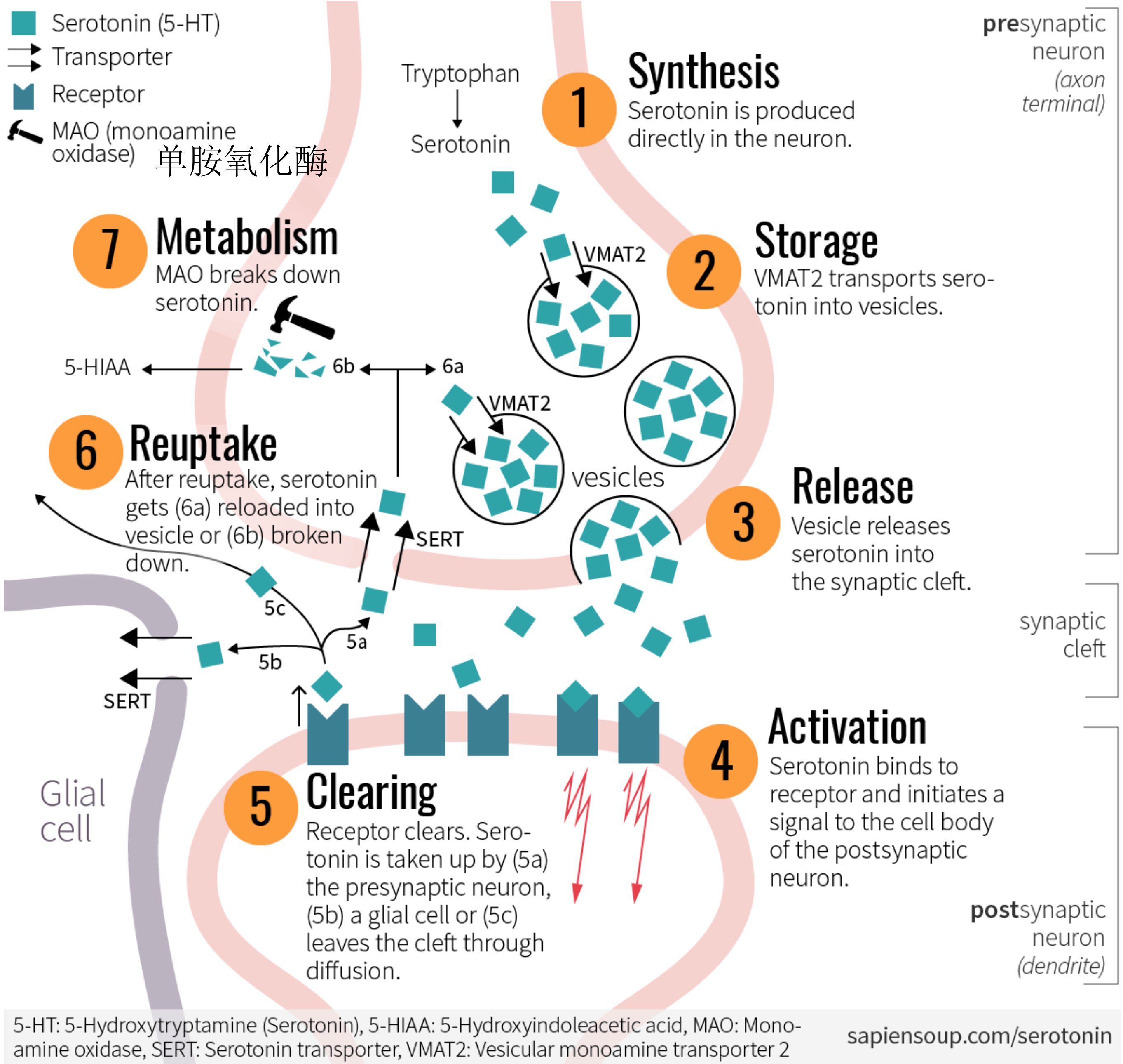
A brief introduction of the serotonergic system in *Drosophila*

- How is serotonin synthesized and acts in vivo?
- What is the mechanism and significance of serotonin recycling?
- How does the serotonergic system interact with other aminergic systems?

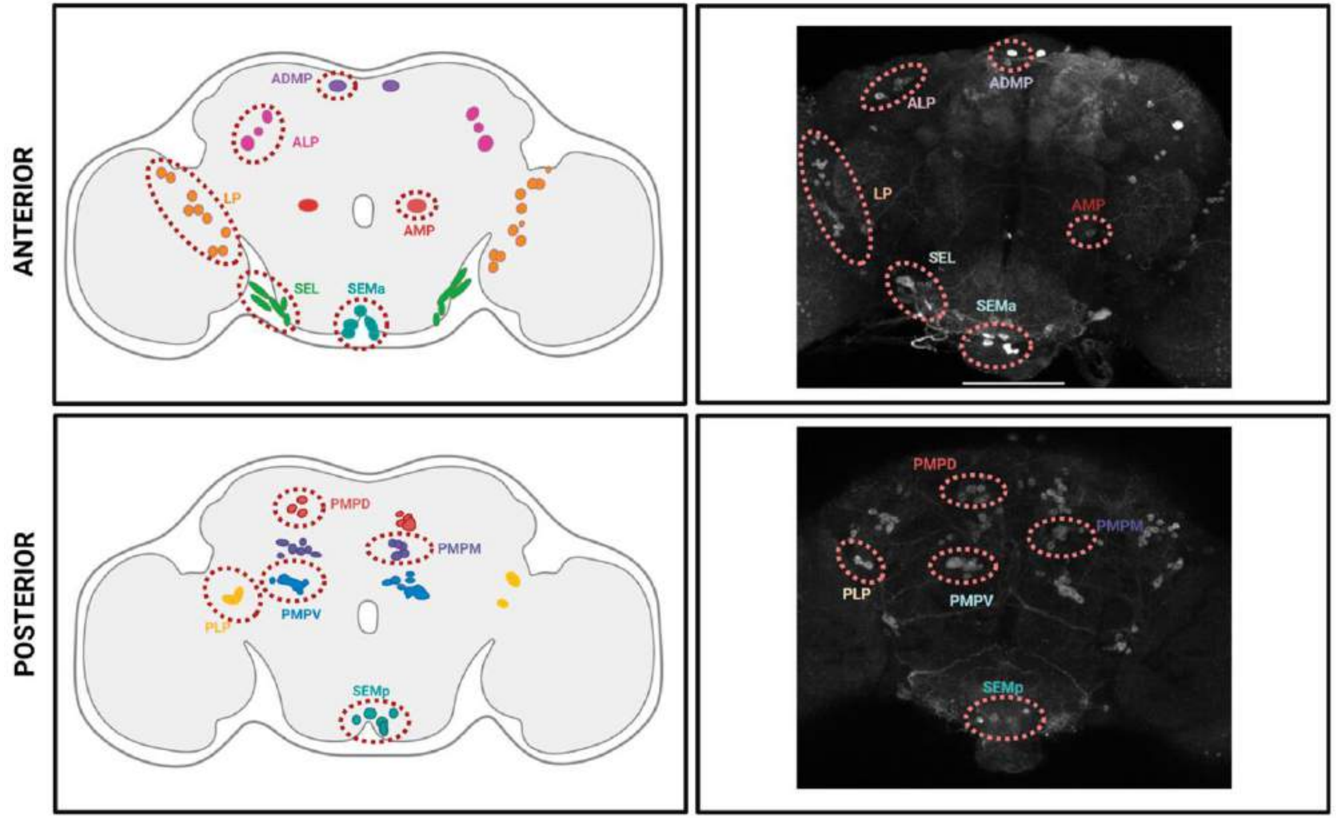
The pathway of serotonin synthesis



The pathway of serotonin function



A map of 5-HT neuron clusters in the central brain



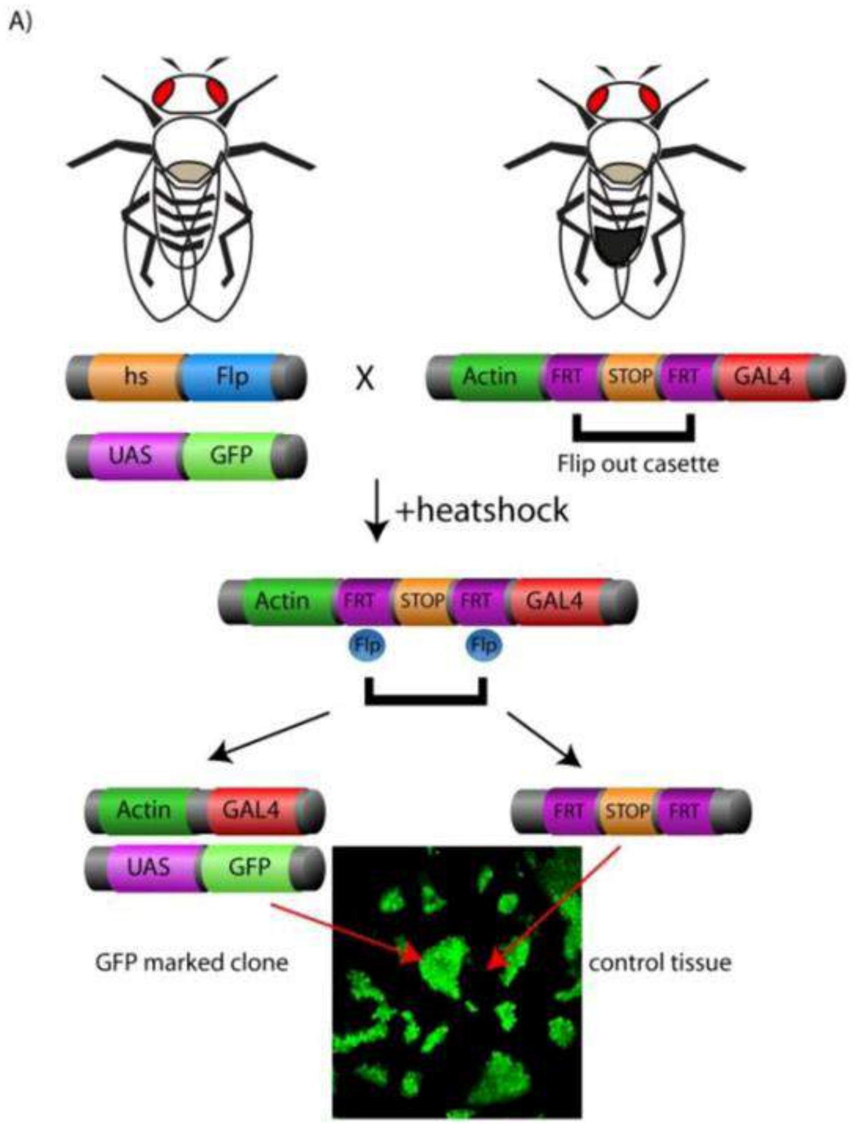
Gajardo I, et al. *Int J Mol Sci*. 2023

5-HT cell cluster	5-HT-positive
ALP	6 ± 0
AMP	2 ± 0
ADMP	2 ± 0
LP	24 ± 3
SEL	10 ± 2
SEM	10 ± 3
PLP	4 ± 0
PMPD	6 ± 0
PMPM	13 ± 2
PMPV	14 ± 3
$\sum$ 5-HT neurons	91 ± 13

Pooryasin A, et al. *J Neurosci*. 2015

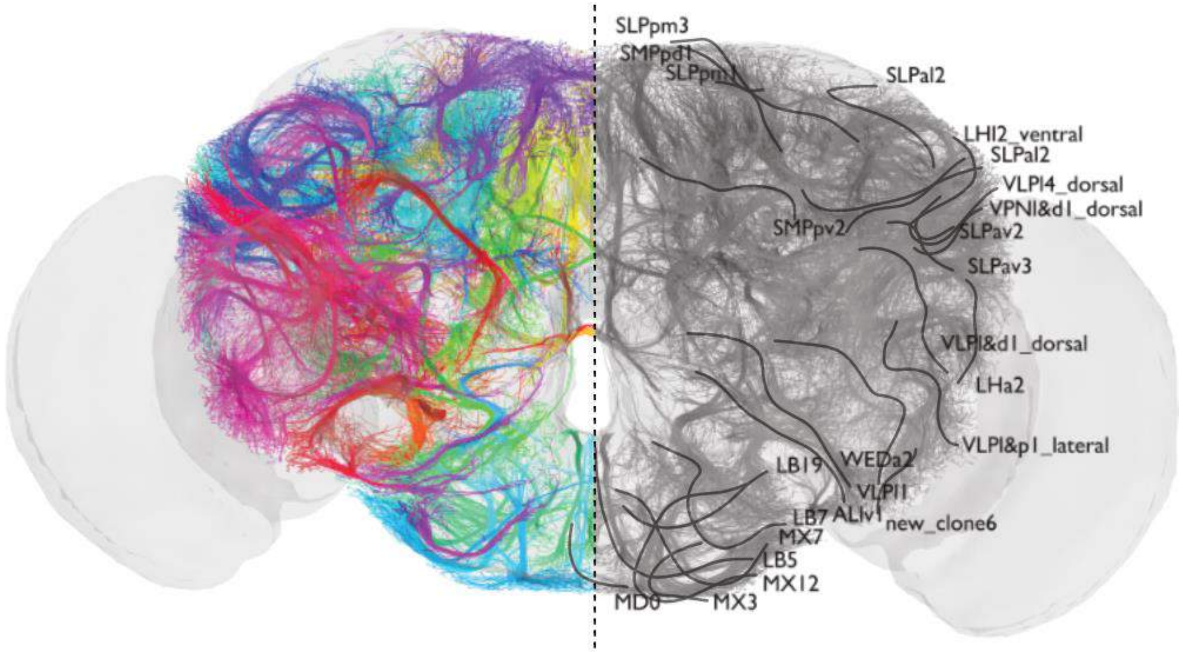
- The adult fly brain contains ~90 serotonin-releasing neurons, and that 11 neuronal populations can be distinguished per hemisphere.

A map of 5-HT neuron clusters in the central brain



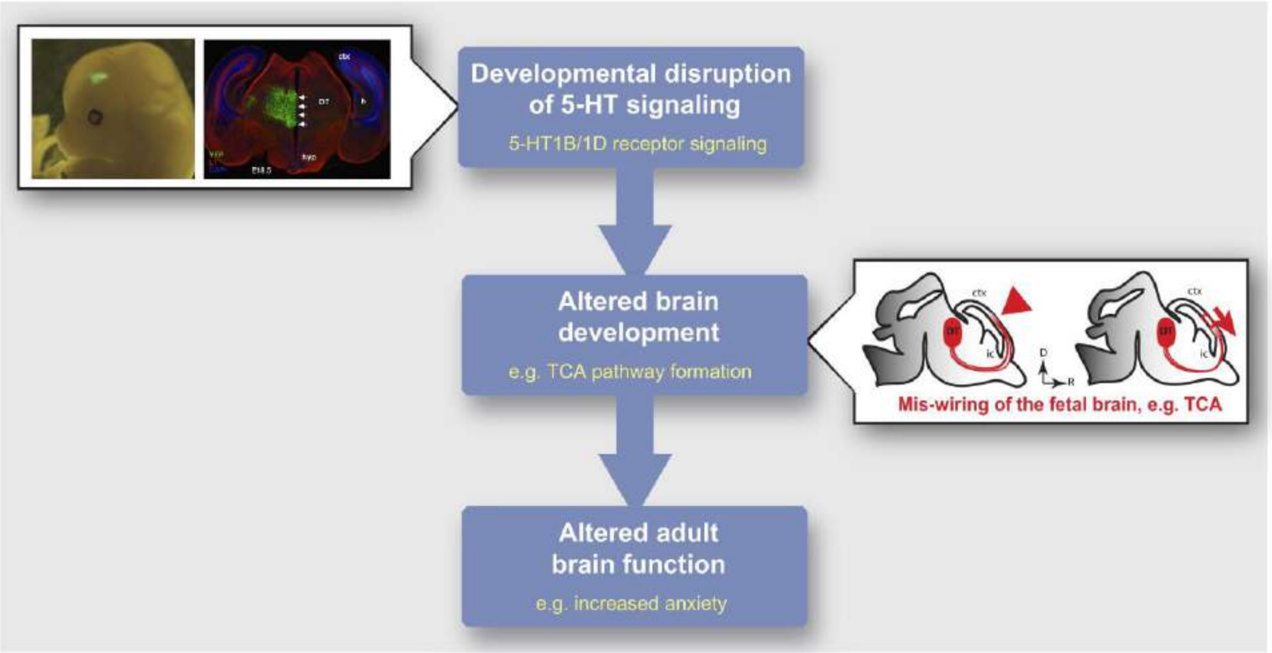
FLP-out system

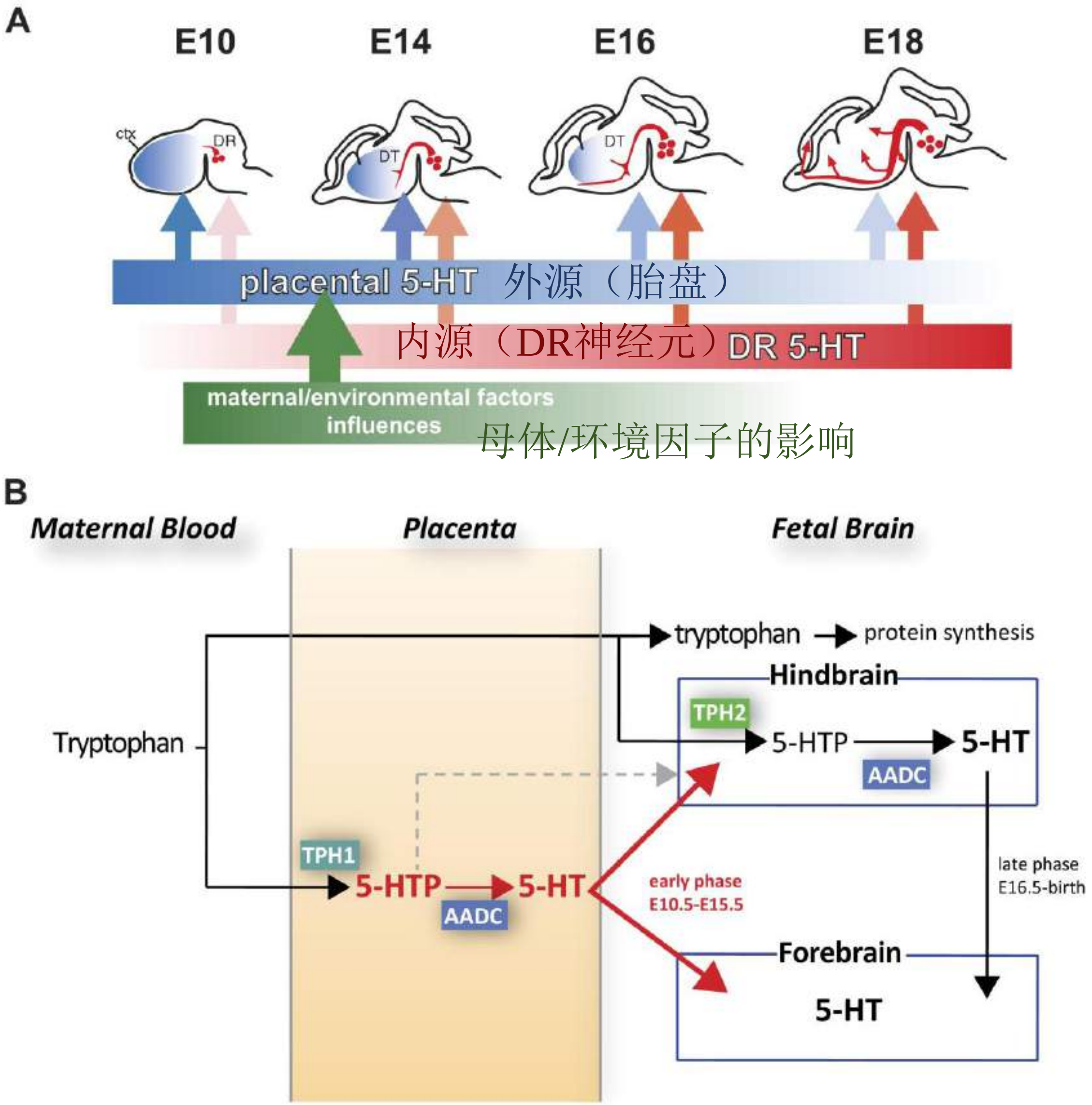
- They can label a smaller number of neurons and even achieve single neuron accuracy, better characterizing serotonergic neuronal projection.



Drosophila brain connectome

Serotonin is acting not only as a classical neurotransmitter, but also as a neurotrophic factor

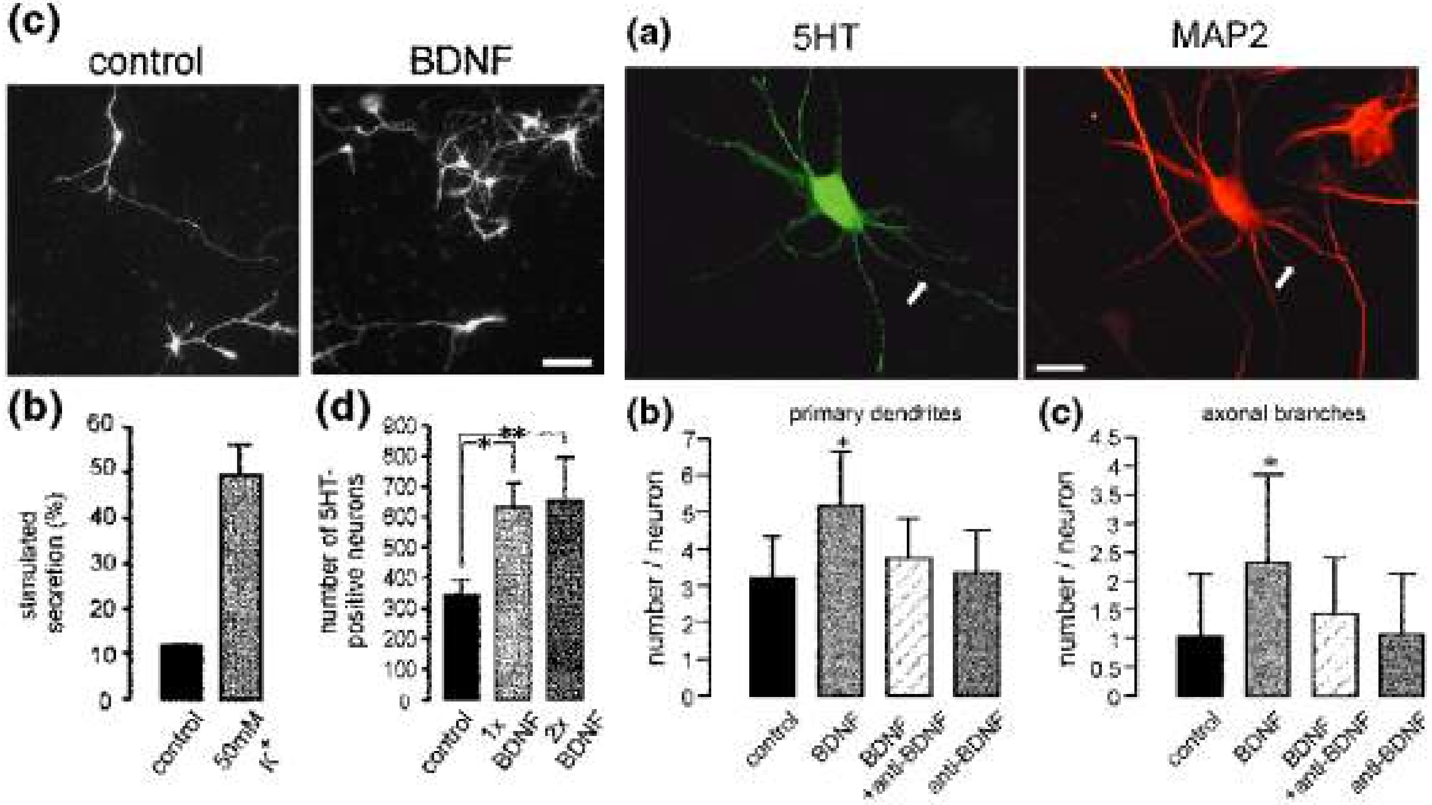


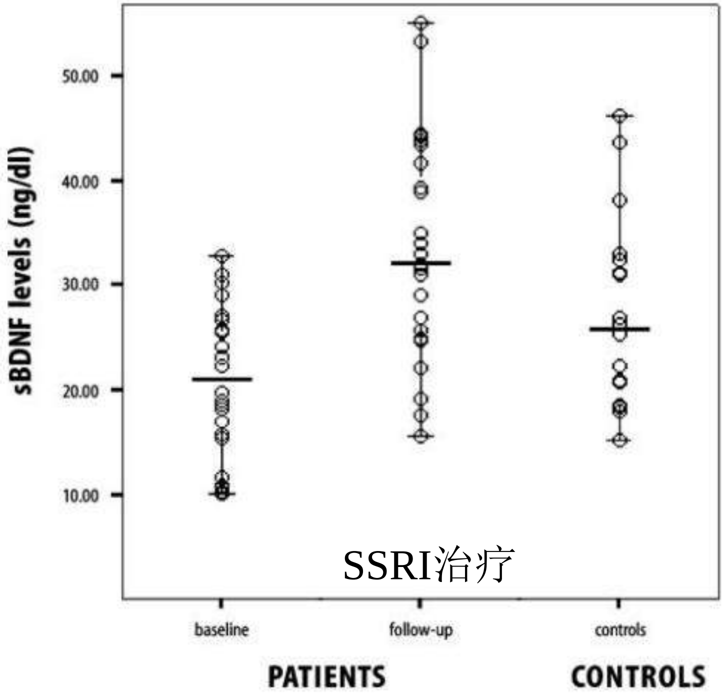


DT：dorsal thalamus/丘脑背侧
TCA：thalamocortical axon/丘脑皮层轴突
DR：dorsal raphe neuron/背侧缝神经元

Bonnin A, et al. *Neuroscience*. 2011

Interaction between serotonin and brain-derived neurotrophic factor (BDNF)

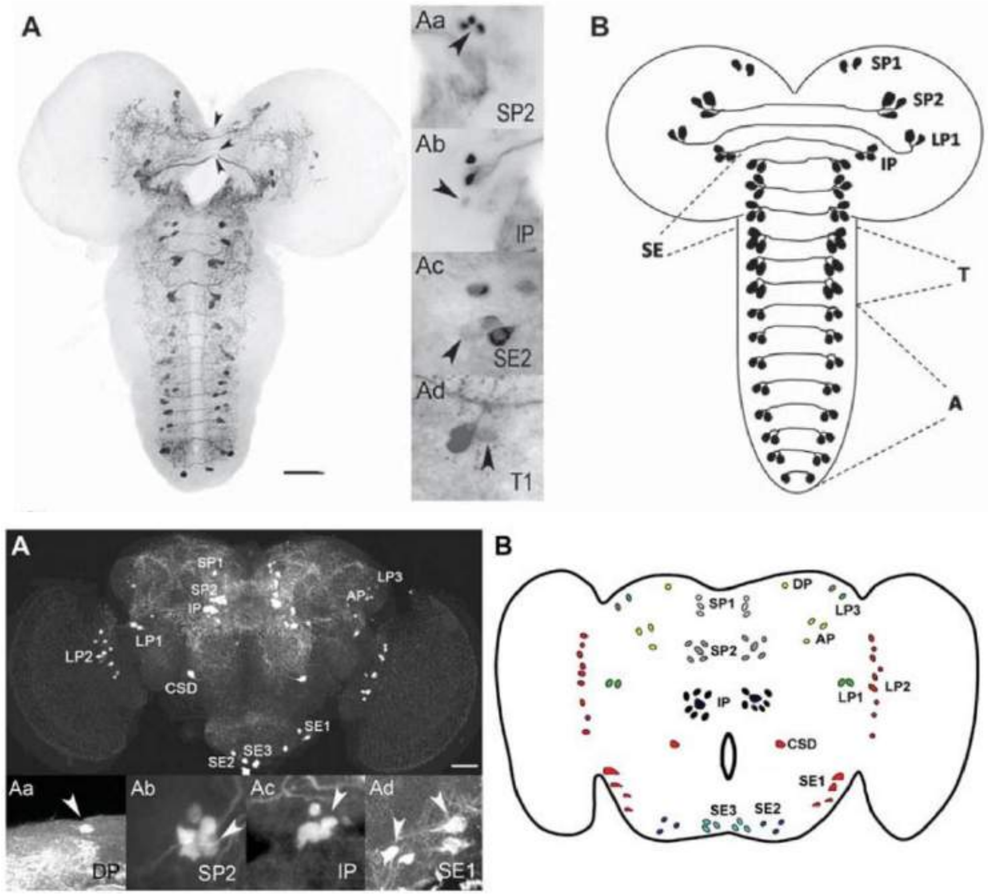




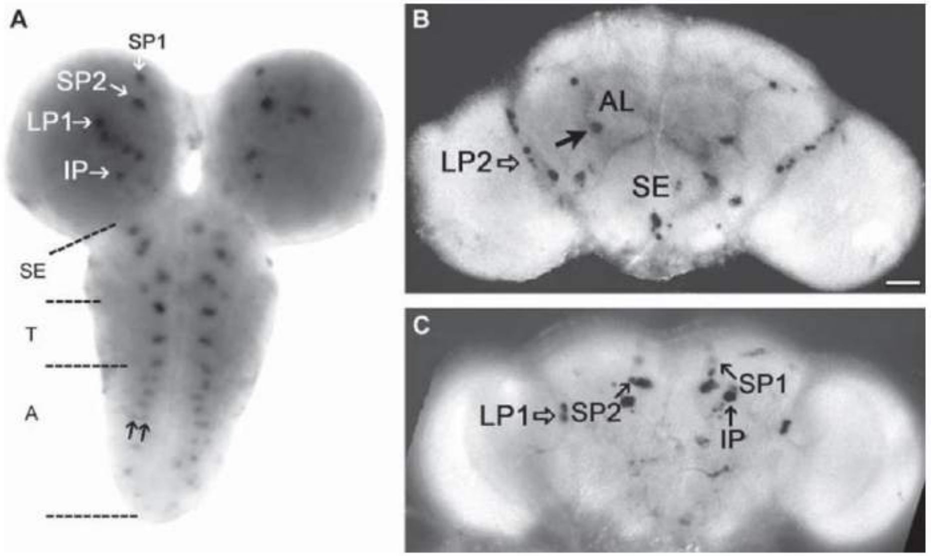
Djalali S, et al. *J Neurochem*. 2005

Gonul AS, et al. *Eur Arch Psychiatry Clin Neurosci*. 2005

Serotonin transporter (SERT) co-localizes with 5-HT in the larval and adult CNS



5-HT expression in the larva and adult

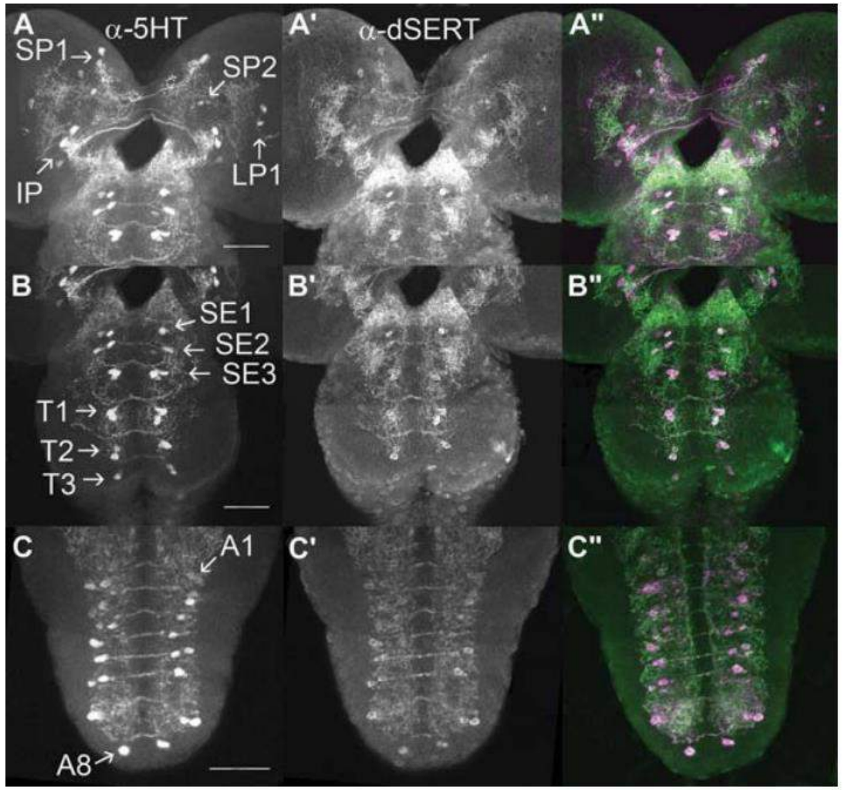


dsert RNA expression in the larva and adult

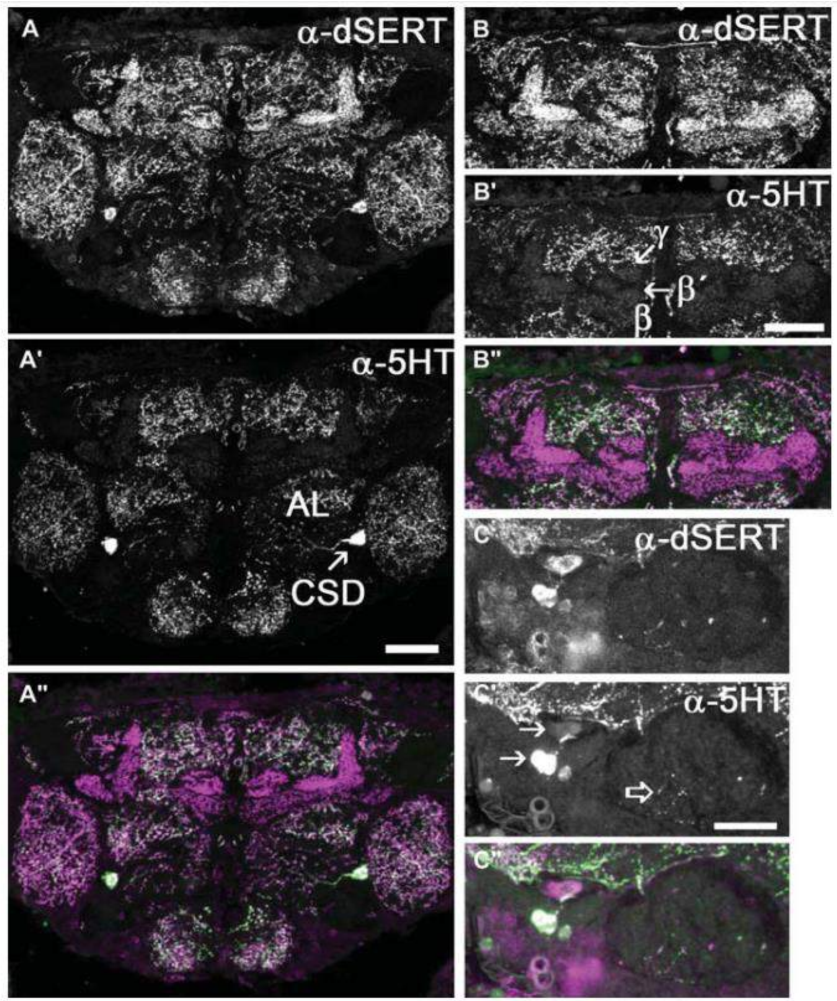
- It seems that 5-HT and dSERT are expressed in the same group of cells.

Giang T, et al. *J Neurogenet*. 2011

Serotonin transporter (SERT) co-localizes with 5-HT in the larval and adult CNS



dSERT and 5-HT expression in the larva CNS

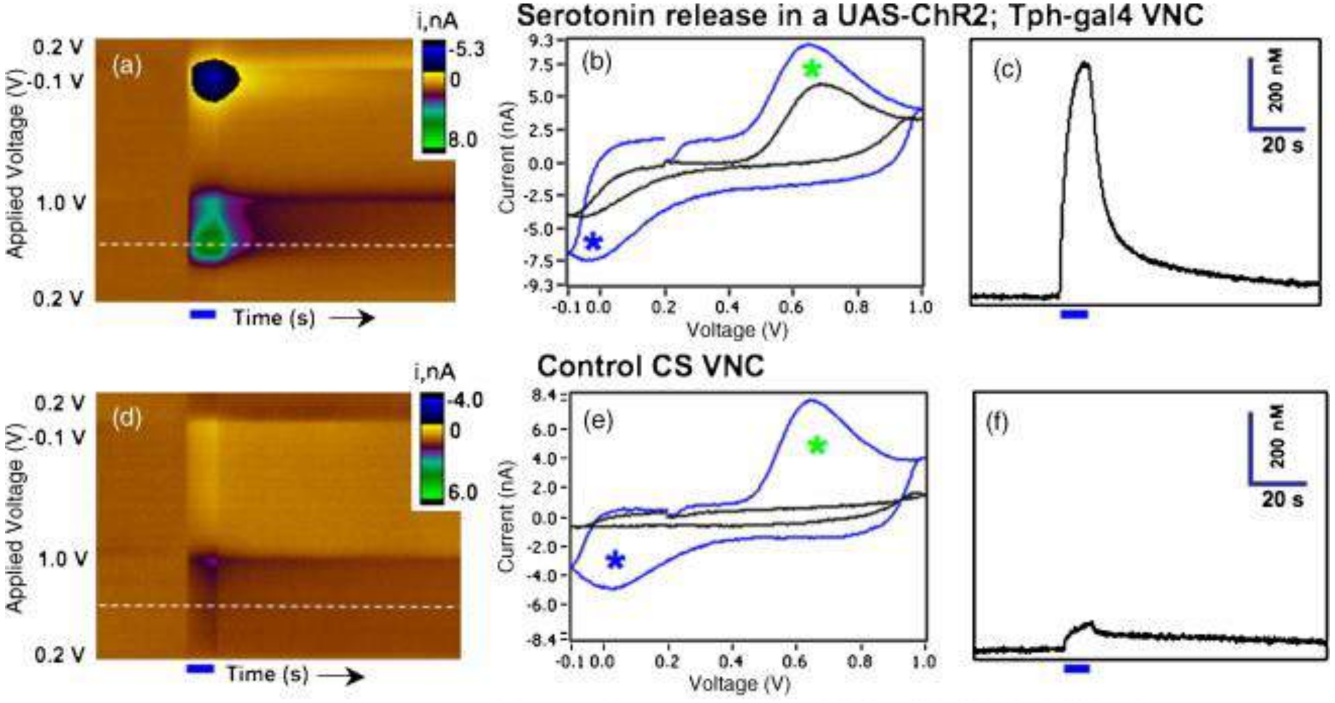


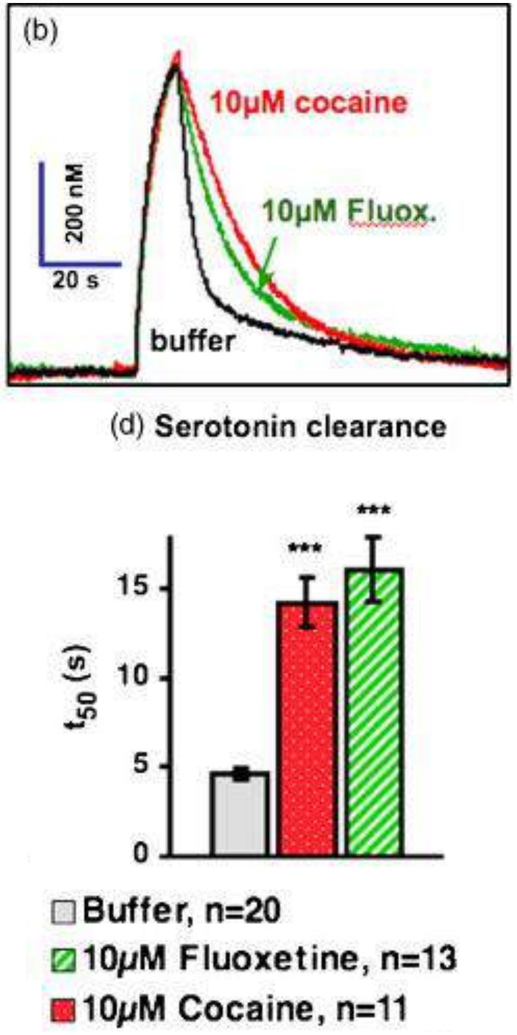
dSERT and 5-HT expression in the adult brain

- The overlap of dSERT and 5-HT expression sites suggests that all serotonergic neurons express dSERT and vice versa.

Giang T, et al. *J Neurogenet*. 2011

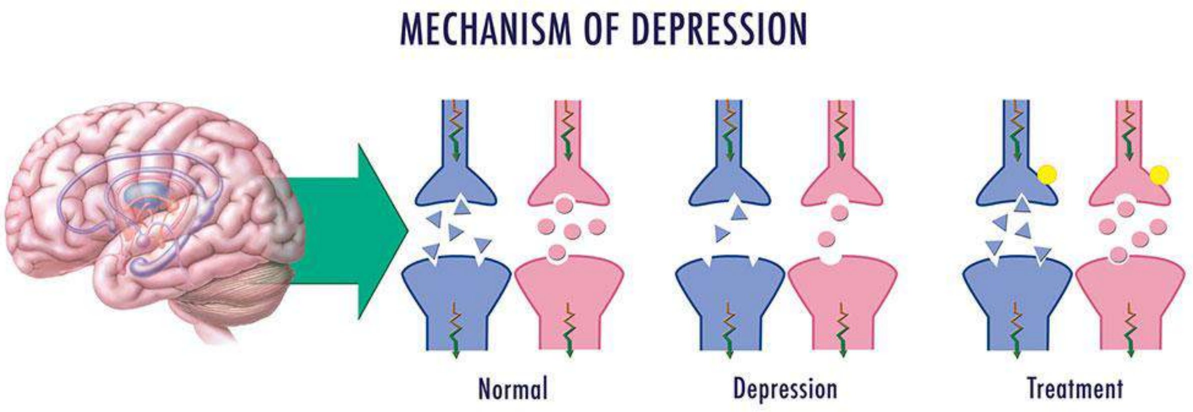
SERT functions as an important factor in the reuptake of serotonin

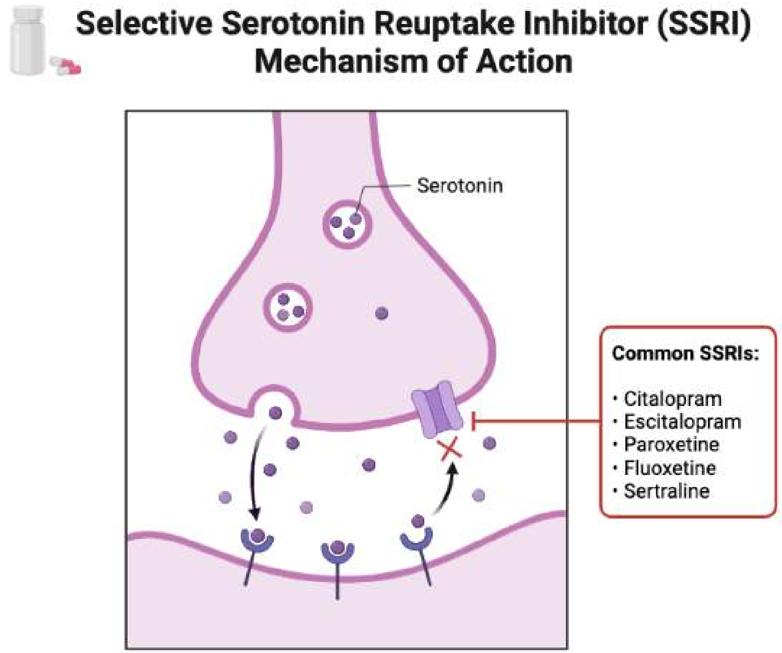


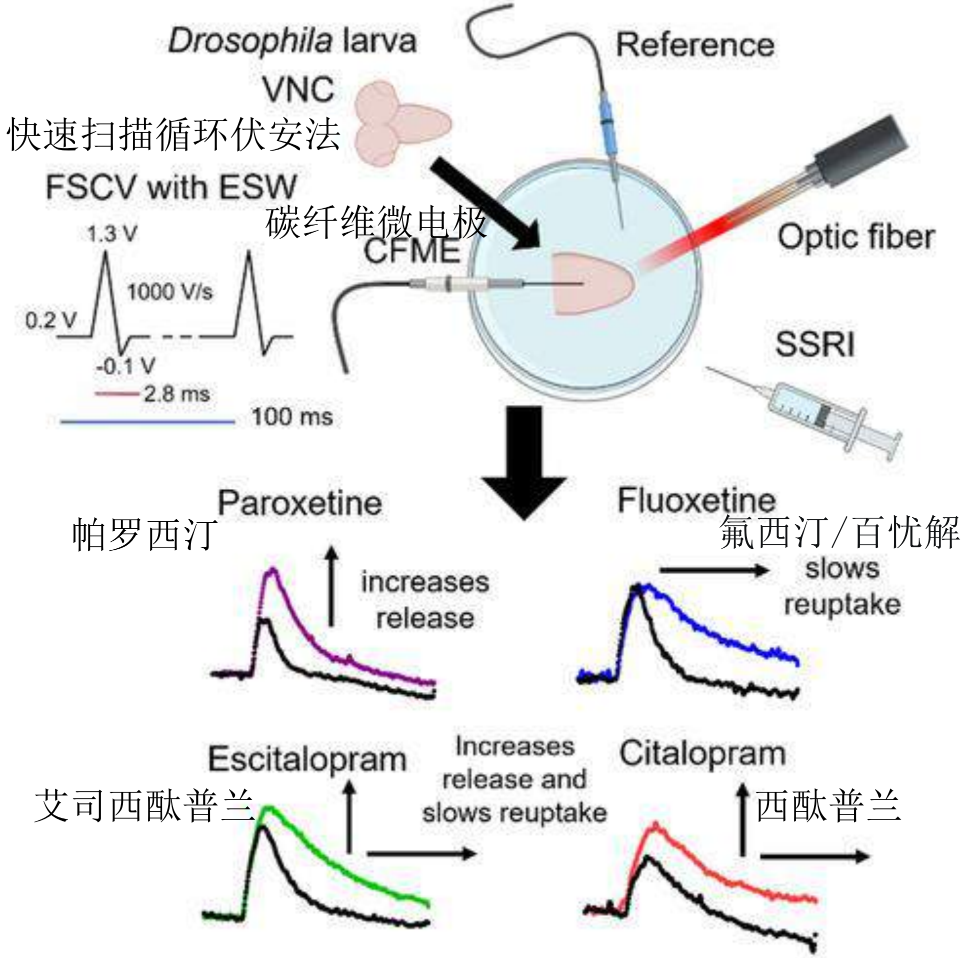


Borue X, et al. *J Neurosci Methods*. 2009

Selective serotonin reuptake inhibitors (SSRIs) are widely used as medicines for depression

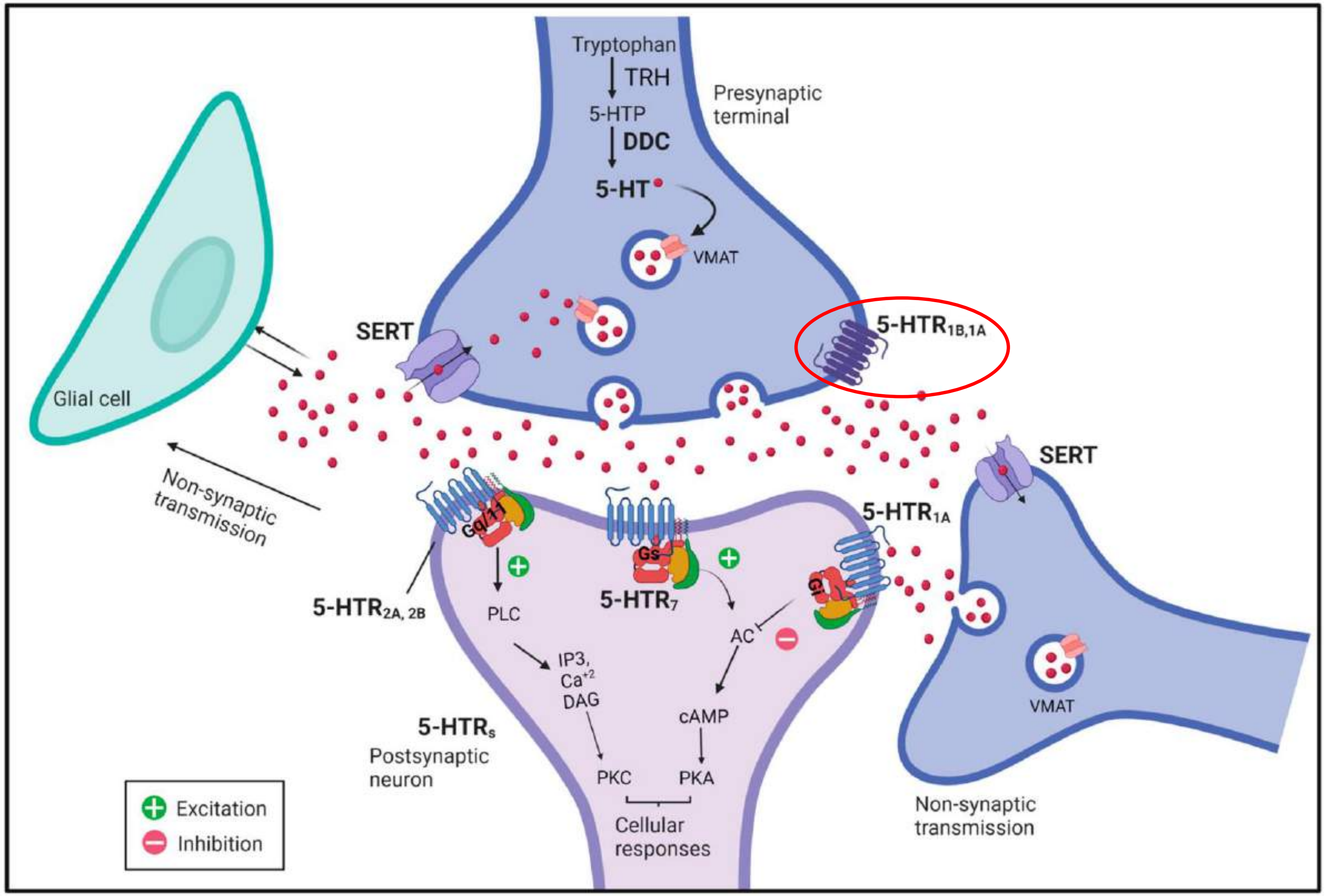






Dunham KE, et al. *J Neurochem*. 2022

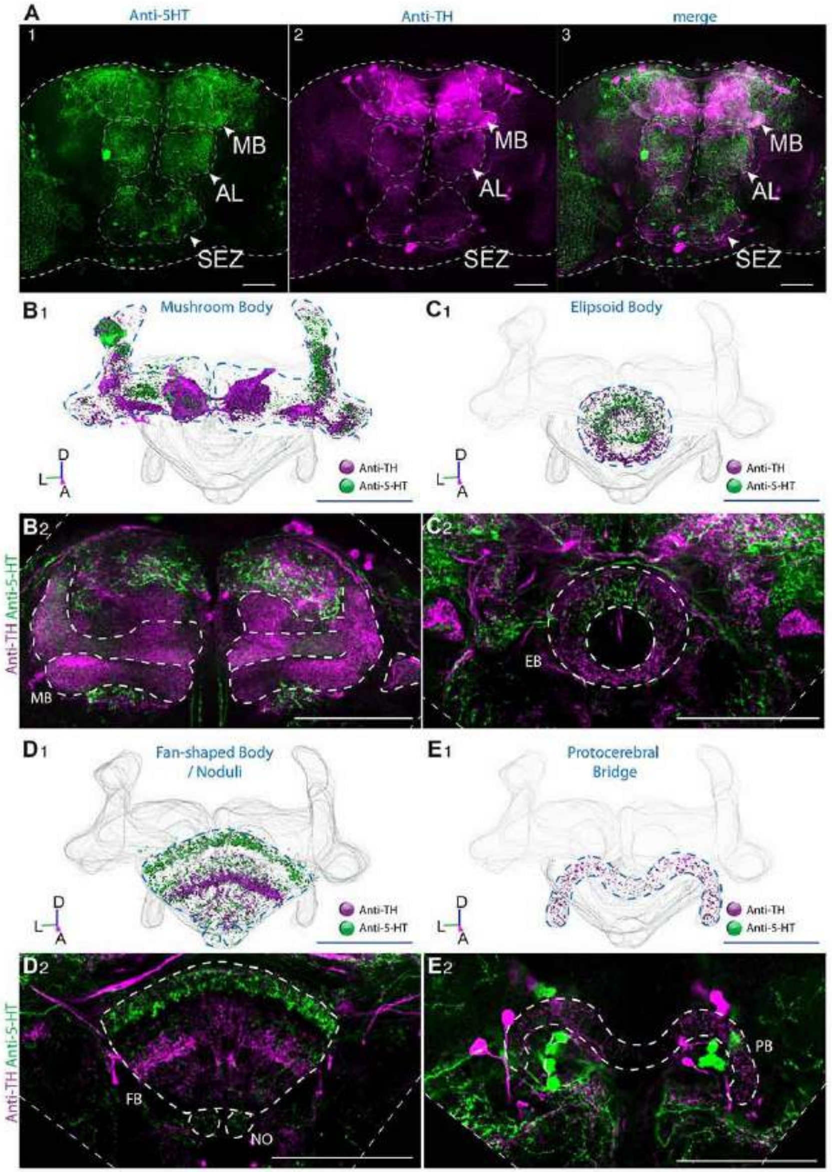
Five 5-HT receptors have been found in fruit flies, which play different roles

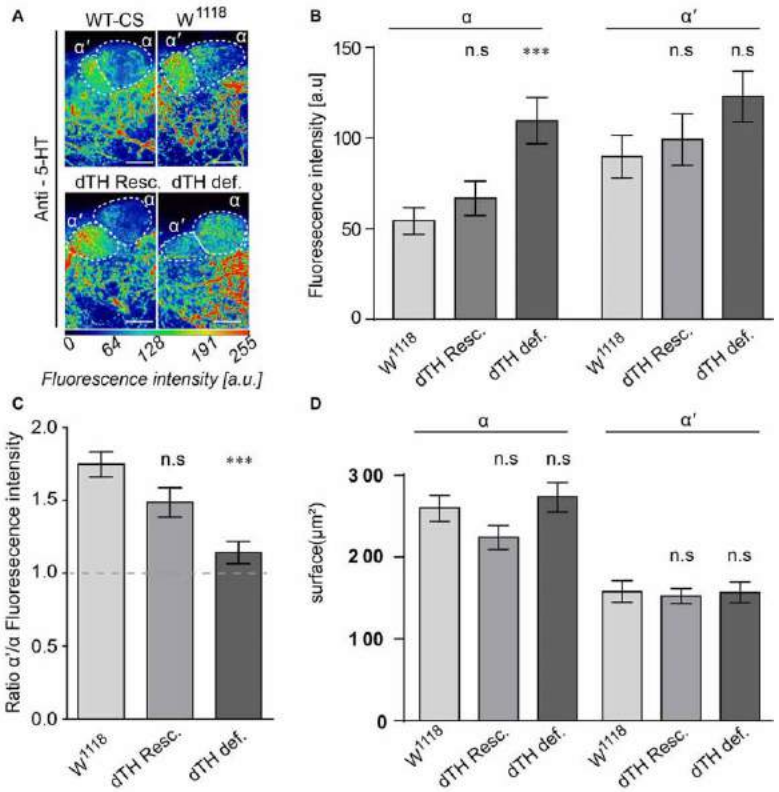


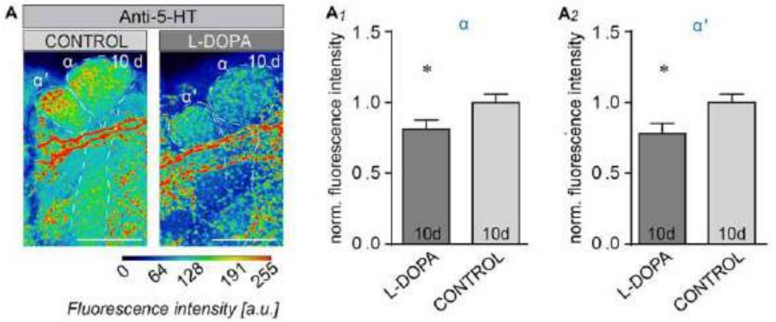
PLC：磷脂酶C

Gajardo I, et al. *Int J Mol Sci*. 2023

Interaction of the serotonergic and other aminergic systems



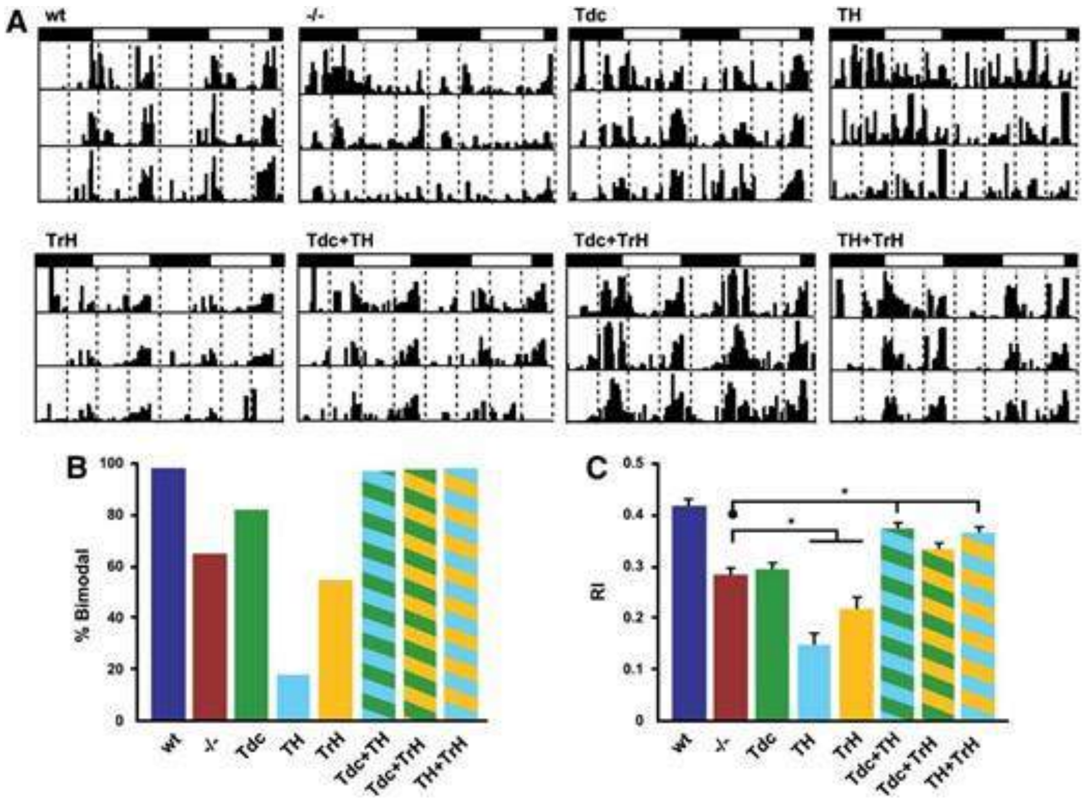




竞争性相互作用

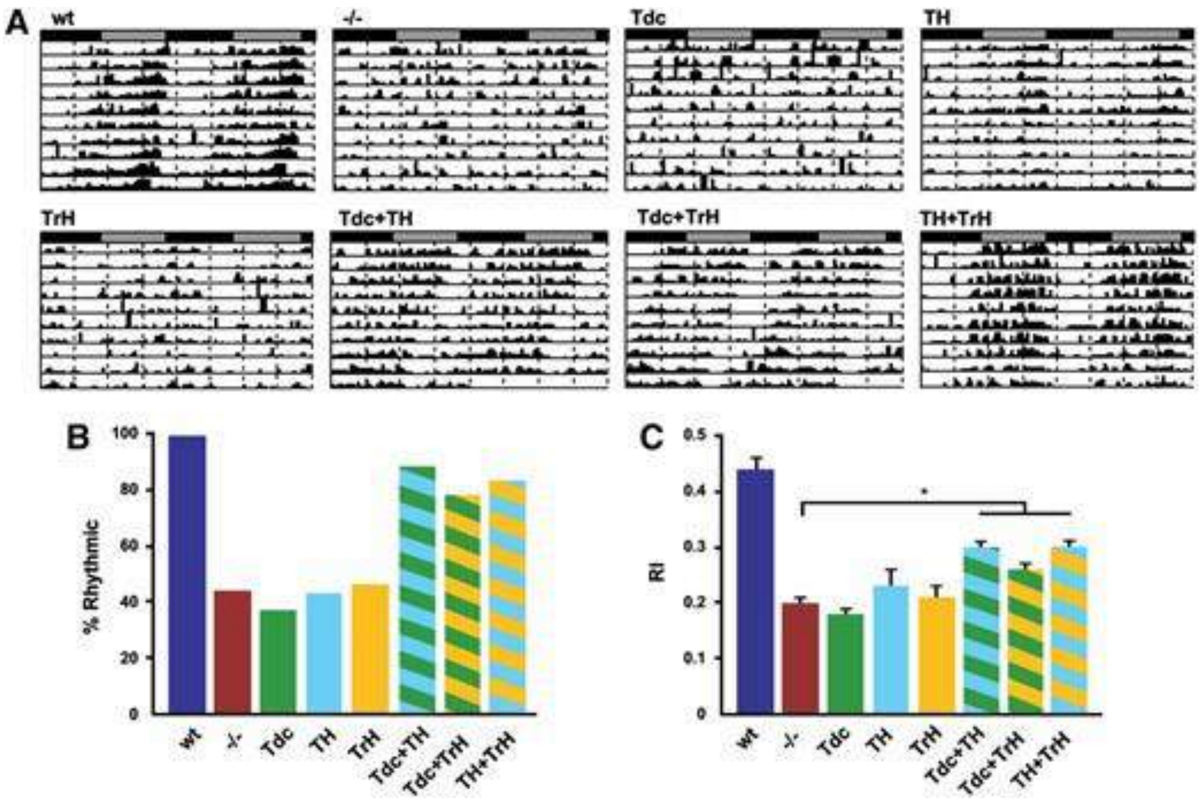
Niens J, et al. *Front Syst Neurosci*. 2017

Interaction of the serotonergic and other aminergic systems



Circadian rhythm of dVMAT mutant
under LD condition

合作性相互作用



Circadian rhythm of dVMAT mutant
under DD condition

Chen A, et al. *Genetics*. 2013

Summary

- Biogenic amines are nitrogenous organic bases of low molecular weight with biological functions.

  DA, OA, TA, 5-HT, HA.

- Serotonin also plays a key role as a signaling/trophic factor in early development.

- SERT is an important component of serotonin regulation and is a target of SSRIs.

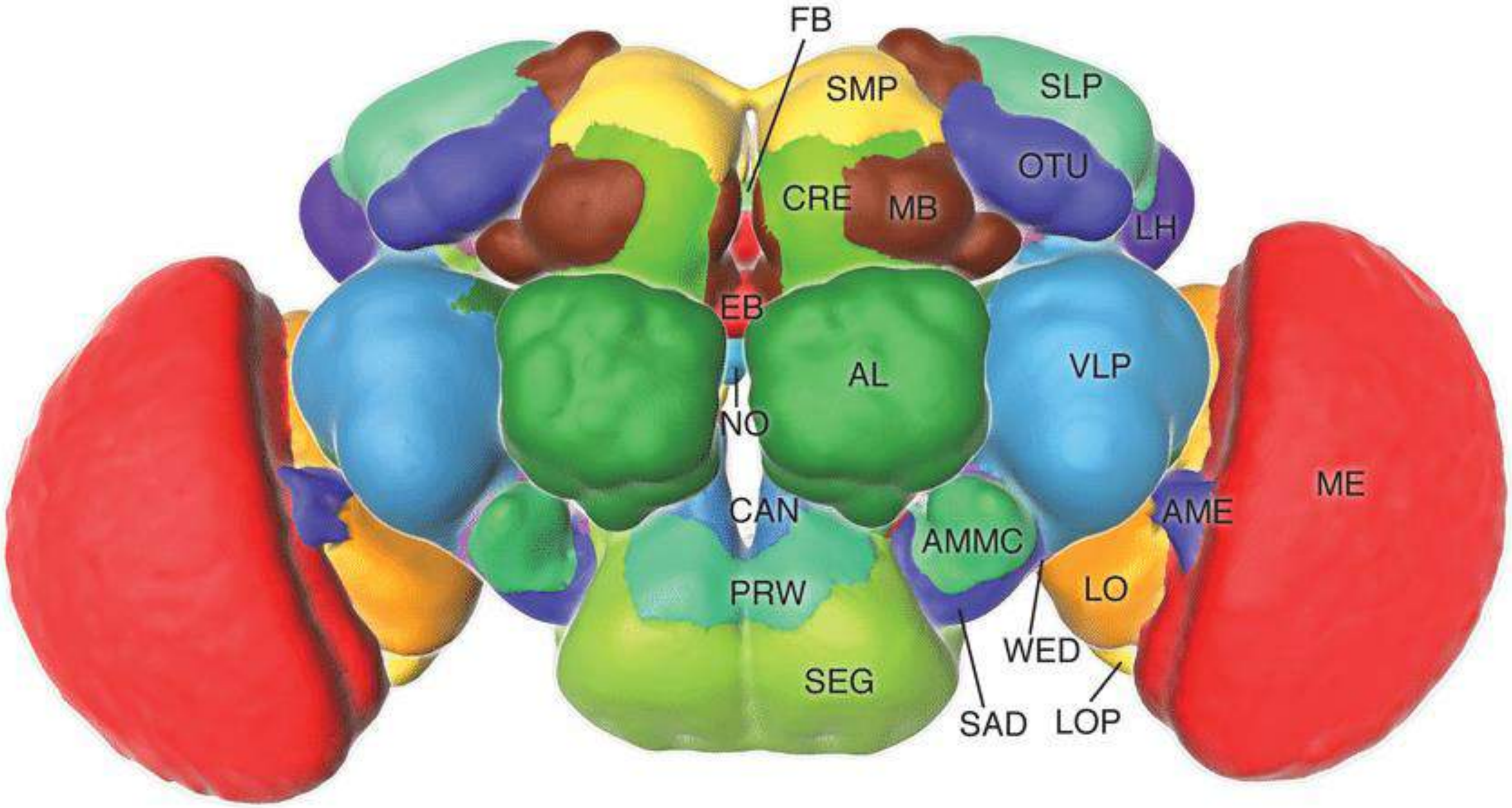
- The serotonergic system interacts strongly with other aminergic systems.

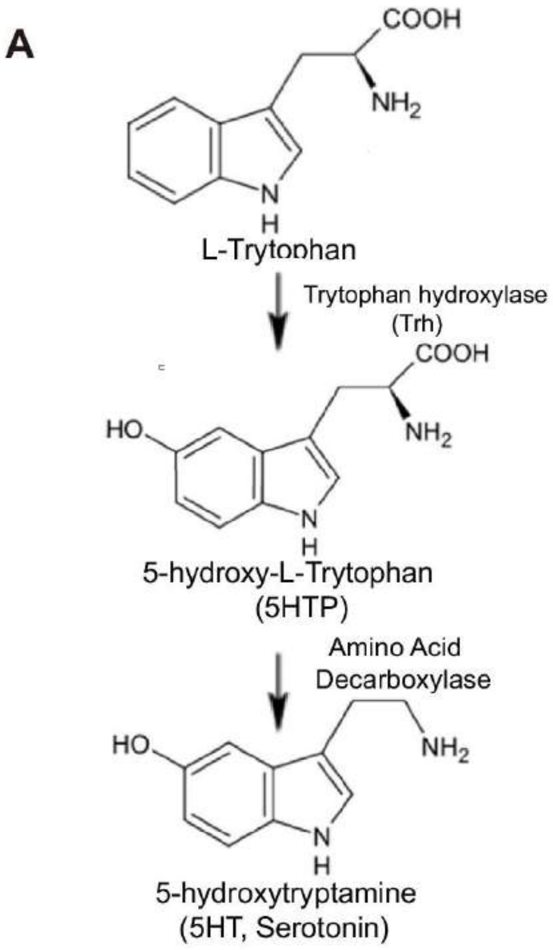
The regulation of different behaviors by serotonin in Drosophila

- What behaviors can 5-HT regulate?
- Where do 5-HT neurons function?
- What are the differences and connections between different subtypes of serotonin receptors in regulating behavior?

ZZK

Elementary knowledge of 5-HT



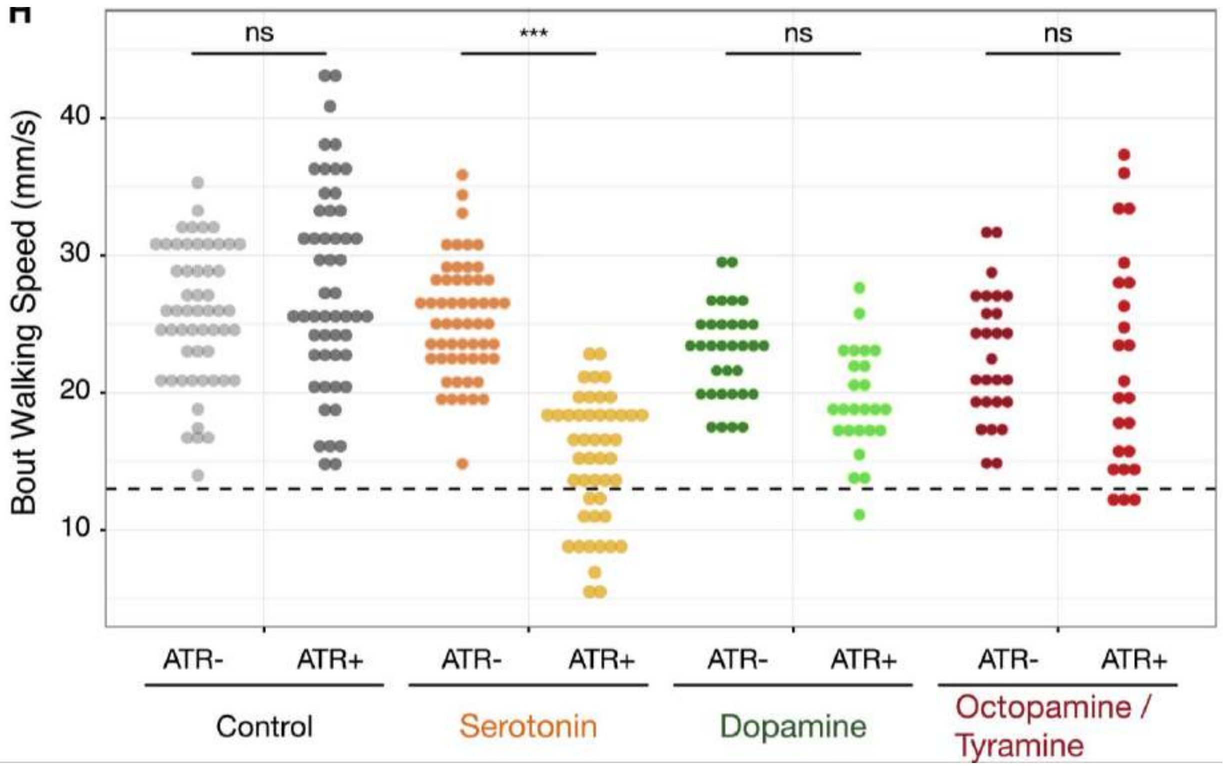


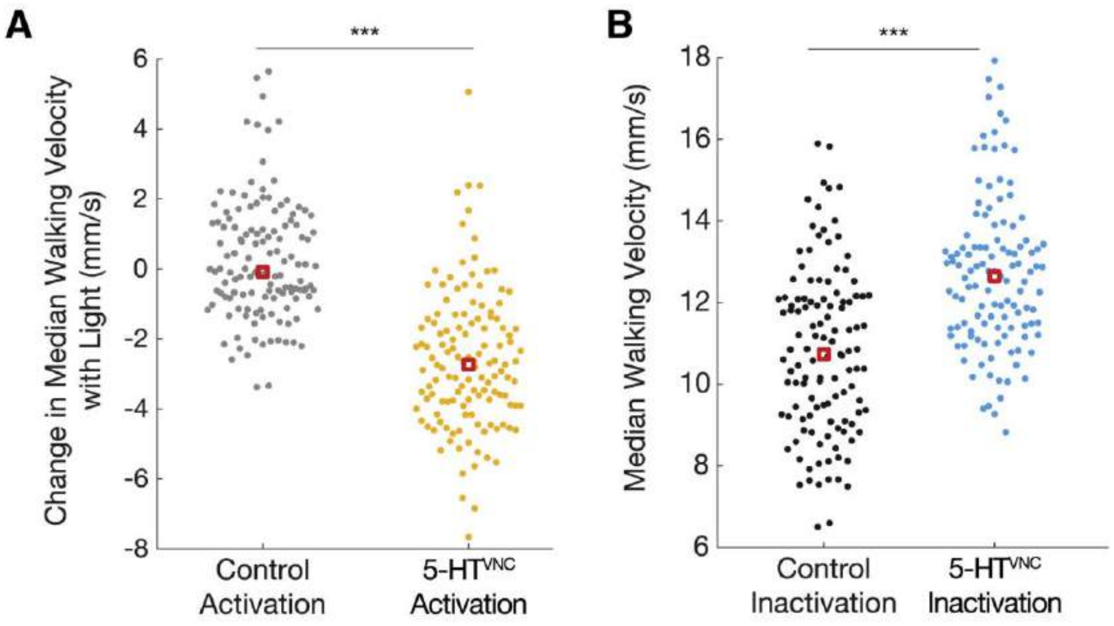
Trh:色氨酸羟化酶
AADC:芳香族脱羧酶

Qian, Yongjun et al. eLife. 2017

5-HT affects the basic states of Drosophila

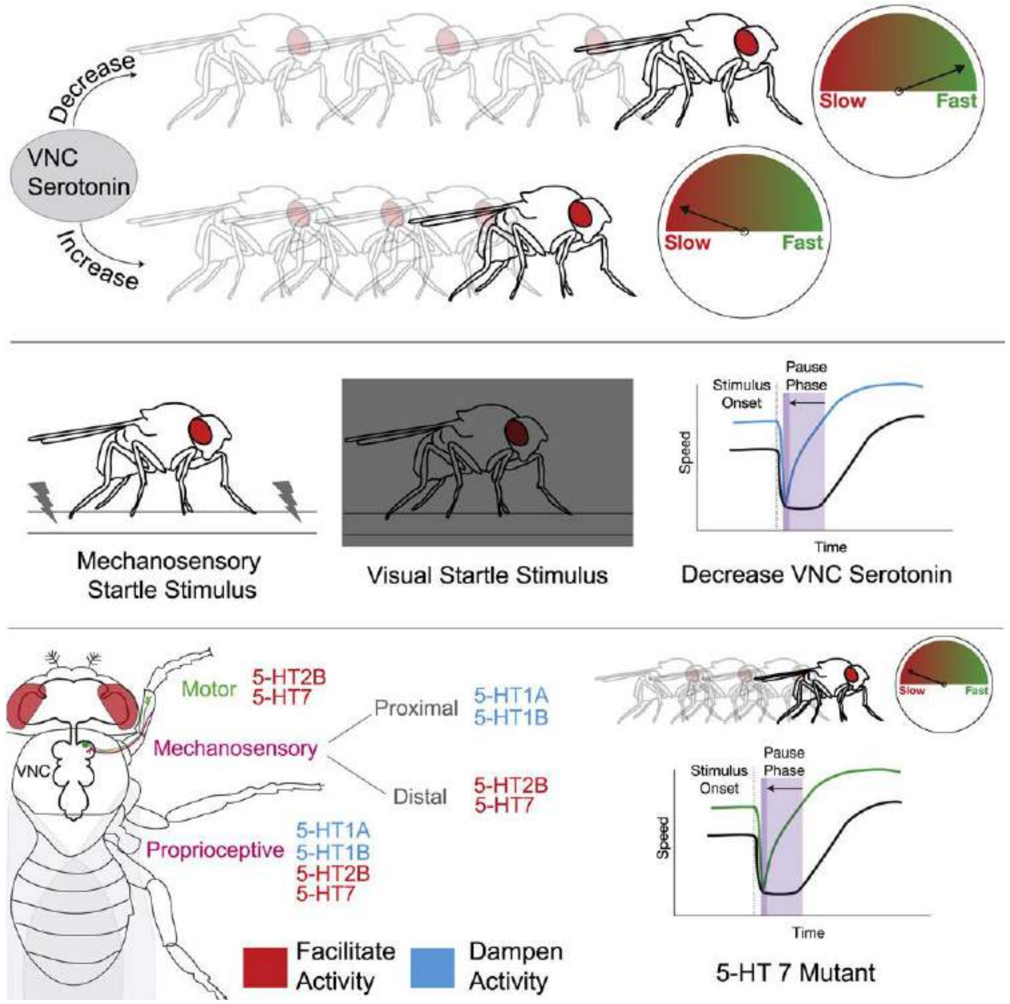
Activation of serotonin neurons may cause slower walking speed

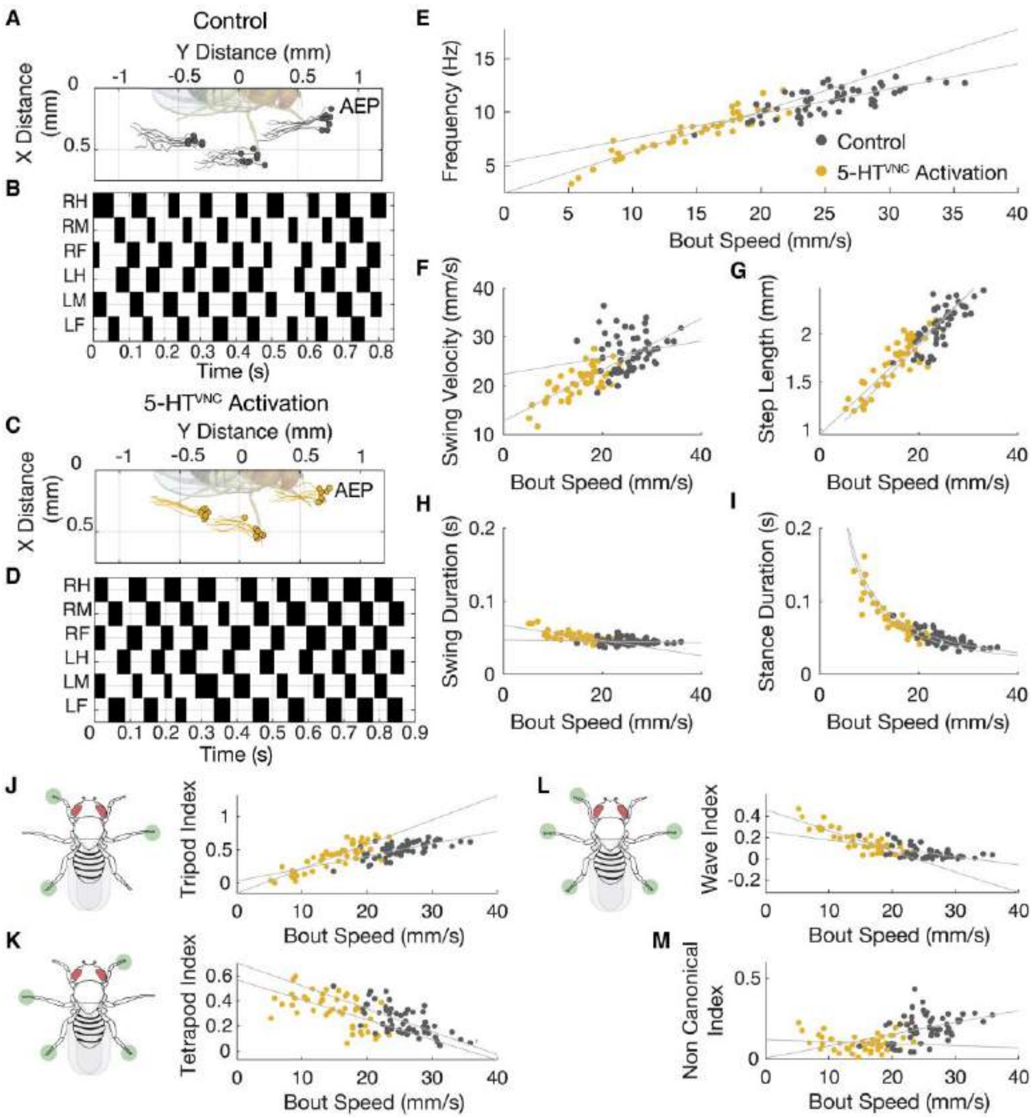




Howard, Clare E et al. Current biology. 2019

The complex role of serotonin in regulating locomotion of Drosophila

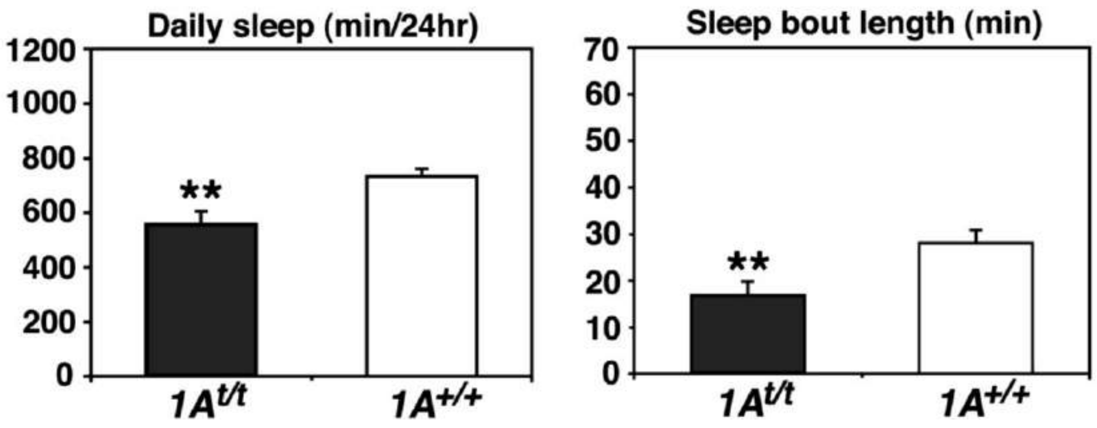




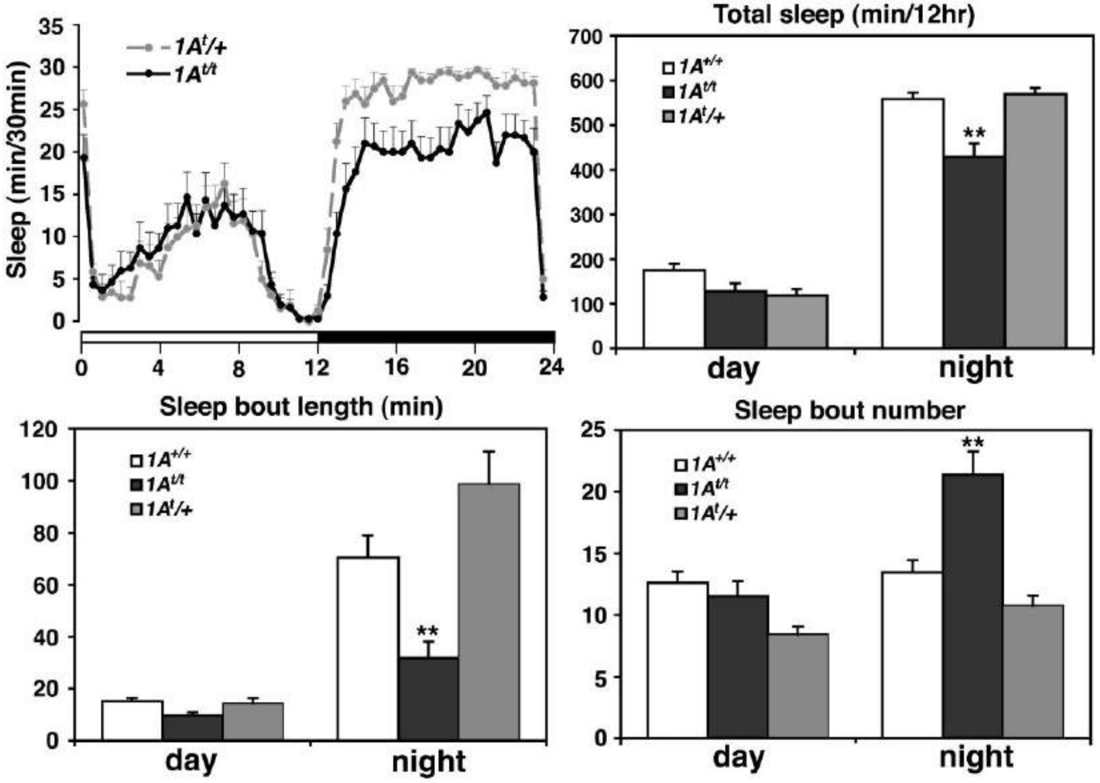
white：站立；black：摆动

Howard, Clare E et al. Current biology. 2019

5-HT has a complex regulation mechanism for sleep



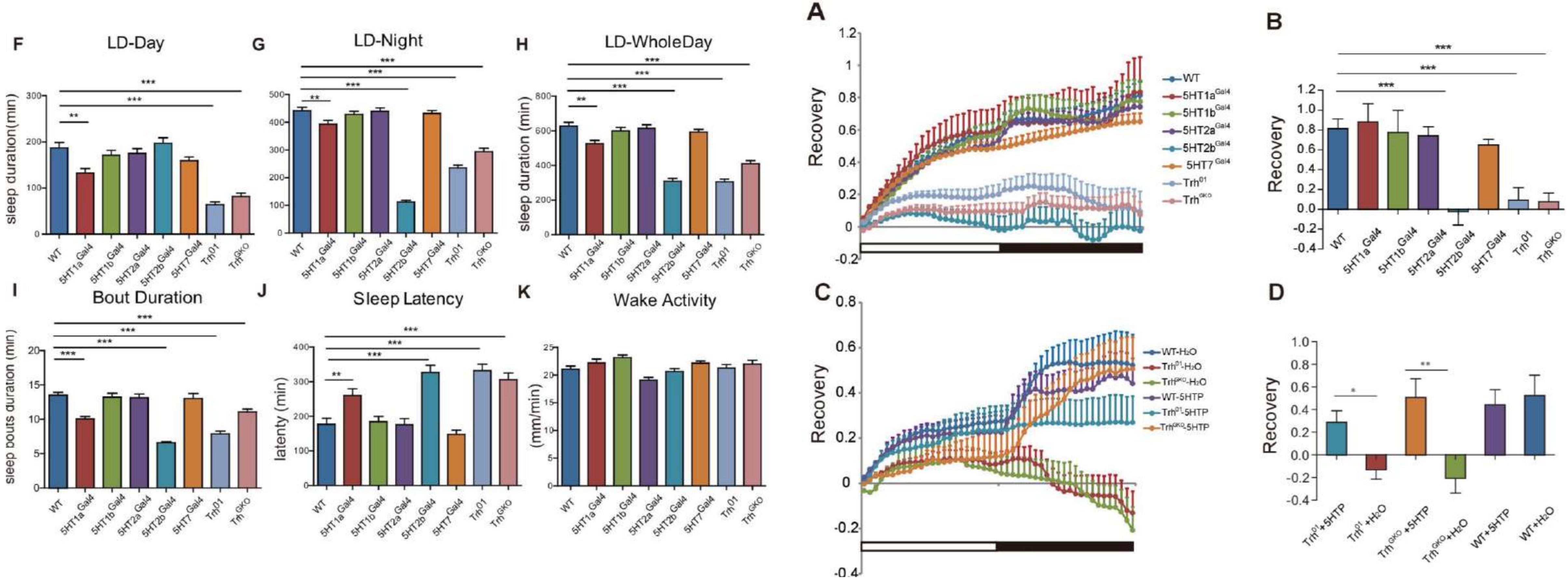
Baseline Sleep



d5-HT1A mutant flies have short and fragmented sleep but normal circadian rhythms

Yuan, Quan et al. Current biology. 2006

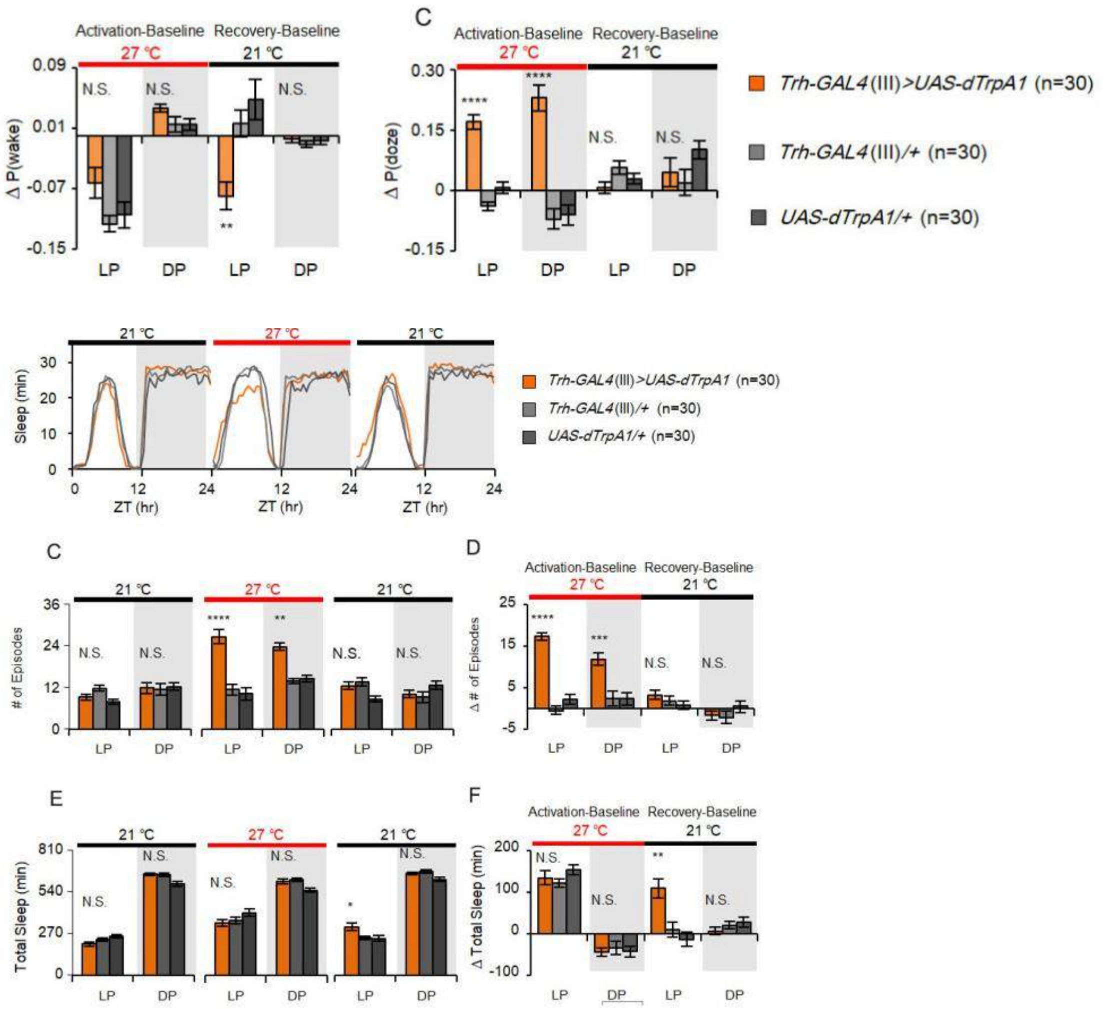
5HT2b gene diminished sleep rebound after sleep deprivation

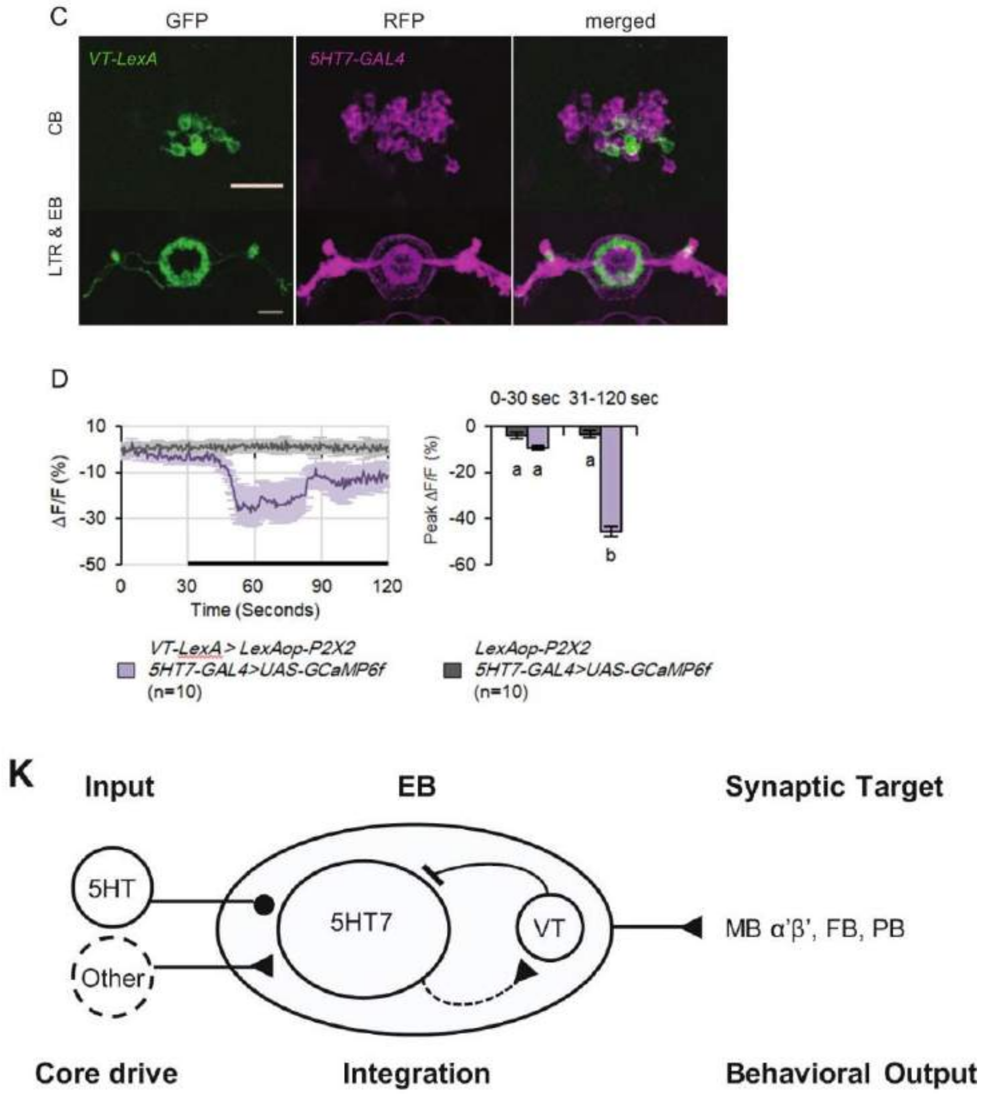


The loss of 5-HT affects sleep rather than mobility

Qian, Yongjun et al. eLife. 2017

5-HT7 receptor neurons are involved in regulating sleep structure but do not affect the total amount of sleep

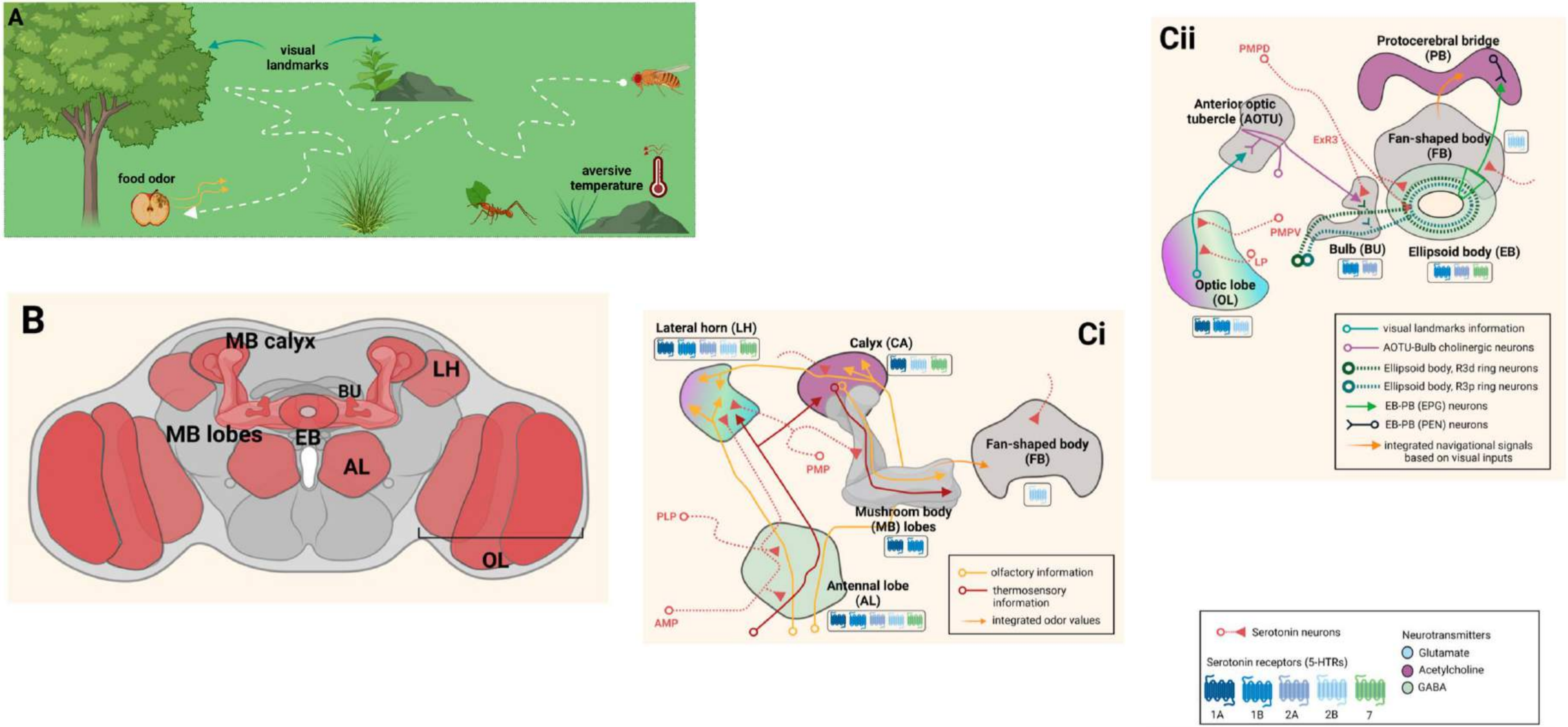




Liu, Chang et al. Current biology. 2019

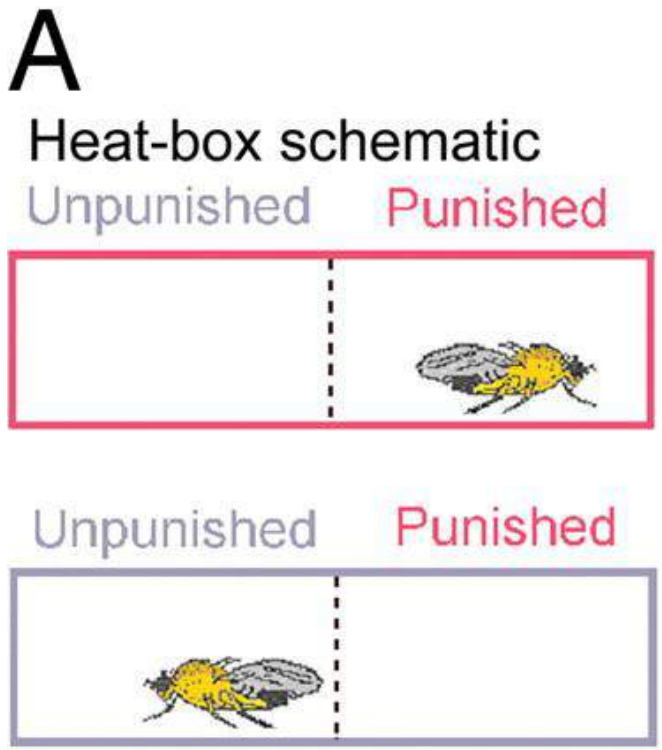
5-HT affects learning and memory in Drosophila

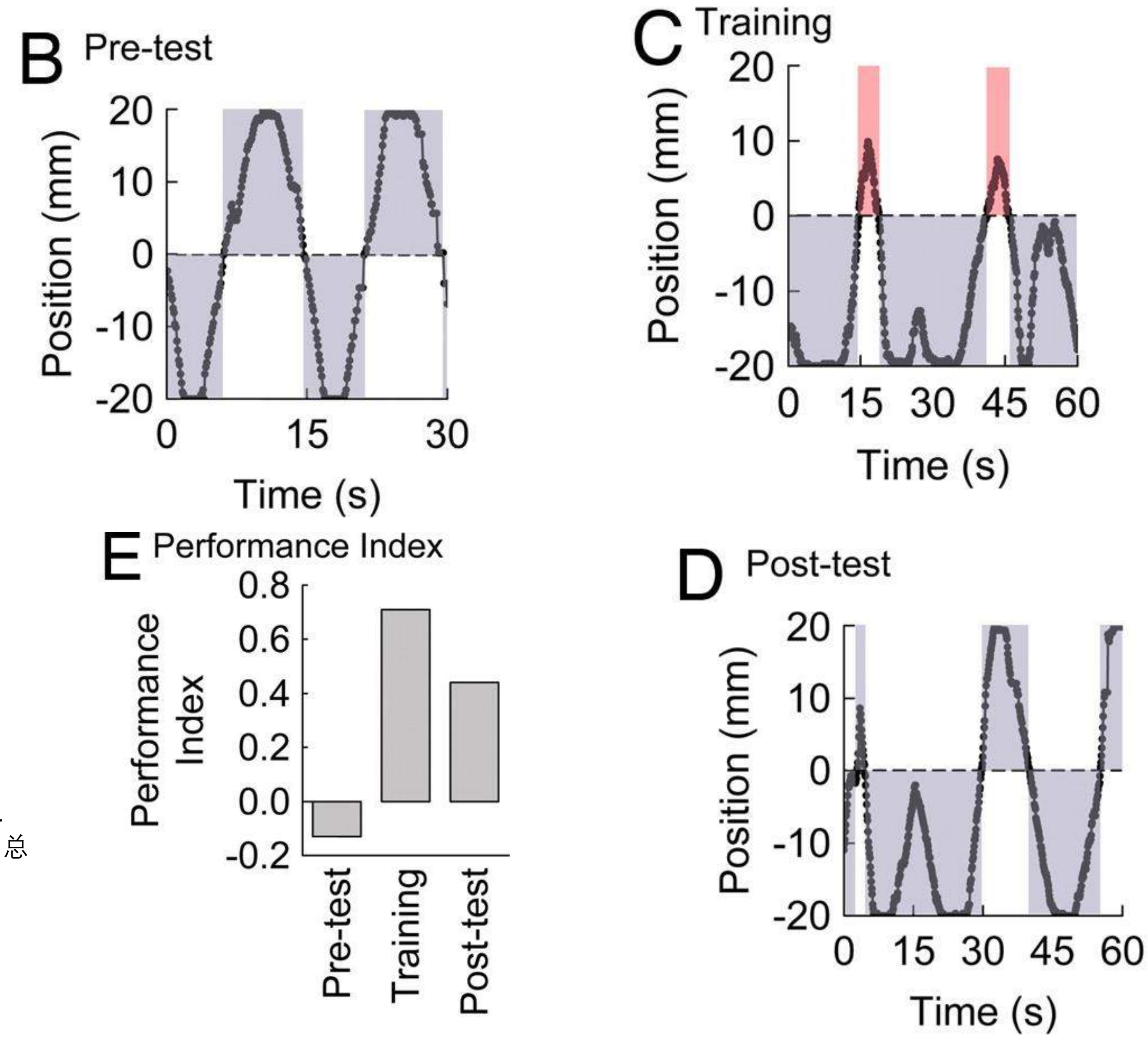
Serotonin is crucial for spatial memory formation in fruit flies



Gajardo, Ivana et al. International journal of molecular sciences vol. 2023

Serotonin is crucial for spatial memory formation in fruit flies

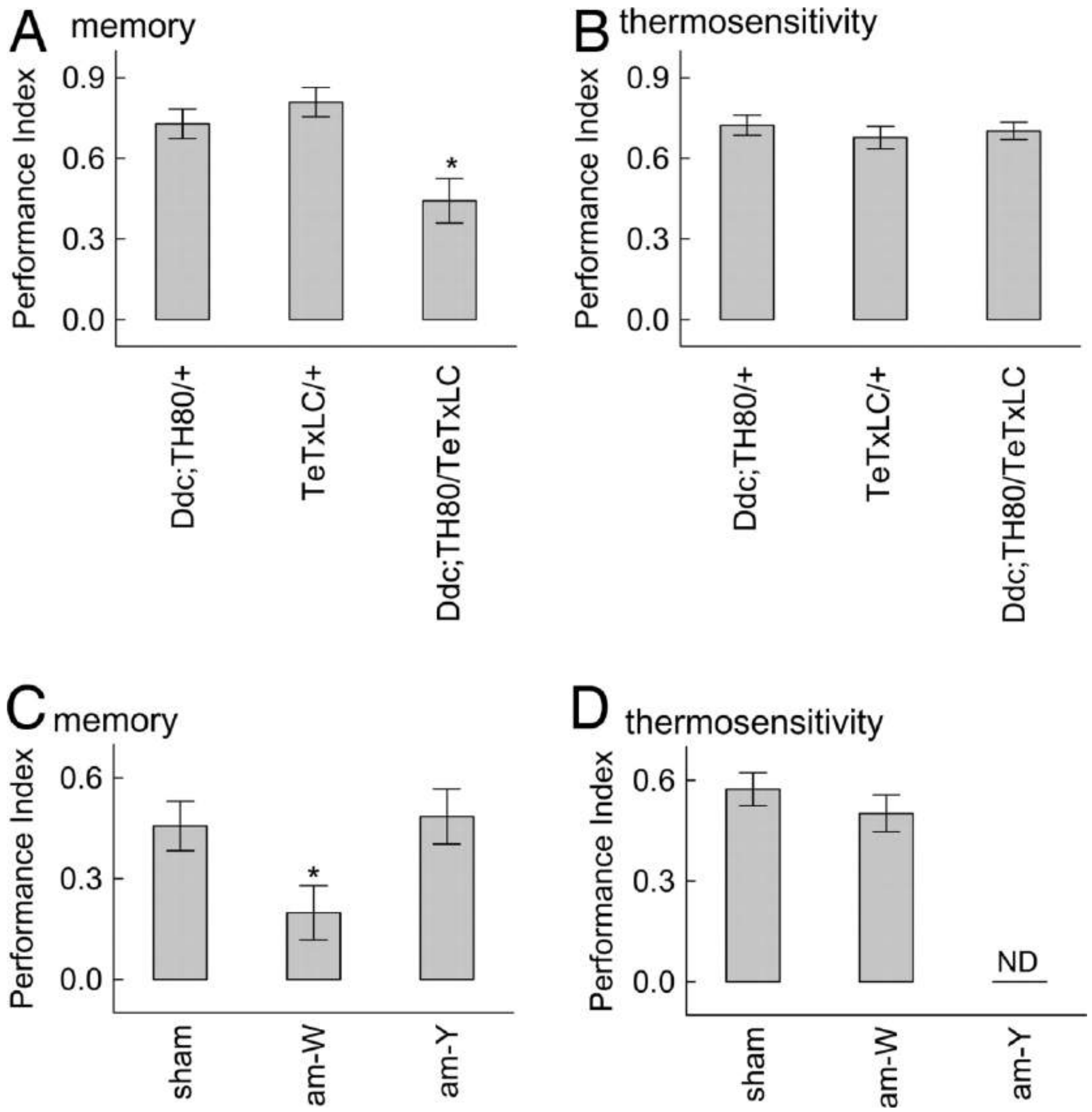


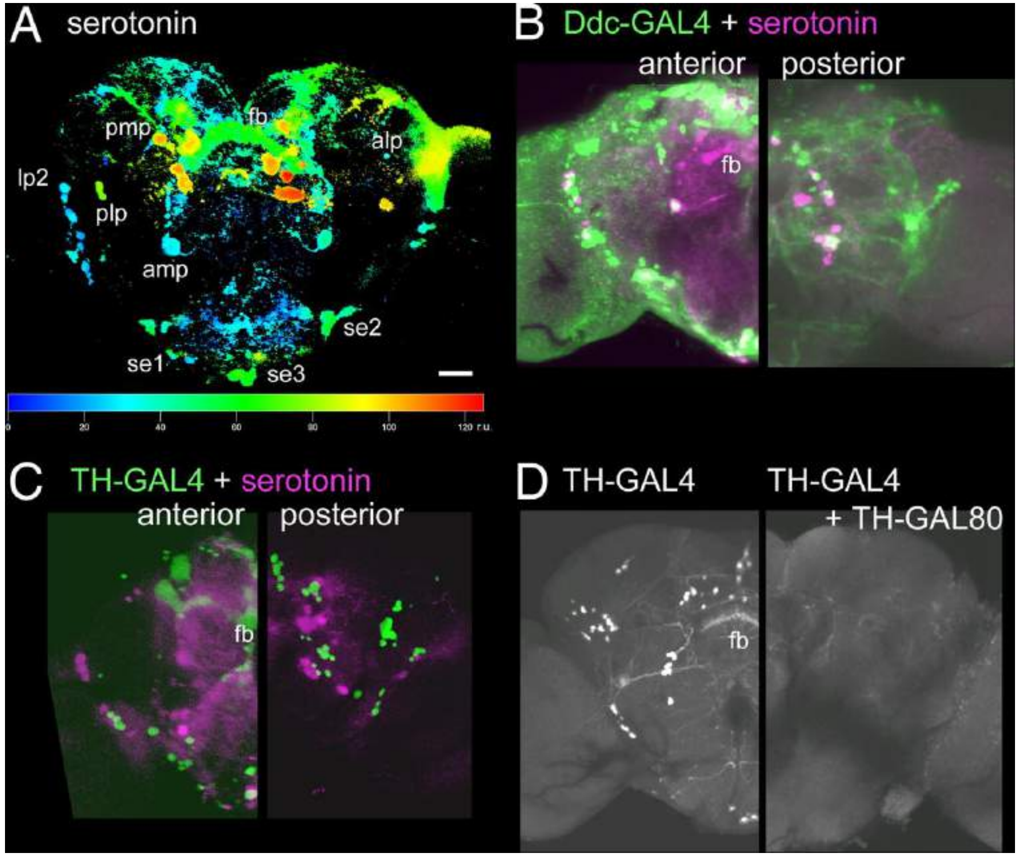


performance index=（T（低温）-T（高温））/T总

Sitaraman, Divya et al. PNAS.2008

Serotonin is crucial for spatial memory formation in fruit flies





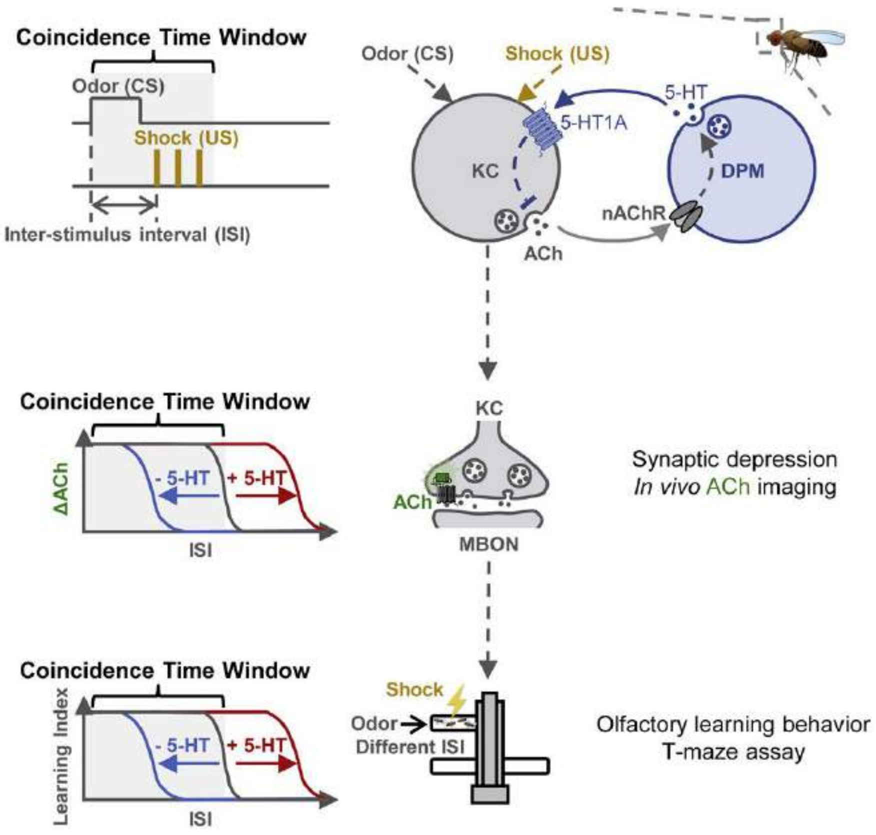
am-W：restrain 5-HT
am-Y：restrain dopamine
ND：未测试

Sitaraman, Divya et al. PNAS.2008

Article

Neuron

Local 5-HT signaling bi-directionally regulates the coincidence time window for associative learning



Principal Investigator

李毓龙

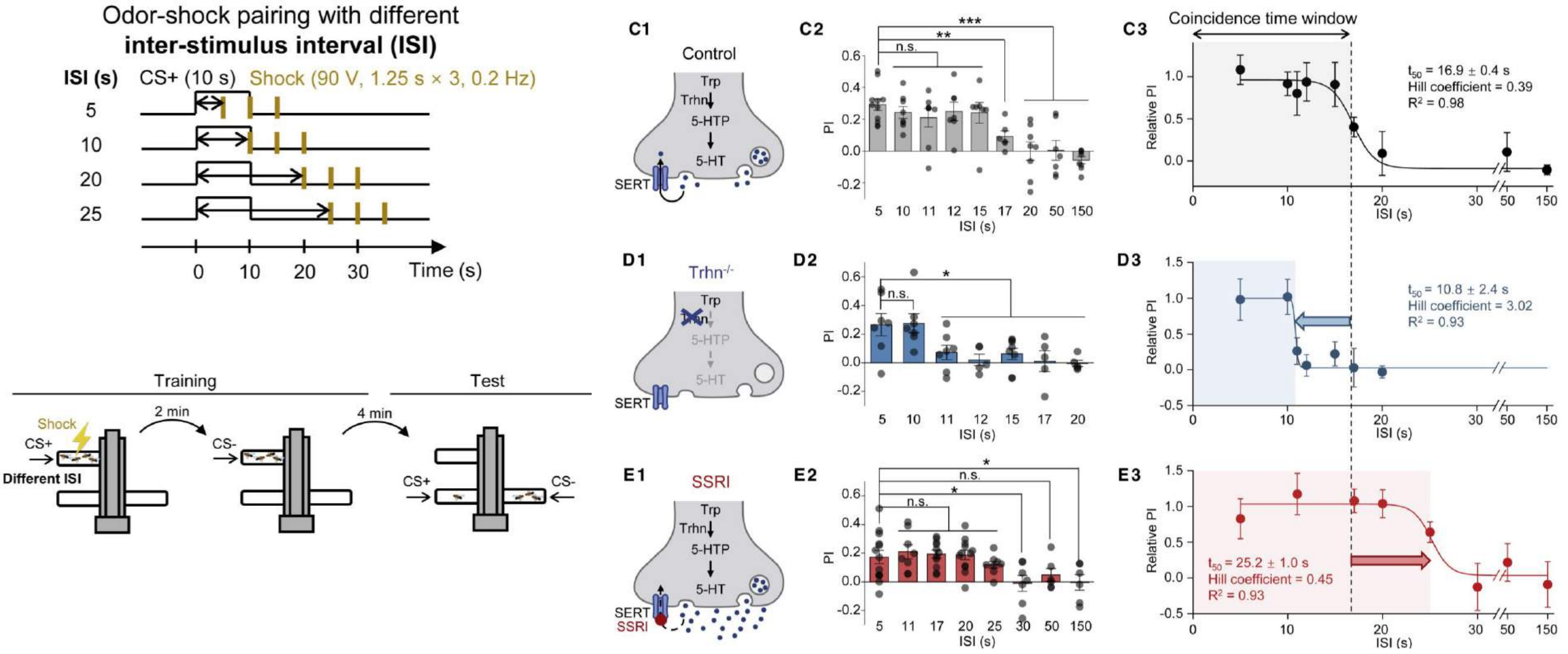
荧光探针、神经成像、突触传递、信号转导、神经疾病

联系电话： 62766905

通信地址： 北京市海淀区颐和园路5号金光生命科学大楼142信箱，100871

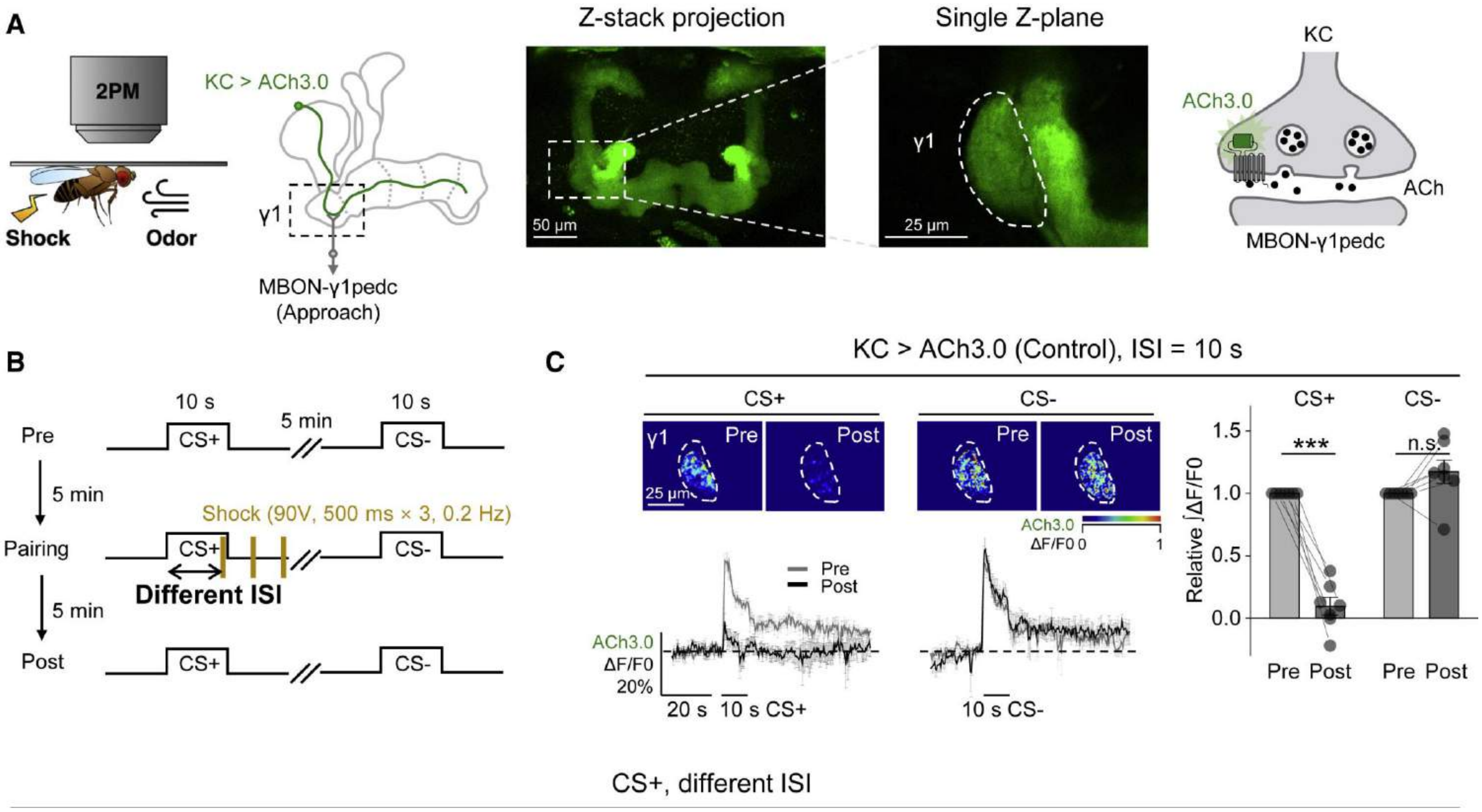
电子邮件： yulongli@pku.edu.cn

5-HT bi-directionally regulates the coincidence time window of olfactory learning



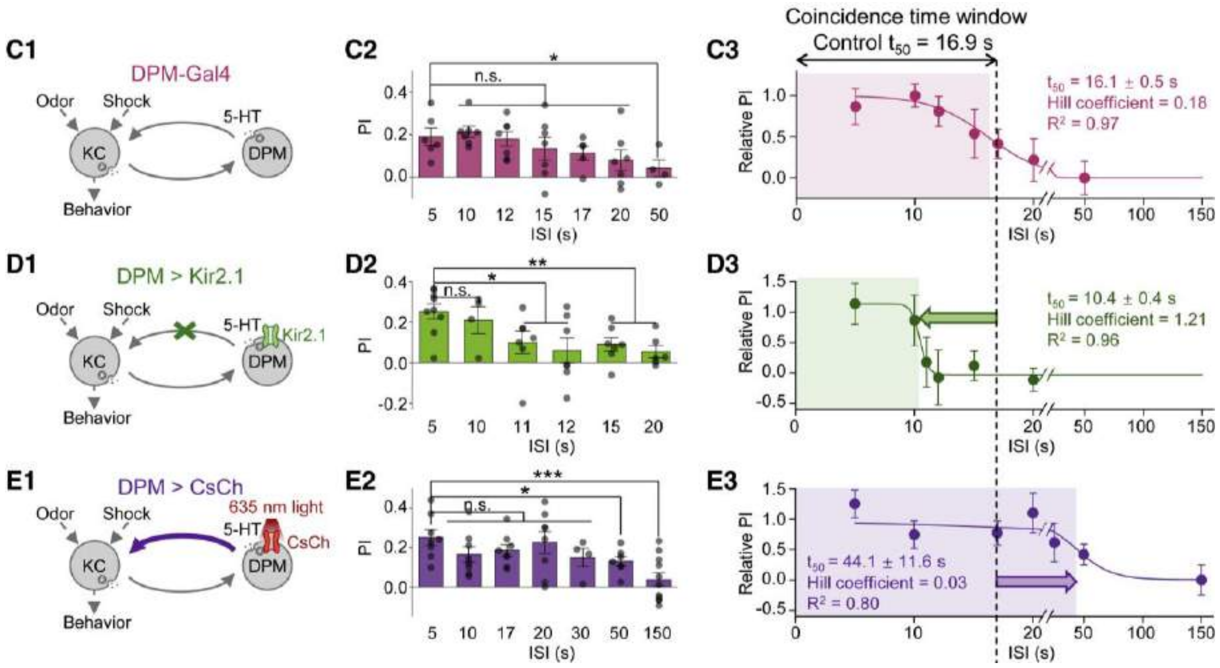
Zeng, Jianzhi et al. Neuron. 2023

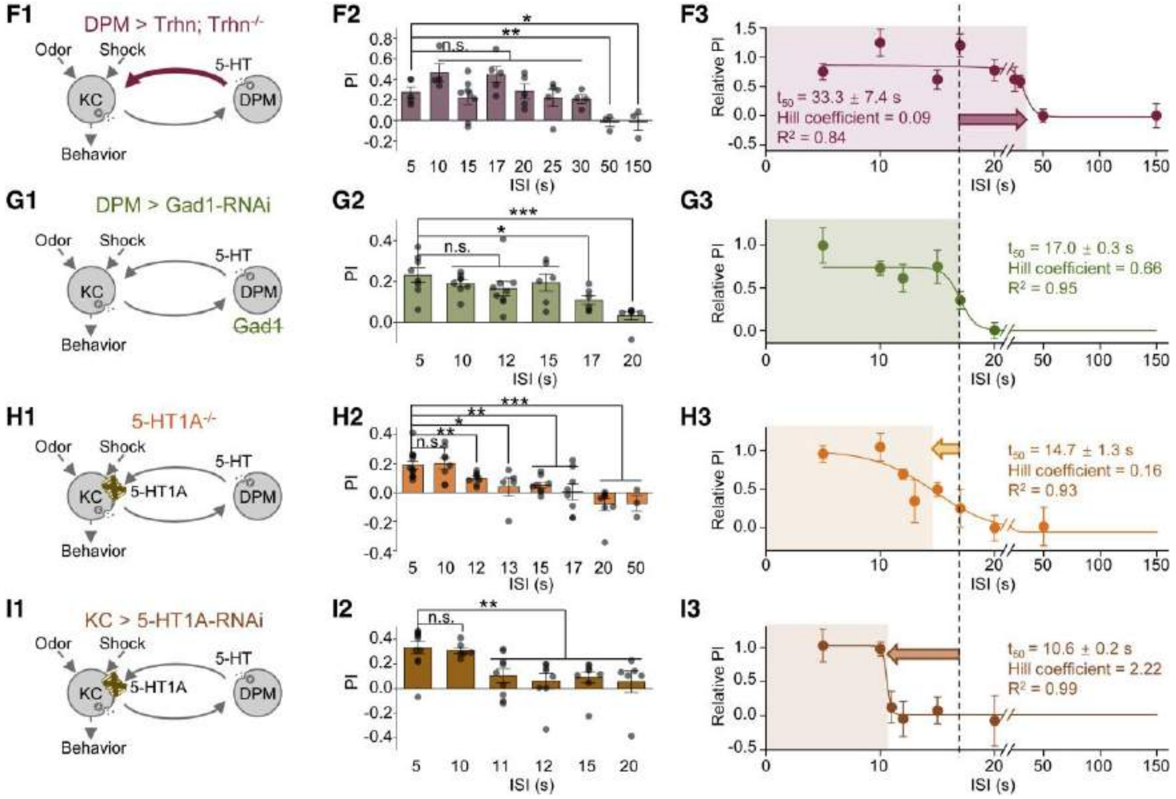
5-HT signaling affects synaptic plasticity in Drosophila brain



Zeng, Jianzhi et al. Neuron. 2023

5-HT from the DPM neuron bi-directionally modulates the coincidence time window of olfactory learning





Zeng, Jianzhi et al. Neuron. 2023

5-HT regulates sociality in other model animals

饶毅

邮　　箱：yrao (AT) pku.edu.cn

职　　称：教授

办公室地址：北京市海淀区颐和园路5号，北京大学，吕志和楼，100871

所属实验室：饶毅实验室

实验室地址：北京市海淀区颐和园路5号，北京大学，吕志和楼，100871

实验室主页

http://www.raolab.cn/

饶毅现任北京大学校务委员会副主任、理学部主任、生物学讲席教授。北大麦戈文研究所创始所长、北大-清华生命科学联合中心创始主任、北京脑科学中心创始主任。

About us

1）用遗传学和分子生物学研究神经发育的分子机理，特别是神经导向分子及其信号转导机理；

2）用分子生物学、遗传学和核磁共振成像揭示社会行为的分子机理，从果蝇打架、小鼠交配、猴的亲母行为到人的脸识别；

3）用生物化学研究睡眠的分子机理，特别是蛋白质磷酸化的作用；

4）用化学分析和生化分离纯化发现新的小分子神经递质；

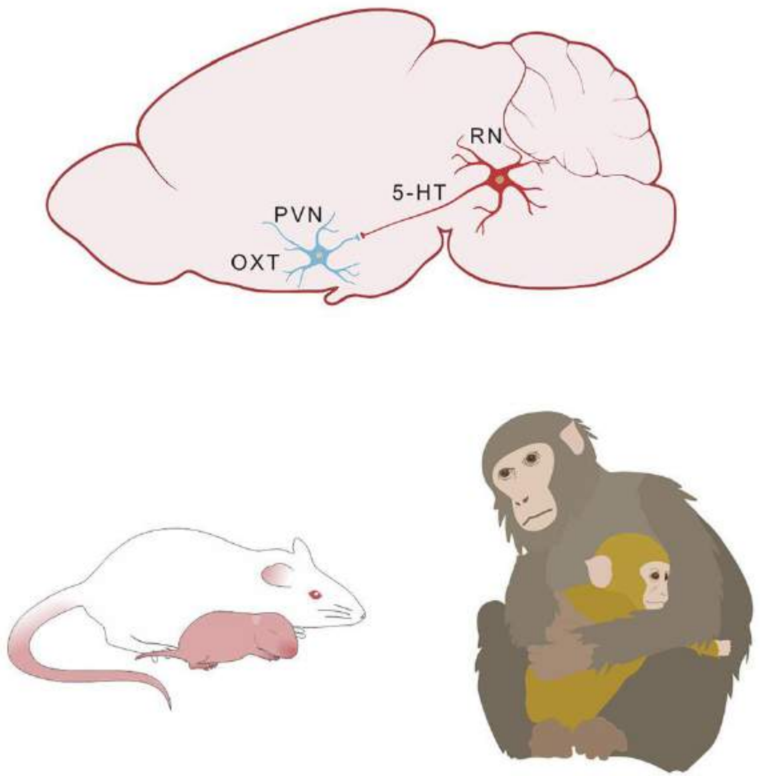
5）用现代光学成像和分子生物学研究GPCR受体的新配体；

6）研究疾病的分子机理和分子治疗方法。

Neuron

Article

Molecular and cellular mechanisms of the first social relationship: A conserved role of 5-HT from mice to monkeys, upstream of oxytocin



Authors

Yan Liu, Liang Shan, Tiane Liu, ...,
Chen Zhang, Jianzhong Xi, Yi Rao

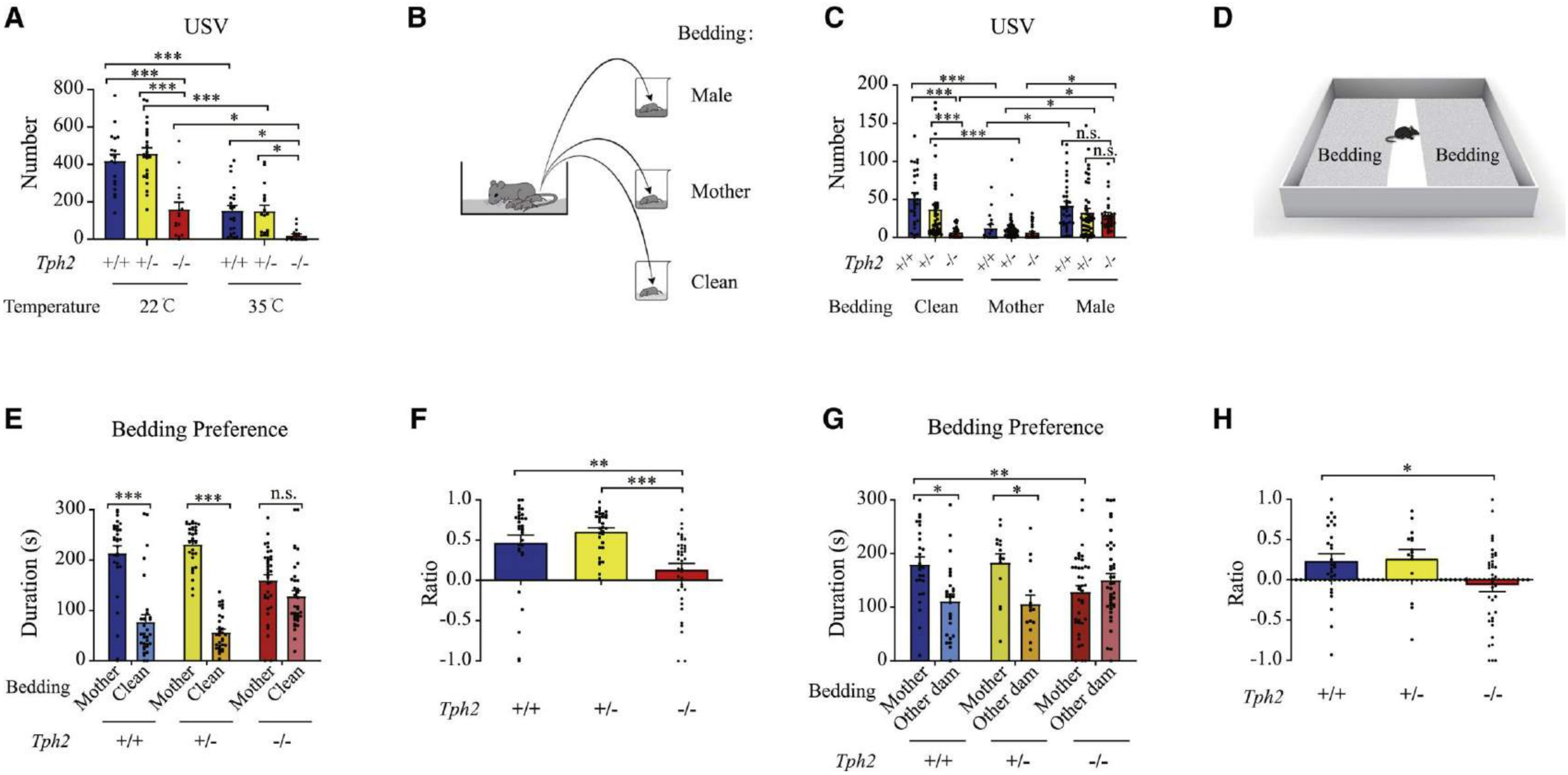
Correspondence

liuyan@ccmu.edu.cn (Y.L.),
yrao@pku.edu.cn (Y.R.)

In brief

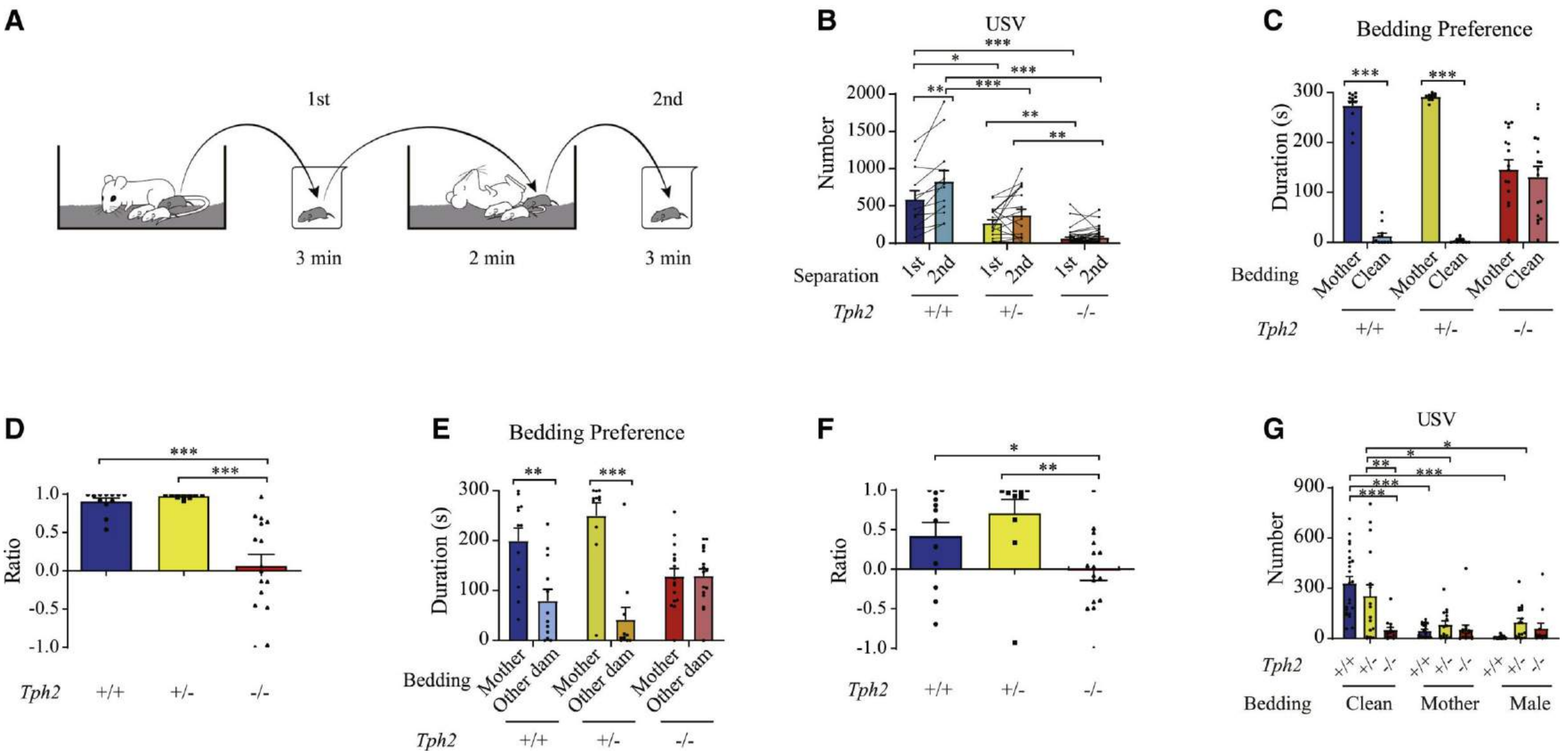
Maternal affiliation by infants is the first social behavior. Liu et al. have discovered a role for serotonin in this behavior conserved from mice and rats to monkeys. Serotonergic neurons from the raphe nucleus innervates oxytocinergic neurons in the paraventricular nucleus with serotonin acting upstream of oxytocin in maternal affiliation.

5-HT affects maternal affiliation in mouse pups



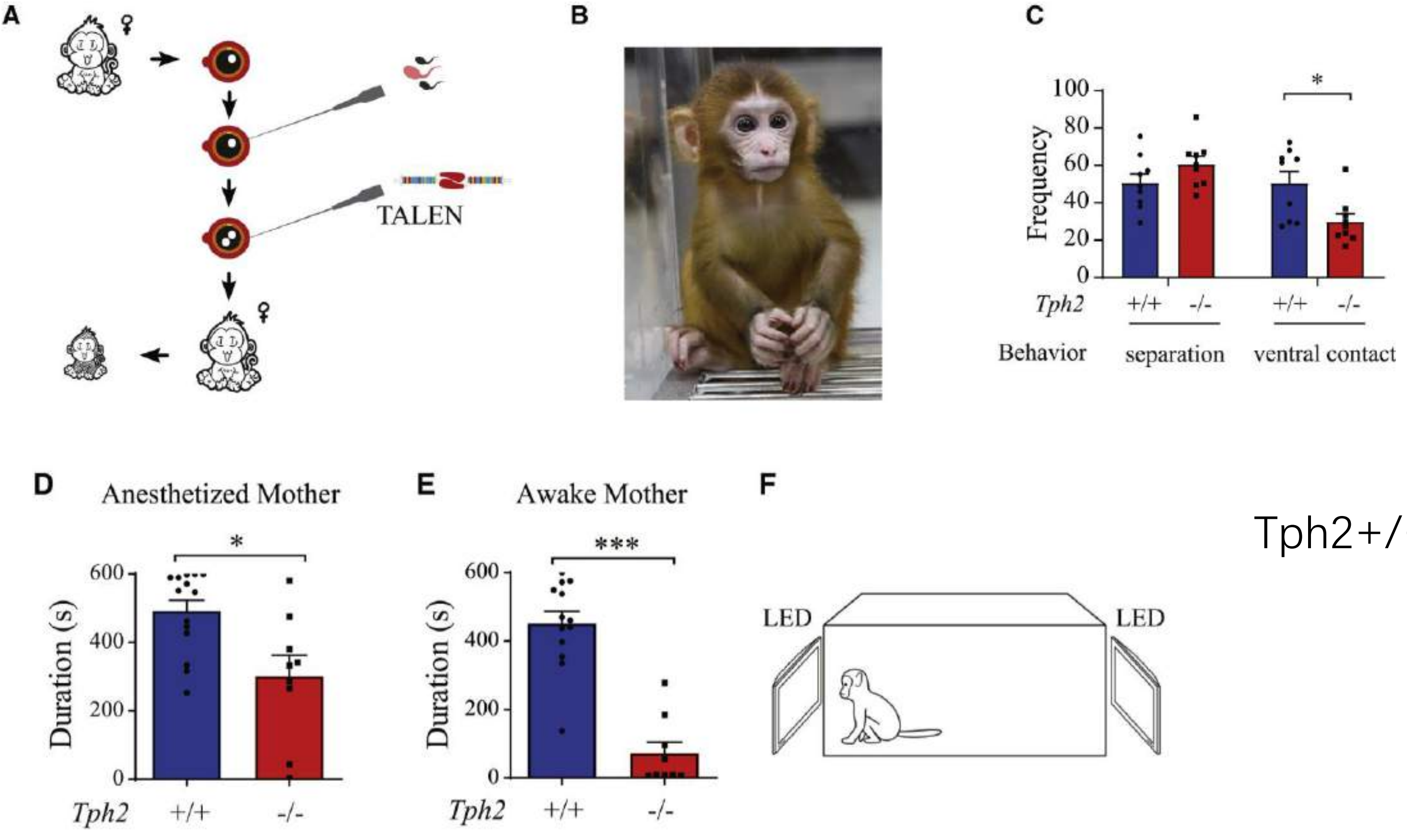
Liu, Yan et al. Neuron.2023

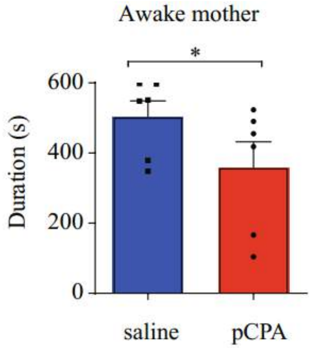
Tph2 mutant affects maternal affiliation in rat pups

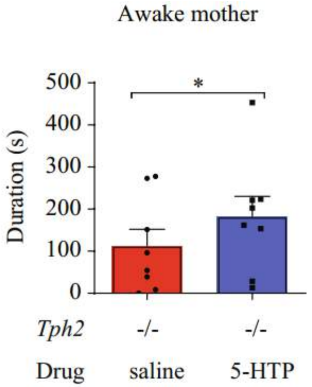


Liu, Yan et al. Neuron.2023

Maternal affiliation by Tph2−/− infant rhesus monkeys





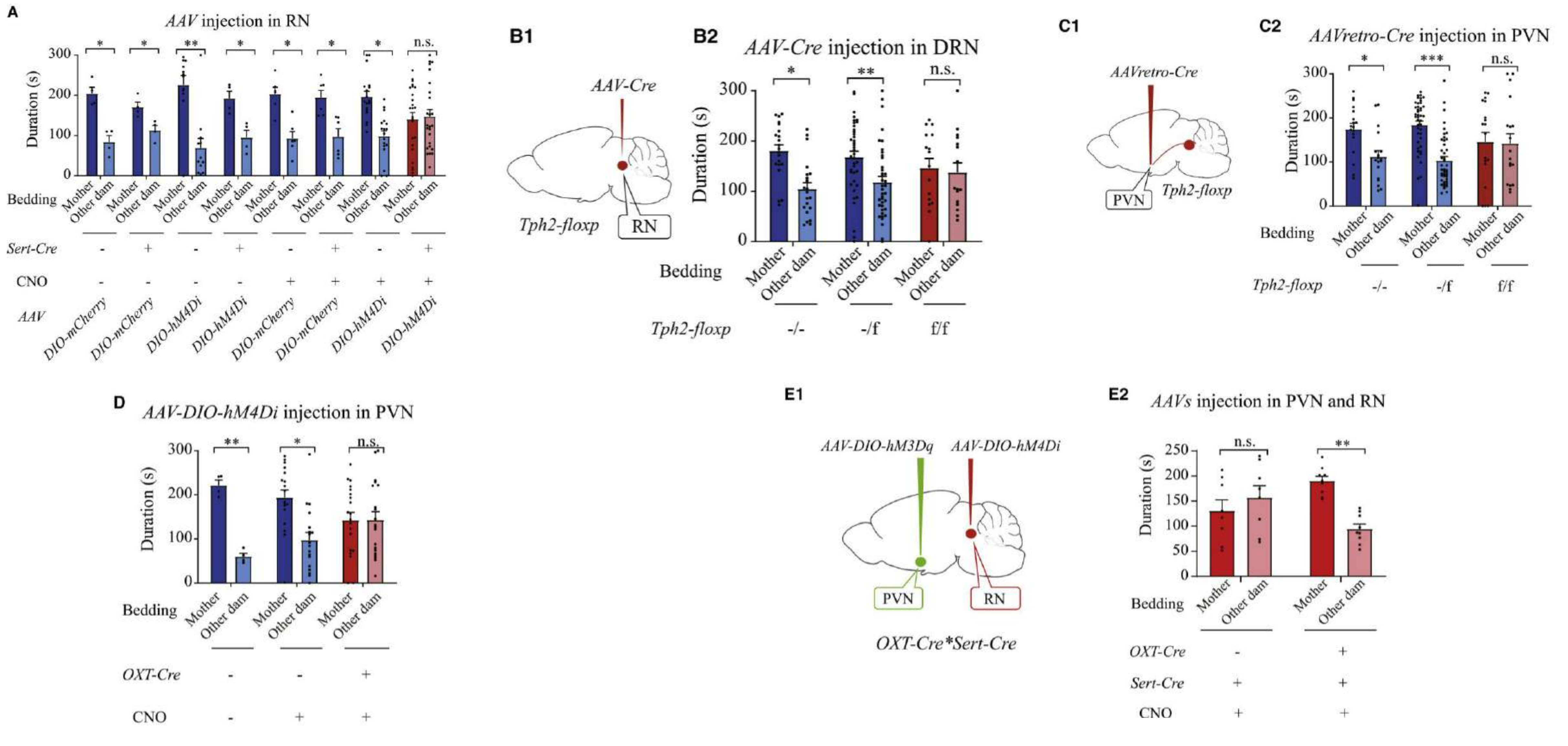


Tph2+/+

Tph2−/−

Liu, Yan et al. Neuron.2023

Oxytocinergic neurons downstream of serotonergic neurons in regulating affiliation



Summary

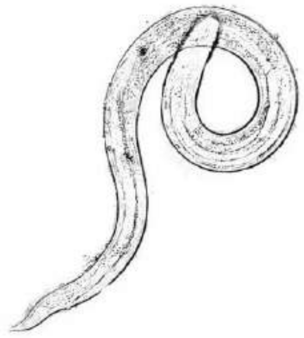
- Serotonergic neurons are involved in the regulation of many behaviors in Drosophila melanogaster, such as locomotion, sleep, aggression, and memory formation.
- Different serotonin receptor subtypes may have different regulation of the same behavior in Drosophila.

Serotonin and disease treatment in animal models

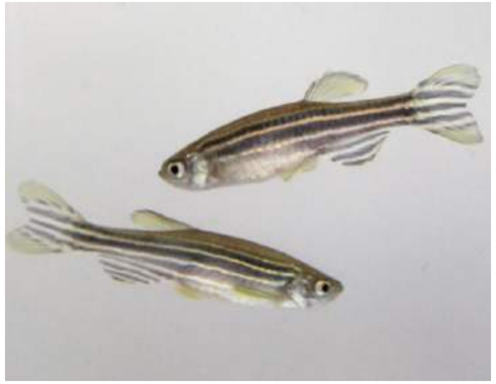
LZQ

2024.06.27

Questions：



1.The treatment principle of serotonin related diseases



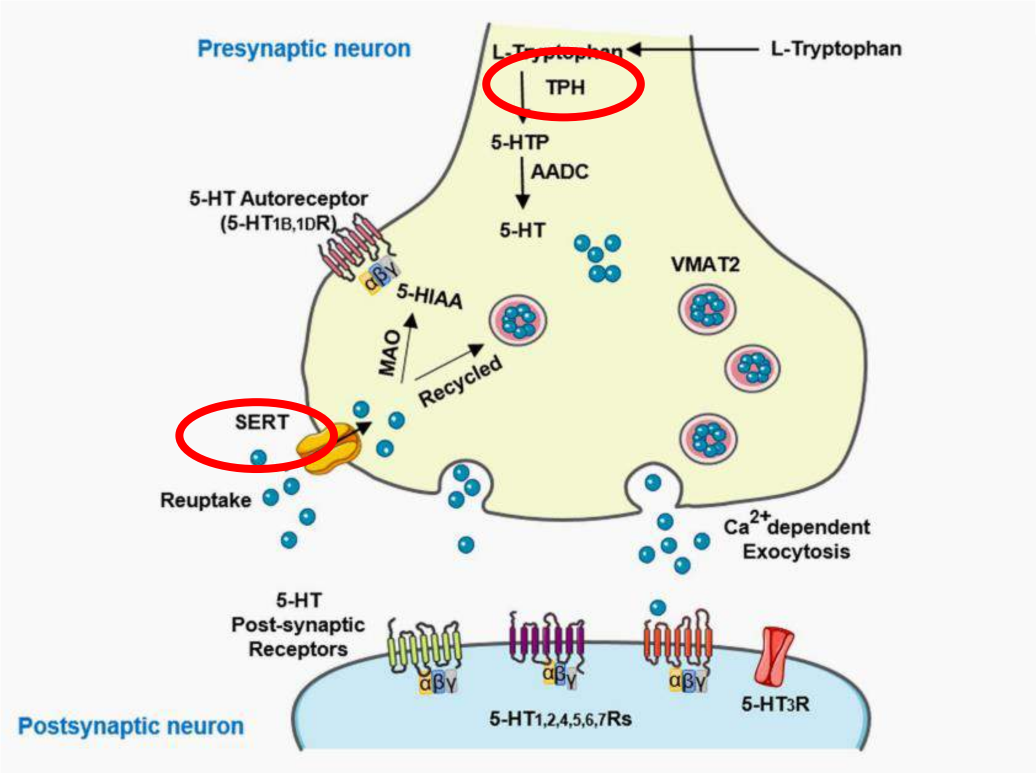
2.What are the serotonin-related diseases in model organisms

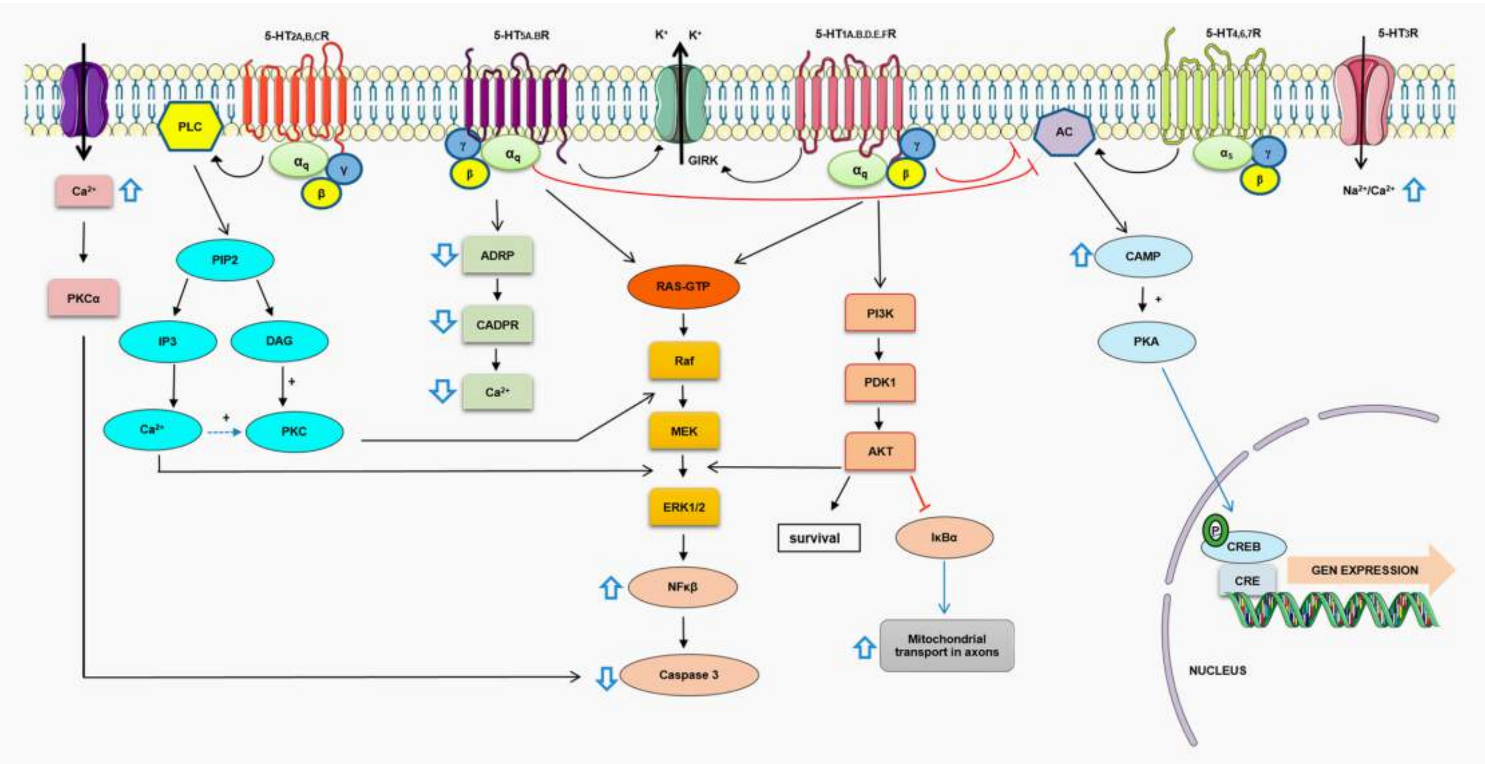
- *C. elegans*
- *Danio rerio*
- *Mus*

3.Serotonin-related drugs for use

1.The treatment principle of serotonin related diseases

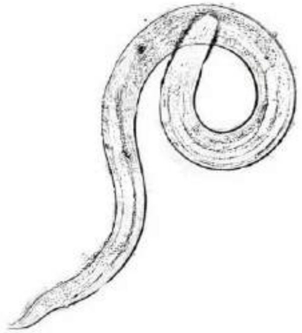
5-HT Synthesis, Metabolism and its receptors



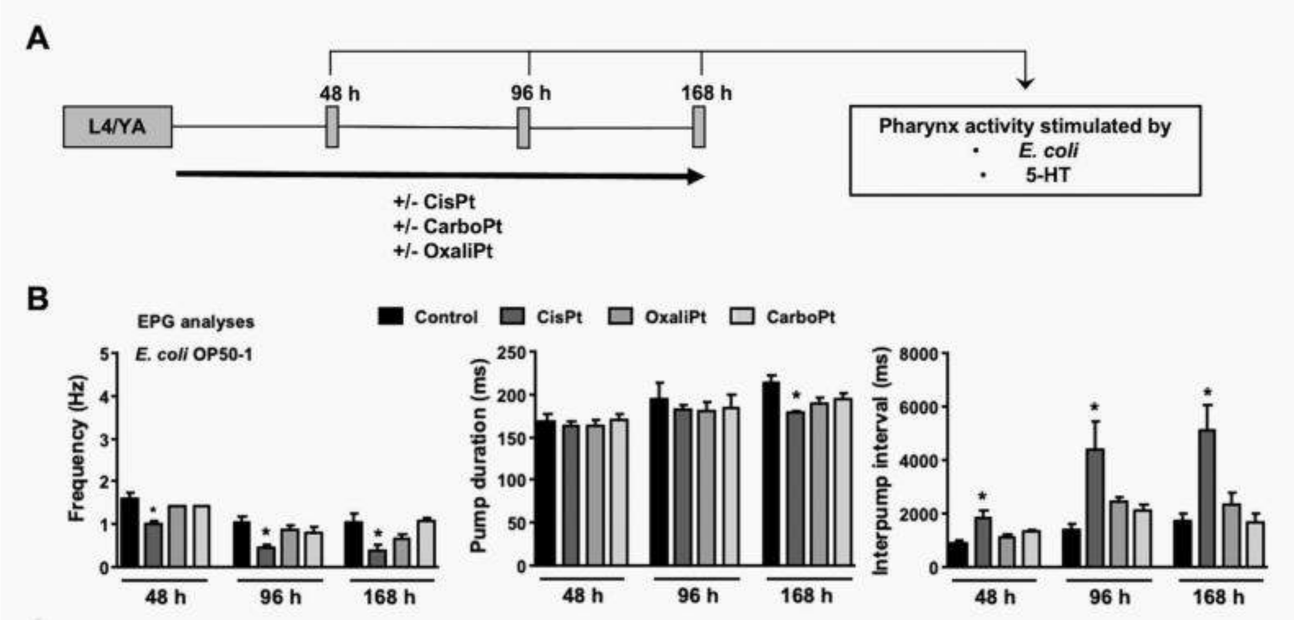


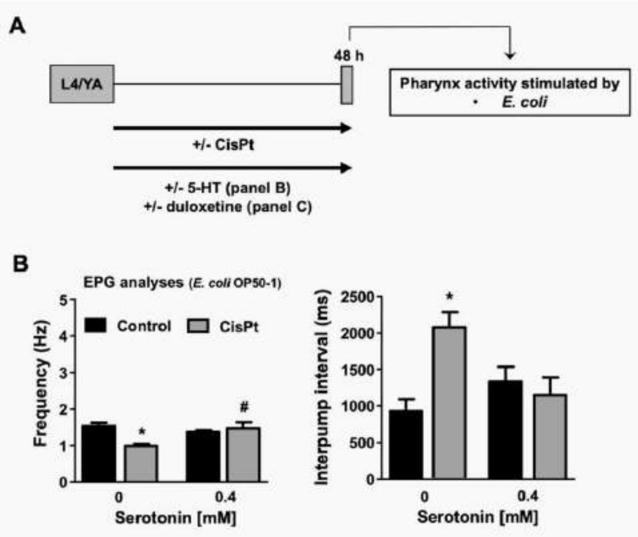
Pourhamzeh M, et al.,Cell Mol Neurobiol, 2022

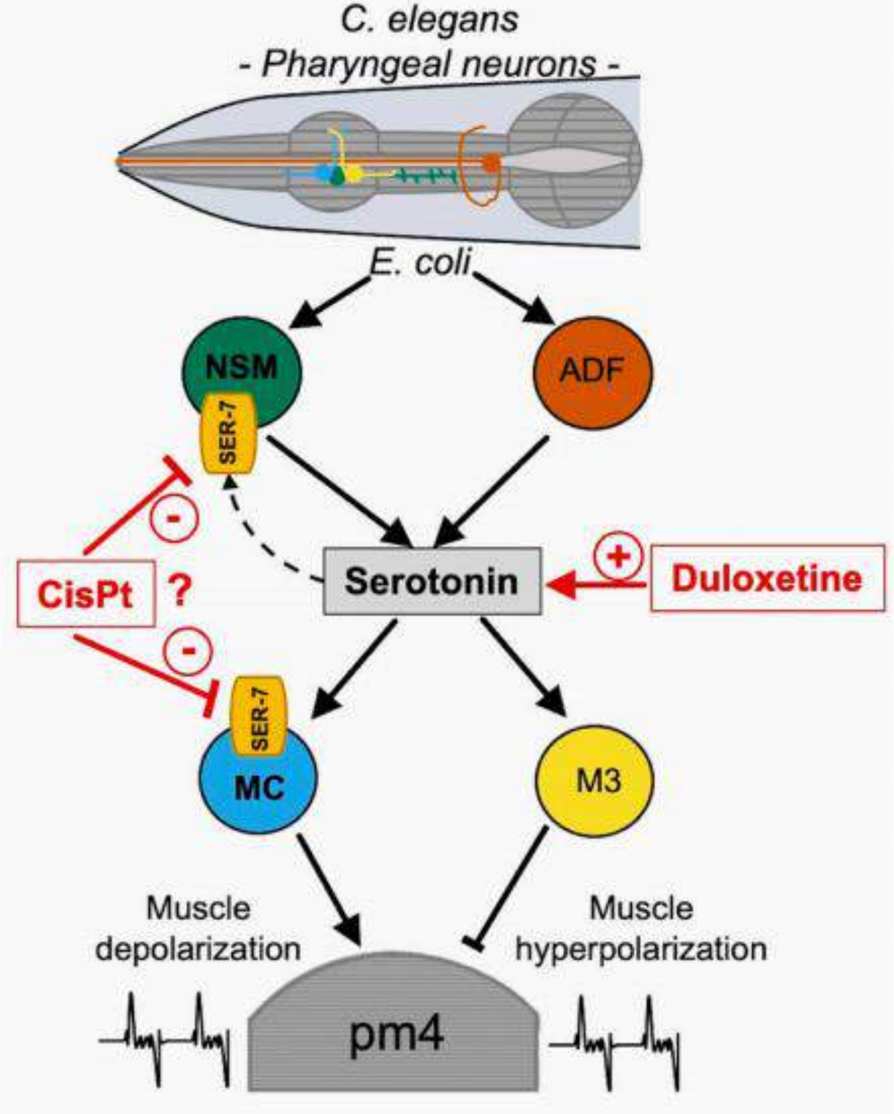
2.What are the serotonin-related diseases in model organisms



Cisplatin-induced neurotoxicity involves the disruption of serotonergic neurotransmission

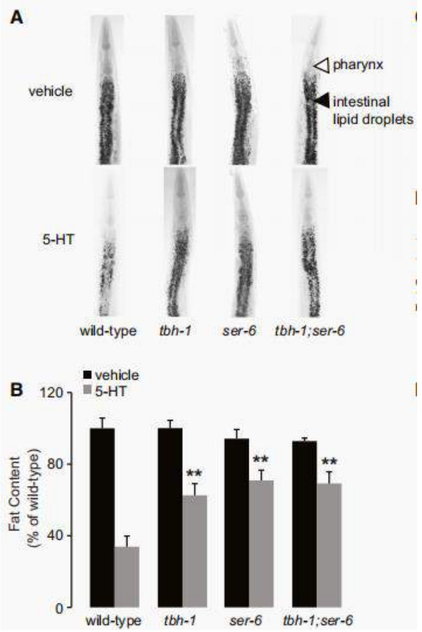


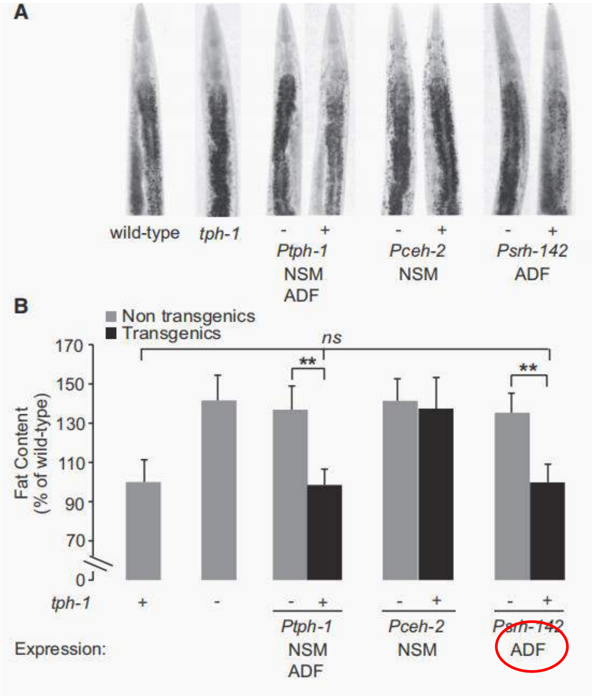


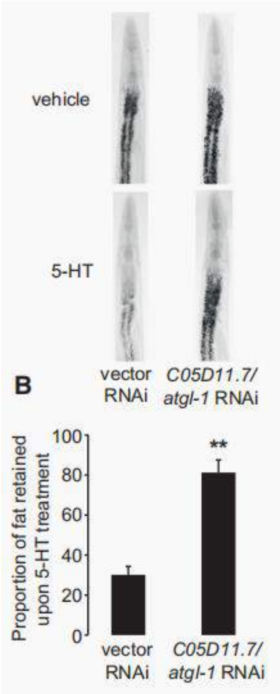


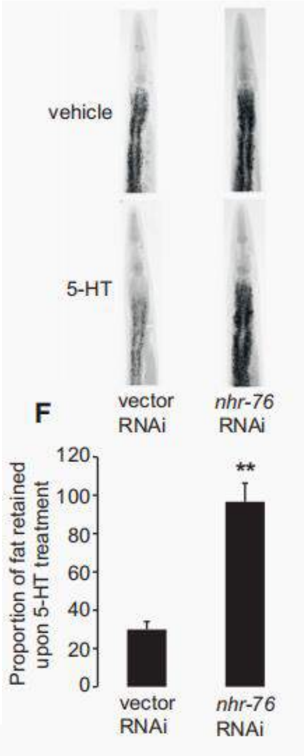
Wellenberg A, et al., Pharmacol Res,2021

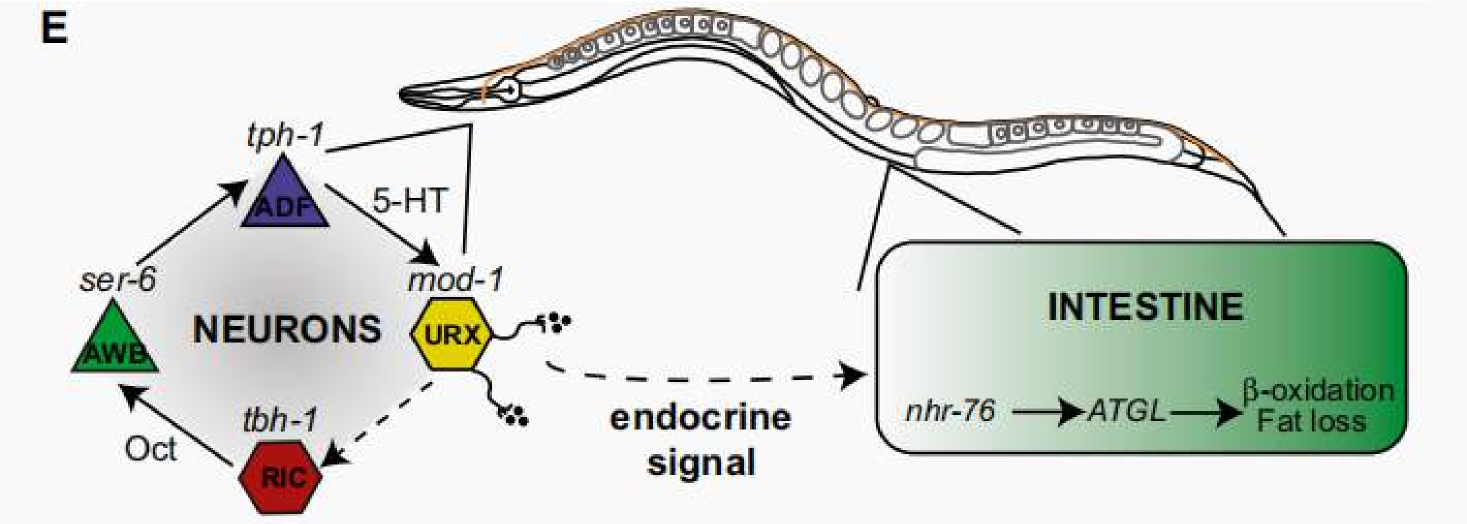
Integrated Serotonin and Octopamine Neuronal Circuit Directs an Endocrine Signal to Control Body Fat





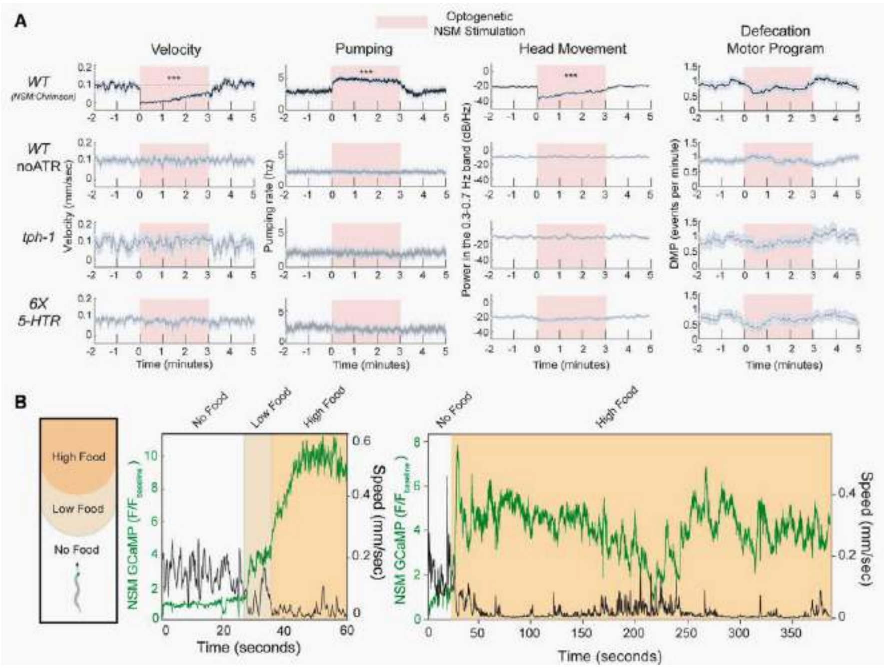


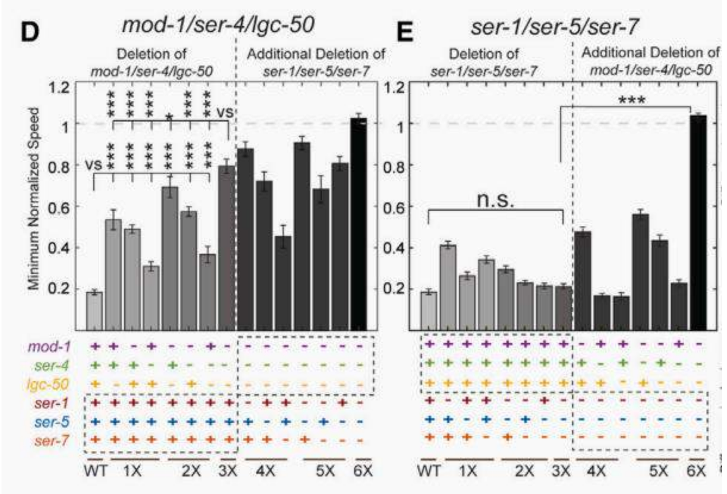


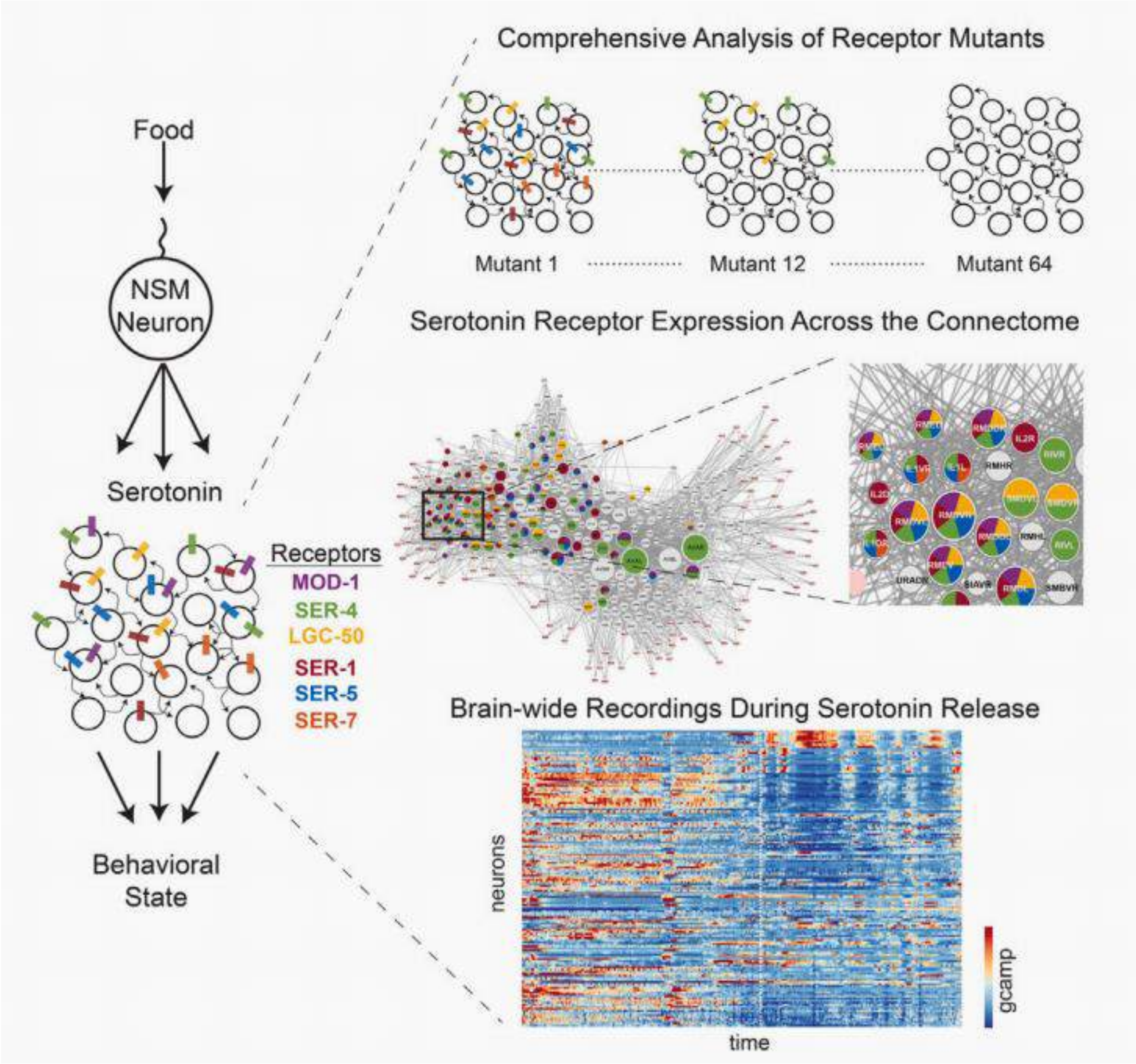


Noble T, et al., Cell Metab. 2013

Dissecting the functional organization of the C. elegans serotonergic system at whole-brain scale

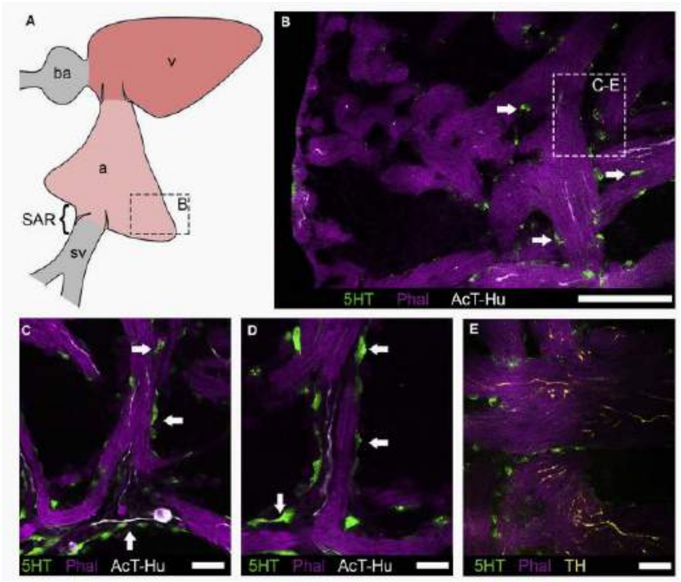


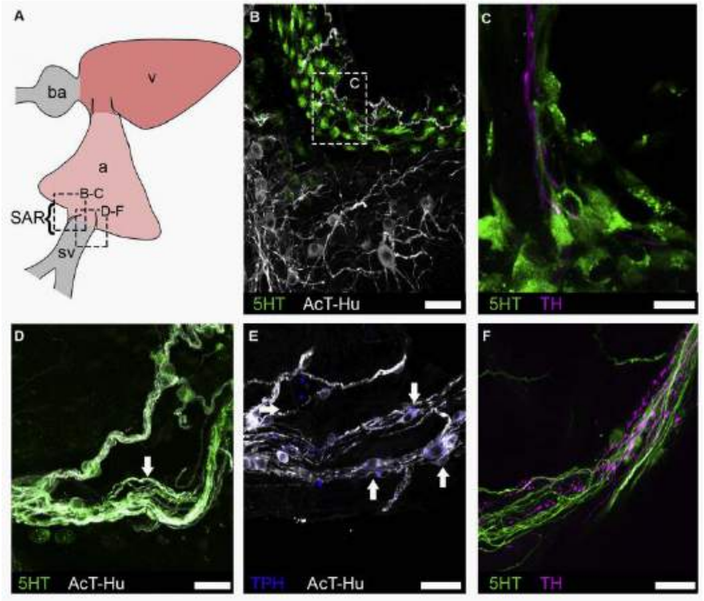




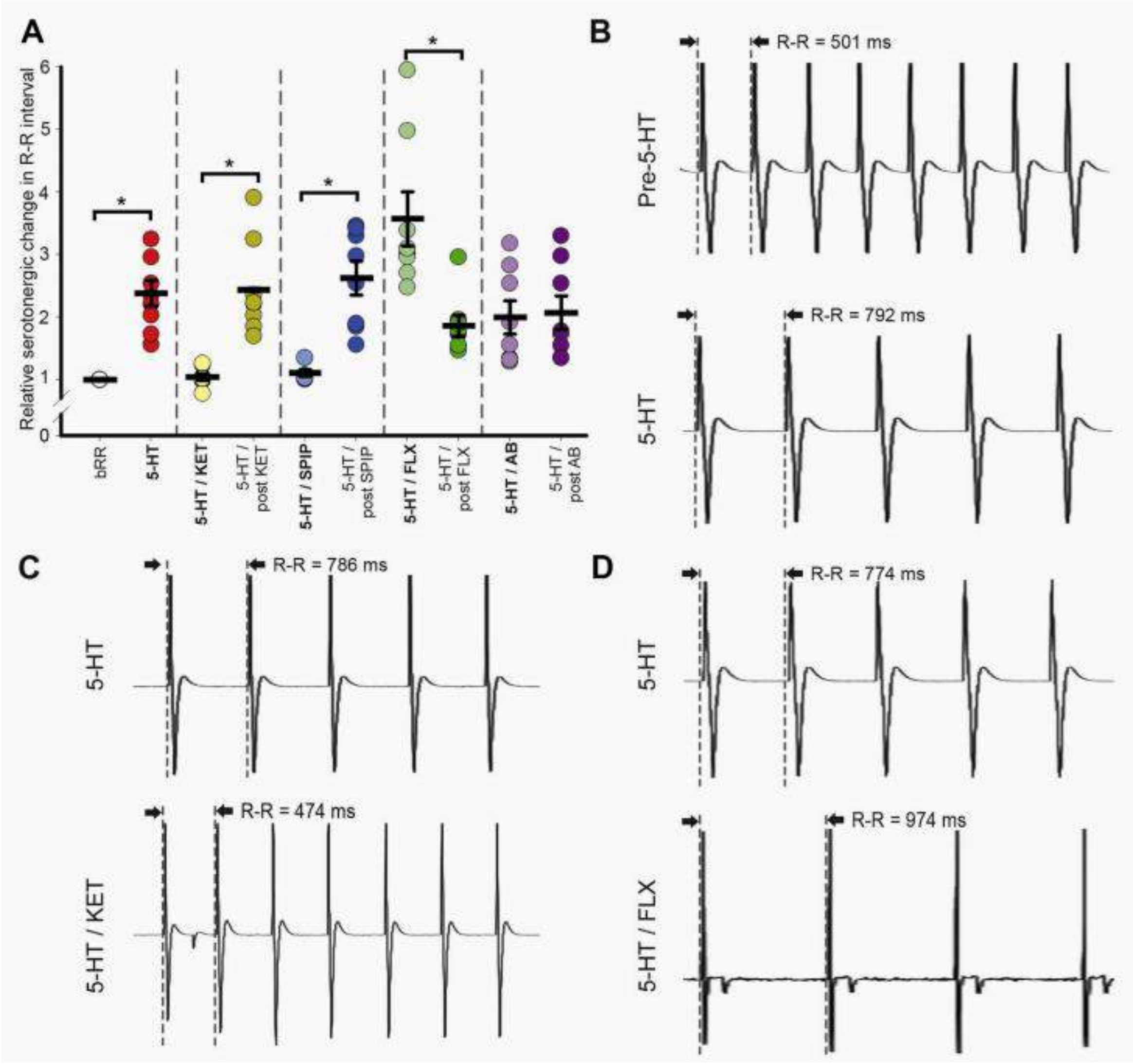
Dag U, et al., Cell, 2023

Distribution and chronotropic effects of serotonin in the zebrafish heart



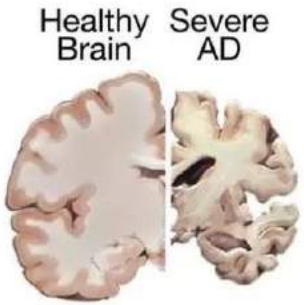


R-R interval



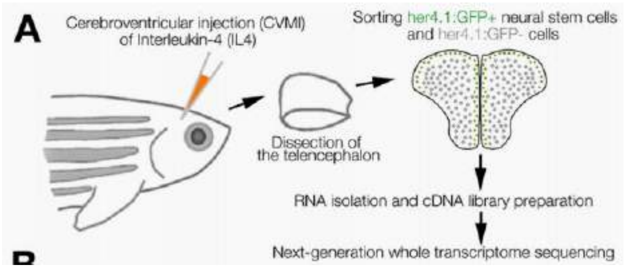
Stoyek MR, et al.,Auton Neurosci, 2017

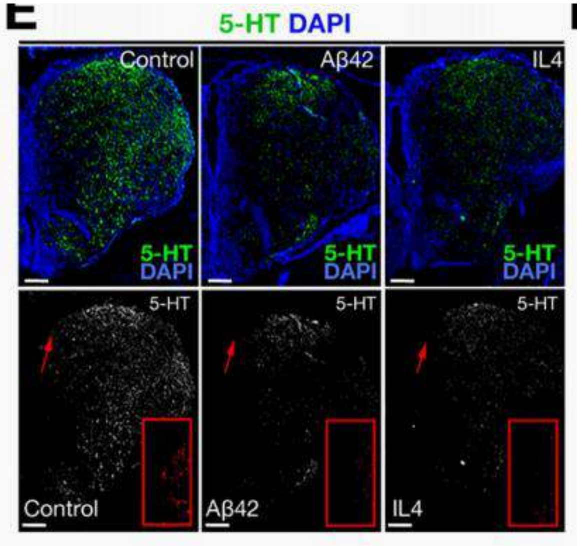
Serotonin-BDNF-NGFR axis enables regenerative neurogenesis in Alzheimer's model

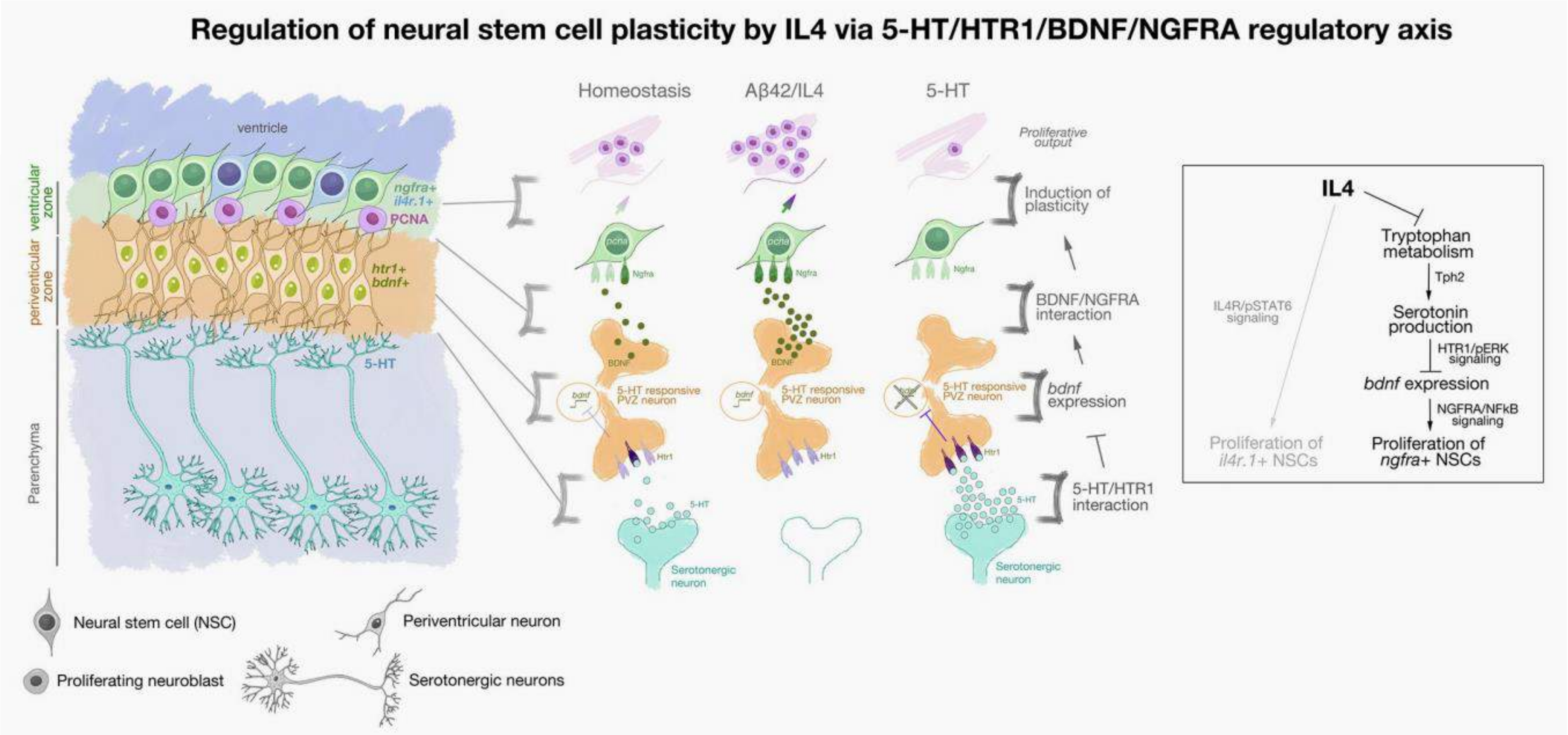


preventing the death of the neurons

increasing the production of new neurons

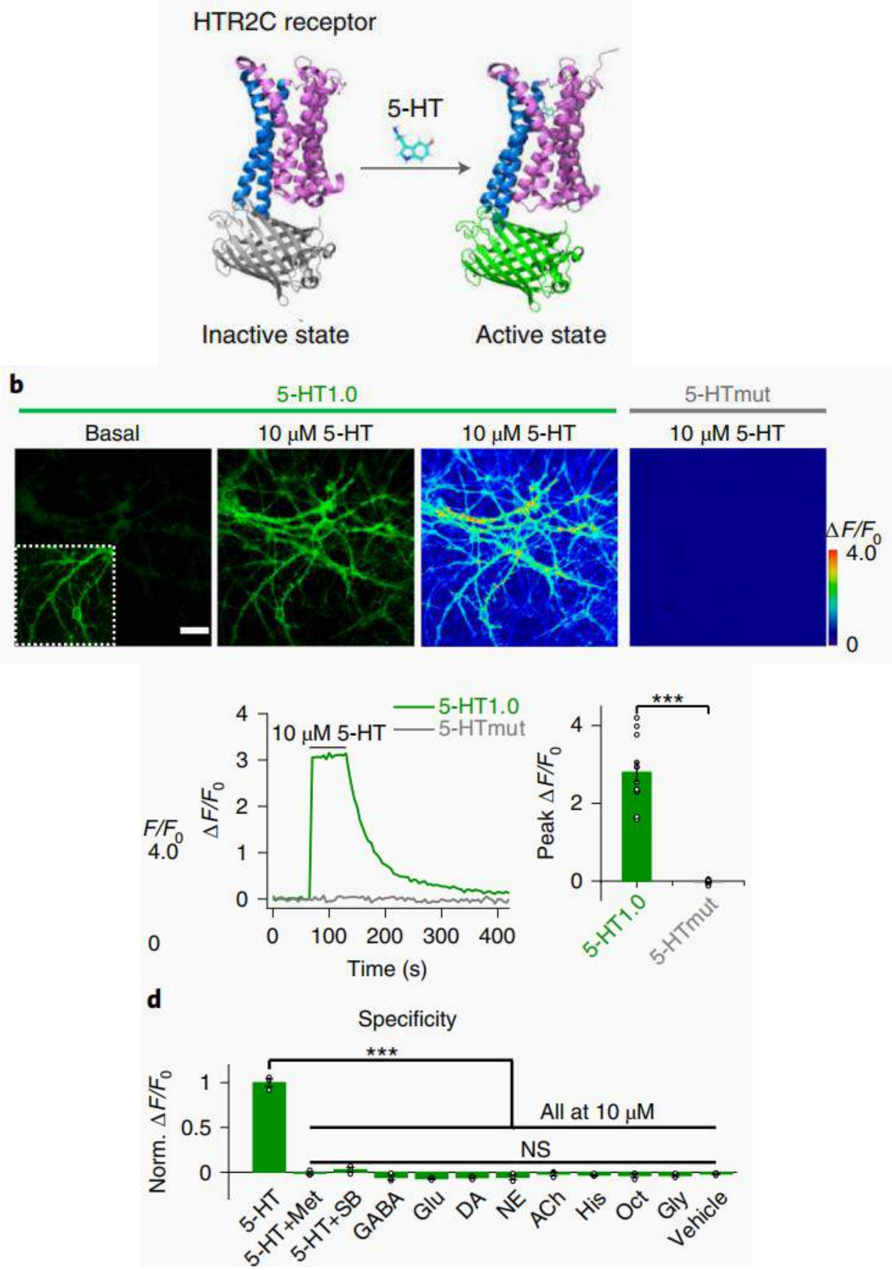


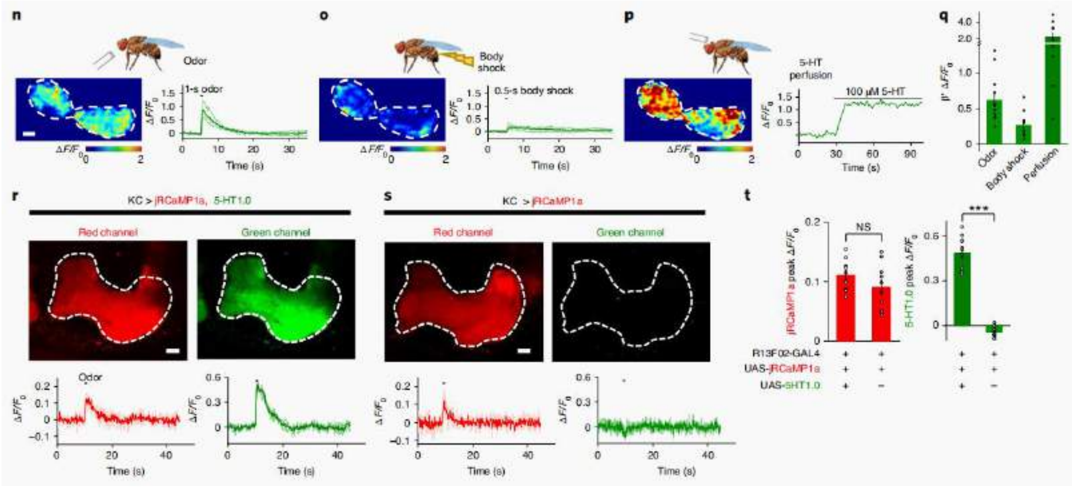


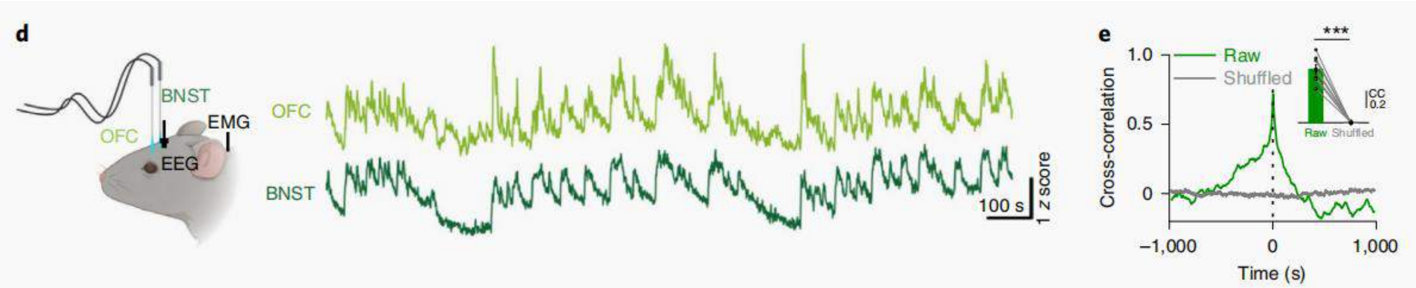


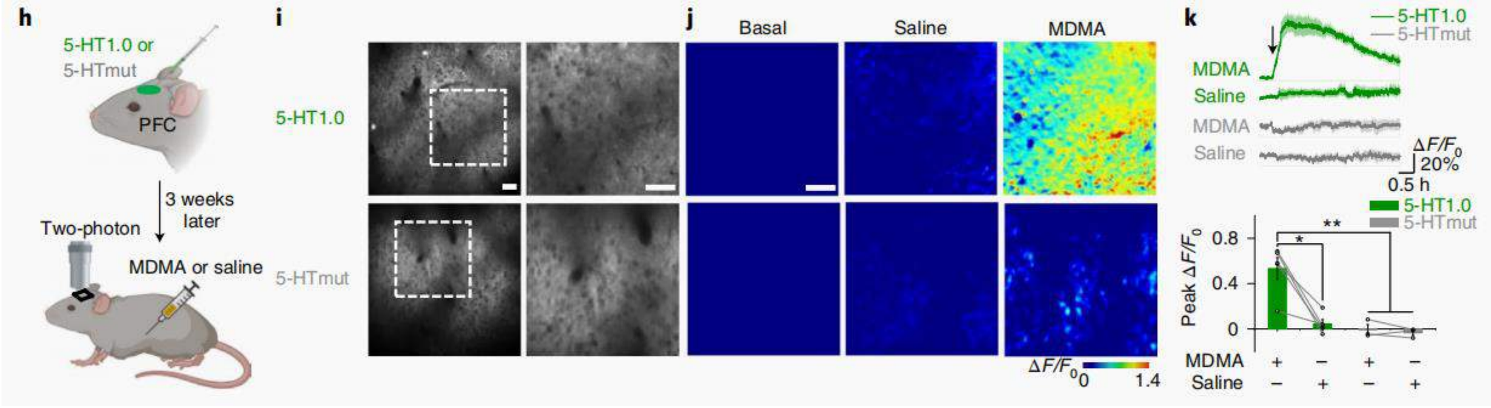
Bhattarai P, et al., PLoS Biol, 2020

A genetically encoded sensor for measuring serotonin dynamics









Wan J, et al., Nat Neurosci, 2021

办公地址：

北京大学吕志和楼436

联系电话：

010-62766905

电子邮箱：

yulongli@pku.edu.cn

个人网页：

http:// yulonglilab.org

李毓龙

教授、博士生导师

北京大学生命科学学院

北京大学麦戈文脑研究所

北大-清华生命科学联合中心

北京大学国家生物医学成像科学中心（兼）

个人简介

人的大脑由数十亿的神经元组成，后者又通过数万亿的突触组成复杂的神经网络。不同种类的神经元经过或远或近的投射，通过突触与其他神经元进行信息交流，实现感知、决策和运动等高级神经功能。

研究大脑的最大挑战在于脑的高度复杂性。实验室集中在神经元通讯的基本结构突触上，从两个层面上开展研究：一是开发前沿的工具，即开发新型成像探针，用于在时间和空间尺度上解析神经系统的复杂功能；二是借助先进的工具探究突触传递的调节机制，特别是在生理及病理条件下对神经递质释放的调节。

具体而言，对于工具开发，集中于：

1.结合光遗传学和荧光成像，无损伤性的研究神经元之间的电突触连接。电突触的异常可导致耳聋、癫痫、脑部肿瘤和心脏功能异常等疾病。

2.开发可遗传编码的检测神经递质/调质的荧光探针。神经递质/调质是神经元化学突触传递的关键介导分子，与感知、学习和记忆以及情绪密切相关。

利用上述荧光探针，针对功能性和生理性的研究集中于：

1.结合生物信息学、分析化学、生物化学、生理学和成像学方法，系统地探索和鉴定潜在的新型小分子神经递质。

2.研究神经元中重要的分泌性囊泡“高密度核心囊泡”的蛋白质组学，分析囊泡内的神经肽组成。这些神经肽对于调节食物摄取、侵犯性行为和生物节律有重要的调节作用。

3.寻找上述新型化学递质/调质小分子的对应受体，即寻找“孤儿”受体的配体。

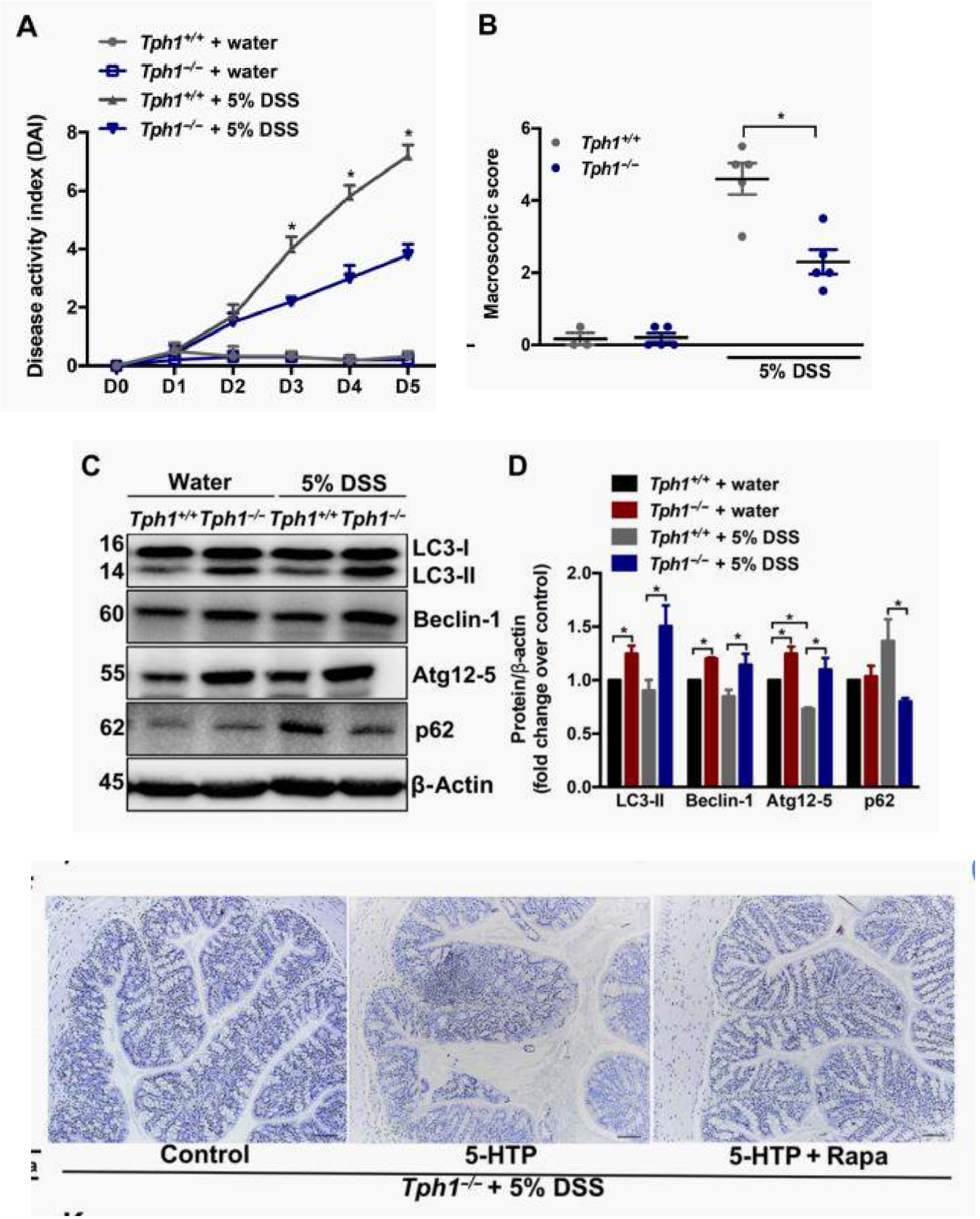
4.结合双光子成像和可遗传编码的荧光探针，使用果蝇和小鼠作为模式生物，研究嗅觉传导或睡眠过程中脑的工作机制。

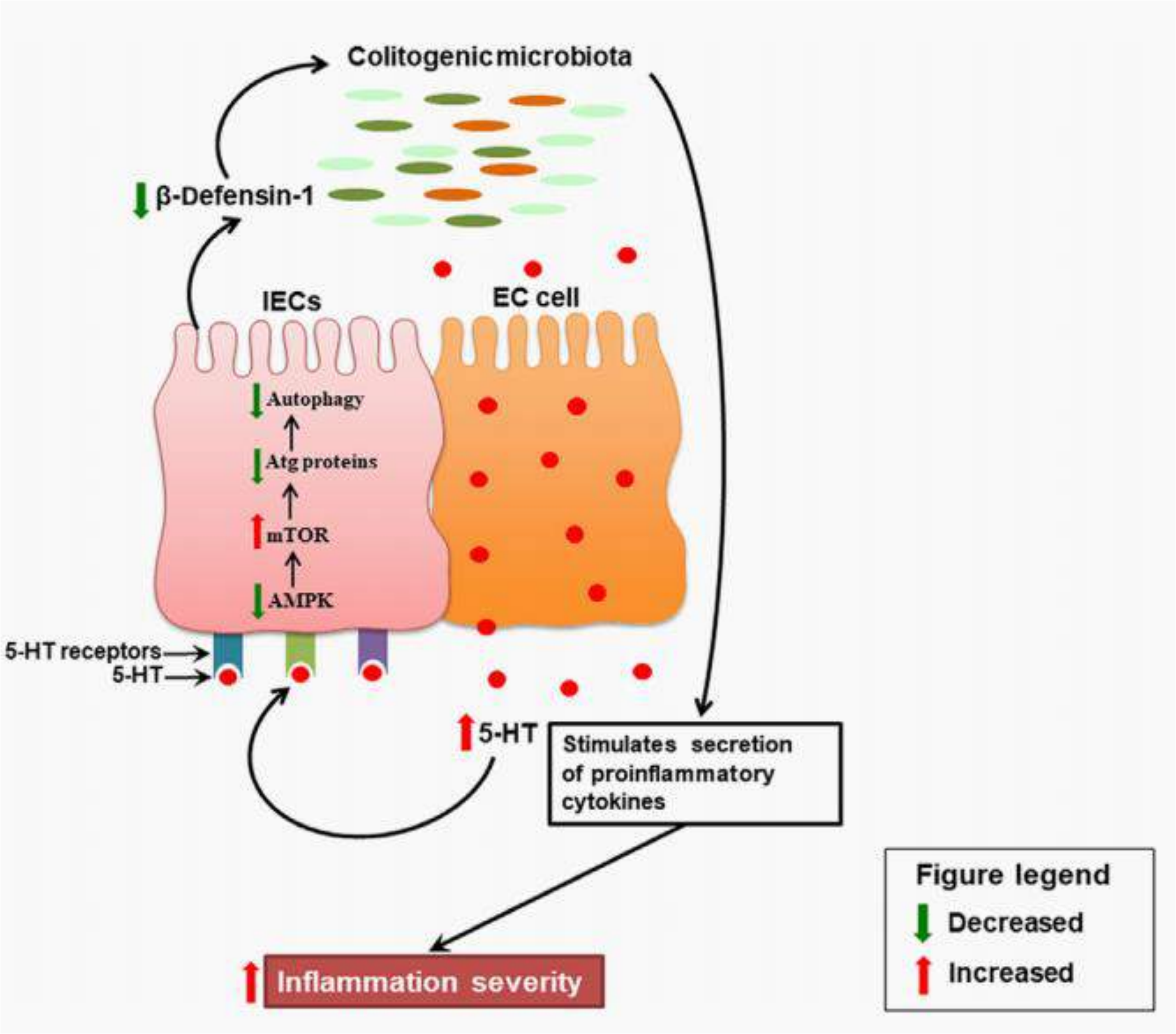
The laboratory focuses on the research of new neurotransmitter receptors, and has independently developed high-efficiency fluorescent probes for acetylcholine, dopamine, norepinephrine, adenosine and other neurotransmitters in recent years.

Representative papers:

1. Jing, M., Zhang, P., Wang, G., Feng, J., … Zhu, JJ. # & Li, Y. # (2018). A genetically-encoded fluorescent acetylcholine indicator for in vitro and in vivo studies. **Nature Biotechnology**, 36(8), 726-737.
2. Sun, F., Zeng, J., Jing, M., Zhou, J., Feng, J., … & Li, Y. # (2018). A genetically-encoded fluorescent sensor enables rapid and specific detection of dopamine in flies, fish, and mice. **Cell**, 174(2), 481-496.
3. Yu, H., Zhao, T., Liu, S., Wu, Q., Johnson, O., Wu, Z., Zhuang, Z., Shi, Y., He, R., Yang, Y., Sun, J., Wang, X., Xu, H., Zeng, Z., Lei, X., Luo, W.# & Li, Y.# (2019). MRGPRX4 is a bile acid receptor for human cholestatic itch. **eLife**, 8, e48431.
4. Wu, L., Dong, A., Dong, L., Wang, S. Q., & Li, Y. # (2019). PARIS, an optogenetic method for functionally mapping gap junctions. **eLife**, 8, e43366.
5. Feng, J., Zhang, C., Lischinsky, JE., Jing, M., … & Li, Y. # (2019). A genetically encoded fluorescent sensor for rapid and specific in vivo detection of norepinephrine. **Neuron**, 102(4), 745-761.
6. Jing, M. #, Li, Y., Zeng, J., Huang, P., … & Li, Y. # (2020). An optimized acetylcholine sensor for monitoring in vivo cholinergic activity. **Nature Methods**, 17(11), 1139-1146.
7. Sun, F., Zhou, J., Dai, B., Qian, T., ⋯, Lin, D. #, Cui, G. #, & Li, Y. # (2020). Next-generation GRAB sensors for monitoring dopaminergic activity in vivo. **Nature Methods**, 17(11), 1156-1166.
8. Qian, C., Wu, Z., Sun, R., Yu, H., Zeng, J., Rao, Y., & Li, Y. # (2021). Localization, proteomics, and metabolite profiling reveal a putative vesicular transporter for UDP-glucose. **eLife**, 10, e65417.
9. Wan, J., Peng, W., Li, X., Qian, T., ⋯, & Li, Y. # (2021). A genetically encoded GRAB sensor for measuring serotonin dynamics. **Nature Neuroscience**, 24(5), 746-752.
10. Wu, Z. #, He, K., Chen, Y., Li, H., Pan, S., Li, B., Liu, T., Wang, H., Du, J., Jing, M., & Li, Y. # (2022). A sensitive GRAB sensor for detecting extracellular ATP in vitro and in vivo. **Neuron**, 110, 770-782 e775.

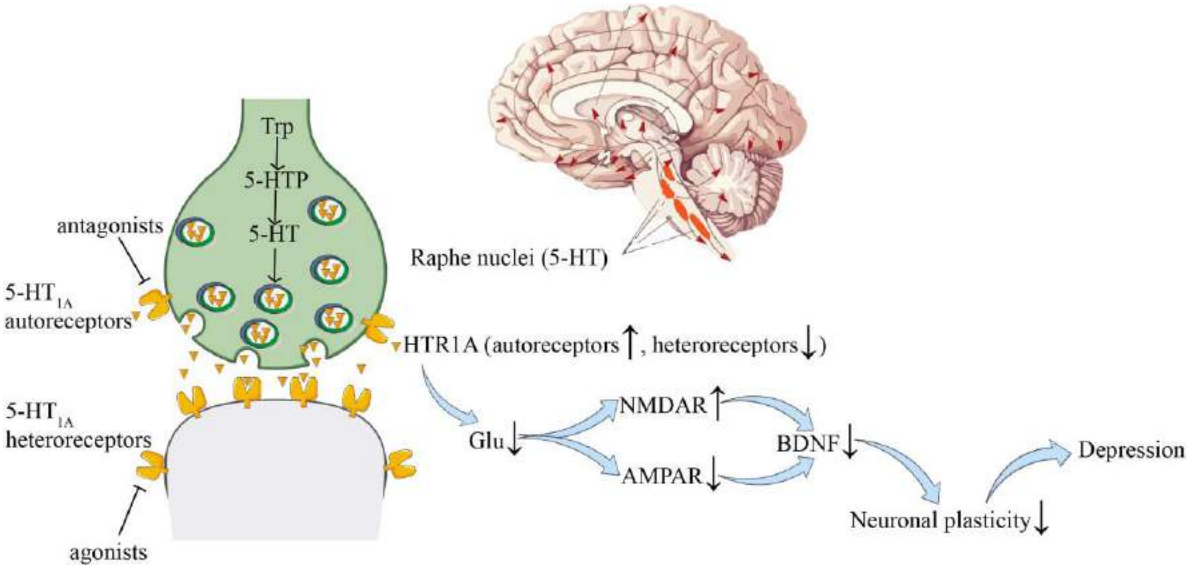
Disruption of autophagy by increased 5-HT alters gut microbiota

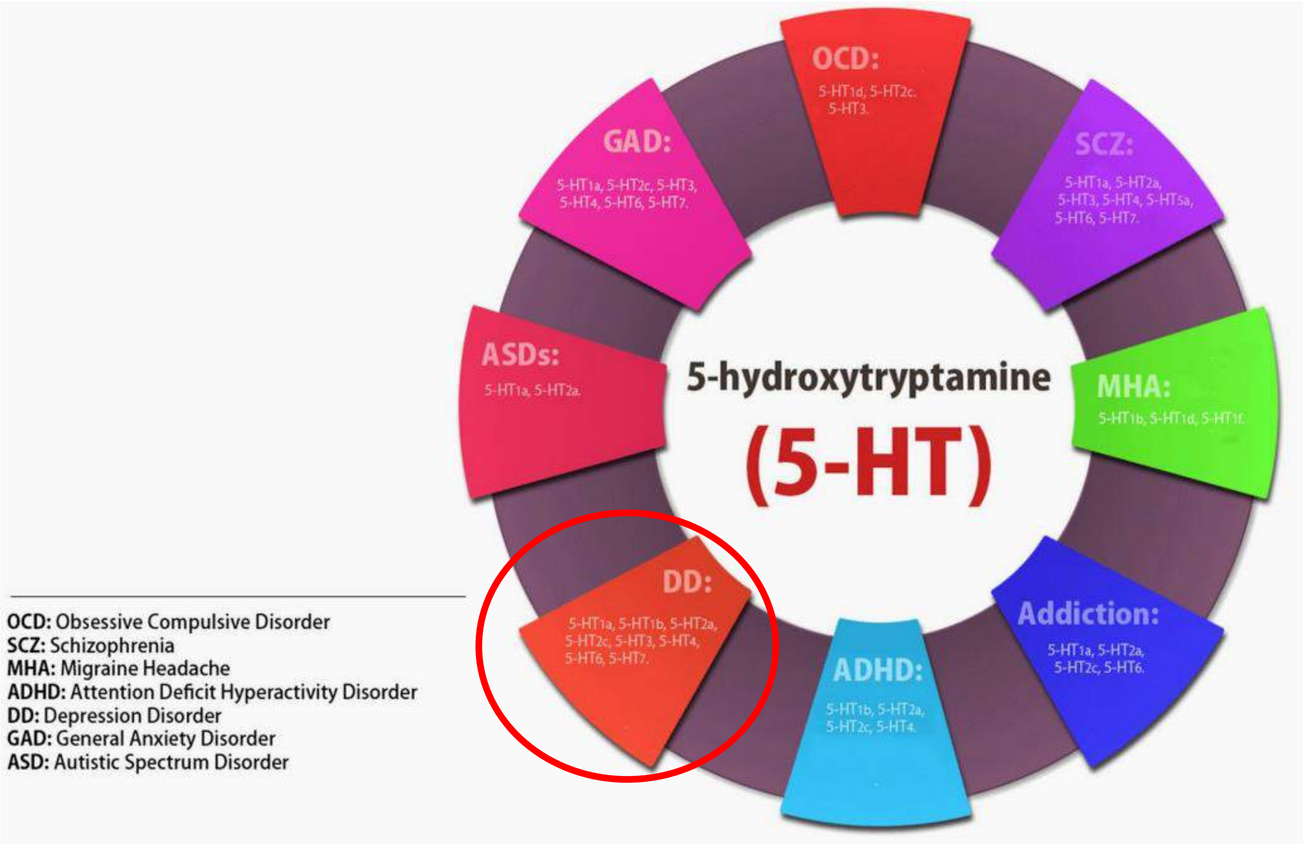




Haq S, et al., Sci Adv, 2021

The serotonin theory of depression



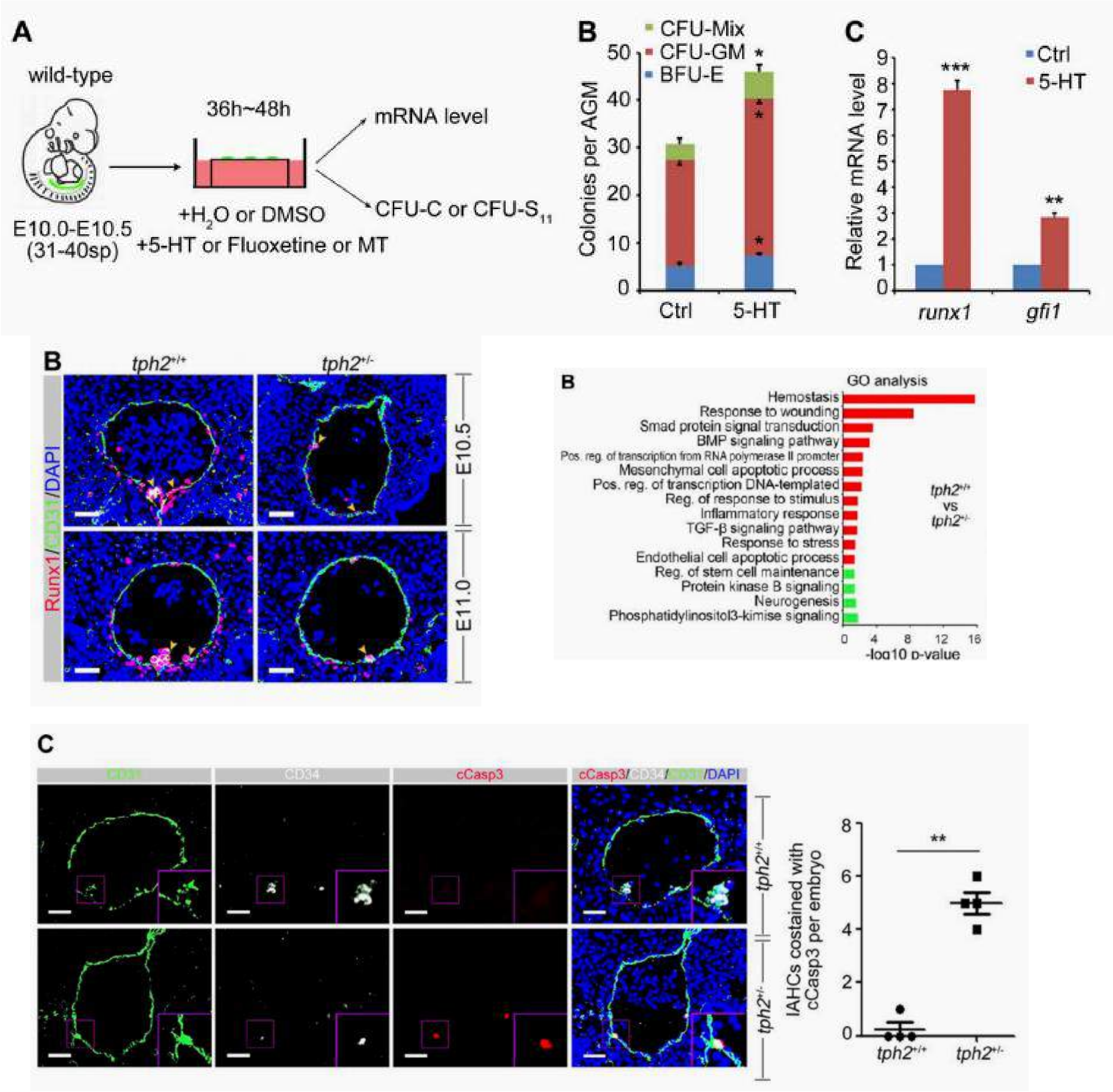


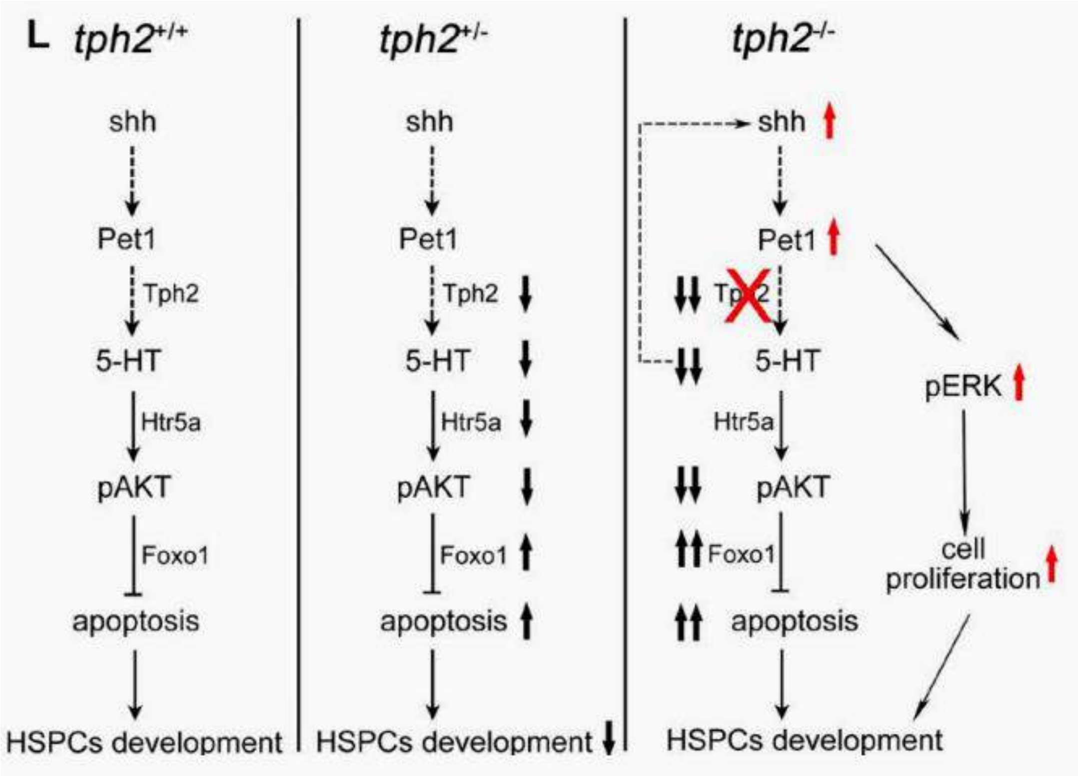
A summary of the major nervous system diseases associated with dysfunctions in serotonergic receptors

Wang HQ, et al., Pharmacol Res. 2021

Pourhamzeh M, et al.,Cell Mol Neurobiol, 2022

5-hydroxytryptamine regulates hematopoietic stem and progenitor cell survival





Lv J, et al., J Exp Med, 2017

3.Serotonin-related drugs for use

SSRIPrescription antidepressants——Inhibit serotonin reuptake into presynaptic cells

Citalopram (Lundbeck)

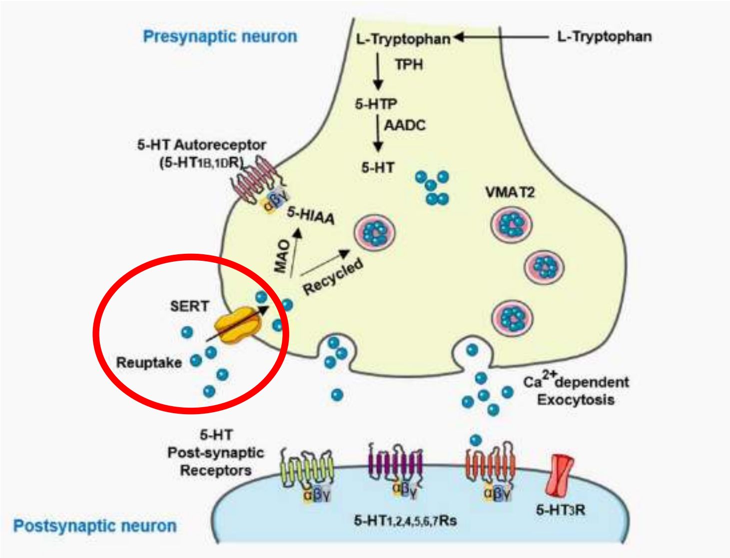
Escitalopram oxalate (Lundbeck)

Fluoxetine (Lilly)

Fluvoxamine (Abbott Solvay)

Paroxetine (GSK Plc)

Sertraline (Pfizer)



Better clinical efficacy and tolerability	Escitalopram	Sertraline
Quickest effect	Escitalopram	
The most exciting effect	Fluoxetine	Sertraline
The most calming effect	Fluvoxamine	Paroxetine
Best treatment for anxiety	Paroxetine	
Best tolerated	Escitalopram	Sertraline

http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId51

Summary：

1.Serotonin has been linked to many diseases, and it has been extensively studied in model organisms

- *C. elegans* : Cisplatin-induced neurotoxicity、Body Fat
- *Danio rerio* : Autonomic cardiac control、Dravet Syndrome、Alzheimer's Disease
- *Mus* : Enteritis、Depression、Hematopoietic stem and progenitor cell survival

2.Technology has been developed to detect serotonin activity in real time

3.SSRI drug targets — inhibit serotonin reuptake into presynaptic cells and increase serotonin levels in the synaptic gap

What can we learn from this journal?

- Serotonin is acting not only as a classical neurotransmitter, but also as a neurotrophic factor. But these studies have focused mainly on mammals.
- The complex cellular and molecular roles of amines are not yet fully understood, and the interactions between amines should not be ignored when conducting related studies.
- Exploring the co-regulation of different serotonin receptor subtypes in Drosophila Drosophila is a focus of current research.
- The distribution of serotonin neurons in different locations may regulate the same behavior in different directions.
- The receptor of serotonin is an important target for many diseases, and there is much room for exploitation.
- Technology has been developed to detect serotonin activity in real time.

Thank you!