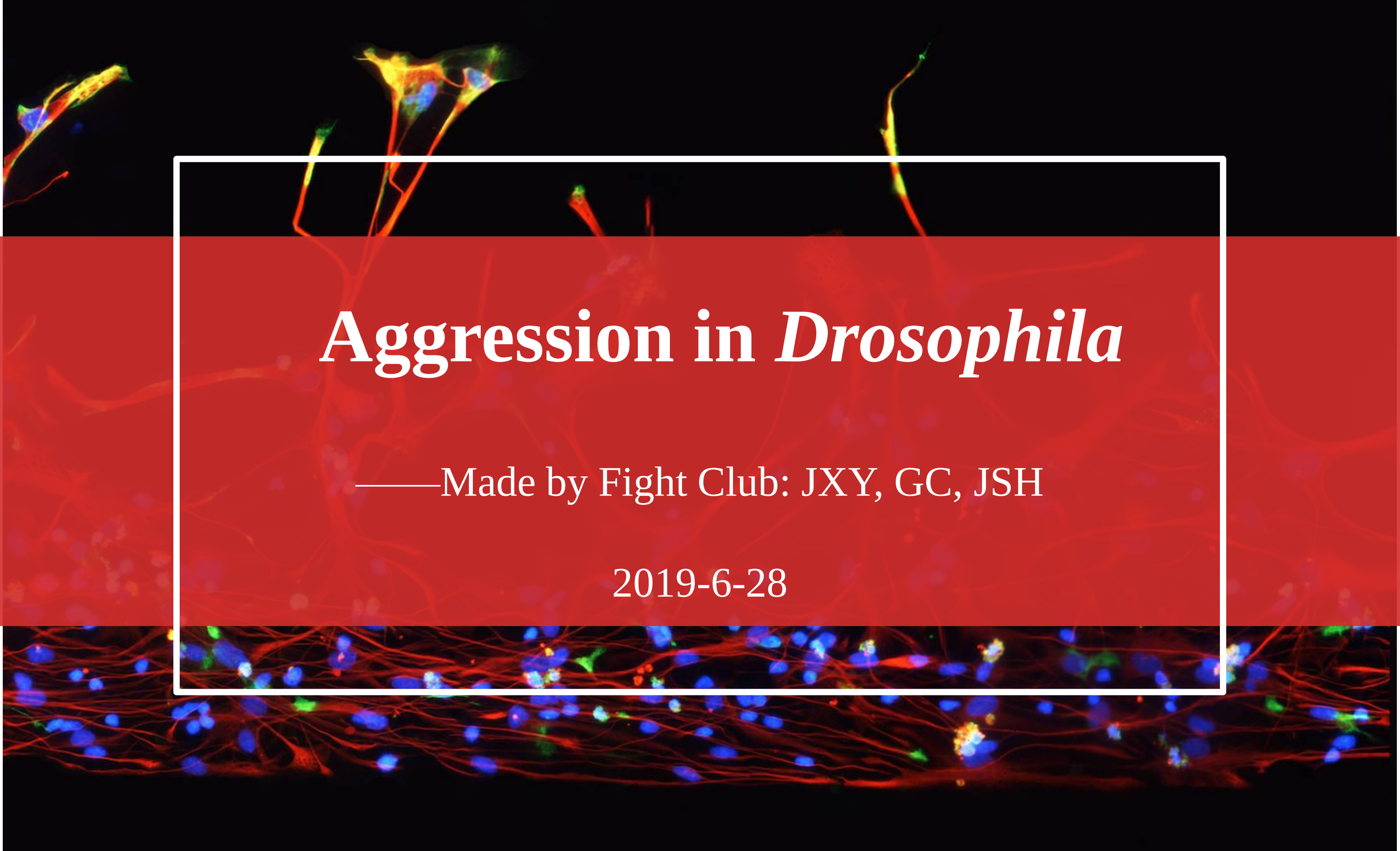


Aggression in *Drosophila*

——Made by Fight Club: JXY, GC, JSH

2019-6-28

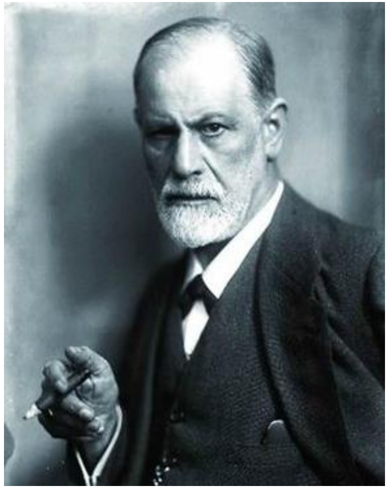
Aggressive behavior is widely present throughout the animal kingdom

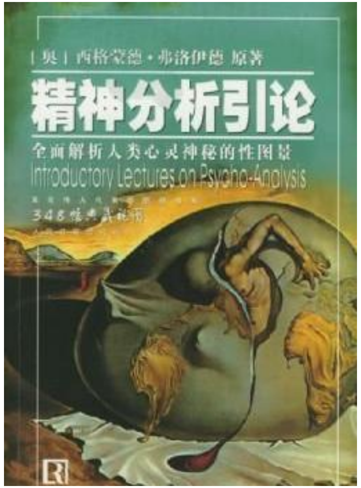
for territory, food or mates

in defense of the predators

establish a social hierarchy

Aggressive behavior is equally important to human





Life instinct

Sexual

reality principle

Death instinct

Aggressive

Why we choose *Drosophila* as a model system for the study of aggression

- Its genetic resources allow researchers to comprehensively identify genes and neurons
- Its stereotypical aggressive actions make classification and quantification straightforward
- Ethological studies in other arthropods provide a framework for interpreting laboratory experiments in *Drosophila*

"Aggression": describe potentially heterologous sets of behaviors

Predatory aggression

Intraspecific aggression

Maternal aggression

Why we choose *Drosophila* as a model system for the study of aggression

Content

Neuromodulation in *Drosophila* aggression

by JXY

Modulation of *Drosophila* aggression by sensory stimuli, social interaction, and prior experience

by GC

Conserved mechanisms of aggression in vertebrates

by JSH

Neuromodulation in *Drosophila* aggression

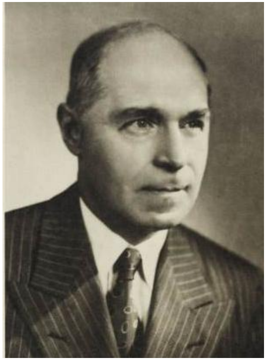
ONE

Xinyu Jiang

Research history of aggression in *Drosophila*

1915

1987



Alfred Henry Sturtevant
QUICK FACTS

BORN
November 21, 1891
Jacksonville, Illinois

DIED
April 5, 1970 (aged 78)
Pasadena, California

SUBJECTS OF STUDY
chromosome map

Ary Hoffmann
School of BioSciences, Bio21 Institute
University of Melbourne
Melbourne, VIC
Australia

Edward Kravitz, Ph.D.
George Packer Berry Professor of Neurobiology

Kravitz Lab
Phone: 617/432-1753
Edward_Kravitz@hms.harvard.edu

The set of components that made up fighting behavior

The proportions of time flies showed the different patterns

The factors that influenced the outcome of fights

"We are very interested in the nature of the changes that take place in the nervous systems of male flies to create the hyper-aggressive 'bully' phenotype. Whatever the nature of those changes, they occur during a short window in development during the pupal life of flies."

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Experiments on sex recognition and the problem of sexual selection in Drosoophilia.

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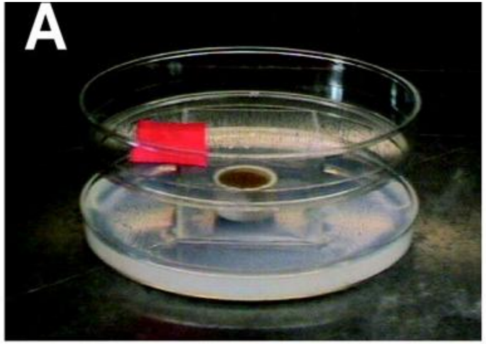
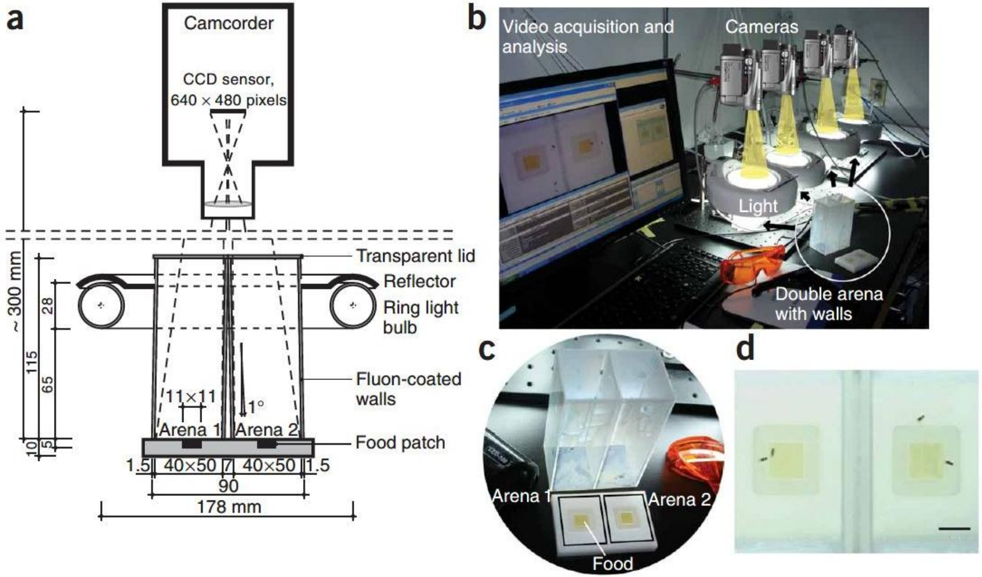
Different set-ups to study aggression in *Drosophila*

Establishing conditions under which only two male flies would fight

Developing a quantitative framework for measuring the behavior

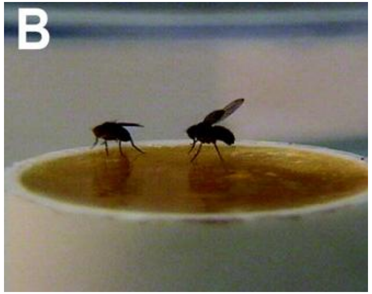




(Mundiyanapurath, Certel et al. 2007) (Zwarts, Versteven et al. 2012) (Dankert, Wang et al. 2009)

Aggression consists of rich ensembles of stereotyped behaviors, which often unfold in a characteristic sequence

Approach



Wing threat

Fencing, Kick

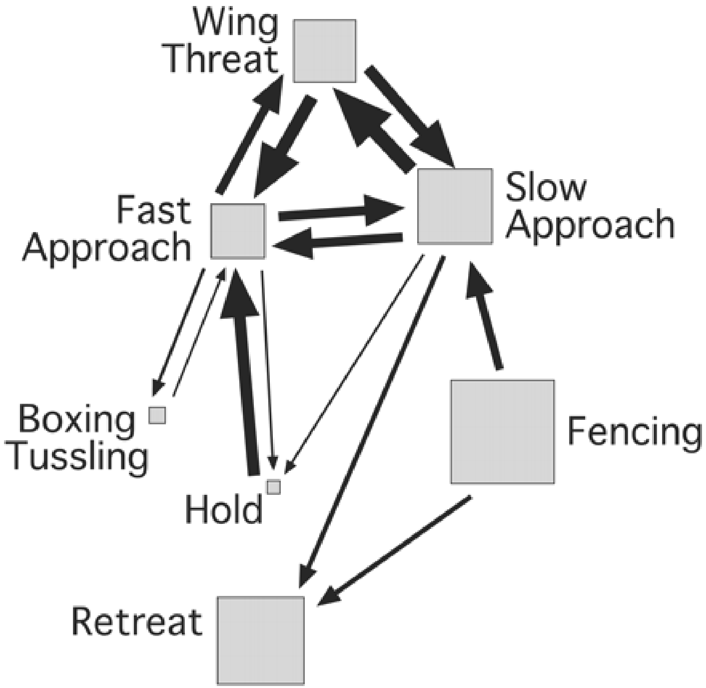
Chasing, Hold

Lunge

Boxing

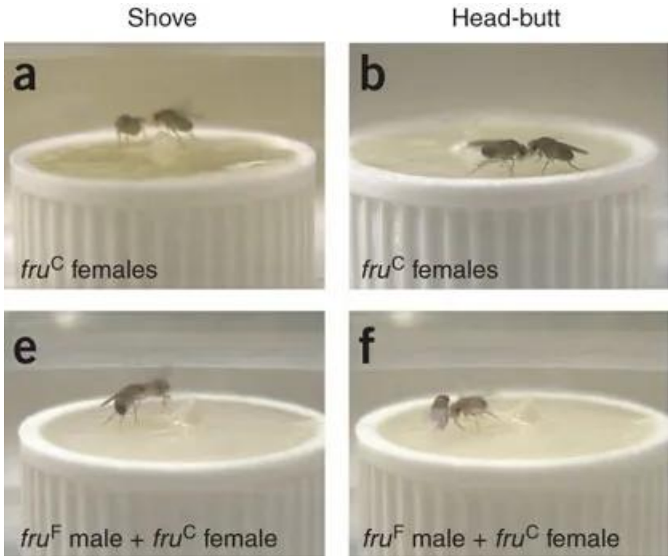
Defensive wing threat

High-intensity Level

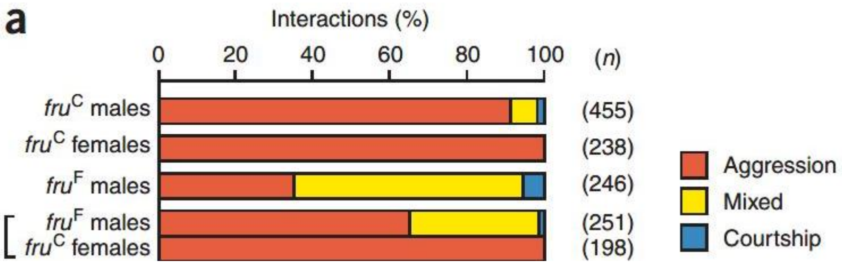


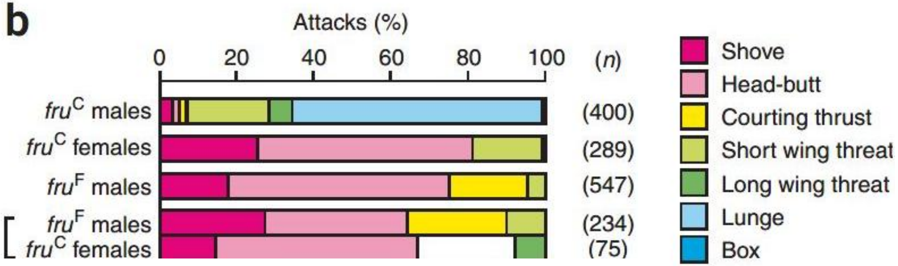
(Chen, Lee et al. 2002)

fru regulates the sex-specific patterns of aggression in both sexes



	Probability of winning				
Pairing	Overall	As prior winner	As prior loser	Dominance index (DI)	*n*
fru^C males	(0.50)	0.88	0.12	0.75	306
fru^C females	(0.50)	0.61	0.39	0.22	156
fru^F males	(0.50)	0.69	0.31	0.39	197



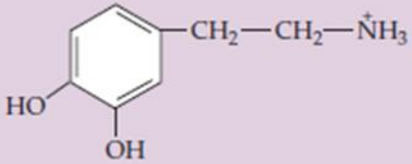


(Vrontou, Nilsen et al. 2006)

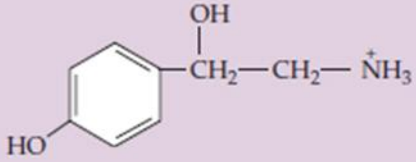
Neuromodulators of aggression in *Drosophila*

BIOGENIC AMINES

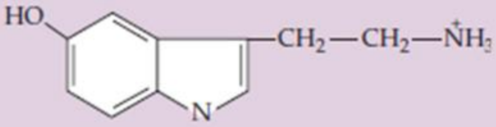
DA



OA



5-HT



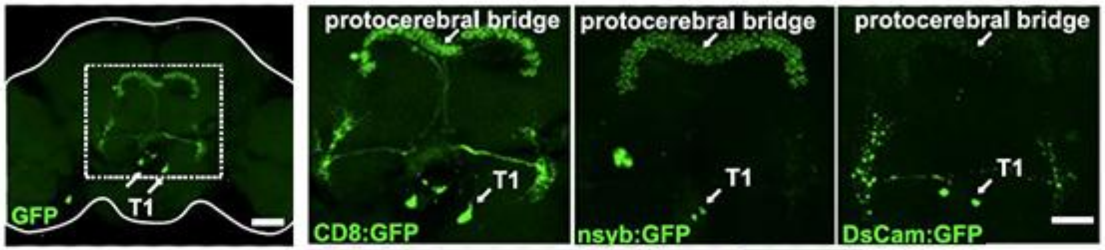
Neuropeptide

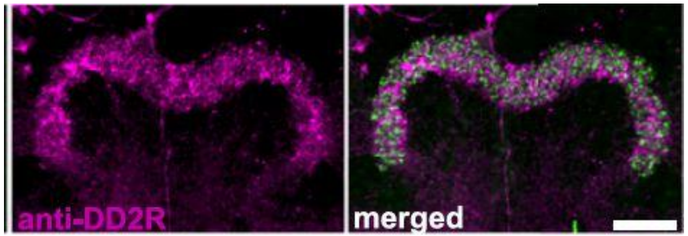
TK

NPF

DSK

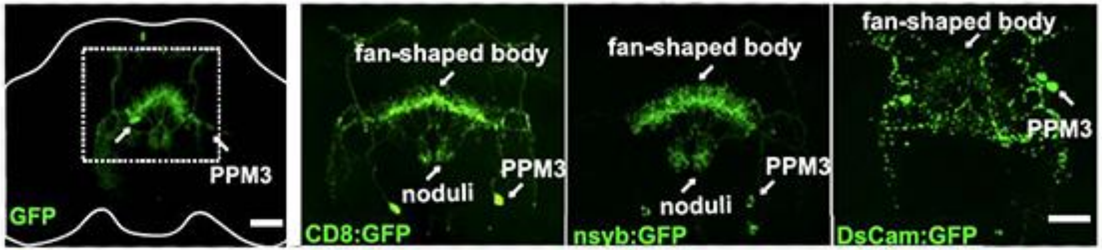
Single dopaminergic neurons promote aggression governed by a “U-shaped” relationship

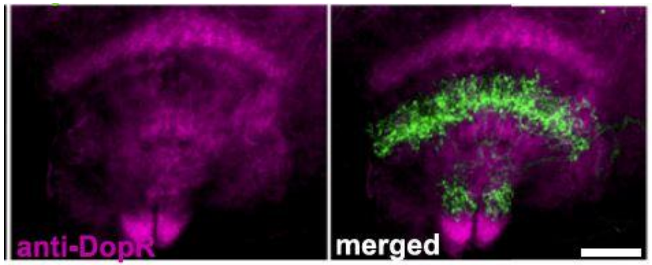




T1 neurons

Presynaptic terminals dendritic arbors





PPM3 neurons

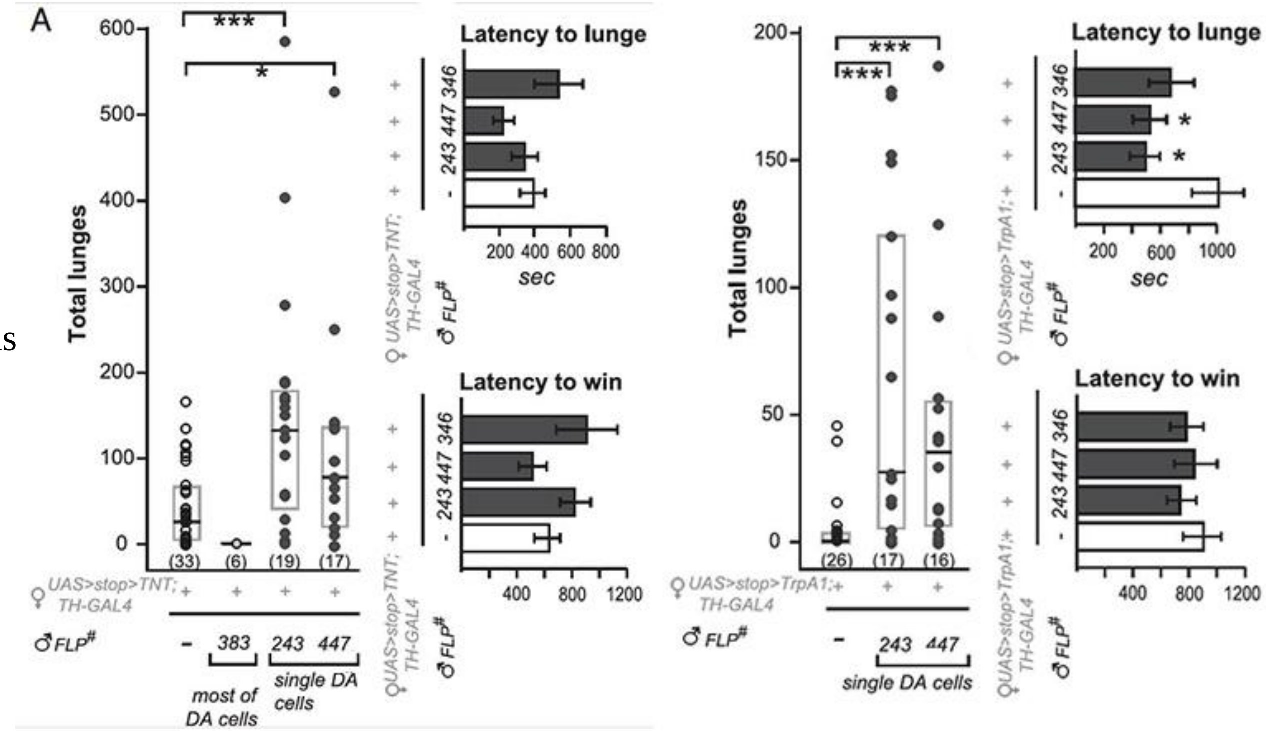
DD2R: D2-like, pre- and postsynaptic, motor control
DopR: D1-like, postsynaptic, hyperactivity

(Alekseyenko, Chan et al. 2013)

Single dopaminergic neurons promote aggression governed by a “U-shaped” relationship

243：T1 neurons

447：PPM3 neurons



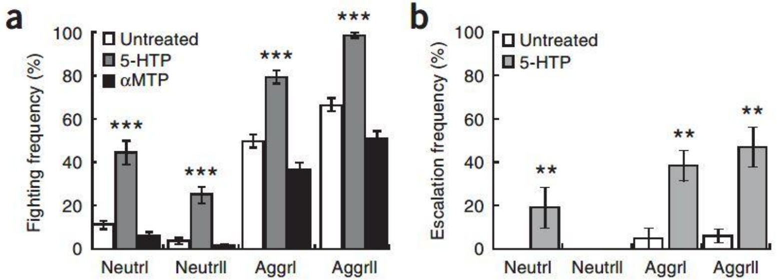
inactivate

activate

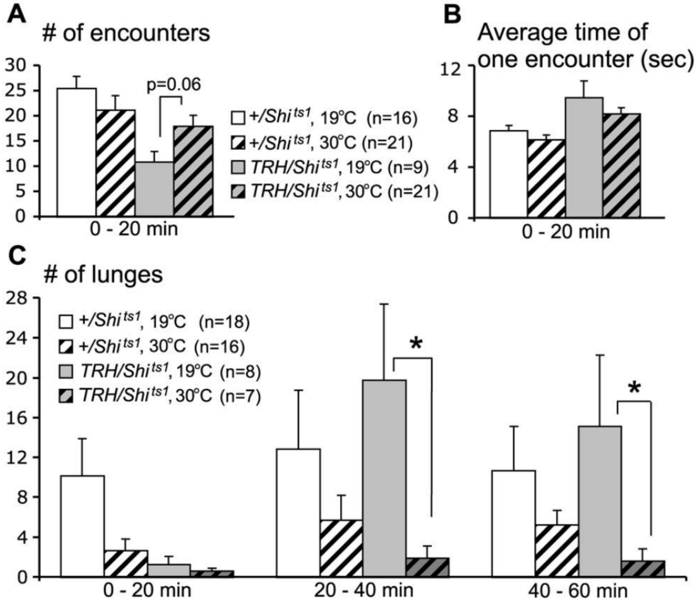
“U shaped ”

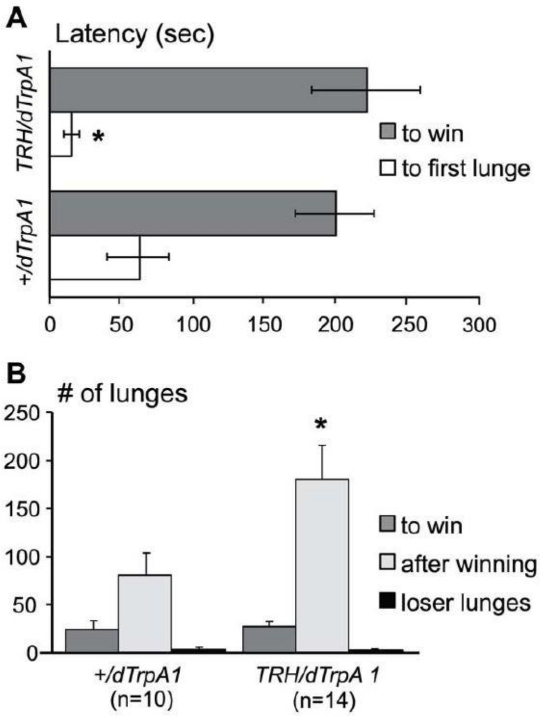
(Alekseyenko, Chan et al. 2013)

5-HT is involved in facilitating the transition to higher-level aggression



5-HTP: 5-HT precursor
αMTP: 5-HT inhibitor

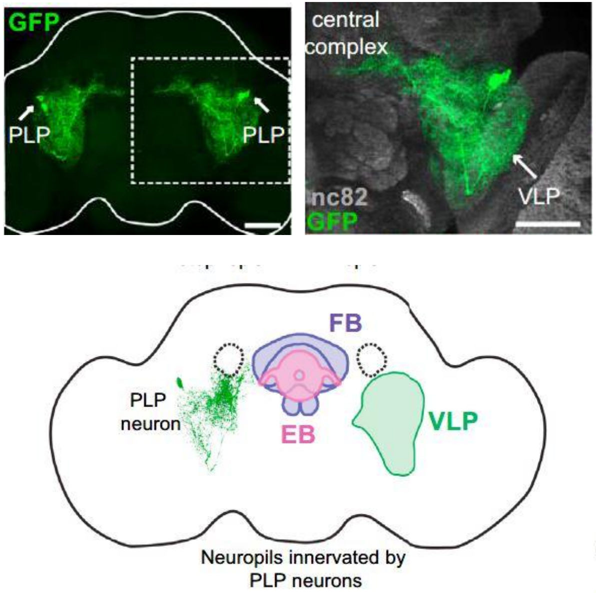


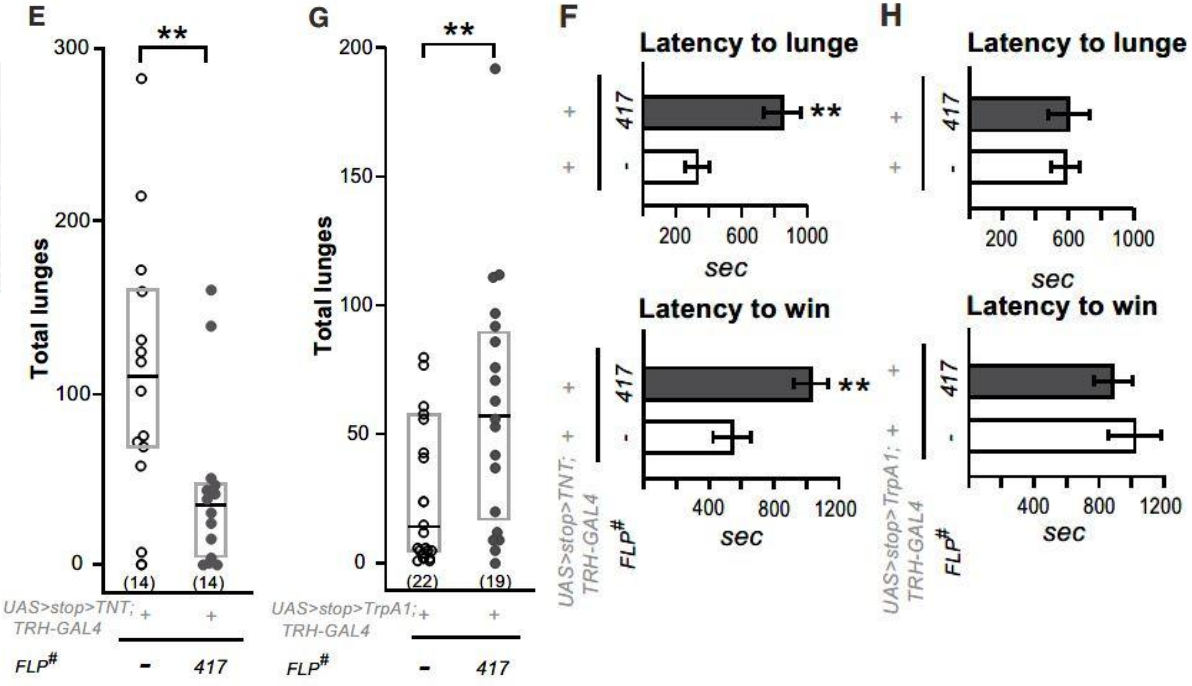


(Dierick and Greenspan 2007)   (Alekseyenko, Lee et al. 2010)

5-HT is involved in facilitating the transition to higher-level aggression

5-HT PLP neurons

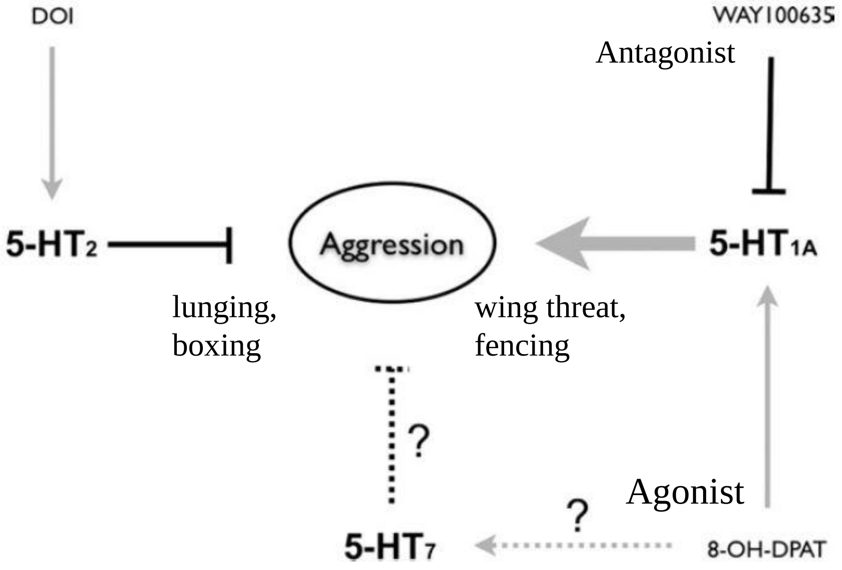




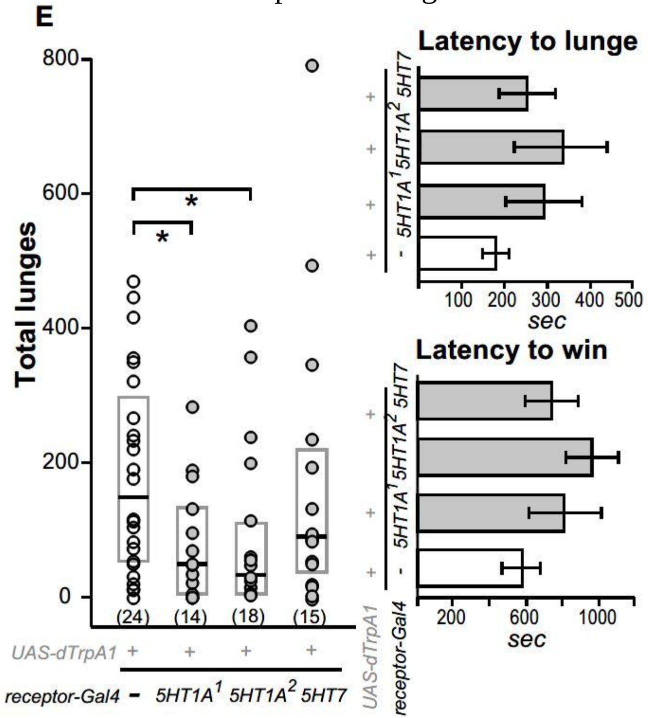
(Alekseyenko, Chan et al. 2014)

5-HT receptors differentially modulate aggressive behaviors

5-HT receptors: $5HT_{1A}$, $5HT_{1B}$, $5HT_{2}$, $5HT_{7}$



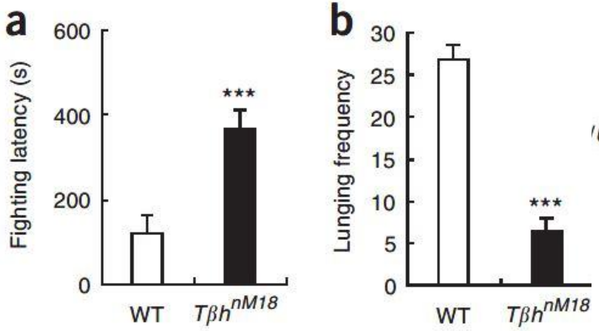
5HT1A Receptor-Bearing Neurons



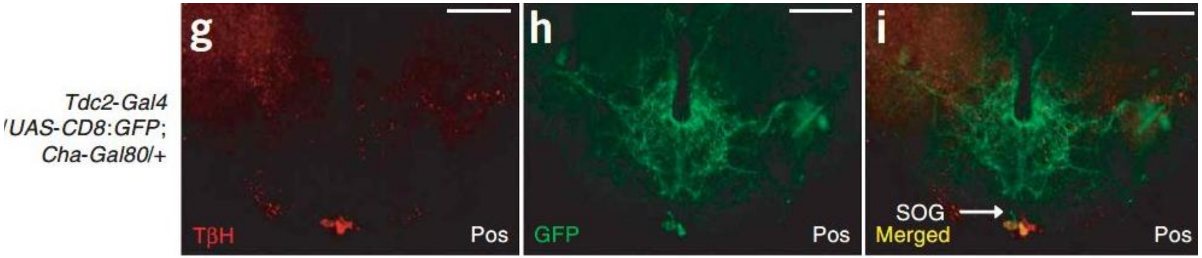
(Johnson, Becnel et al. 2009)

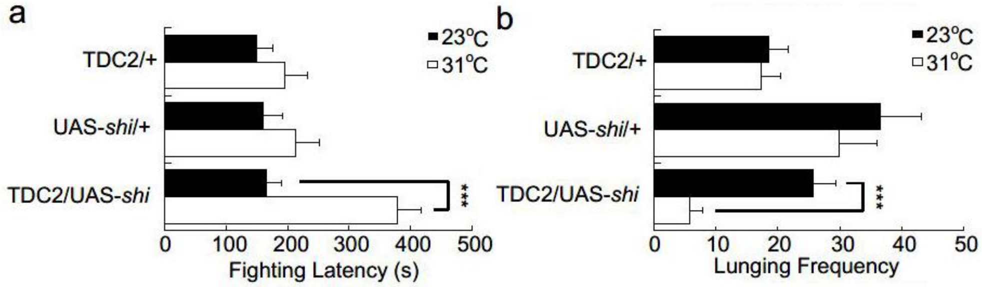
(Alekseyenko, Chan et al. 2014)

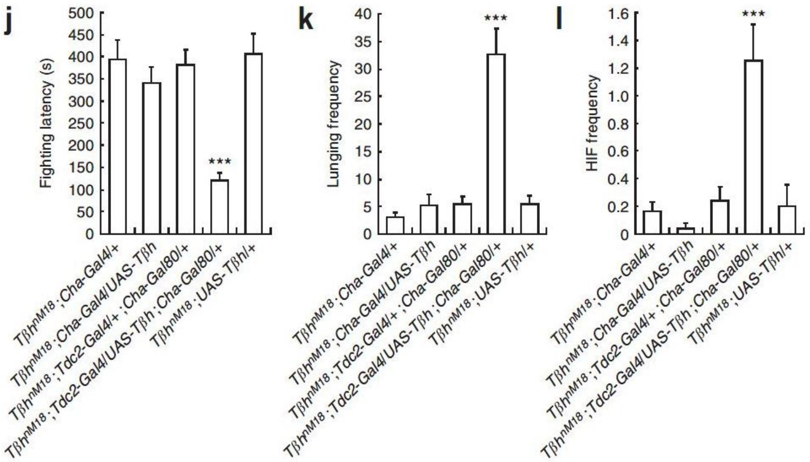
OA is essential for normal levels of aggression



OA neurons in SOG

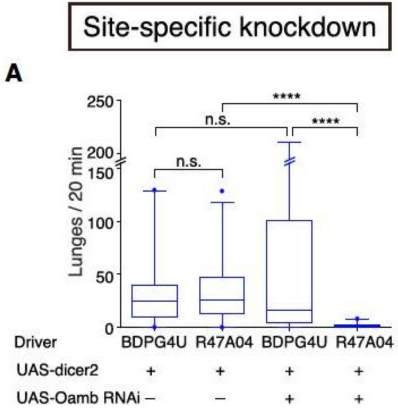


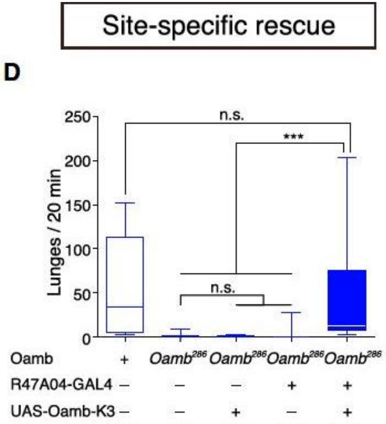




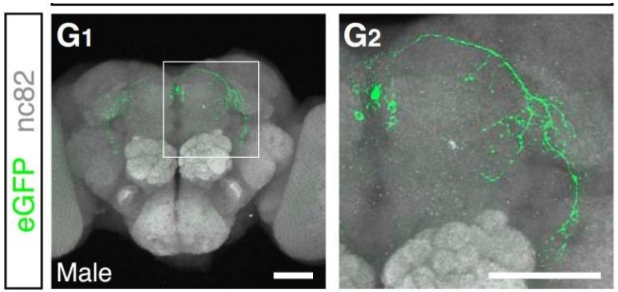
(Hoyer, Eckart et al. 2008) (Zhou, Rao et al. 2008)

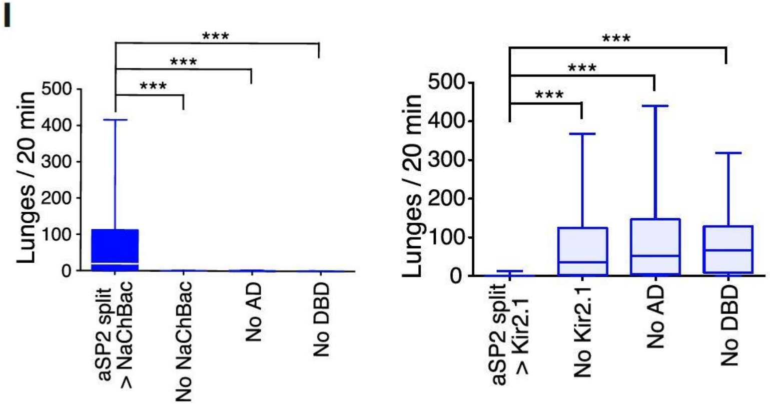
OA-sensitive aSP2 neurons are required for normal levels of aggressiveness

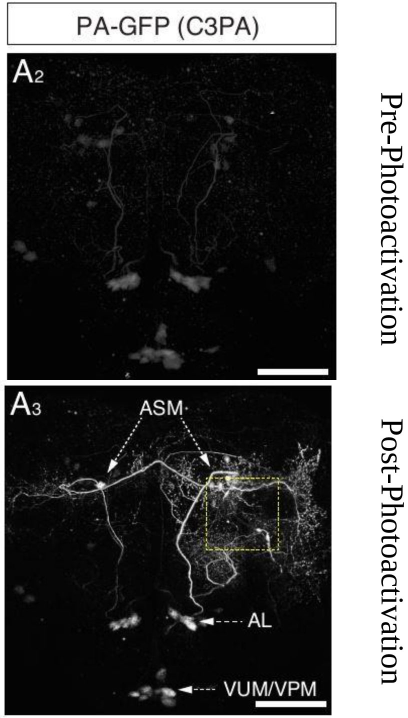




Fru^{M+} aSP2 neurons



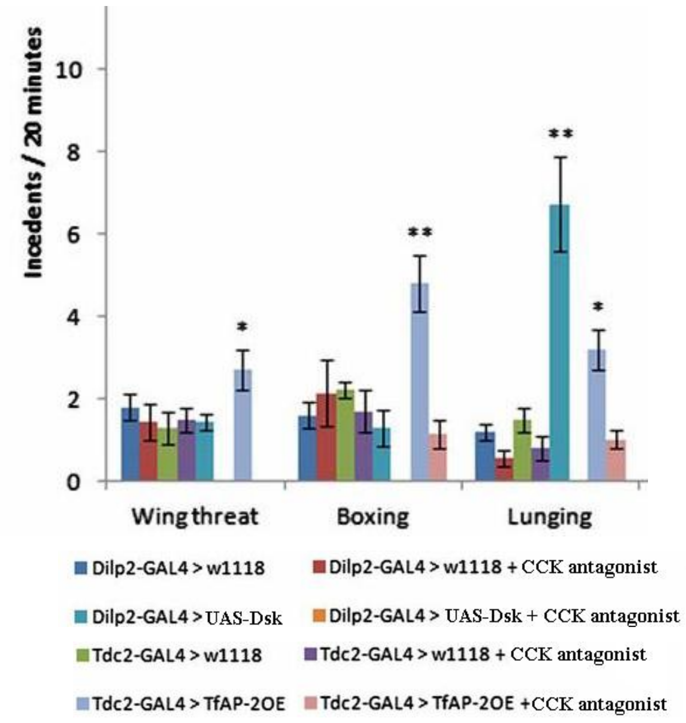


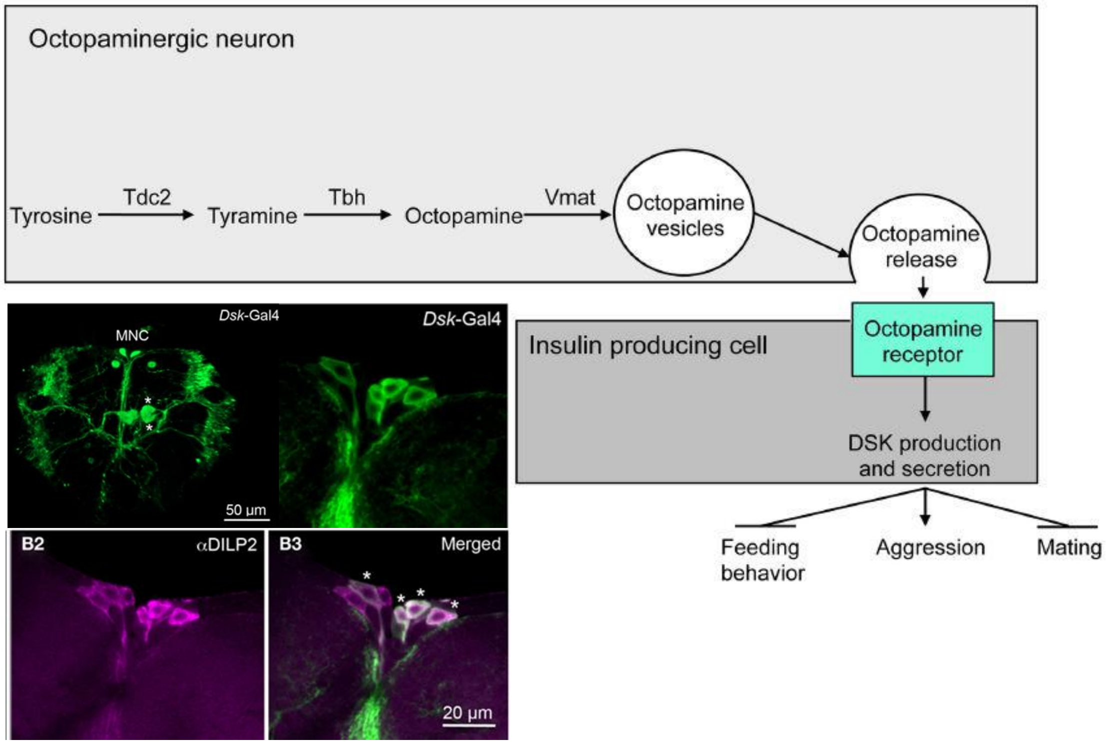


Tdc-2

(Watanabe, Chiu et al. 2017)

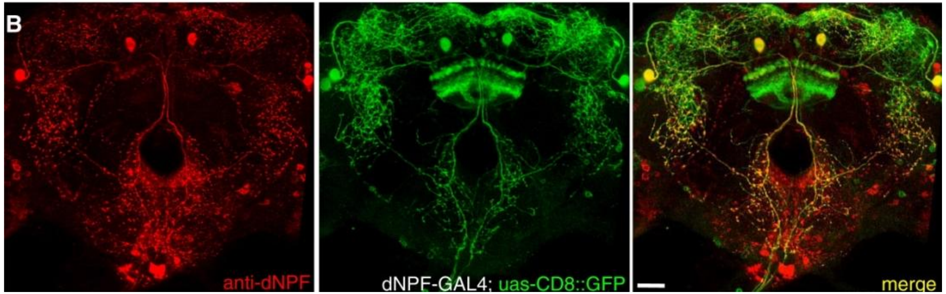
Satiation hormone DSK modulates aggression controlled by OA



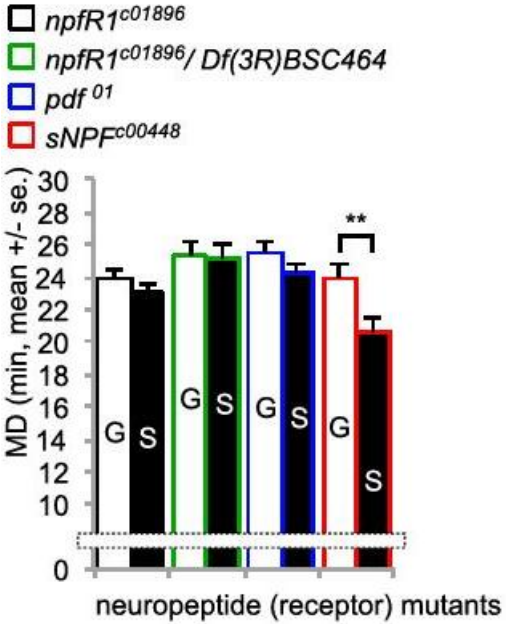


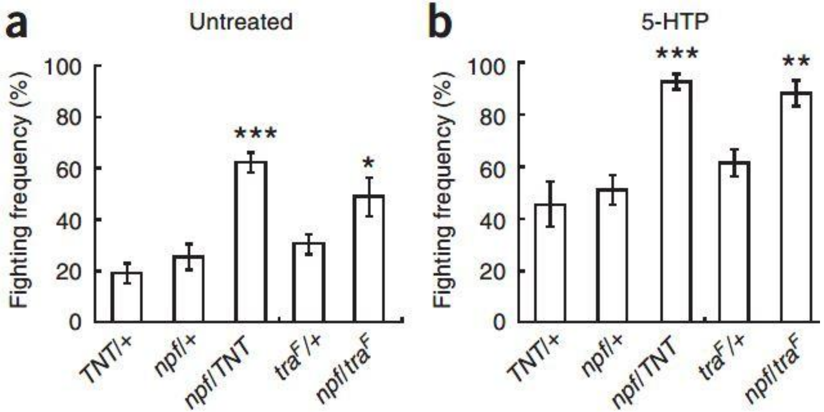
(Williams, Goergen et al. 2014)

NPF-expressing neurons may play a more general role in modulating male behavioral patterns rather than aggression



rival-induced prolonged mating



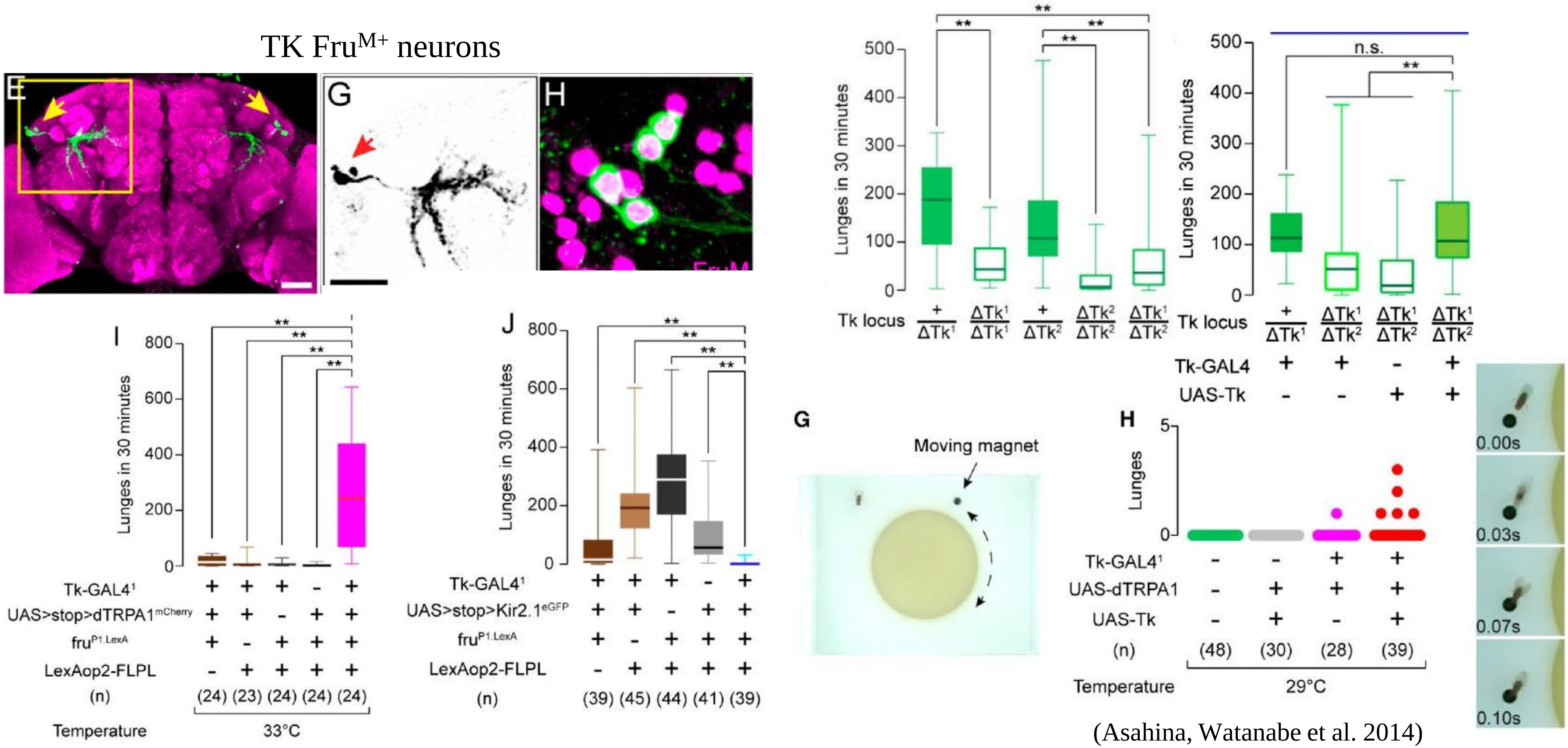


NPF acts as a brake on the aggressive and the roles of NPF and 5-HT are independent

(Kim, Jan et al. 2013) (Dierick and Greenspan 2007)

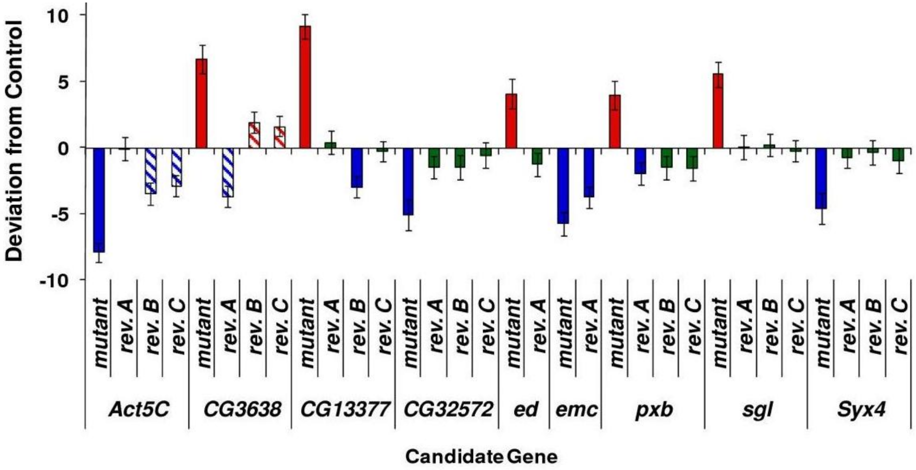
TK-expressing neurons control higher levels of aggression and aggressive arousal

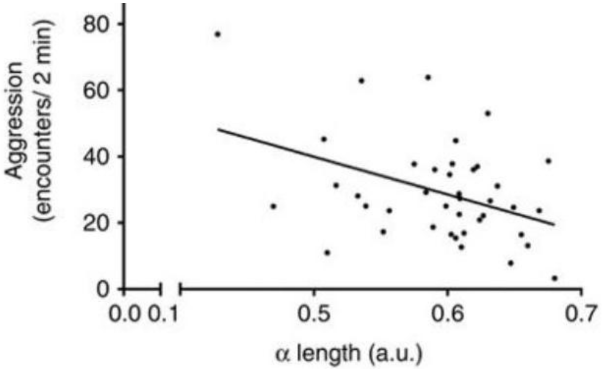
TK Fru^{M+} neurons



(Asahina, Watanabe et al. 2014)

The mushroom bodies have been implicated in aggression

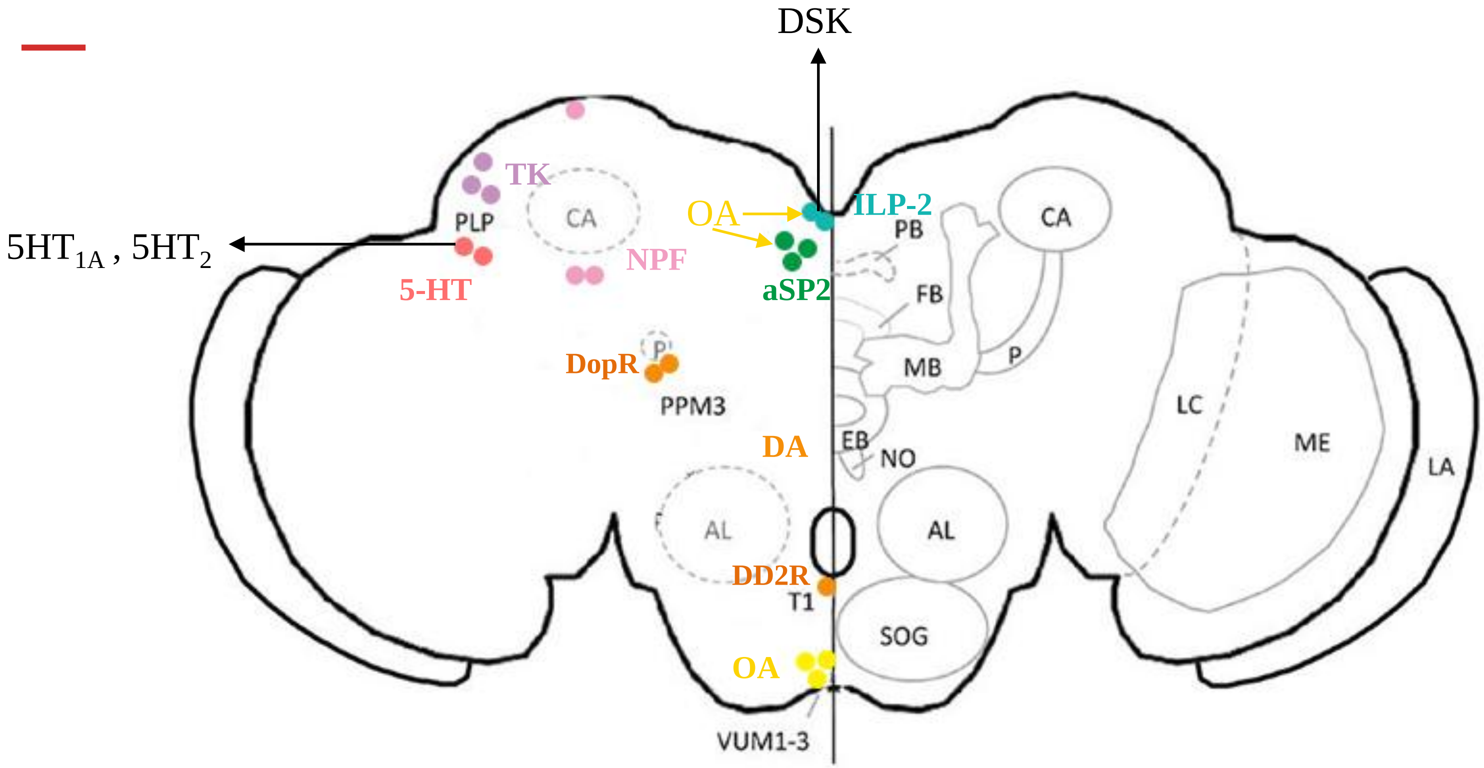




	Alpha lobes		Beta lobes	
Mutant	Length (SE)	Width (SE)	Length (SE)	Width (SE)
Canton S B	6.03 (0.09)	0.6925 (0.0170)	4.28 (0.03)	0.7901 (0.0236)
Act5C	6.35 (0.13)*	0.6648 (0.0185)	4.18 (0.04)	0.7746 (0.0282)
CG3638	6.07 (0.13)	0.8372 (0.0323)***	4.26 (0.06)	0.8866 (0.0303)*
CG13377	5.99 (0.12)***	0.8036 (0.0222)	4.22 (0.04)	0.8273 (0.0342)
CG32572	6.56 (0.09)***	0.8218 (0.0169)***	4.23 (0.04)	0.8085 (0.0345)
ed	5.99 (0.16)	0.8330 (0.0299)***	4.09 (0.08)*	0.8683 (0.0389)
emc	6.23 (0.17)	0.7174 (0.0216)	4.29 (0.05)	0.8622 (0.0300)
pxb	6.12 (0.08)	0.8070 (0.0230)***	4.15 (0.05)*	0.8729 (0.0281)*
sgl	5.60 (0.13)**	0.7631 (0.0214)*	4.25 (0.07)	0.8263 (0.0312)
Syx4	5.94 (0.14)	0.7044 (0.0170)	4.13 (0.05)*	0.8504 (0.0194)

(Edwards and Mackay 2009) (Zwarts, Vanden Broeck et al. 2015)

Summary



DSK
5HT1A , 5HT2
TK
PLP
CA
OA
ILP-2
PB
CA
NPF
5-HT
aSP2
FB
P
DopR
MB
PPM3
LC
DA
EB
NO
ME
LA
AL
AL
DD2R
T1
SOG
OA
VUM1-3

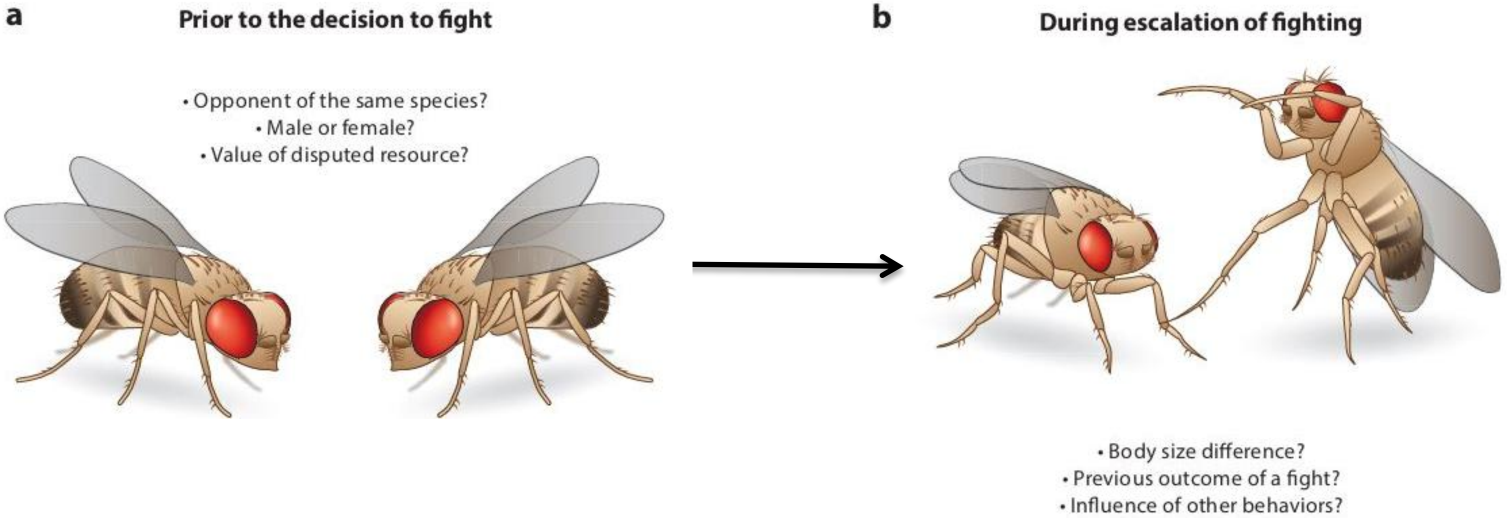
Questions

What is the neuromodulator that can completely suppress the aggression?

What are the interactions between neuromodulators?

What is the classification and function of receptor neurons?

What are the neurons that regulate the sexual differences in aggression?


a
Prior to the decision to fight
• Opponent of the same species?
• Male or female?
• Value of disputed resource?
b
During escalation of fighting
• Body size difference?
• Previous outcome of a fight?
• Influence of other behaviors?

Modulation of *Drosophila* aggression by sensory stimuli, social interaction, and prior experience

TWO

Chao Guo

Modulation of *Drosophila* aggression by sensory stimuli, social interaction, and prior experience

- Modulation of *Drosophila* aggression by sensory stimuli
  - Inter-male aggression is prone
  - Acoustic regulation of aggression
  - The kind of food to fight over
- Modulation of *Drosophila* aggression by social interaction
  - Isolated male is more aggressive than group housed male
  - Female contact inhibit male aggression
- Modulation of *Drosophila* aggression by prior experience
  - Dynamics of aggression of Drosophila
  - Defeated fly fight less
- Other factors

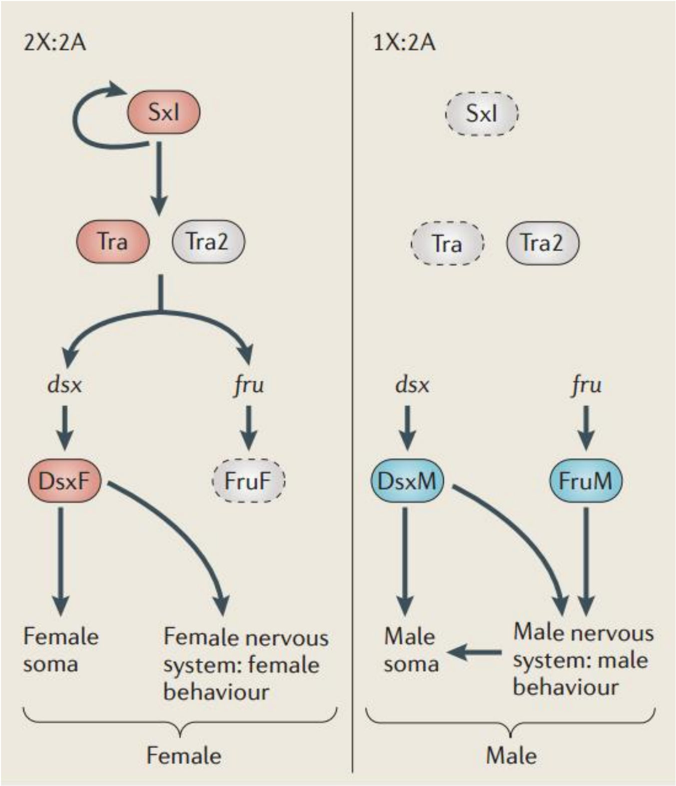
WHY MALE IS AGGRESSIVE TOWARD MALES BUT NOT FEMALE?

Male pheromone induce aggression in males

Sex-determination cascade and masculinization of either pheromone profiles or behavioral patterns

oe^{traIR}

elav^{traIR}

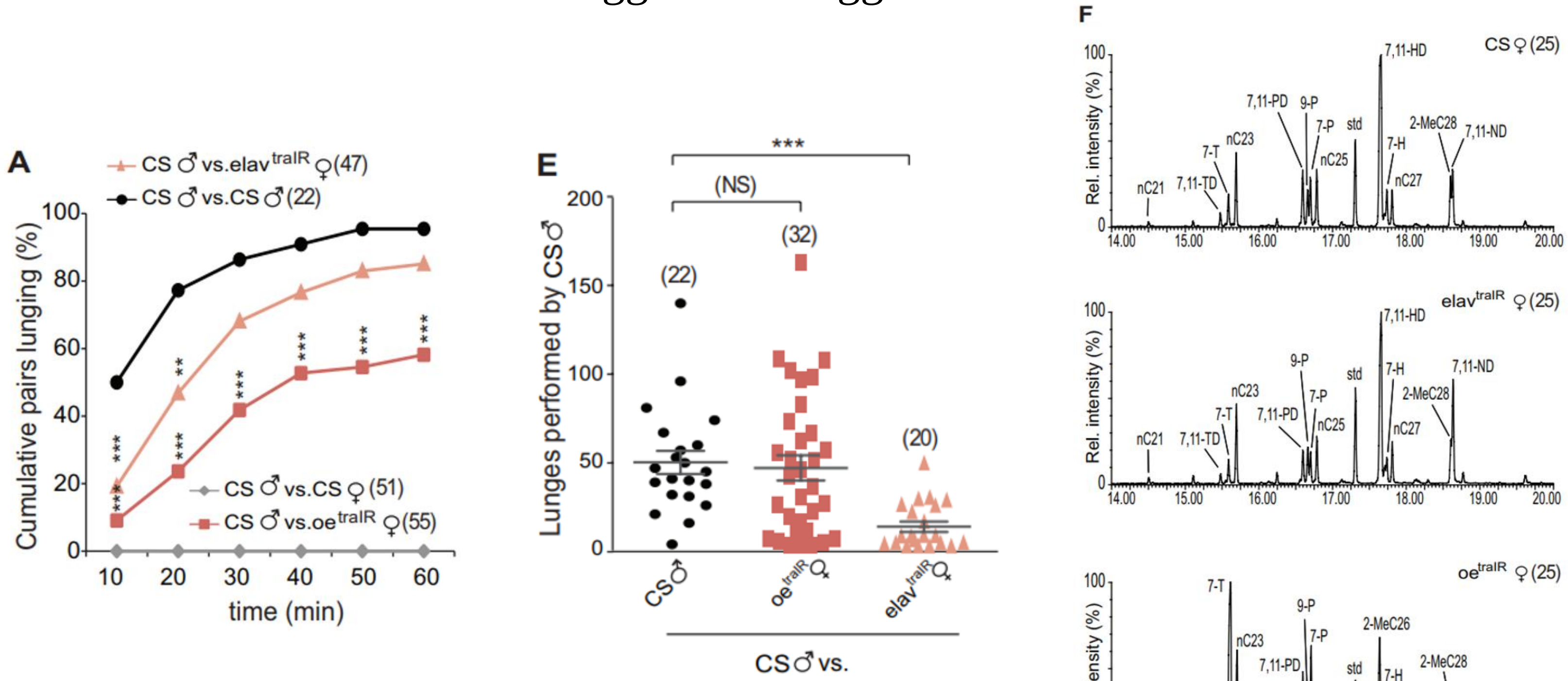


oet^{raF}

elav^{traF}

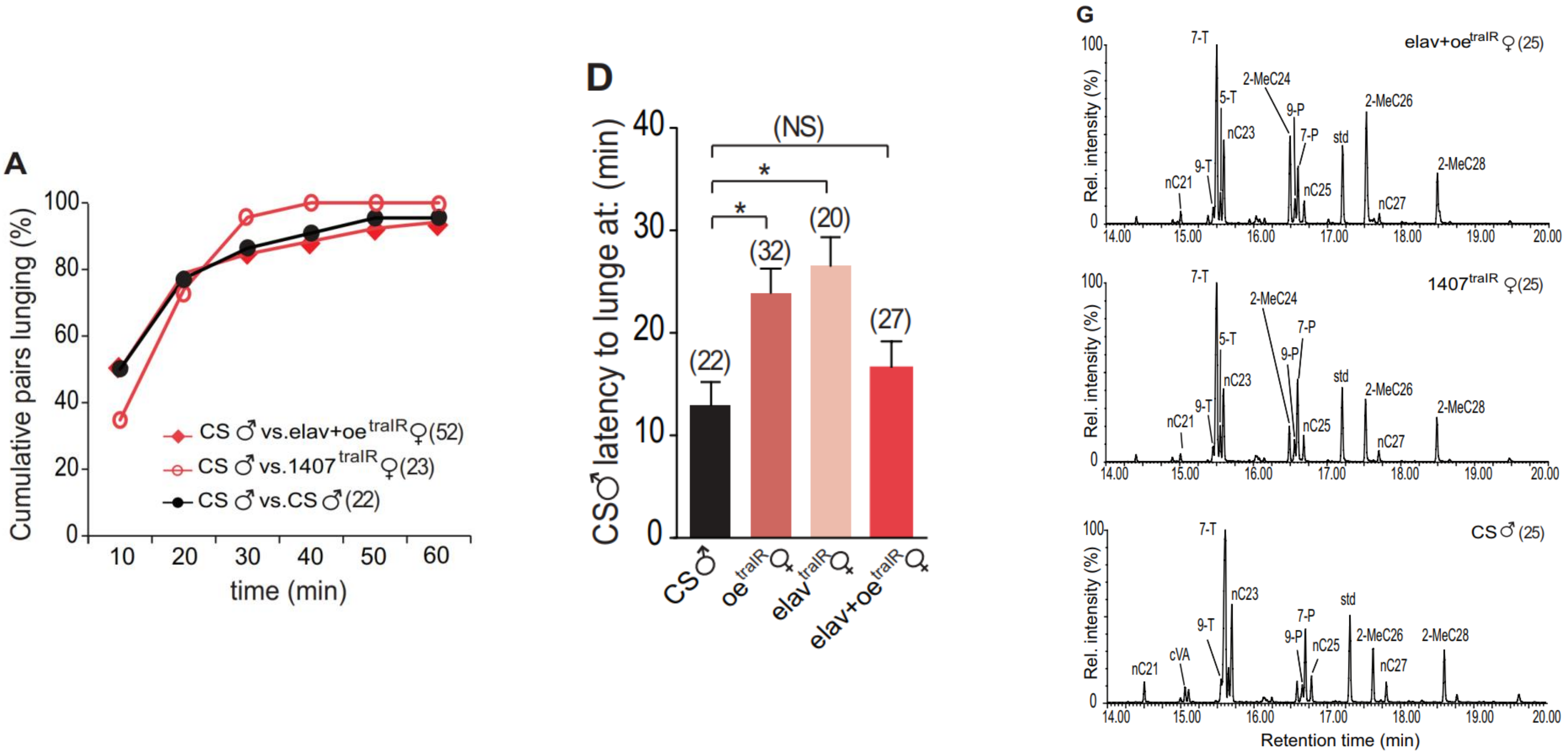
Yamamoto, D., & Koganezawa, M. (2013). Genes and circuits of courtship behaviour in Drosophila males. Nature Reviews Neuroscience, 14(10), 681-692.

Masculinization of either pheromone profiles or fighting patterns in females triggers male aggression



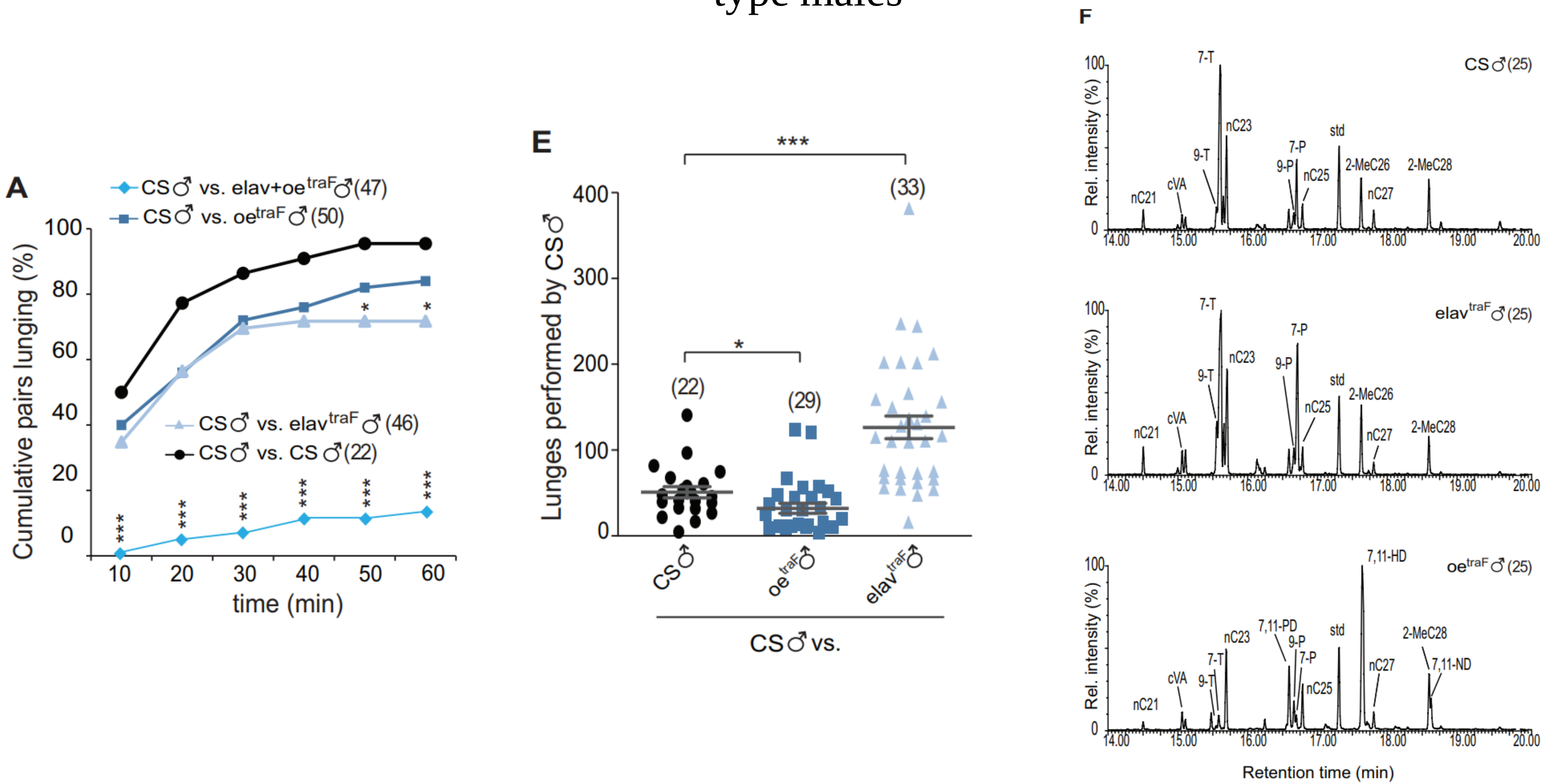
Fernandez, M. P., Y. B. Chan, J. Y. Yew, J. C. Billeter, K. Dreisewerd, J. D. Levine and E. A. Kravitz (2010). "Pheromonal and behavioral cues trigger male-to-female aggression in Drosophila." PLoS Biol 8(11): e1000541.

Simultaneous masculinization of pheromones and behavior invert normal male-female dynamics



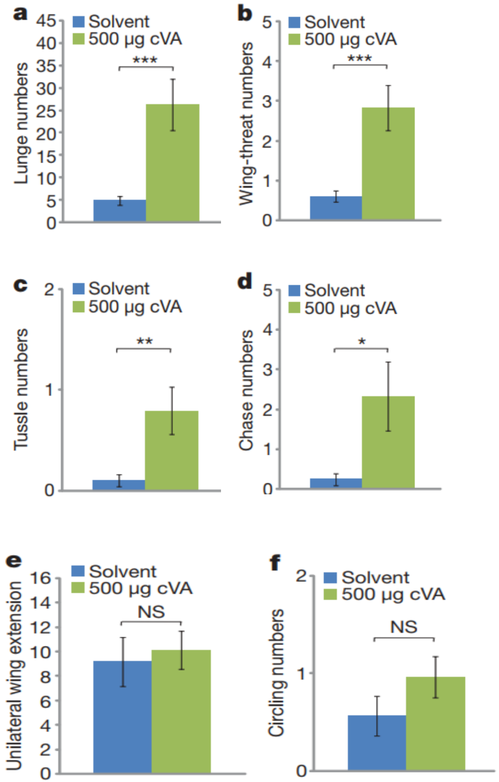
Fernandez, M. P., Y. B. Chan, J. Y. Yew, J. C. Billeter, K. Dreisewerd, J. D. Levine and E. A. Kravitz (2010). "Pheromonal and behavioral cues trigger male-to-female aggression in Drosophila." PLoS Biol 8(11): e1000541.

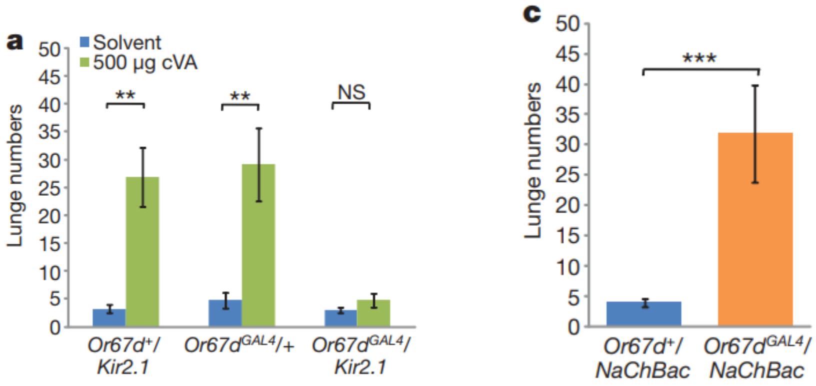
Feminization of pheromones and behavior in males inhibits aggression from wild type males



Fernandez, M. P., Y. B. Chan, J. Y. Yew, J. C. Billeter, K. Dreisewerd, J. D. Levine and E. A. Kravitz (2010). "Pheromonal and behavioral cues trigger male-to-female aggression in Drosophila." PLoS Biol 8(11): e1000541.

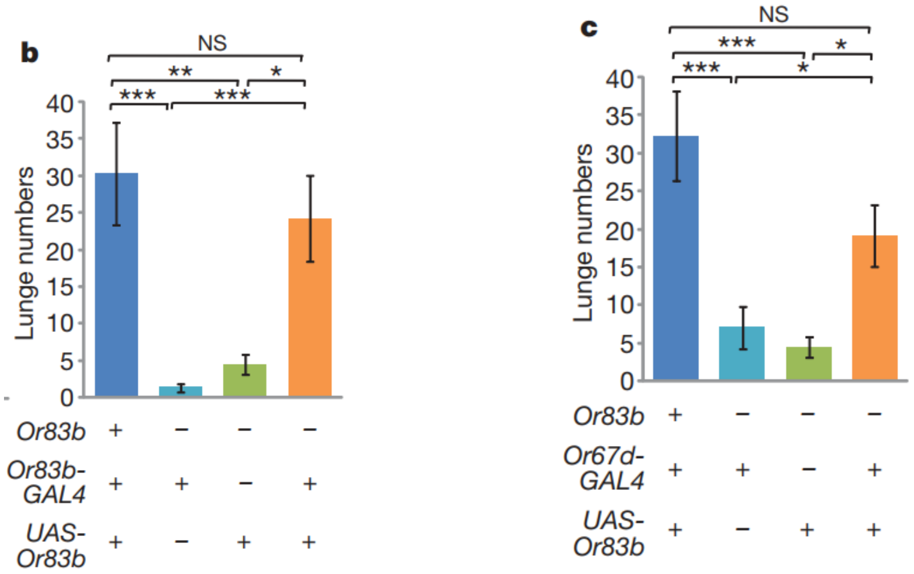
Synthetic cVA promotes aggression mediated by Or67d-expressing OSNs mediate





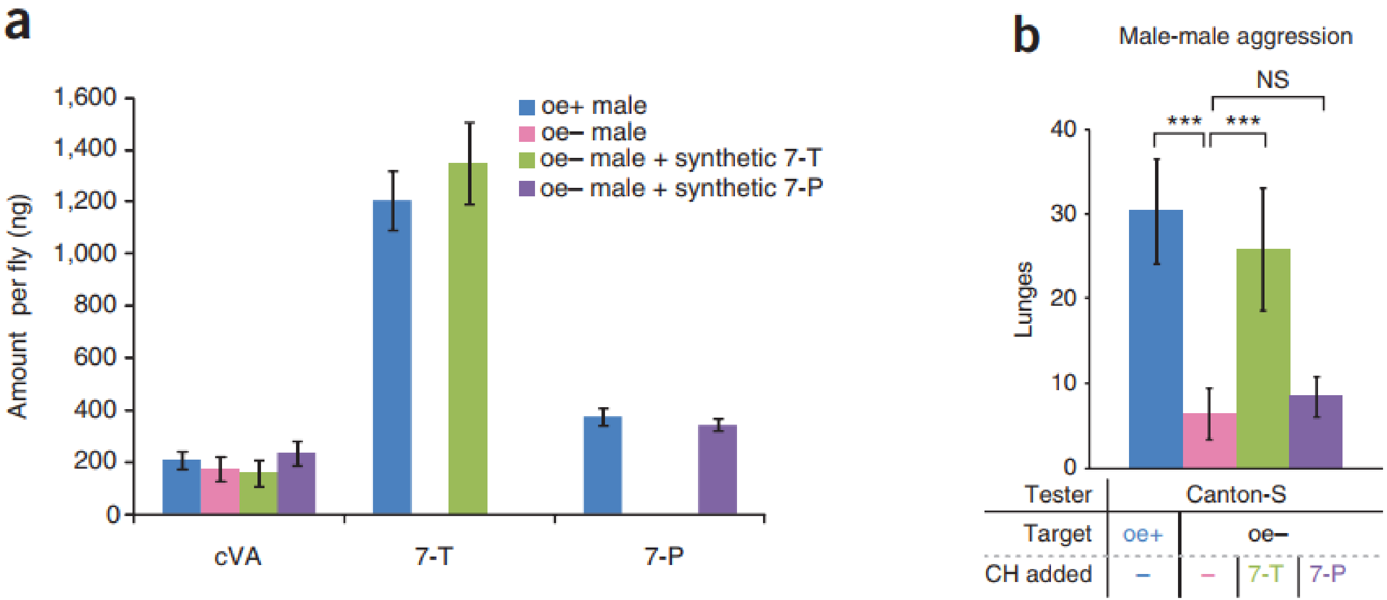
Wang, L. and D. J. Anderson (2010). "Identification of an aggression-promoting pheromone and its receptor neurons in Drosophila." Nature 463(7278): 227-231.

Or67d-expressing OSNs are sufficient to mediate the aggression-promoting effect of endogenously produced cVA



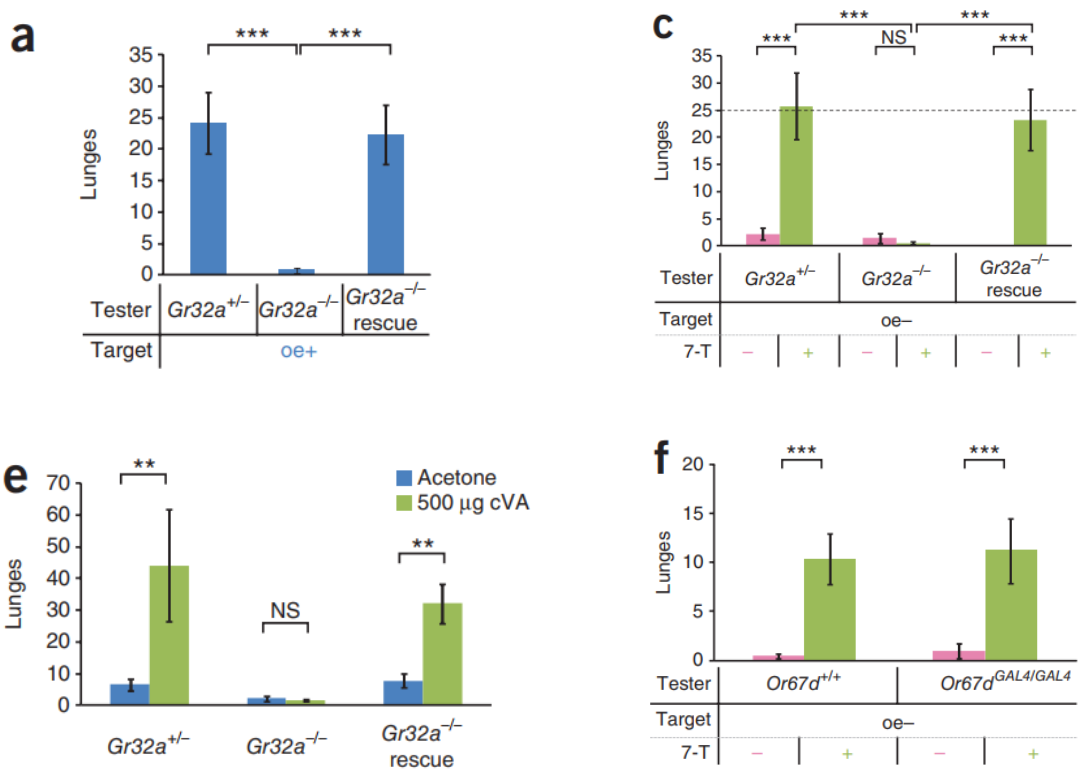
Wang, L. and D. J. Anderson (2010). "Identification of an aggression-promoting pheromone and its receptor neurons in Drosophila." Nature 463(7278): 227-231.

(z)-7-tricosene regulates male-male aggression



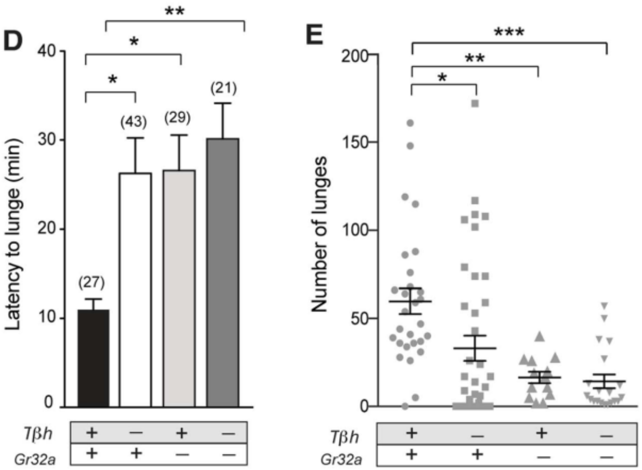
Wang, L., X. Han, J. Mehren, M. Hiroi, J. C. Billeter, T. Miyamoto, H. Amrein, J. D. Levine and D. J. Anderson (2011). "Hierarchical chemosensory regulation of male-male social interactions in Drosophila." Nat Neurosci 14(6): 757-762.

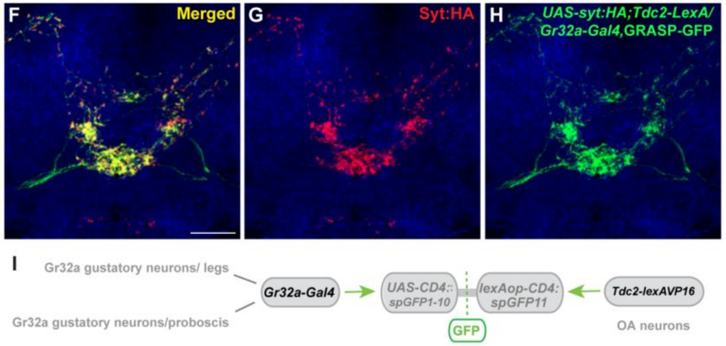
Gr32a mediates the behavioral effects of (*z*)-7-tricosene and permits the aggression-promoting effect of cVA

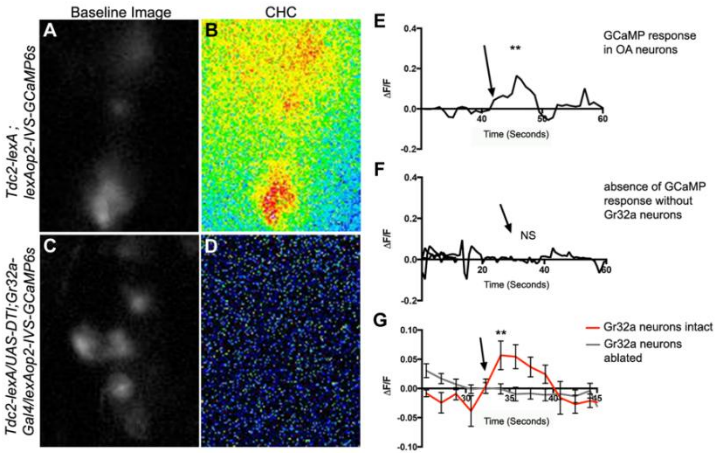


Wang, L., X. Han, J. Mehren, M. Hiroi, J. C. Billeter, T. Miyamoto, H. Amrein, J. D. Levine and D. J. Anderson (2011). "Hierarchical chemosensory regulation of male-male social interactions in Drosophila." Nat Neurosci 14(6): 757-762.

Gr32a neurons contact OA neurons in the suboesophageal ganglion







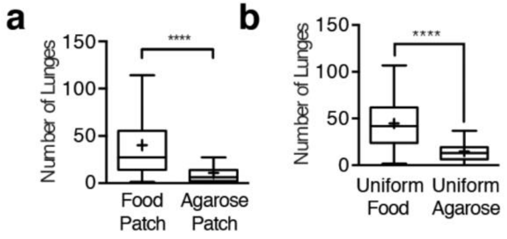
Andrews, J. C., M. P. Fernandez, Q. Yu, G. P. Leary, A. K. Leung, M. P. Kavanaugh, E. A. Kravitz and S. J. Certel (2014). "Octopamine neuromodulation regulates Gr32a-linked aggression and courtship pathways in Drosophila males." PLoS Genet 10(5): e1004356.

HOW FOOD MODULATE MALE AGGRESSION?

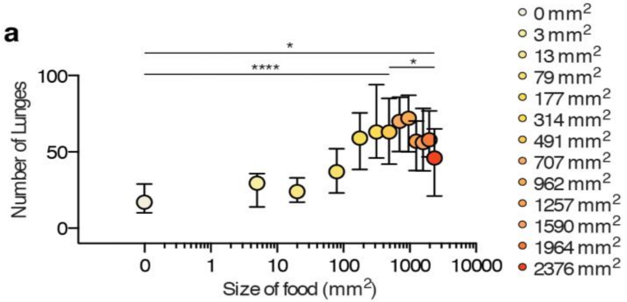
Evaluation of food resource and effect of starvation

Level of aggression modulated by the availability of food

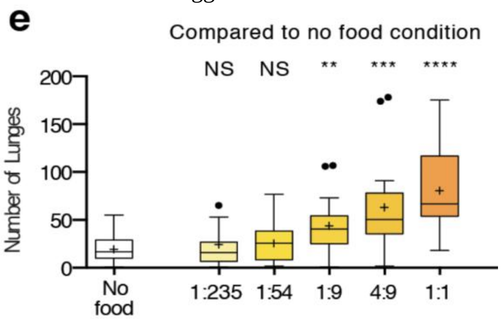
Food is necessary for normal levels of male-male aggression



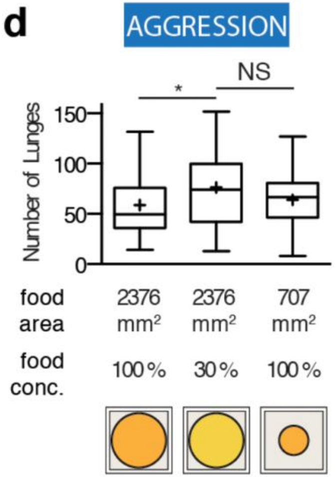
The relationship between aggression and the amount of food



Increasing the concentration of food while keeping the size of food constant increases aggression



The decrease in aggression seen in the largest food patch tested can be reversed by decreasing the concentration of food to 30%



Lim, R. S., E. Eyjolfsdottir, E. Shin, P. Perona and D. J. Anderson (2014). "How food controls aggression in Drosophila." PLoS One **9**(8): e105626.

Food deprivation influence intermediate-level aggressive behavior

Table 1. χ^2 analysis of deviance of Poisson GLMs testing the effect of strain, food deprivation and their interaction on nine aggressive behaviours. The *p*-values that are below 0.05 after the Bonferroni correction are bolded. Rover, sitter and s2 differ in all the aggressive behaviours except retreat. Food deprivation influenced intermediate-level aggressive behaviours: fencing and wing threat, but did not influence other behaviours. There were significant interaction effects on lunging, chasing and offensive wing threat.

	strain effect			food deprivation effect			interaction effect		
behaviour	$\Delta\chi^2_{(d.f.=2)}$	p	$p_{Bonferroni}$	$\Delta\chi^2_{(d.f.=1)}$	p	$p_{Bonferroni}$	$\Delta\chi^2_{(d.f.=2)}$	P	$p_{Bonferroni}$
head-to-head interaction	24.134	0.00001	**0.00005**	0.896	0.34390	1.00000	8.076	0.01763	0.15870
lunging	101.749	0.00000	**0.00000**	0.101	0.75017	1.00000	111.695	0.00000	**0.00000**
approach	100.480	0.00000	**0.00000**	2.551	0.11023	0.99203	7.558	0.02285	0.20562
chasing	11.718	0.00285	**0.02569**	0.003	0.95696	1.00000	36.193	0.00000	**0.00000**
offensive wing threat	530.351	0.00000	**0.00000**	128.577	0.00000	**0.00000**	49.580	0.00000	**0.00000**
defensive wing threat	201.492	0.00000	**0.00000**	207.264	0.00000	**0.00000**	1.331	0.51401	1.00000
offensive fencing	387.516	0.00000	**0.00000**	80.899	0.00000	**0.00000**	10.281	0.00585	0.05268
defensive fencing	247.996	0.00000	**0.00000**	19.740	0.00001	**0.00008**	0.224	0.89414	1.00000
retreat	2.143	0.34247	1.00000	4.797	0.02850	0.25652	1.447	0.48514	1.00000

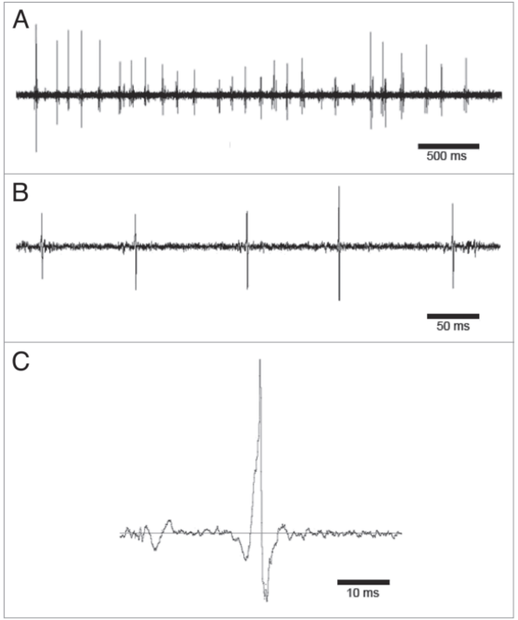
Wang, S. and M. B. Sokolowski (2017). "Aggressive behaviours, food deprivation and the foraging gene." R Soc Open Sci **4**(4): 170042.

HOW ACOUSTIC SIGNAL MODULATE MALE AGGRESSION?

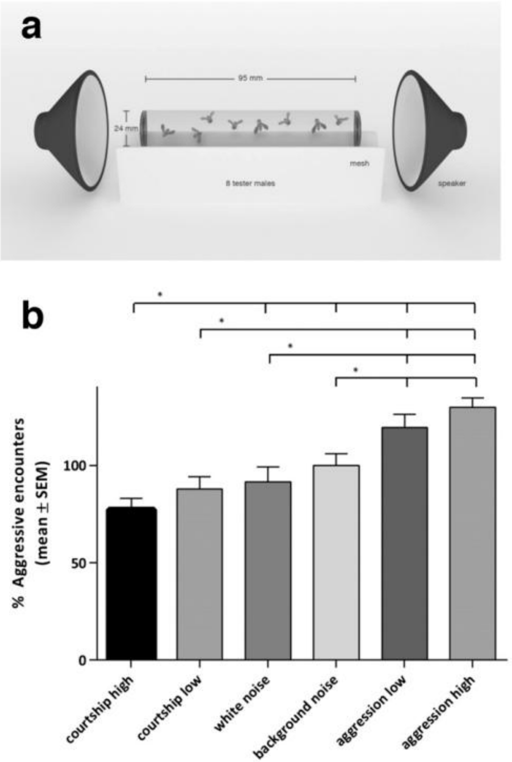
Antagonistic acoustic signals escalate aggression

Acoustic signals in *Drosophila* aggression

Acoustic signals produced by male *D. melanogaster* during agonistic encounters



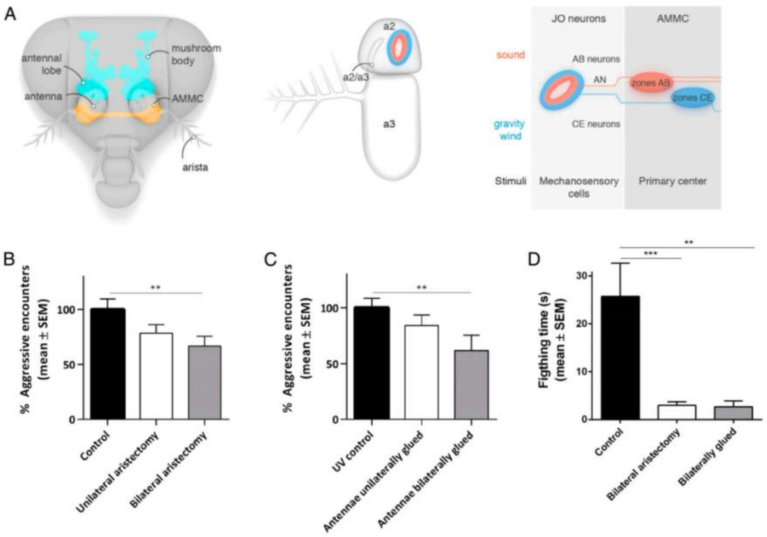
Agonistic sound promotes aggression in flies



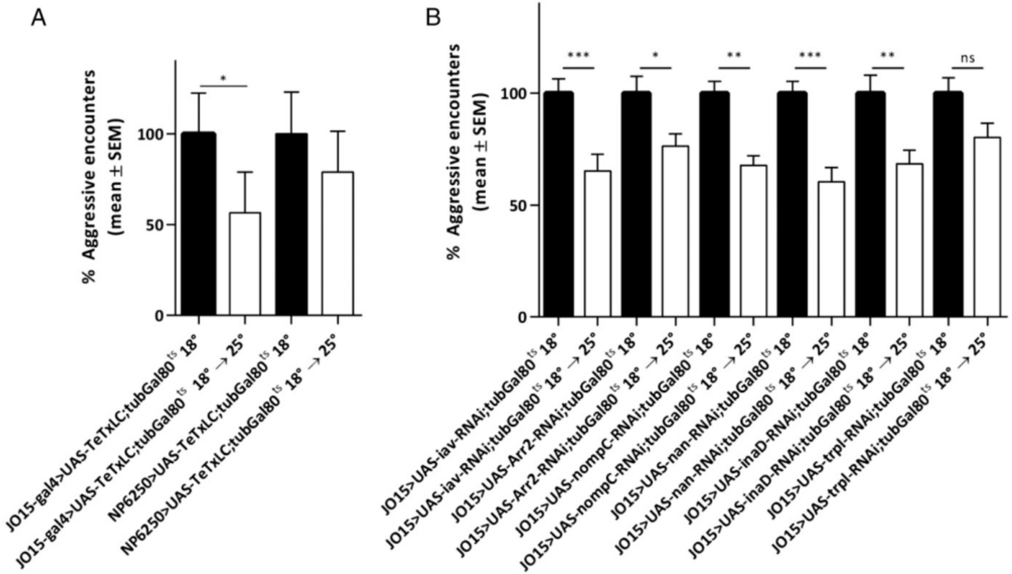
Jonsson, T., E. A. Kravitz and R. Heinrich (2011). "Sound production during agonistic behavior of male Drosophila melanogaster." Fly (Austin) **5**(1): 29-38.
Versteven, M., L. Vanden Broeck, B. Geurten, L. Zwarts, L. Decraecker, M. Beelen, M. C. Gopfert, R. Heinrich and P. Callaerts (2017). "Hearing regulates Drosophila aggression." Proc Natl Acad Sci U S A 114(8): 1958-1963.

Hearing organs and neuronal signaling required for normal aggressive behavior

Mechanical disruption of hearing organs reduces aggressive behavior



Neuronal silencing and genetic disruption of Johnston's organ results in reduced aggression

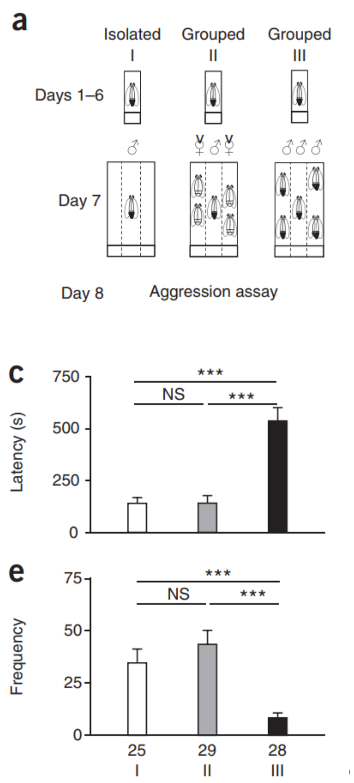


Versteven, M., L. Vanden Broeck, B. Geurten, L. Zwarts, L. Decraecker, M. Beelen, M. C. Gopfert, R. Heinrich and P. Callaerts (2017). "Hearing regulates Drosophila aggression." Proc Natl Acad Sci U S A 114(8): 1958-1963.

MODULATION OF *DROSOPHILA* AGGRESSION BY SOCIAL INTERACTION

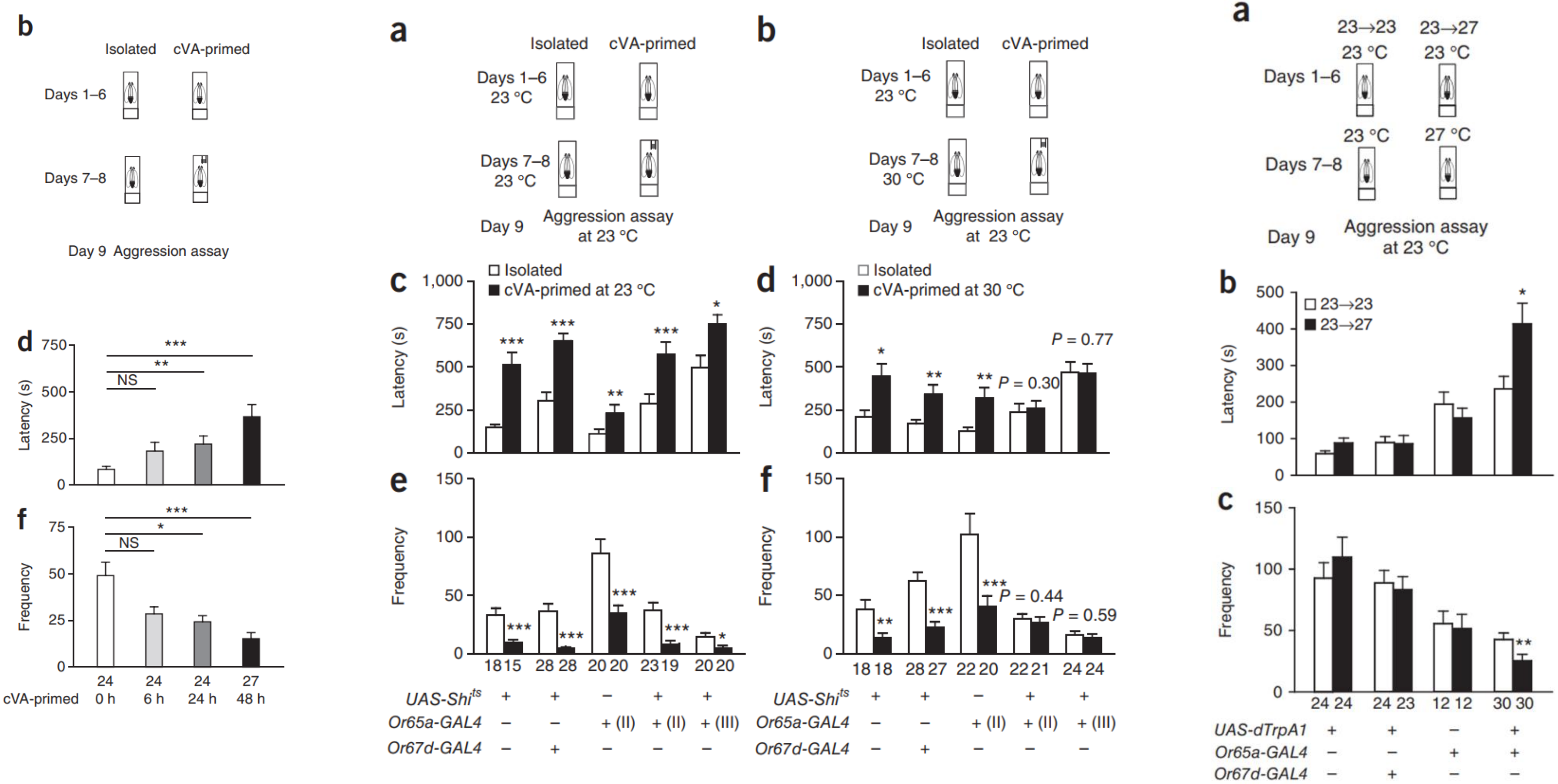
How isolated male is more aggressive than group housed male?

Social regulation of aggression



Liu, W., X. Liang, J. Gong, Z. Yang, Y. H. Zhang, J. X. Zhang and Y. Rao (2011). "Social regulation of aggression by pheromonal activation of Or65a olfactory neurons in Drosophila." Nat Neurosci 14(7): 896-902.

Aggression-suppressing effect of chronic cVA exposure mediated by Or65a ORNs

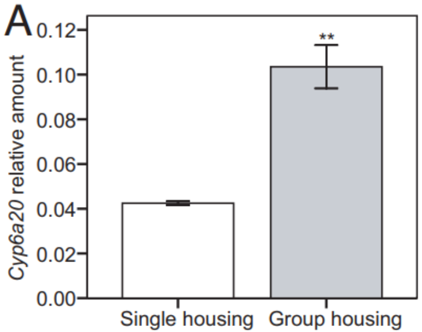


Liu, W., X. Liang, J. Gong, Z. Yang, Y. H. Zhang, J. X. Zhang and Y. Rao (2011). "Social regulation of aggression by pheromonal activation of Or65a olfactory neurons in Drosophila." Nat Neurosci 14(7): 896-902.

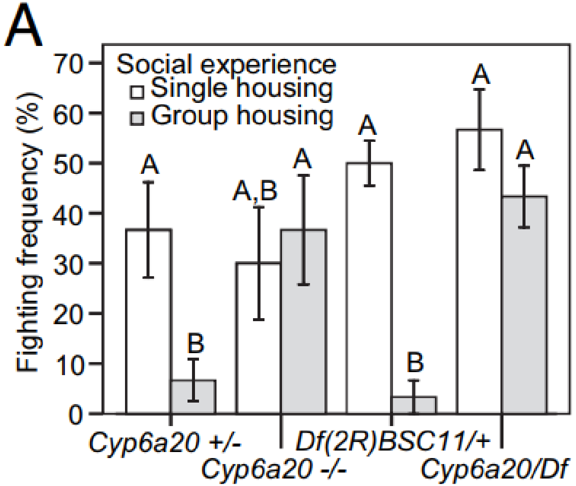
Cyp6a20 (cytochrome P450) regulates aggressiveness under group housing condition

gene expression is correlated with social experience

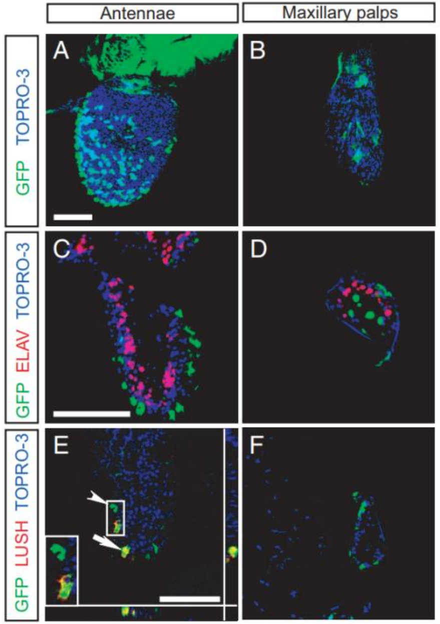
	Single housing	Group housing
0-3day	1 fly/vial	10 flies/vial
3-6day		



Cyp6a20 mutants exhibit increased aggressiveness only under group housing conditions



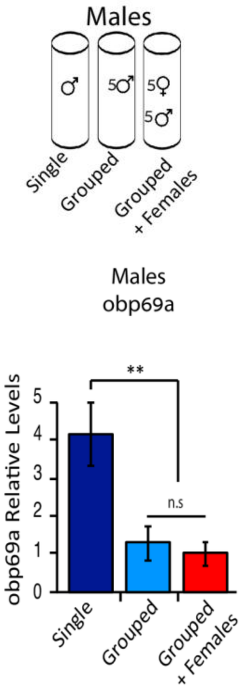
Cyp6a20 expression in olfactory sensory organs



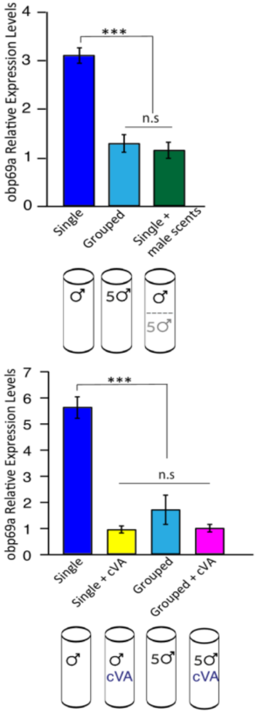
Wang, L., H. Dankert, P. Perona and D. J. Anderson (2008). "A common genetic target for environmental and heritable influences on aggressiveness in Drosophila." Proc Natl Acad Sci U S A 105(15): 5657-5663.

Odorant binding protein 69a (*Obp69a*) links prior social interaction to modulation of social responsivity

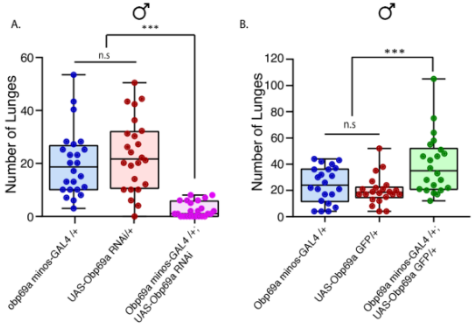
Obp69a expression levels regulated by social conditions



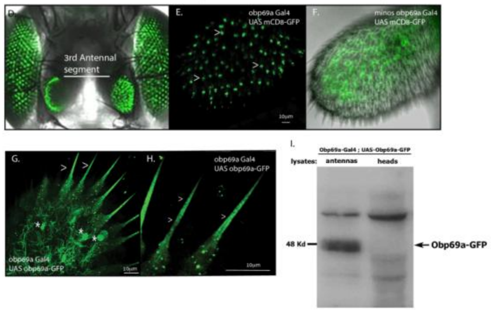
Obp69a transcription is regulated in response to male scents, and exposure to the male pheromone cVA



Obp69a links prior social interaction to modulation of social responsivity



Obp69a is expressed in cells within the third antennal segment and is exported to the lymph

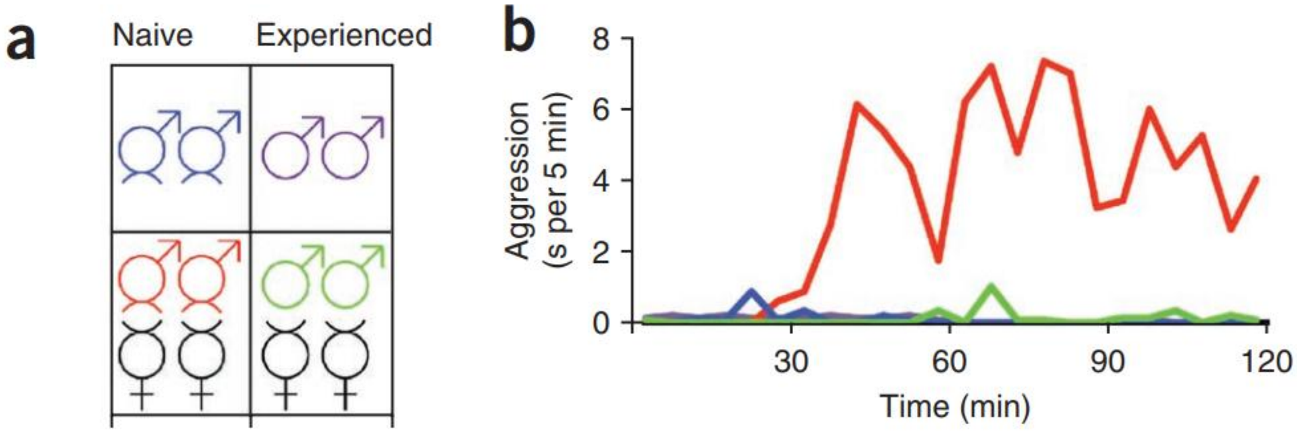


Bentzur, A., A. Shmueli, L. Omesi, J. Ryvkin, J. M. Knapp, M. Parnas, F. P. Davis and G. Shohat-Ophir (2018). "Odorant binding protein 69a connects social interaction to modulation of social responsiveness in Drosophila." PLoS Genet 14(4): e1007328.

HOW FEMALE CONTACT MODULATES MALE AGGRESSION?

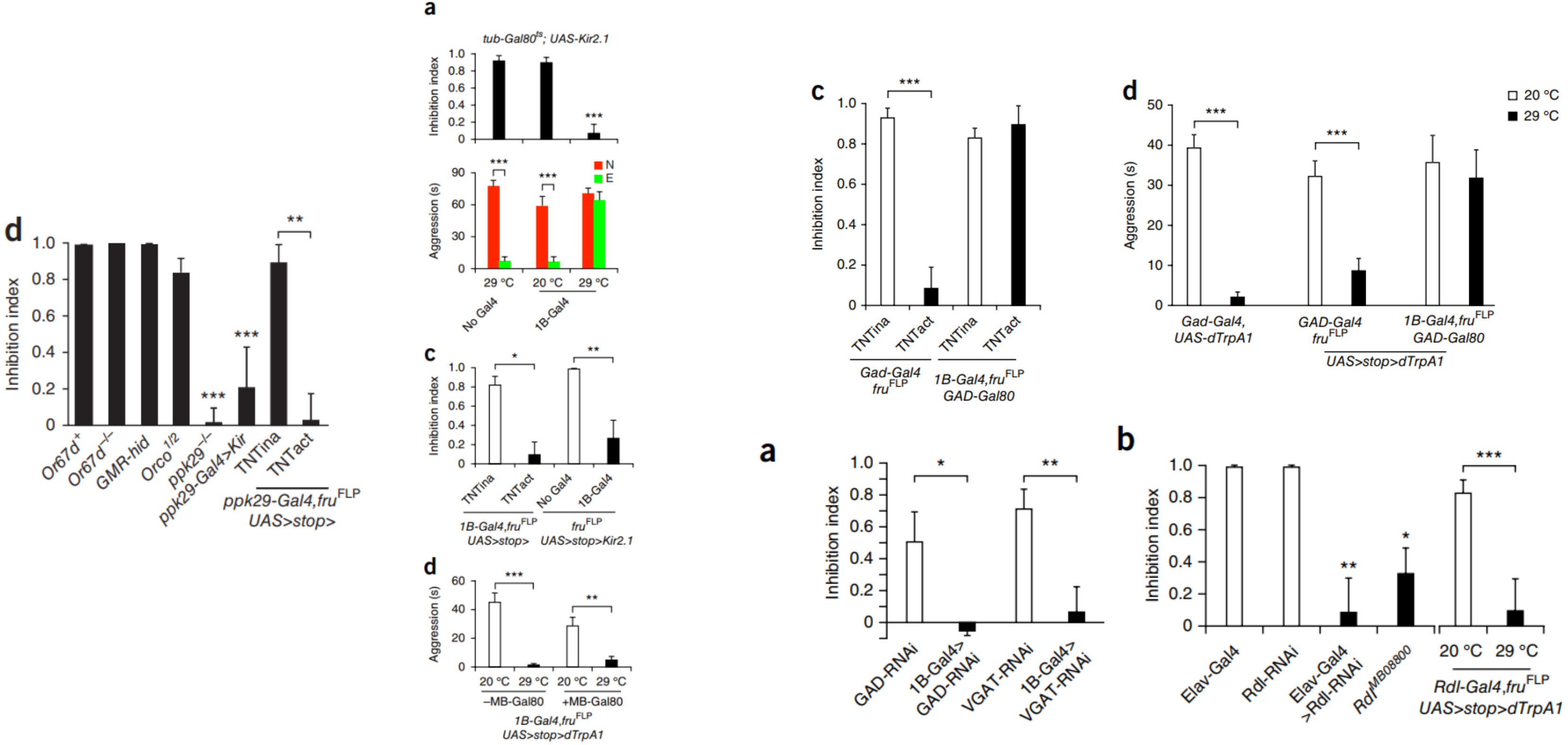
inhibit

Prior female experience inhibits sex-related male-male aggression



Yuan, Q., Y. Song, C. H. Yang, L. Y. Jan and Y. N. Jan (2014). "Female contact modulates male aggression via a sexually dimorphic GABAergic circuit in Drosophila." Nat Neurosci 17(1): 81-88.

Prior female contact–dependent inhibition of aggression mediated by pheromone-sensing channel ppk29, GABAergic neurotransmission in sexually dimorphic fru^{+}, GABA^{+} and d5HT1B^{+} neurons, the GABAA receptor RDL and Rdl^{+} fru^{+} sexually dimorphic neurons

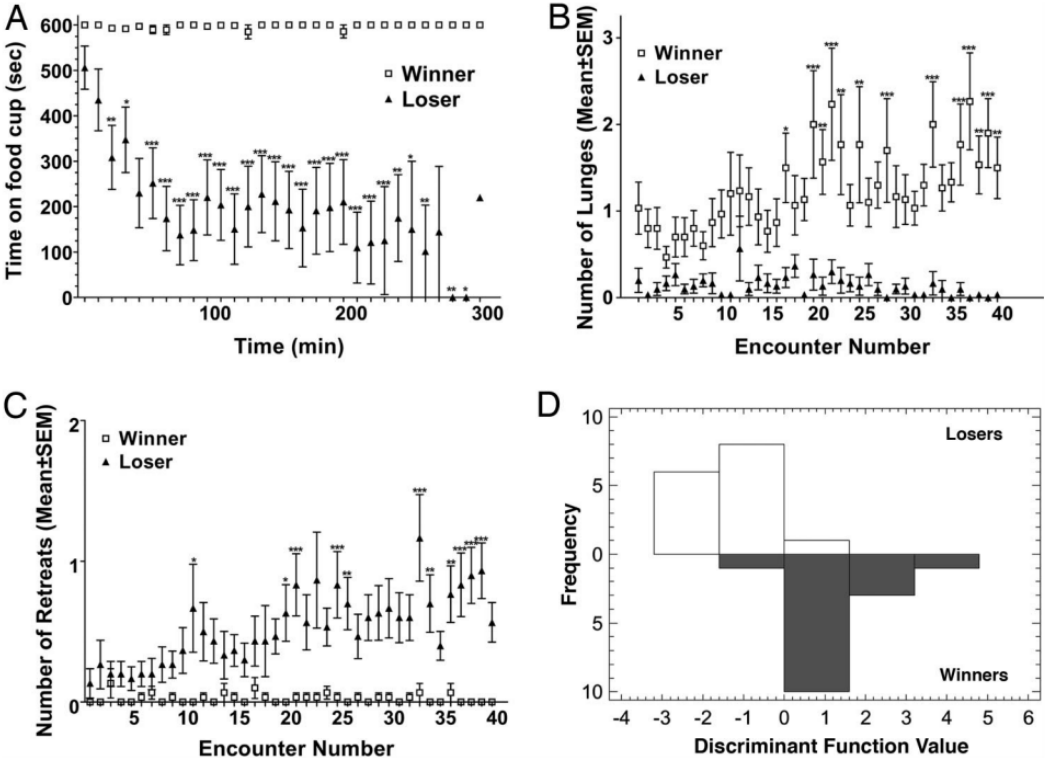


Yuan, Q., Y. Song, C. H. Yang, L. Y. Jan and Y. N. Jan (2014). "Female contact modulates male aggression via a sexually dimorphic GABAergic circuit in Drosophila." Nat Neurosci 17(1): 81-88.

MODULATION OF *DROSOPHILA* AGGRESSION BY PRIOR EXPERIENCE

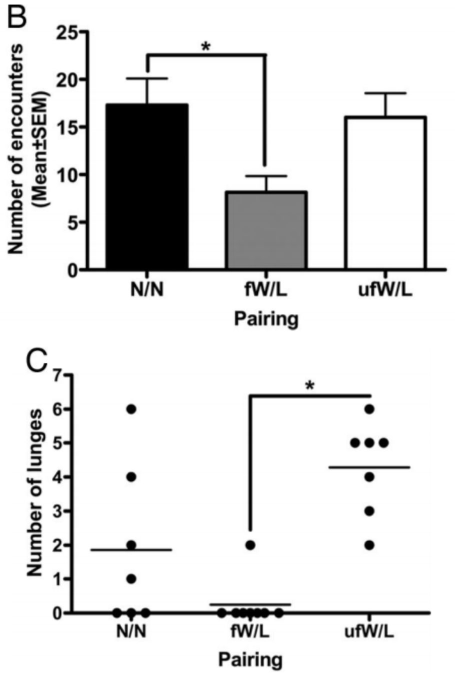
Social defeat reduces aggression

Indicators of dominant and subordinate status



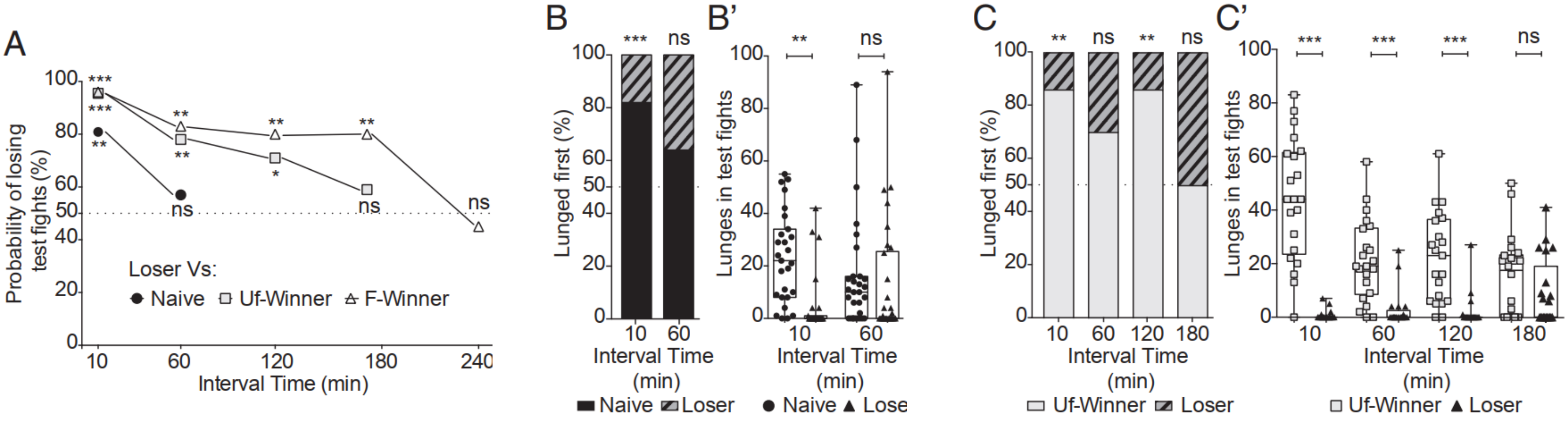
Yurkovic, A., O. Wang, A. C. Basu and E. A. Kravitz (2006). "Learning and memory associated with aggression in Drosophila melanogaster." Proc Natl Acad Sci U S A **103**(46): 17519-17524.

Persistence of dominance relationship and individual recognition



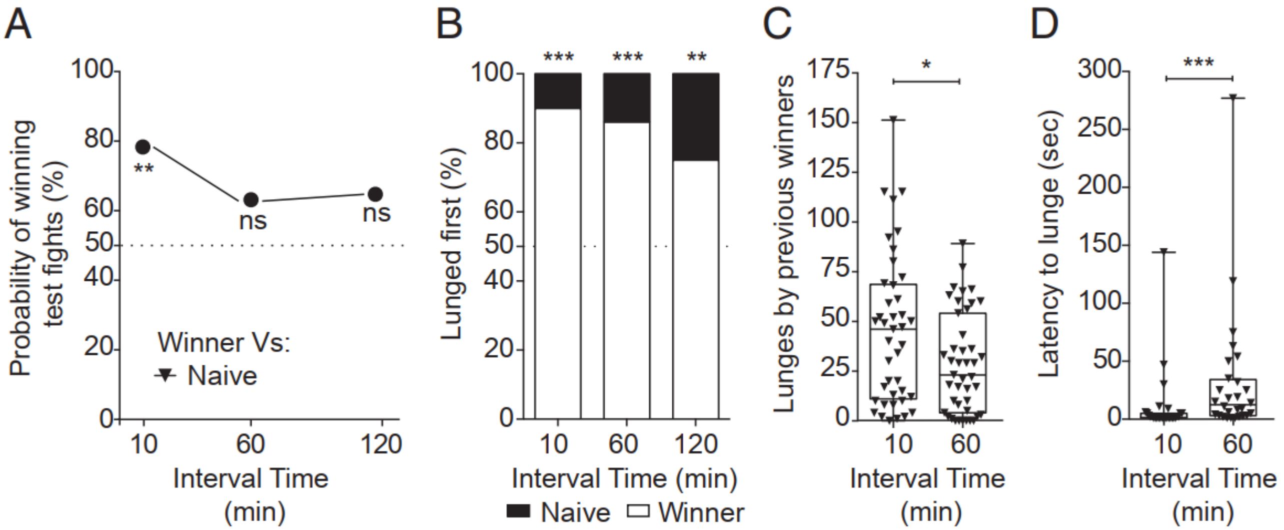
Yurkovic, A., O. Wang, A. C. Basu and E. A. Kravitz (2006). "Learning and memory associated with aggression in Drosophila melanogaster." Proc Natl Acad Sci U S A **103**(46): 17519-17524.

Prior defeat induces submissive behavior and drives short-term loser effect formation



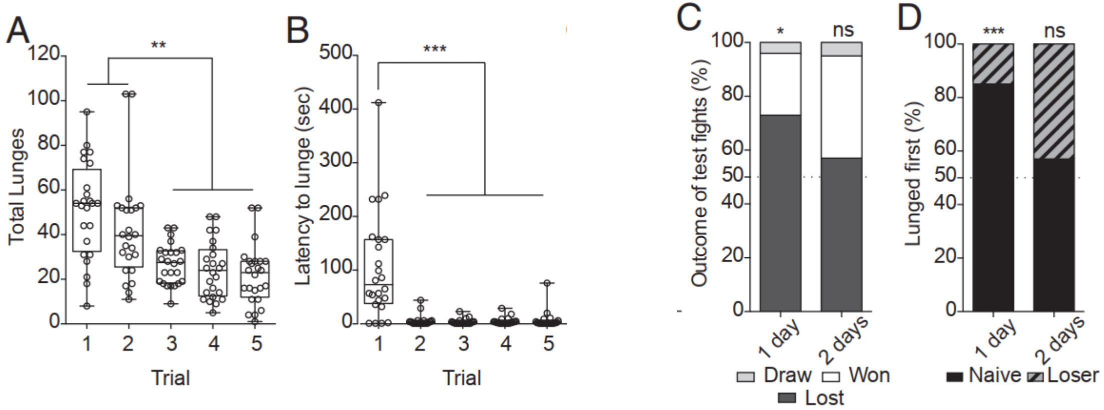
Trannoy, S., J. Penn, K. Lucey, D. Popovic and E. A. Kravitz (2016). "Short and long-lasting behavioral consequences of agonistic encounters between male Drosophila melanogaster." Proc Natl Acad Sci U S A **113**(17): 4818-4823.

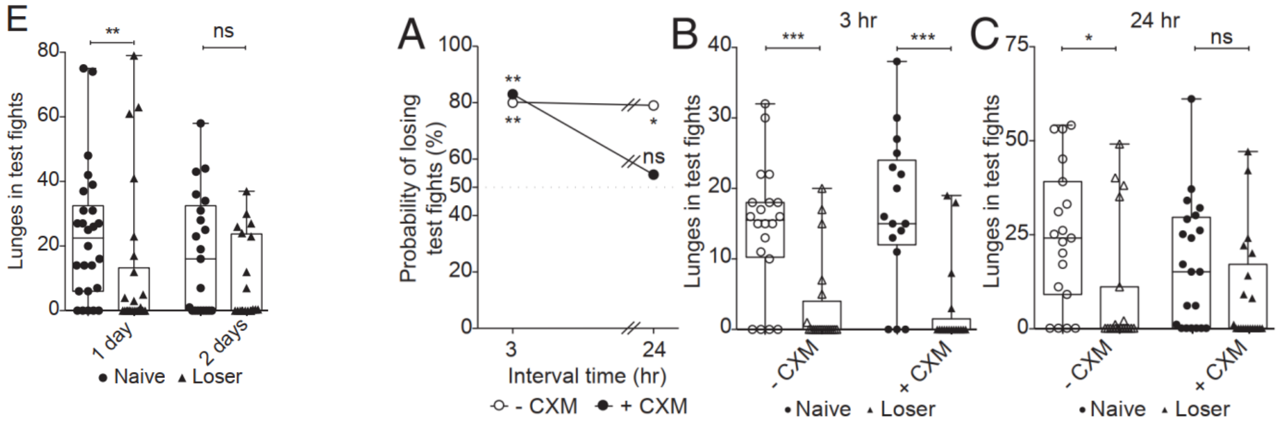
Previous victory enhances aggressive behavior and promotes the formation of a short-term winner effect



Trannoy, S., J. Penn, K. Lucey, D. Popovic and E. A. Kravitz (2016). "Short and long-lasting behavioral consequences of agonistic encounters between male Drosophila melanogaster." Proc Natl Acad Sci U S A **113**(17): 4818-4823.

Repeated defeats lead to long-lasting consequences that requires de novo protein synthesis

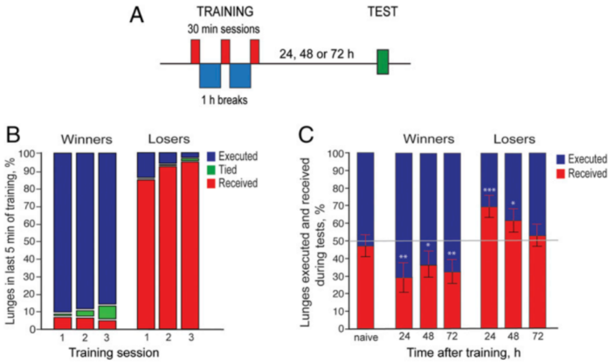




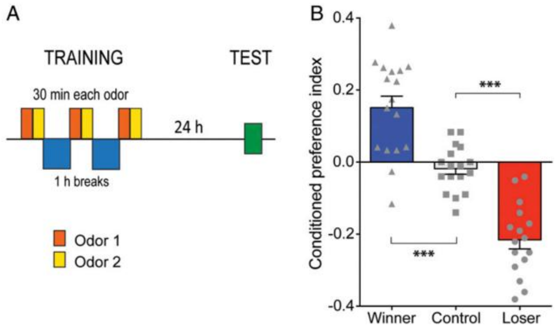
Trannoy, S., J. Penn, K. Lucey, D. Popovic and E. A. Kravitz (2016). "Short and long-lasting behavioral consequences of agonistic encounters between male Drosophila melanogaster." Proc Natl Acad Sci U S A **113**(17): 4818-4823.

Repetitive aggressive encounters generate a long-lasting internal state in *Drosophila* males

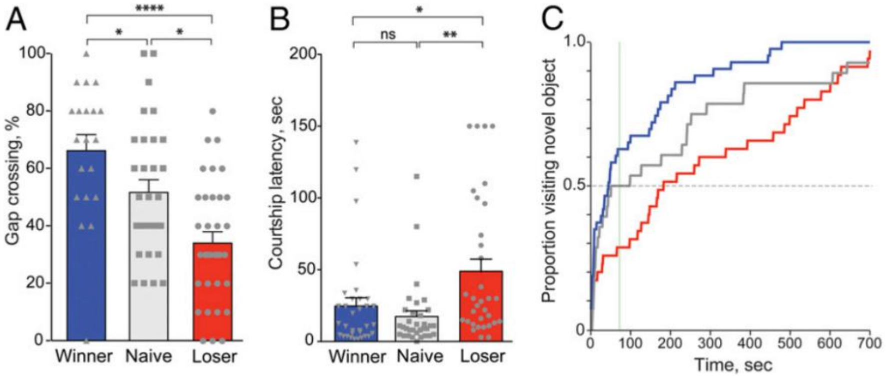
Generation of a persistent winner and loser effect



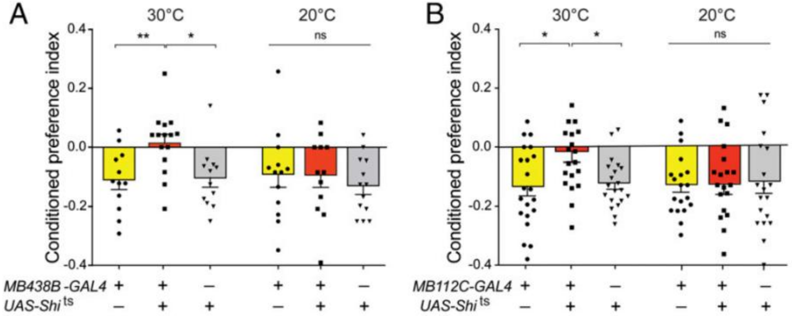
Valence of the winning and losing.



Generalization of the loser and winner effect



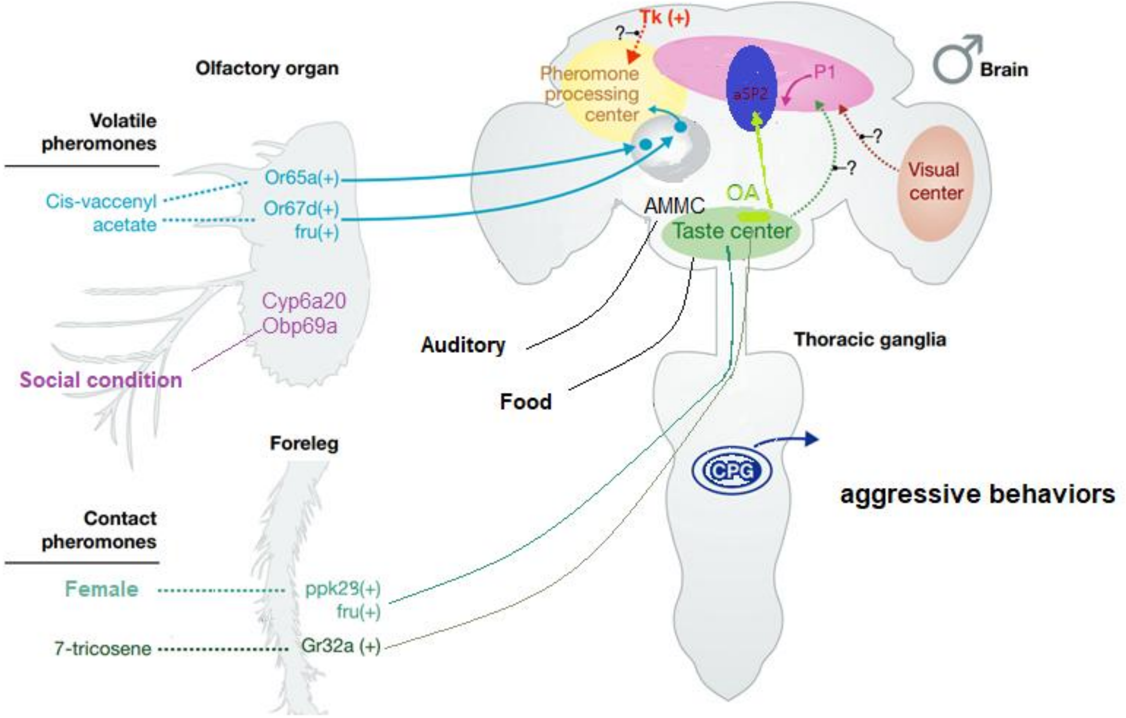
The activities of PPL1- γ1pedc dopamine neuron and MBON-γ1pedc>α/β mushroom body output neurons are required for the memory of a cue associated with losing



Kim, Y. K., M. Saver, J. Simon, C. F. Kent, L. Shao, M. Eddison, P. Agrawal, M. Texada, J. W. Truman and U. Heberlein (2018). "Repetitive aggressive encounters generate a long-lasting internal state in Drosophila melanogaster males." Proc Natl Acad Sci U S A 115(5): 1099-1104.

Summary

Aggression in *Drosophila* males



Conserved mechanisms of aggression in vertebrates

THREE

Sihui Jin

A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system

Article *in* The American journal of physiology 84:490-515 · January 1928

PNAS

Connectional architecture of a mouse hypothalamic circuit node controlling social behavior

Liching Lo[a,b,c,1], Shenqin Yao[d,1], Dong-Wook Kim[a,c], Ali Cetin[d], Julie Harris[d], Hongkui Zeng[d], David J. Anderson[a,b,c,2], and Brandon Weissbourd[a,b,c,2]

[a]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA 91125; [b]Howard Hughes Medical Institute, California Institute of Technology, Pasadena, CA 91125; [c]Tianqiao and Chrissy Chen Institute for Neuroscience, California Institute of Technology, Pasadena, CA 91125; and [d]Allen Institute for Brain Science, Seattle, WA 98109

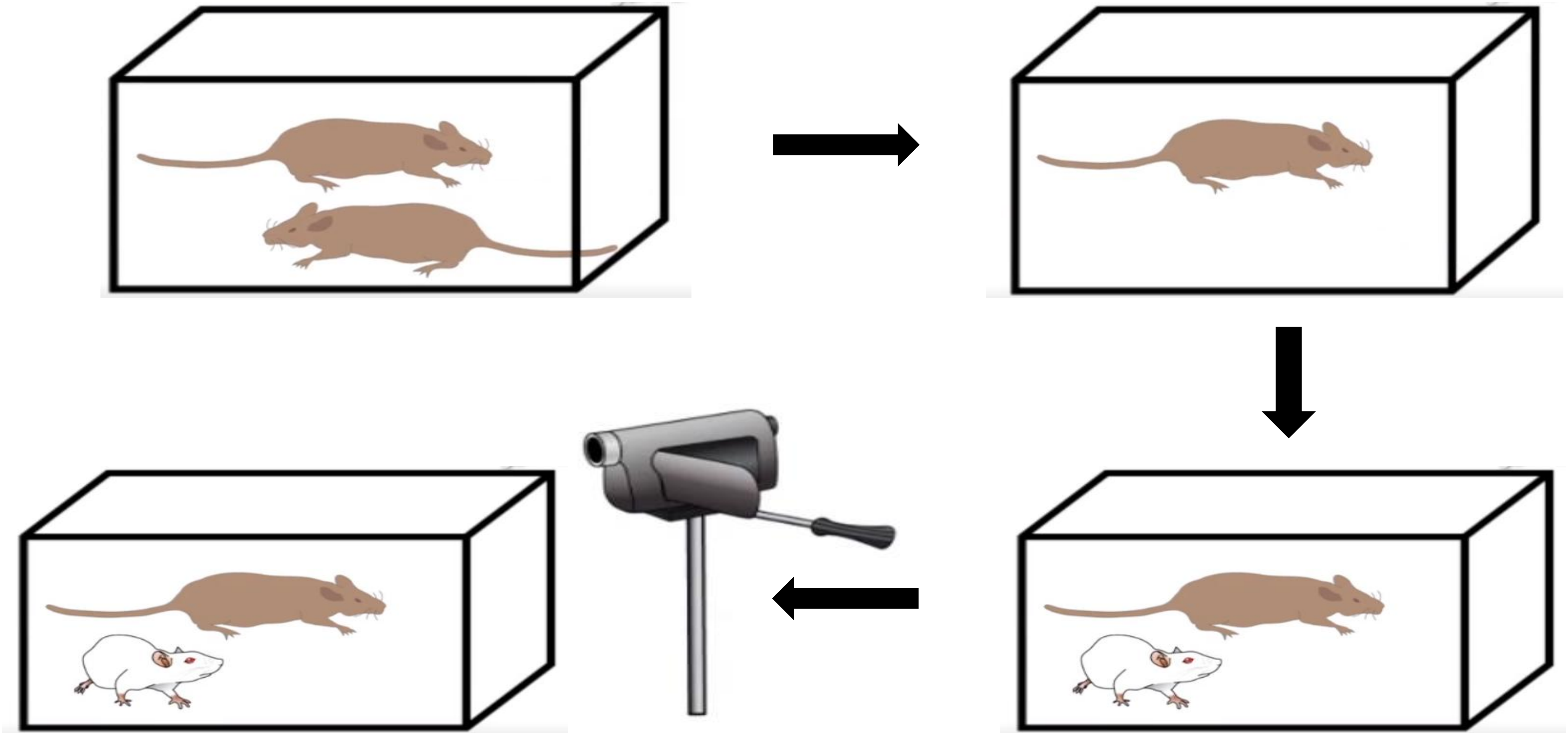
Contributed by David J. Anderson, December 12, 2018 (sent for review October 11, 2018; reviewed by Clifford B. Saper and Richard B. Simerly)

Brain, Behavior and Evolution

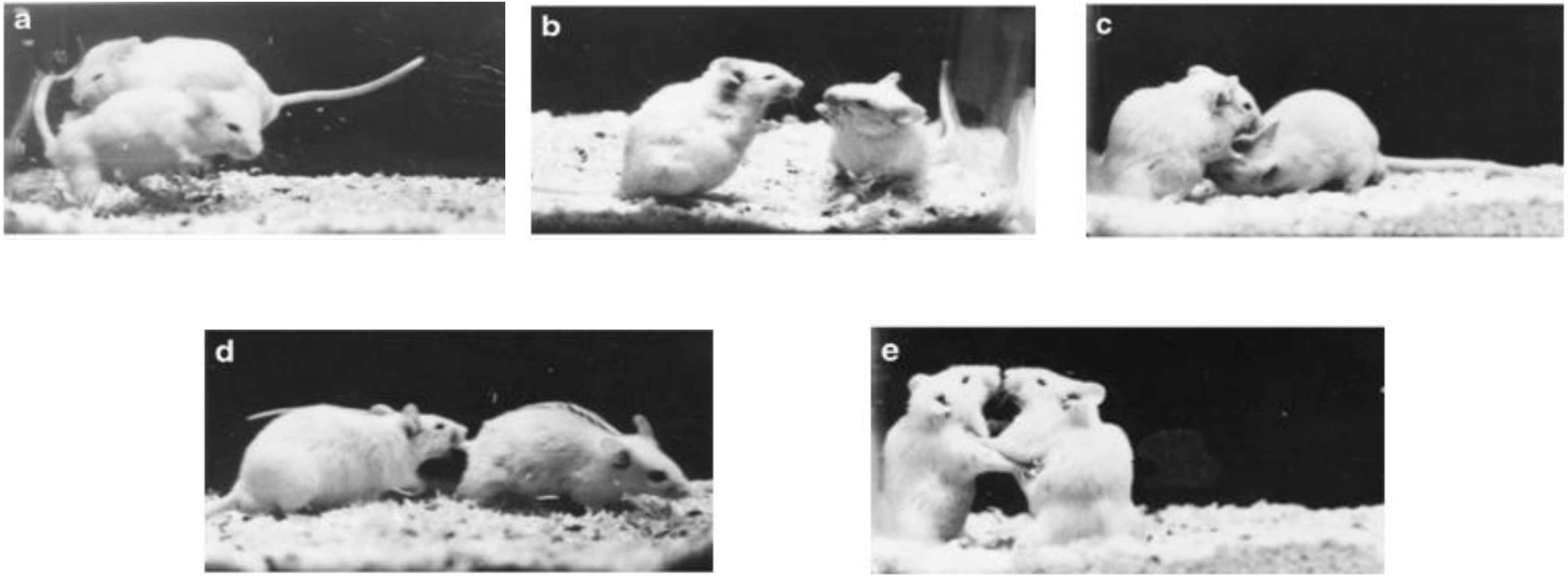
Threat, Attack and Flight Elicited by Electrical Stimulation of the Ventromedial Hypothalamus of the Marmoset Monkey *Callithrix jacchus*; pp. 260–275

Lipp H.P. · Hunsperger R.W.

The Resident-intruder Paradigm: A Standardized Test for Aggression



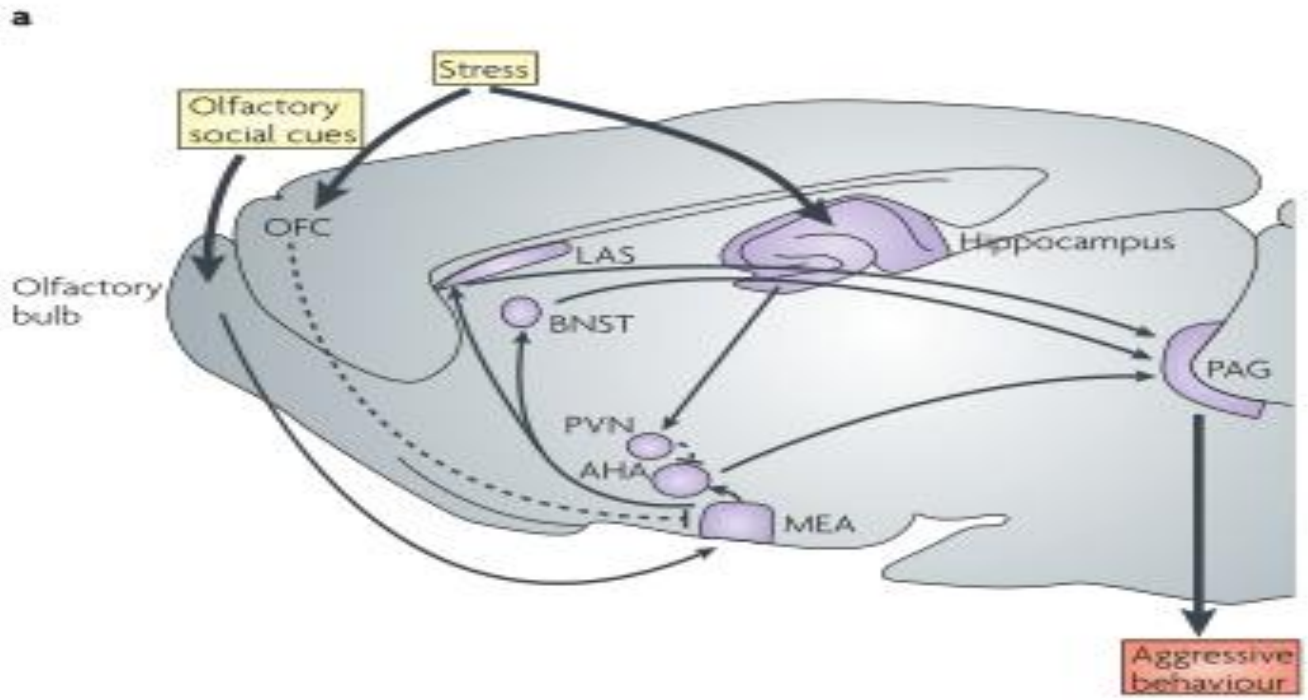
Mouse agonistic behavior



Aki Takahashi.,*Brain serotonin receptors and transporters: initiation vs. termination of escalated aggression*,2011

- Neuroanatomical pathways of aggression in rodent
- Signalling molecules of aggression in rodents
- The neural circuits of mating and fighting in male mice

Neuroanatomical pathways of aggression in rodents



Randy J. Nelson and Brian C. Trainor, *Neural mechanisms of aggression*,Nature,2007

Previous

Articles, Systems/Circuits

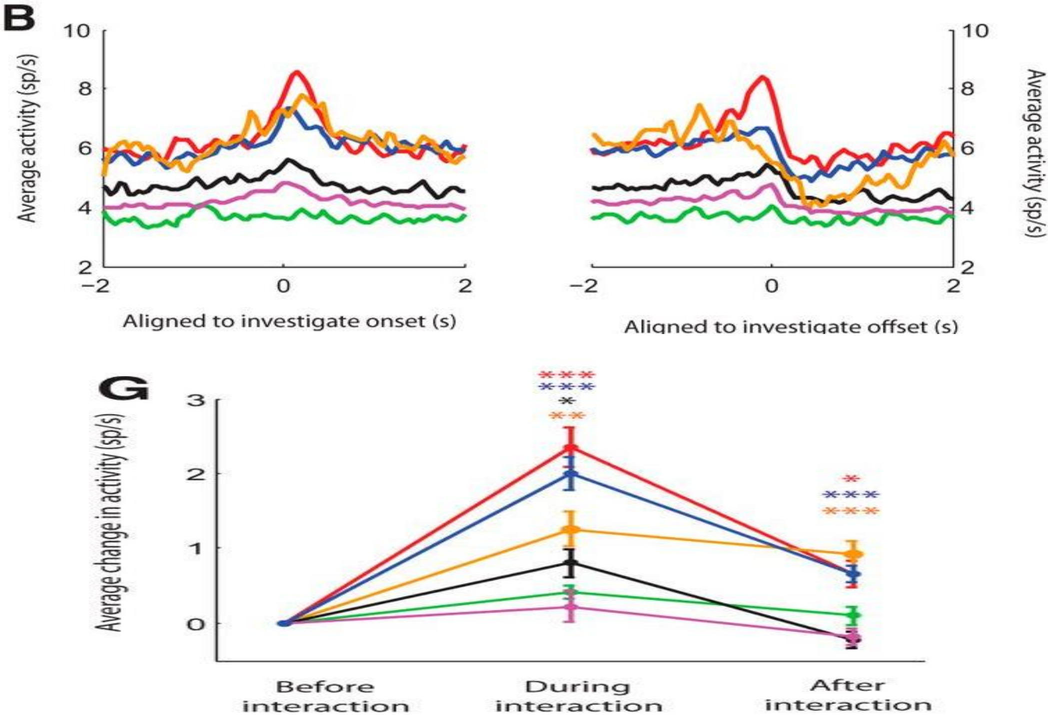
Decoding Ventromedial Hypothalamic Neural Activity during Male Mouse Aggression

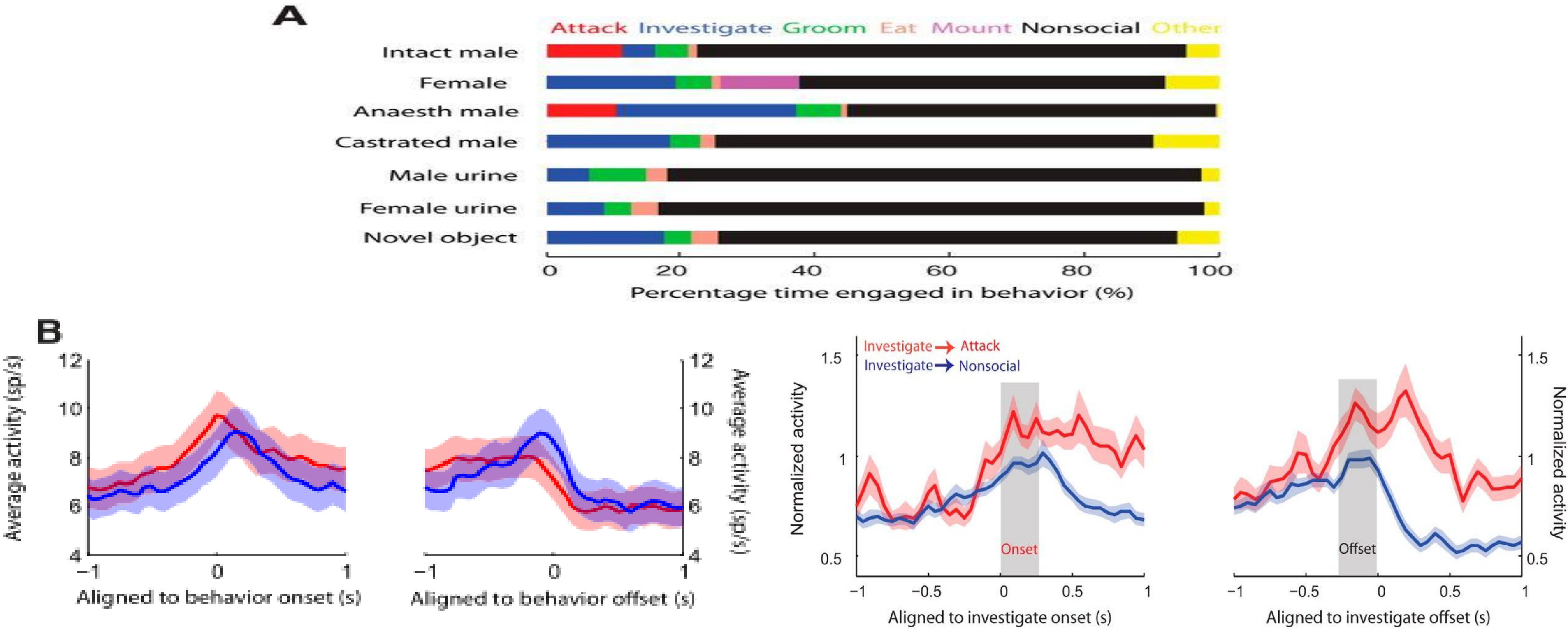
Annegret L. Falkner, Piotr Dollar, Pietro Perona, David J. Anderson, and Dayu Lin

Journal of Neuroscience 23 April 2014, 34 (17) 5971-5984; DOI: https://doi.org/10.1523/JNEUROSCI.5109-13.2014

Sensory contribution

	Presence of animal (sight)	Movement cues (sound)	Social odor cues	Act of investigat
Intact male	+	+	+	+
Anaesth male	+	-	+	+
Castrated male	+	+	reduced	+
Female	+	+	+	+
Male mouse urine	-	-	+	+
Novel object	-	-	-	+





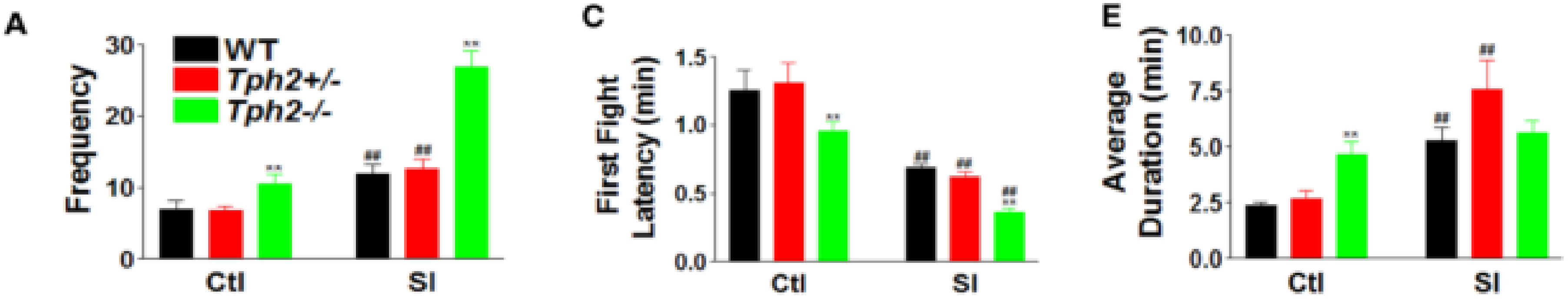
The ventromedial hypothalamus, ventrolateral area(VMHvl) neurons transiently increase activity during attack and investigation of male mice.

VMHvl activity during investigation correlates with the likelihood of a future attack.

Signalling molecules of aggression in rodents

- 5-HT
- Dopamine
- GABA
- Monoamine oxidase A (MAOA)
- Steroid hormones

5-HT—lower 5-HT signalling increases aggression

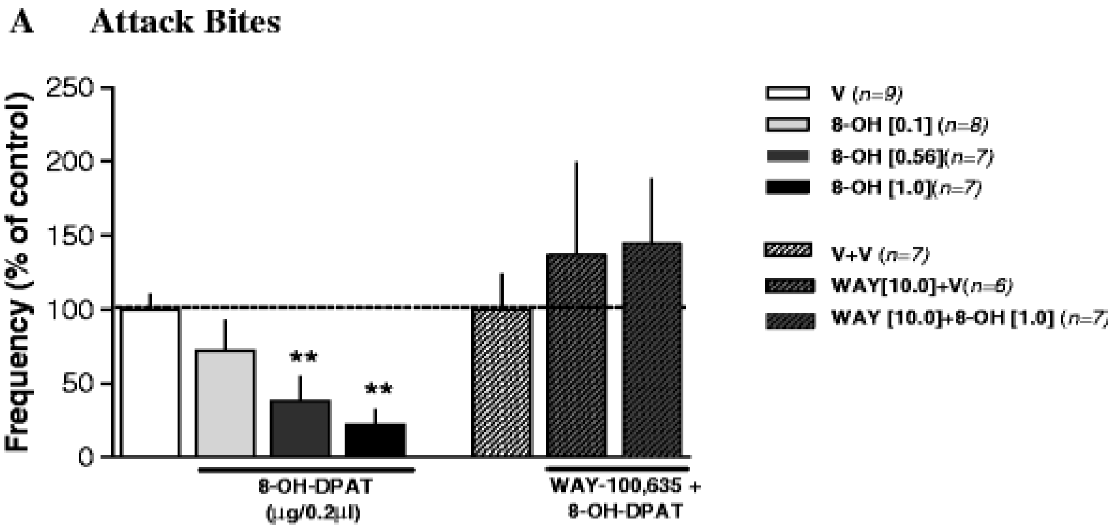


Yiqiong Liu, *Neurosci*,2019

TPH2 knockout mice showed a decrease of brain serotonin levels.

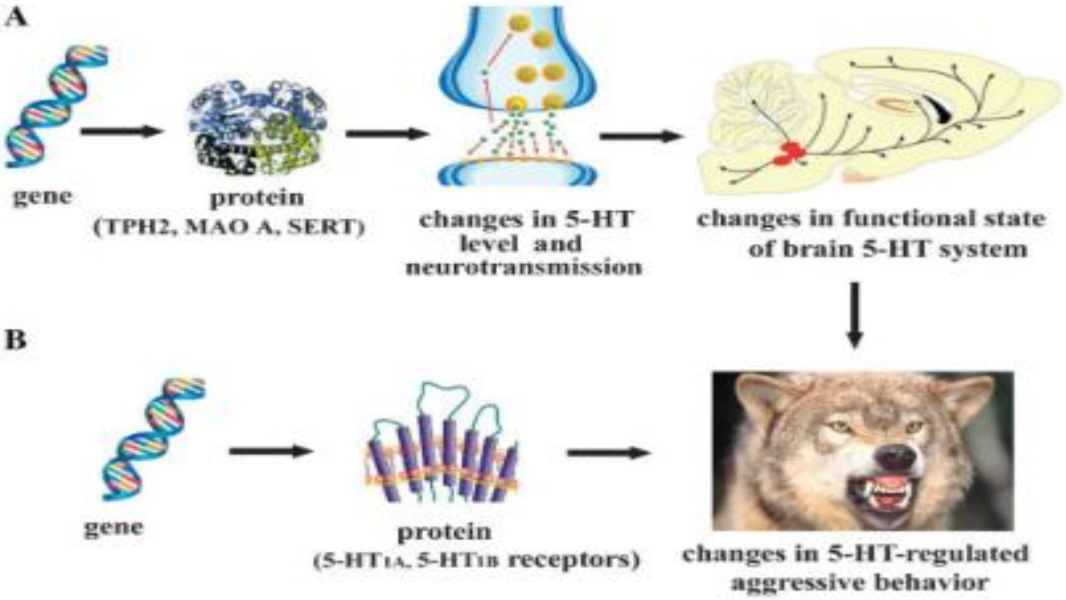
The decrease of brain serotonin level enhances aggression.

Effects of 5-HT_{1A} receptor agonist and antagonist on aggression



L ǵia Aline Centenaro, et.al, *role of 5-HT 1A and 5-HT 1B receptors in the prefrontal cortex*, 2008

Schematic model of the pathway from gene to aggressive behavior



Via key enzymes in 5-HT synthesis (TPH2)

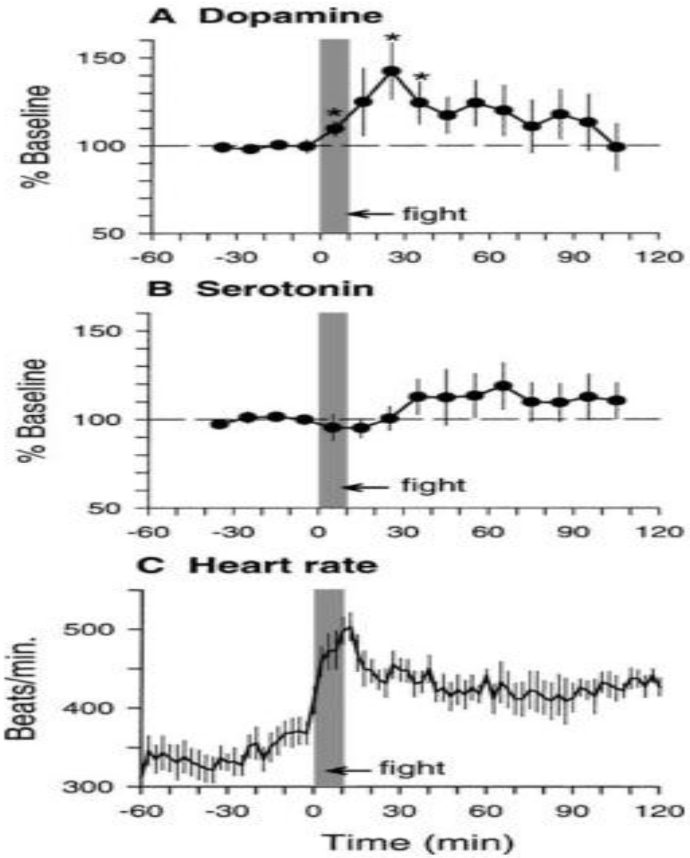
Via shorter way involving 5-HT receptors

Nina K. Popova, *From genes to aggressive behavior: the role of serotonergic system*,2006

Study	Correlation between serotonergic activity and aggressive behavior?	Aggressive behavior studied in
(Valzelli, 1973)	Negative	Prolonged socially isolated mice
(Saudou et al., 1994)	Negative	Knockout mice
(Holmes et al., 2002)	Negative	Knockout mice
(Caramaschi et al., 2007)	Negative	Mouse strains particularly selected for aggressive behavior
(Mosienko et al., 2012)	Negative	Knockout mice
(Van der Vegt et al., 2003b)	Positive	Wildtype rats
(Kulikov et al., 2012)	Positive	Conventionally used mouse strains (CC57BR and C57BL/6J)

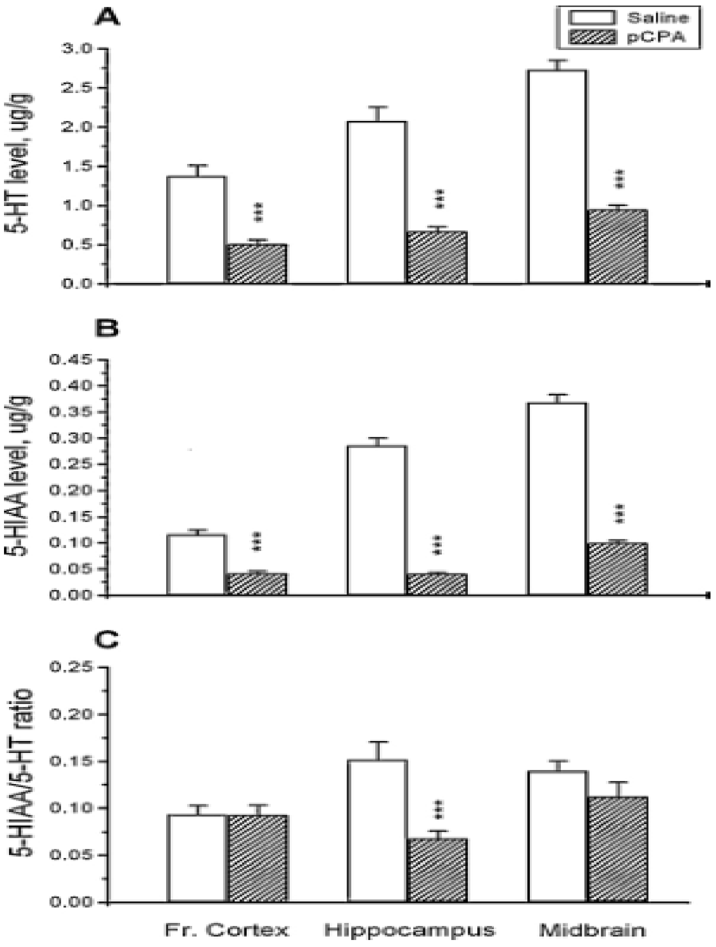
However, some studies also show an opposite correlation.

Dopamine



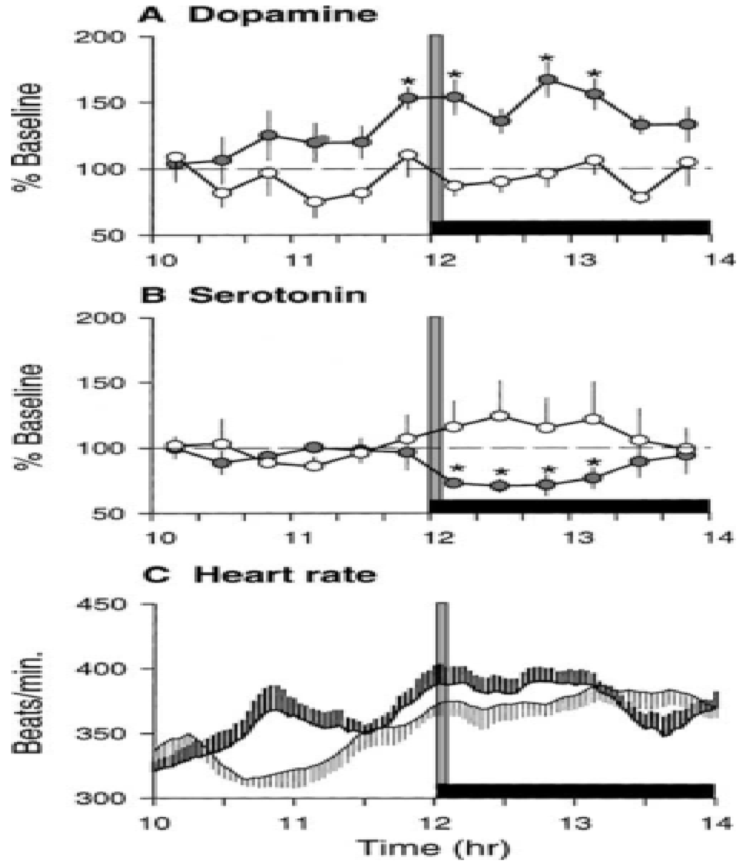
During an acute confrontation NAc serotonin is not a key factor in the modulation of aggressive behavior.

P. F. Ferrari, et.al, *Neuronsci*,2003



Administration of TPH2 inhibitor p-chlorophenylalanine (pCPA) reduced the 5-HT and 5-HIAA contents in brain structures and attenuated the frequency and the duration of aggressive attacks.

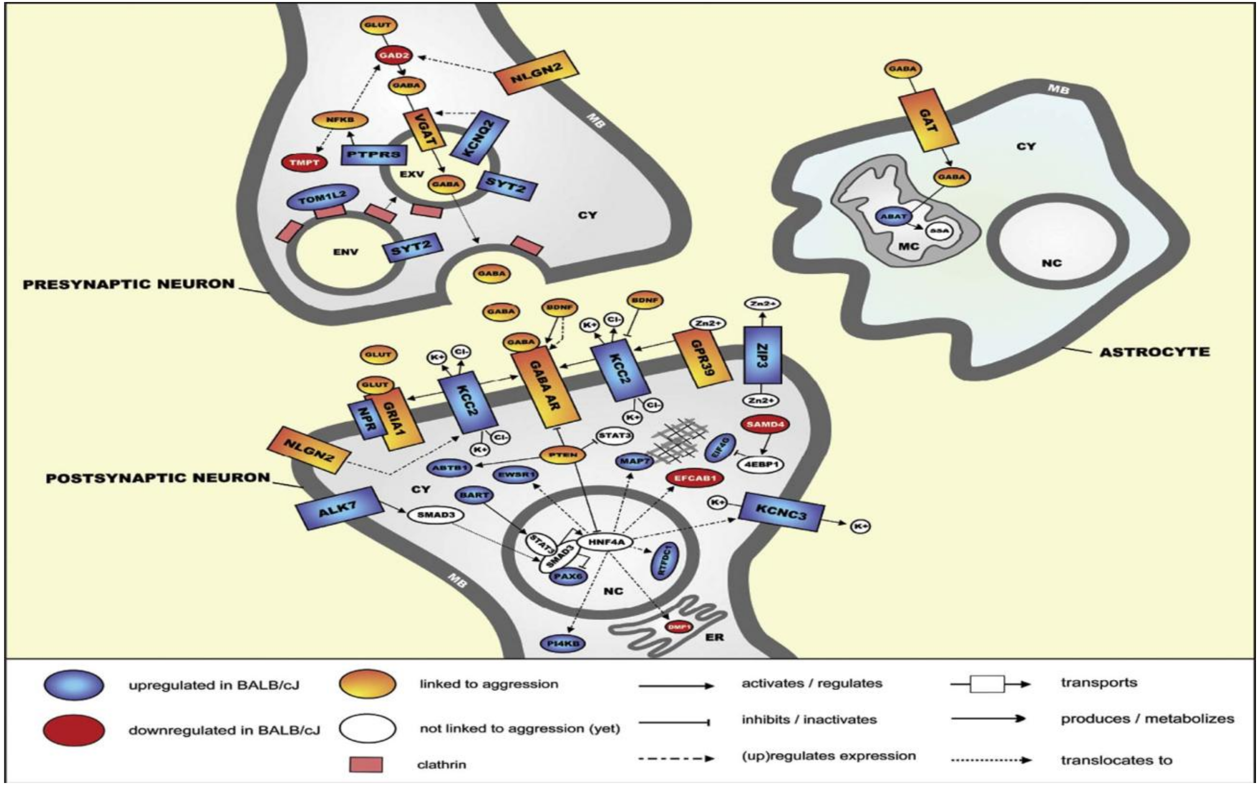
A.V. Kulikov, et.al, *Behavioural Brain Research*,2012



Dopaminergic neurons in the NAc may be activated at the start of aggression and the prolonged elevation persists beyond the removal of the intruder.

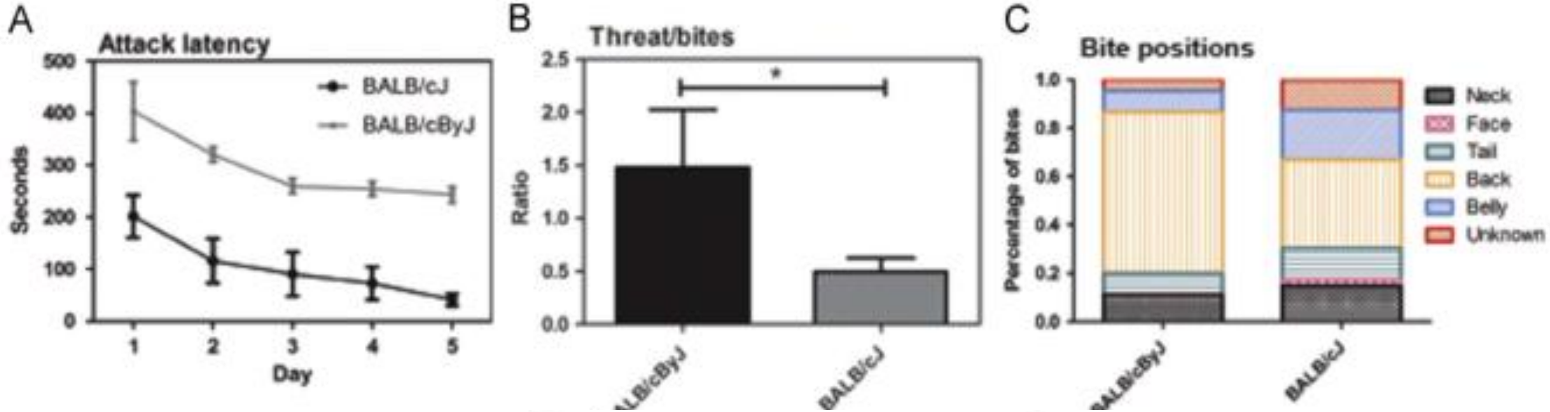
P. F. Ferrari, et.al, *Neuronsci*,2003

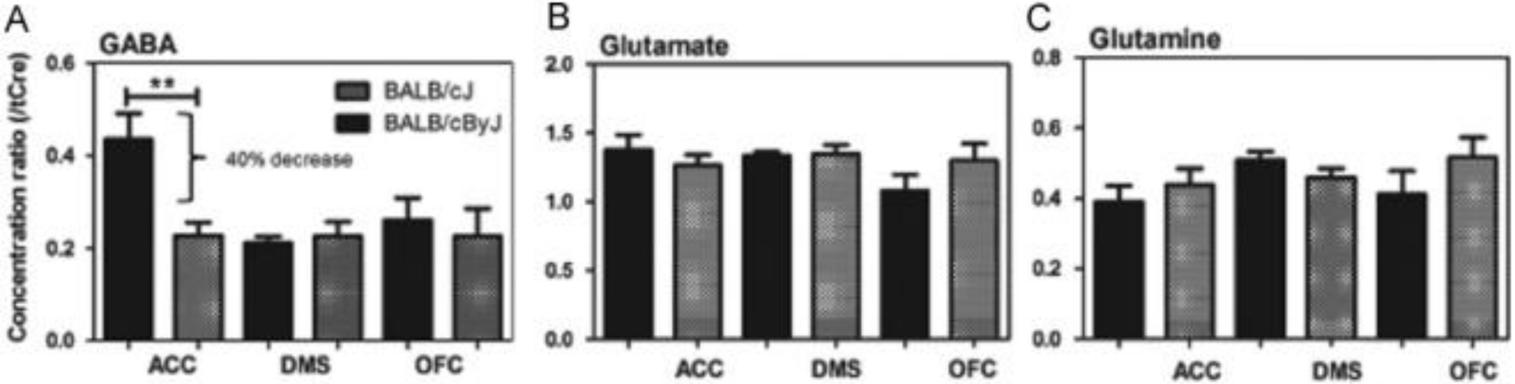
GABA



Amanda Jager, et.al, Cortical control of aggression: GABA signalling in the anterior cingulate cortex, 2017

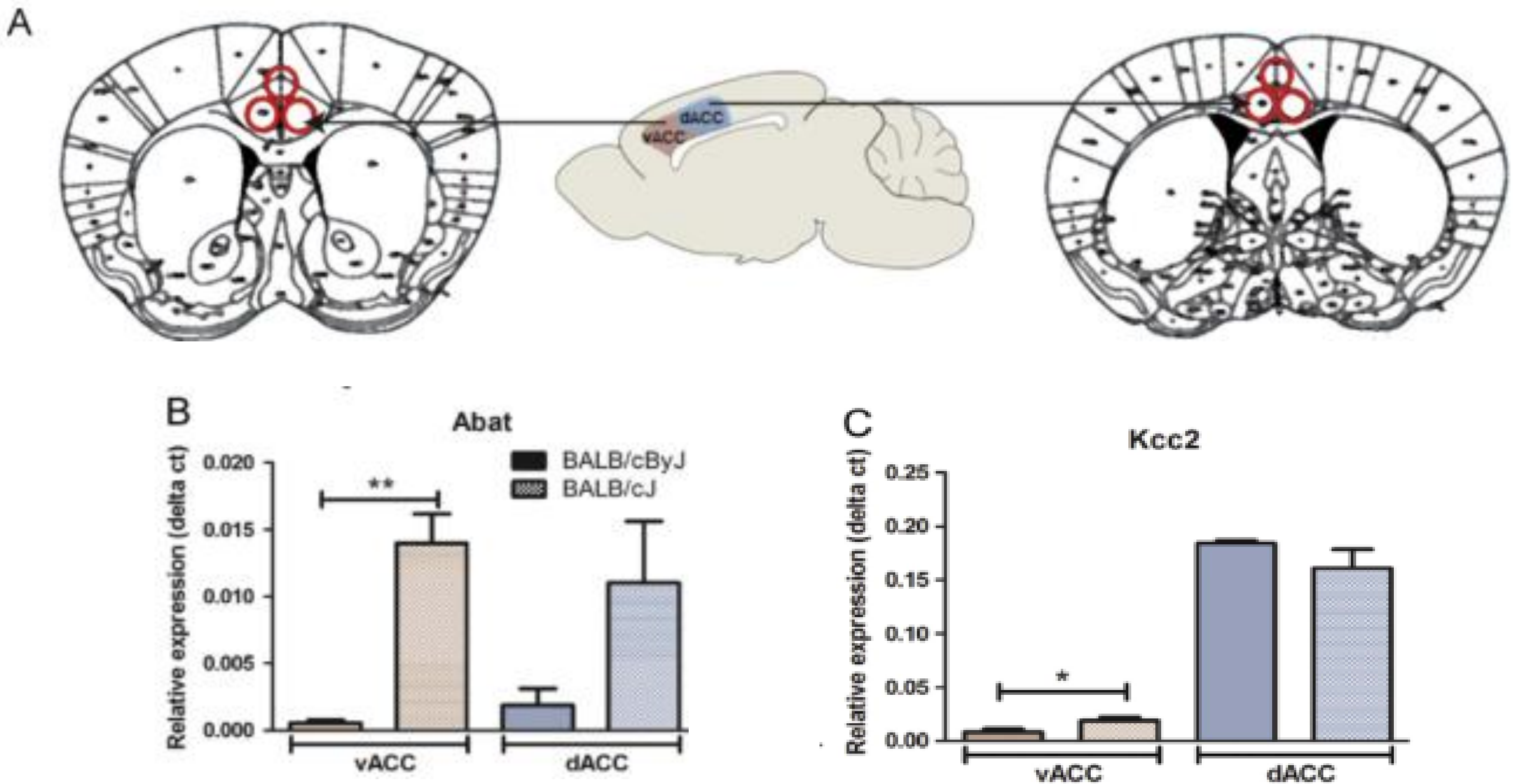
There is a decrease in GABA in ACC brain regions





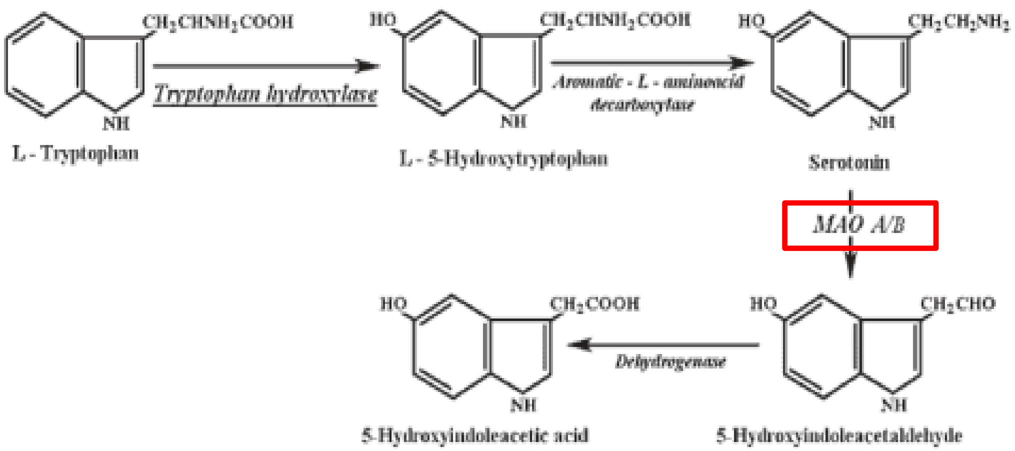
Amanda Jager, et.al, Cortical control of aggression: GABA signalling in the anterior cingulate cortex, 2017

Abat and Kcc2 are involved in modulating aggressive behaviour



Amanda Jager, et.al, Cortical control of aggression: GABA signalling in the anterior cingulate cortex, 2017

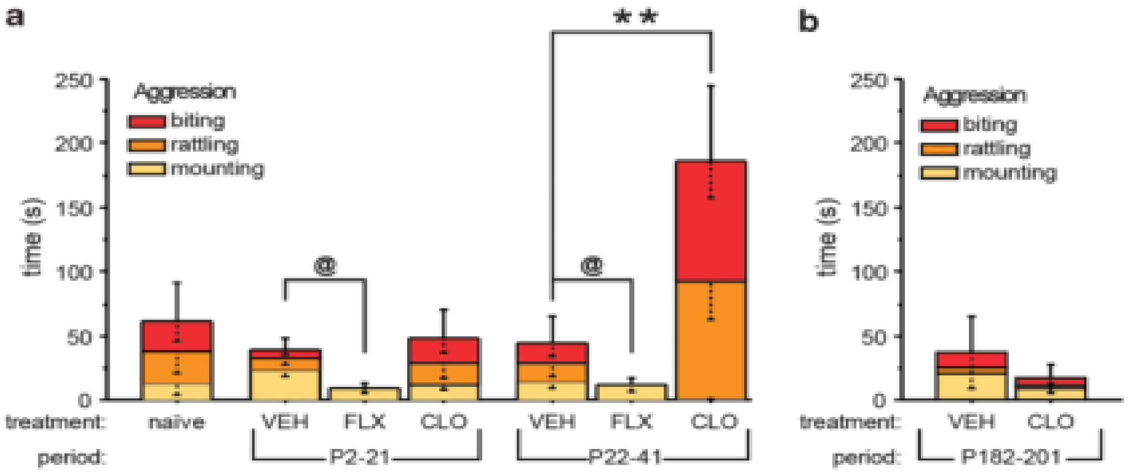
MAOA



Nina K. Popova, *From genes to aggressive behavior: the role of serotonergic system*,2006

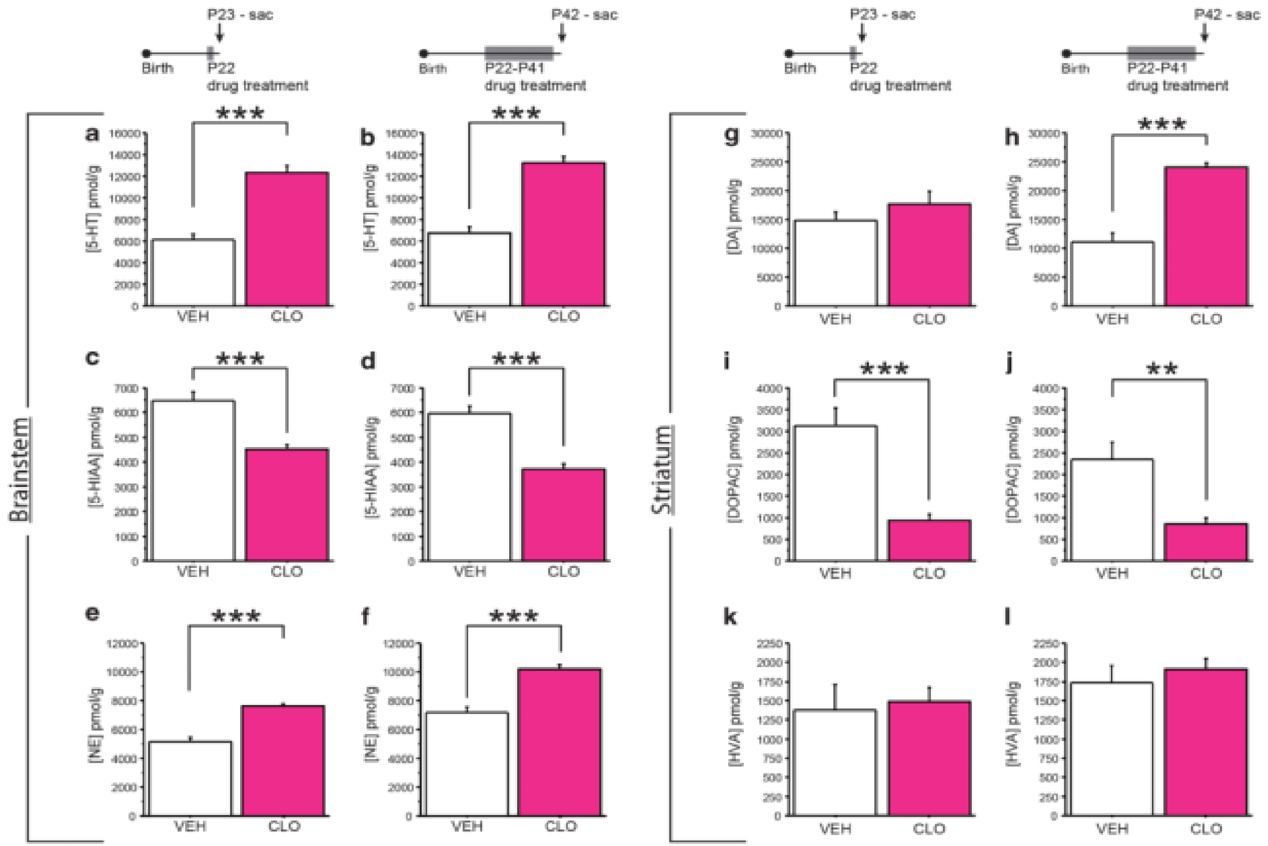
Monoamine oxidase A (MAOA) inactivates bioamines, including serotonin , norepinephrine, dopamine (DA) and trace amines through oxidative deamination.

Peri-adolescent MAOA blockade increases aggression



Q *Yu,Molecular Psychiatry, 2014*

CLO treatment from P22–P41 but not from P2–P21 increased aggressive behavior.

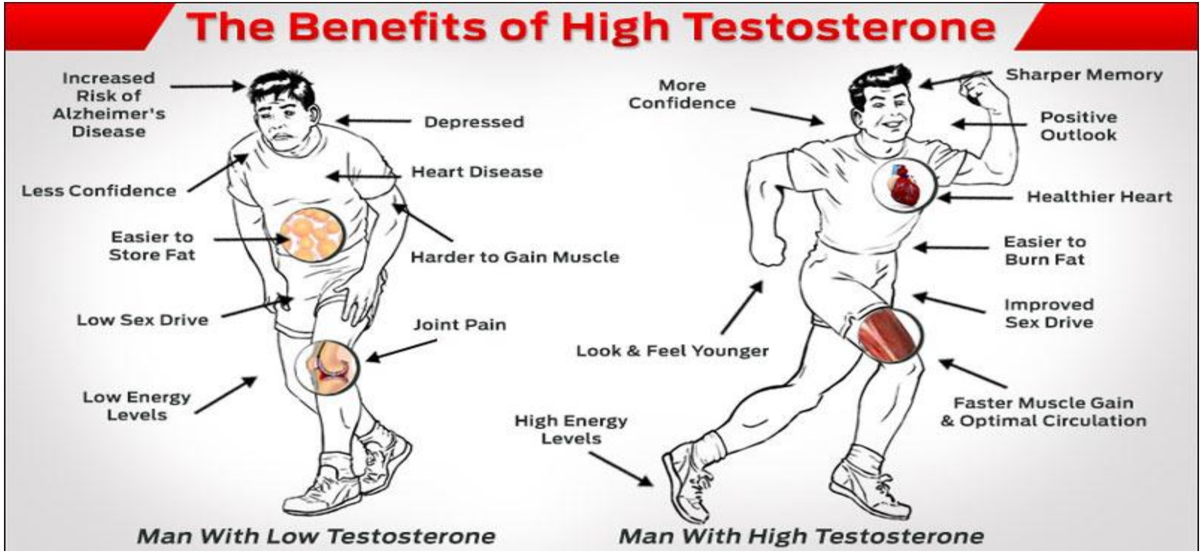


Q *Yu,Molecular Psychiatry, 2014*

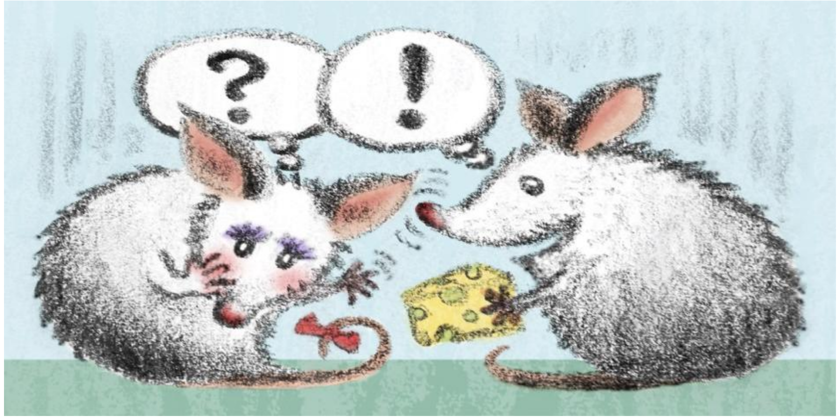
MAOA blockade using CLO treatment during peri-adolescence inhibits 5-HT, NE and DA metabolism and raises levels of 5-HT, DA and NE.

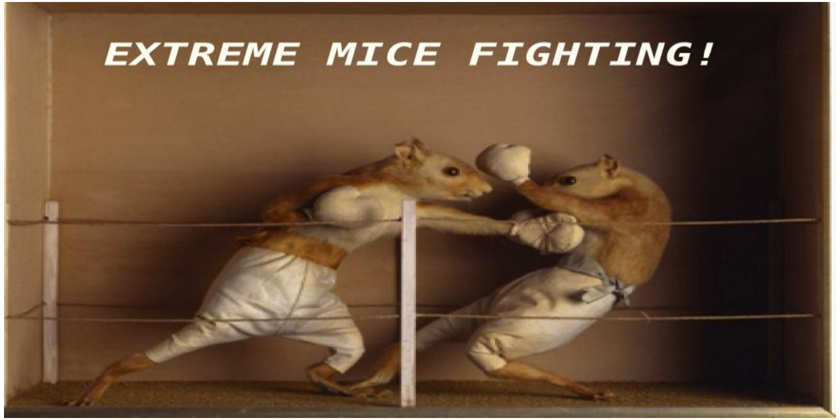
Steroid hormones

Testosterone have both organizational and activational effects on aggression.

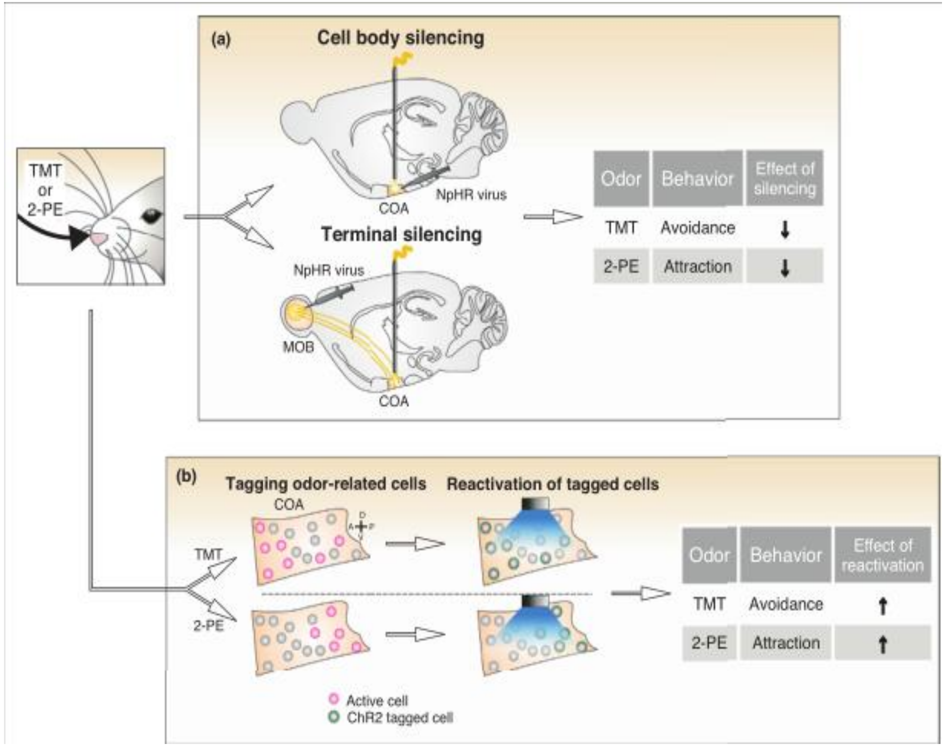


The neural circuits of mating and fighting in male mice





Mating and aggression can be triggered by sensory cues

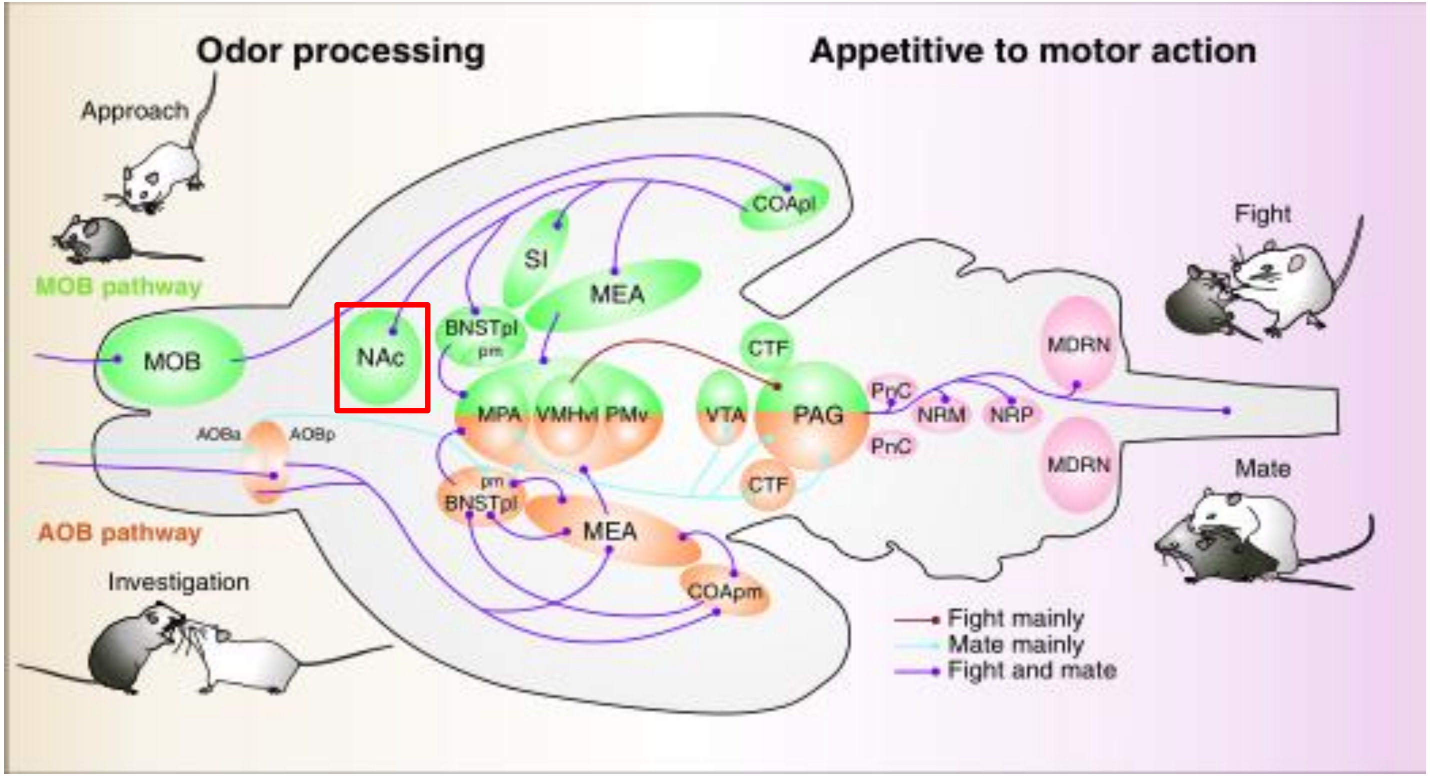


Koichi Hashikawa, Neurobiology, 2016

Odors can be detected through the main olfactory system (MOS)

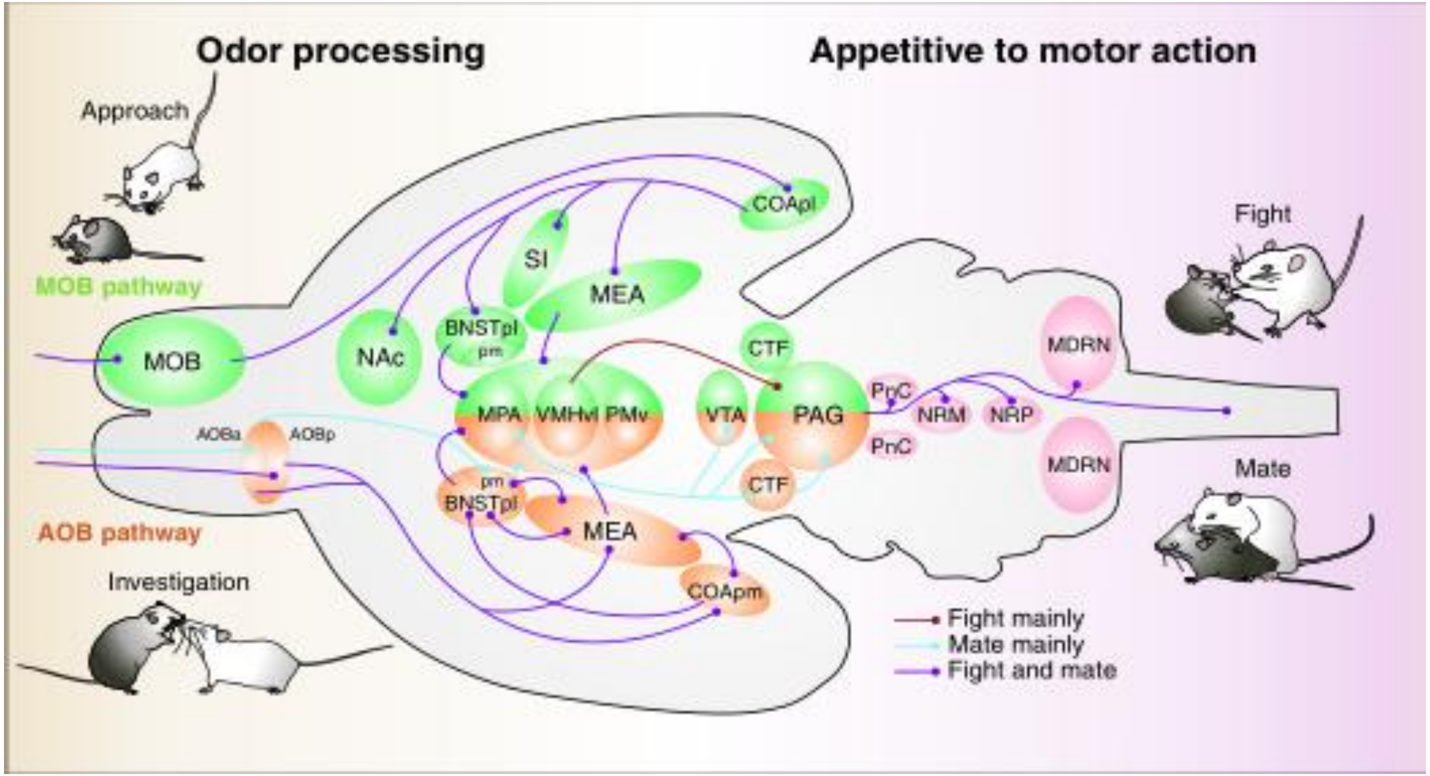
⇩

COApl neurons are essential for innate odor driven avoidance and attraction.



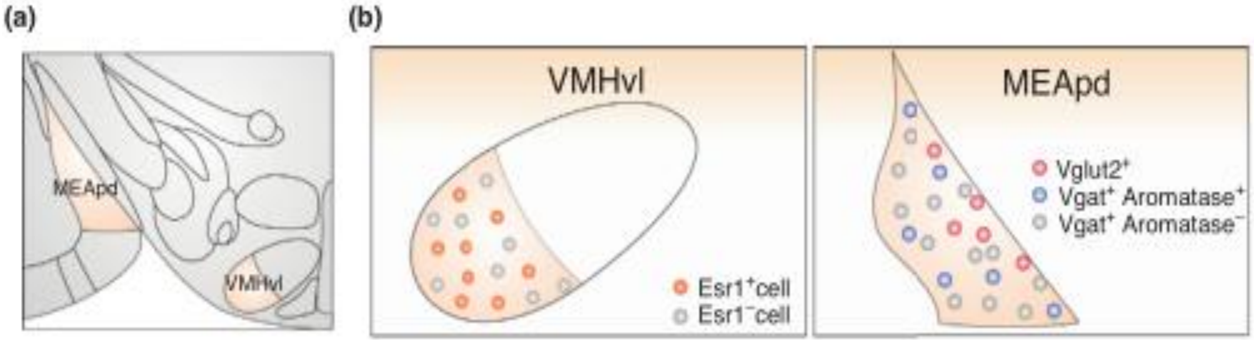
Koichi Hashikawa, Neurobiology, 2016

Investigation of male and female pheromones results differential activation patterns in the AOB



BNSTpm may be preferentially activated during female but not male investigation.

Subpopulations in the MEA that are more critically involved in mating



(d)

Region	Neuronal activity during behaviors						Reference
	Investigate male odor	Investigate female odor	Attack	Mount	Thrust	Ejaculate	
VMHvl	↑↑	↑	↑↑↑	↑	↓	↓	Wong et al., 2016 Falkner et al., 2014 Lin et al., 2011
MEApd	↑	↑↑	–	–	–	–	Bergan et al., 2014
MEApd	–	↑	–	↑	↑	–	Minerbo et al., 1994

Current Opinion in Neurobiology

The roles of the MEApd and VMHvl in male mouse aggression and mating.

(c)

Region	Population	Manipulation	Attack	Mount	Reference
VMHvl	Non-selective	Activation (ChR)	↑	→	Lin et al., 2011
	Non-selective	Silencing (GluCl)	↓	→	Lin et al., 2011
	Esr1	Activation (ChR)	↑	↑	Lee et al., 2014
	Esr1	Silencing (NpHR)	↓	→	Lee et al., 2014
	Esr1 (-)	Activation (ChR)	→	–	Lee et al., 2014
	PR	Ablation (TaCasp3)	↓	↓	Yang et al., 2013
MEApd	Vgat	Activation (ChR)	↑	↑	Hong et al., 2014
	Vgat	Silencing (NpHR)	↓	→	Hong et al., 2014
	Vglut2	Activation (ChR)	↓	↓	Hong et al., 2014
	Aromatase	Ablation (TaCasp3)	↓	→	Unger et al., 2014
	Aromatase	Silencing (hM4Di)	↓	→	Unger et al., 2014
	Aromatase	Activation (hM3Dq)	→	→	Unger et al., 2014

Koichi Hashikawa, Neurobiology, 2016

	Drosophila	*Mice*
Similar Action Pattern	Approach, Threat, Physical conflict, Retreat Low-intensity → High-intensity Dominance Sexual dimorphism	Approach, Threat, Attack, Chase, Defence Low-intensity → High-intensity Dominance Sexual dimorphism
Similar External Triggers	Male specific pheromone through olfactory system	The accessory olfactory system
Conserved Neuromodulator Signaling	**5-HT:** facilitate the transition to higher-level aggression **DA**: promote aggression **OA**: required for normal levels of aggression **TK**: promote aggression **DSK**: promote aggression **NPF**: suppress aggression	**5-HT**:both increase and decrease in aggression in different brain areas **DA**:the modulation of aggressive behavior **NA**:premote aggression **GABA**:suppress aggression **MAOA**:suppress aggression **Steroid hormones:**promote aggression
Conserved brain structure		**'hypothalamic attack area (HAA)'** induce aggression

Love and Peace