Neuromodulation and Strategic Action Choice in *Drosophila* Agg ession

Overview of The Drosophila Aggression Study;

- Strategic Action Choices in Drosophila Aggression;
- □ The winner and loser effect in *Drosophila*.

2021/3/4 Can Gao , Xiaoxiao Ji , Caihong Han



What is the purpose of aggression?

Food

Mating partners

Habitats

Stable dominance hierarchies (among social animals)



Overview of The Drosophila Aggression Study

Gao Can

The history of *Drosophila* aggression study



Alfred Henry Sturtevant (1891–1970)



Geographic Variation in the Territorial Success of Drosophila melanogaster Males

Ary A. Hoffmann¹



Ary Hoffmann



Edward Kravitz





David Anderson 🏑

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A common genetic target for environmental and heritable influences on aggressiveness in Drosophila

Liming Wang*, Heiko Dankert*[†], Pietro Perona[†], and David J. Anderson*^{‡§}

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Contributed by David J. Anderson, February 11, 2008 (sent for review November 12, 2007)







Werner Heisenberg

Theoretical Physicist

Werner Karl Heisenberg was a German theoretical physicist and one of the key pioneers of quantum mechanics. He published his work in 1925 in a breakthrough paper. In the subsequent series of papers with Max Born and Pascual Jordan, during the same year, this matrix formulation of quantum mechanics was substantially elaborated. He is known for the uncertainty principle, which he published in 1927. Heisenberg was awarded the 1932 Nobel Prize in Physics "for the creation of quantum mechanics".

W Wikipedia

Lived: Dec 05, 1901 - Feb 01, 1976 (age 74) Spouse: Elisabeth Heisenberg (m. 1937) Academic advisors: Max Born - Arnold Sommerfeld - Niels Bohr Awards: Nobel Prize in Physics (1932) - Max Planck Medal (1933) Education: Ludwig Maximilian University of Munich (1920 - 1923) -University of Göttingen

Children: <u>Barbara Heisenberg</u> (Daughter) · Martin Heisenberg (Son) · Jochen Heisenberg (Son) · Maria Heisenberg (Daughter) +

Martin Heisenberg



Martin Heisenberg is a German neurobiologist and geneticist. Before his retirement in 2008, he held the professorial chair for genetics and neurobiology at the Bio Centre of the University of Würzburg. Since then, he continues his research with a senior professorship at the Rudolf Virchow Center of the University of

Würzburg. Heisenberg studied chemistry and molecular biology in Munich, Tübingen and Pasadena. In 1975 he became Professor of genetics and neurobiology at the University of Würzburg. Heisenberg's work has focused on the neurogenetics of Drosophila, with the aim of investigating the genetic foundations of the Drosophila brain by studying the effect of genetic mutations on brain function. In addition, Heisenberg contributed a number of essays on the topics of science in society, perception, as well as the question of the freedom of the will. He was elected as a member of the Leopoldina in 1989.

W Wikipedia

Born: Aug 07, 1940 (age 80) · Munich, Germany

Spouse: Apollonia Gräfin zu Eulenburg

Parents: Werner Heisenberg (Father) · Elisabeth Heisenberg (Mother)

Siblings: Jochen Heisenberg (Brother) · Barbara Heisenberg (Sister) · Maria Heisenberg (Sister) · Wolfgang Heisenberg (Brother) +

Children: Benjamin Heisenberg (Son)

Education: University of Tübingen



Benjamin Heisenberg German Film Director

Benjamin Heisenberg is a German film director and screenwriter. He has directed sixteen films since 1995. His film Schläfer was screened in the Un Certain Regard section at the 2005 Cannes Film Festival. His 2010 film, The Robber, was nominated for the Golden Bear at the 60th Berlin International Film Festival. He is also the grandson of Nobel Prize winning physicist Werner Heisenberg via father Martin Heisenberg. He is co-editor and co-publisher of the German film magazine Revolver.



Born: Jun 09, 1974 (age 46) · Tübingen, Germany

Parents: Martin Heisenberg (Father) · Apollonia Gräfin zu Eulenburg (Mother)

Education: Academy of Fine Arts, Munich

Siblings: Jochen Heisenberg (Brother)

Two main paradigms of *Drosophila* aggression study







Even the second second

Behavioral System

- Arena
- Food
- Female

Recording System

- Camera
- Computer
- Light

Analysis System

- Human
- Semi-automatic software
- Fully-automatic software

Comp	utation	nal Visi	011 at CALT	ECH	
Home	Research	Publications	Data Sets	Courses	People
_					

People







PhD Student



Caroline Murphy * Group Administrator









Mason McGill

PhD Student

* = Photo by <u>Ruud</u>

Barth

Jennifer Sun PhD Student



Joe Marino

* PhD Student

Pietro Perona *Principal Investigator ce

Vision Lab Alumni

PhDs

Matteo Ruggero Ronchi 2020 Grant Van Horn 2019 Ron Appel 2017 David Hall 2017 Krzysztof Chalupka 2017 Bo Chen 2016 Eyrun Eyjolfsdottir 2014 Carlos Gonzáles 2015 Greg Griffin 2013 Peter Welinder 2012 Ryan Gomes 2011 Marco Andreetto 2011 Mohamed Aly 2011 Merrielle Spain 2011 Anelia Angelova 2008 Claudio Fanti 2008 Pierre Moreels 2008 Anelia Angelova 2008 Christophe Basset 2007 Alex Holub 2007 Fei Fei Li 2005 SIlvio Savarese 2005 Domitilla del Vecchio 2005 Yang Song 2003 Xiaolin Feng 2002 Luis Goncalves 2000 Markus Weber 2000 Jean-Yves Bouguet 1999 Mike Burl 1997 Christophe Kolb 1997 Stefano Soatto 1996 Jennifer Sun 1996

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Mario Enrique Munich 2000

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Pietro Perona

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Fighting fruit flies: A model system for the study of aggression

Selby Chen, Ann Yeelin Lee, Nina M. Bowens, Robert Huber, and Edward A. Kravitz





	Slow Approach	Fast Approach	Wing Threat	Fencing	Holding	Boxing Tussling	Retreat	Σ
Slow Approach	-	188	330	479	13	9	243	1262
Fast Approach	330	-	126	187	7	8	13	671
Wing Threat	437	148	-	213	6	5	35	844
Fencing	1437	112	214	-	8	20	421	2212
Holding	6	34	0	1	-	0	0	41
Boxing/ Tussling	19	4	4	14	1	-	4	46
Retreat	75	36	82	1059	1	7	-	1260
Σ	2304	522	756	1953	36	49	716	6336





Gender-selective patterns of aggressive behavior in *Drosophila melanogaster*

Steven P. Nilsen, Yick-Bun Chan, Robert Huber, and Edward A. Kravitz





Learning and memory associated with aggression in *Drosophila melanogaster*



Alexandra Yurkovic, Oulu Wang, Alo C. Basu, and Edward A. Kravitz





fruitless regulates aggression and dominance in *Drosophila*

Eleftheria Vrontou¹, Steven P Nilsen², Ebru Demir¹, Edward A Kravitz² & Barry J Dickson¹



Specific subgroups of Fru^M neurons control sexually dimorphic patterns of aggression in *Drosophila melanogaster*







Group	Cell cluster	Canton- S (18)	1(3)31- GAL4/VAS- tra ^{IR} (F)	1407- GAL4/UAS- tra ^{IR} (F)	c1003- GAL4/VAS- tra ^{IR} (F)	60IIA- GAL4/UAS- tra ^{IR} (F)
1	fru-nAL	23 ± 2	25 ± 3	23 ± 5	17 ± 4	9 ± 4
	fru-PrMs	73 ± 7	68 ± 6	64 ± 6	54 ± 6	33 ± 3
2	<i>fru</i> -aSP2	42 ± 5	37 ± 6	38 ± 5	26 ± 6	12 ± 2
	fru-ncAL	31 ± 1	23 ± 4	25 ± 3	16 ± 4	12 ± 2
3	fru-AL	52 ± 6	40 ± 3	45 ± 8	37 ± 5	39 ± 5
	fru-P	56 ± 7	31 ± 5	32 ± 7	31 ± 5	38 ± 8
	<i>fru</i> -MsMt	38 ± 8	30 ± 4	33 ± 4	28 ± 6	18 ± 2
4	fru-aSP1	12 ± 2	12 ± 2	11 ± 3	11 ± 3	10 ± 2
	fru-aSP3	29 ± 5	31 ± 4	31 ± 3	24 ± 2	28 ± 5
	fru-SG	11 ± 2	3 ± 1	6 ± 2	1 ± 1	2 ± 1
	<i>fru</i> -pSP1	9 ± 2	3 ± 2	5 ± 2	3 ± 2	4 ± 1
	fru-pSP2	18 ± 3	16 ± 1	15 ± 1	12 ± 2	13 ± 2
	fru-pL	12 ± 2	10 ± 1	8 ± 4	5 ± 3	6 ± 3



A common genetic target for environmental and heritable influences on aggressiveness in *Drosophila*



Liming Wang*, Heiko Dankert*[†], Pietro Perona[†], and David J. Anderson*^{‡§}









Feminizing cholinergic neurons in a male Drosophila nervous system enhances aggression Sibu Mundiyanapurath, Yick-Bun Chan, Adelaine K.W. Leung & Edward A. Kravitz

Lunges per Fight (1 h)





nature **methods**

Automated monitoring and analysis of social behavior in *Drosophila*

Heiko Dankert^{1,2}, Liming Wang², Eric D Hoopfer², David J Anderson² & Pietro Perona¹







A single social defeat reduces aggression in a highly aggressive strain of *Drosophila*

Jill K. M. Penn, Michael F. Zito, and Edward A. Kravitz







Identification of an aggression-promoting pheromone and its receptor neurons in *Drosophila*



2011

Functional identification of an aggression locus in the mouse hypothalamus

nature International weekly journal of science Dayu Lin^{1,2,5}, Maureen P. Boyle³, Piotr Dollar⁴, Hyosang Lee¹, Pietro Perona⁴, Ed S. Lein³, and David J. Anderson^{1,2,5}





2013

PNAS



Olga V. Alekseyenko, Yick-Bun Chan, Ran Li, and Edward A. Kravitz

UAS>stop>GFP;





UAS>stop>GFP;





Octopamine Neuromodulation Regulates Gr32a-Linked Aggression and Courtship Pathways in *Drosophila* Males

Jonathan C. Andrews, María Paz Fernández, Qin Yu, Greg P. Leary, Adelaine K. W. Leung, Michael P. Kavanaugh, Edward A. Kravitz, Sarah J. Certel









Single Serotonergic Neurons that Modulate Aggression in *Drosophila*

Olga V. Alekseyenko ¹ ∧ ⊠, Yick-Bun Chan ¹, Maria de la Paz Fernandez ², Torsten Bülow ³, Michael J. Pankratz ³, Edward A. Kravitz ¹





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Tachykinin-expressing neurons control male-specific aggressive

arousal in Drosophila

Kenta Asahina^{1,2}, Kiichi Watanabe^{1,2}, Brian J. Duistermars^{1,2}, Eric Hoopfer^{1,2,4}, Carlos Roberto González³, Eyrún Arna Eyjólfsdóttir³, Pietro Perona³, and David J. Anderson^{1,2}

















Tk specifically affect male-male aggression

control male-male aggression do not modulate courtship behavior





eLIFE

P1 interneurons promote a persistent internal state that enhances inter-male aggression in Drosophila

Eric D Hoopfer^{1,2}, Yonil Jung², Hidehiko K Inagaki², Gerald M Rubin¹, David J Anderson^{2,3*}











Short and long-lasting behavioral consequences of agonistic encounters between male Drosophila melanogaster

Séverine Trannoy, Jill Penn, Kenia Lucey, David Popovic, and Edward A. Kravitz



Neuron

Putative transmembrane transporter modulates higher-level aggression in *Drosophila*

Budhaditya Chowdhury, Yick-Bun Chan, and Edward A. Kravitz



A circuit node that integrates convergent input from neuromodulatory and social behavior-promoting neurons to control aggression in *Drosophila*

Kiichi Watanabe^{1,2}, Hui Chiu^{1,2}, Barret D. Pfeiffer^{2,3,4}, Allan Wong^{2,4}, Eric D. Hoopfer¹, Gerald M. Rubin⁴, and David J. Anderson^{1,2,5,*}





PSI

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Chorion Protein^{RN} 2019

Current

Biology

Serotonergic Modulation of Aggression in *Drosophila* Involves GABAergic and Cholinergic Opposing Pathways

Olga V. Alekseyenko ^{1, 2, 3, 5} ∧ ⊠, Yick-Bun Chan ^{1, 3}, Benjamin W. Okaty ², YoonJeung Chang ², Susan M. Dymecki ^{2, 4}, Edward A. Kravitz ^{1, 4}





A small number of cholinergic neurons mediate hyperaggression in female *Drosophila*

D Caroline B. Palavicino-Maggio, Yick-Bun Chan, Claire McKellar, and Edward A. Kravitz



250

200

UAS-mCD8::GFP; R26E01-Gal4







2020

Neuron

Neurons that Function within an Integrator to Promote a Persistent Behavioral State in Drosophila

Yonil Jung ¹, Ann Kennedy ¹, Hui Chiu ¹, Farhan Mohammad ^{2, 3, 4}, Adam Claridge-Chang ^{2, 3}, David J. Anderson ^{1, 5} ∧ ⊠



Article

Article



Cell

A circuit logic for sexually shared and dimorphic aggressive behaviors in *Drosophila*





- Model establishment (male & female)
- Loser effect
- DA, OA, 5-HT neuromodulation of aggression

- Automated analysis of aggression
- cVA
- TK
- Persistent internal state
- Sexually dimorphic aggression circuit



Strategic Action Choices in Drosophila Aggression

Ji Xiaoxiao

To fight or not to fight



Whether the fly is a Competitor?



(Hoopfer, Curr Opin Neurobiol, 2016)

Olfactory cues



cVA promotes aggression by activating Or67d-expressing OSNs



(Wang and Anderson, Nature, 2010)

Gustatory cues



(z)-7-tricosene (7T) induced aggression required the gustatory receptor Gr32a



(Wang et al., Nat Neurosci, 2011)



alPg and pC1d are two key groups of neurons involved in female aggressive behaviors



(Schretter et al., Elife, 2020)

Absence of visual information alters aggressive behaviors following alPg activation



(Schretter et al., Elife, 2020)

A conceptual model for gating of visual information by alPg neurons in females during aggression



(Schretter et al., Elife, 2020)

Fight for resource



How food controls aggression in Drosophila



(Lim et al., PLoS One, 2014)

Flies measure the level of total nutrients to increase the level of aggression rather than the area of food



Note: Left and right bars (e.g. 1:235 diluted and 3 mm²) are calorically matched)



(Lim et al., PLoS One, 2014)

Flies use sweet-sensing Gr5a⁺ GRNs to detect the concentration of sucrose in the food and tune the level of aggression accordingly





(Lim et al., PLoS One, 2014)

Influence of prior experience on aggression



Group flies are exposured to chronic cVA which reduced aggression through Or65a ORNs



(Liu et al., Nat Neurosci, 2011)

Sexually monomorphic and dimorphic aggressive actions in males and females





Identification of sexually monomorphic and dimorphic aggression-promoting cell types





MAP stimulation elicits dimorphic attacks in males



Functional connectivity between monomorphic and dimorphic circuit modules



Social isolation enhances aggressiveness by strengthening circuit functional connectivity



To fight or not to fight



The winner and loser effect in *Drosophila*

Han Caihong

What sets the odds of winning and losing?



• Body size difference?

Asahina, K., et al. <u>Cell (2014)</u>.



Kayser, M. S., et al. <u>Elife</u> (2015).

• Previous outcome of a fight?

Winner effect and loser effect

winner effect:

the winners are more likely to win again. **loser effect:**

the losers more likely to lose again.



Such effects have been observed in many species, including fish, birds, and mammals.

Indicators of dominant and subordinate status



Yurkovic, A., et al. (2006).

Persistence of dominance relationship and individual recognition



how long flies fight;

Table 1.	Outcomes	of	second	fights	and	control	fights
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VS.	Winner						Loser					Naive			
	W	fL	ufL	Ν	Total	L	fW	ufW	Ν	Total	Ν	W	L	Total	
Win	1	5	6	4	16	3	0	0	0	3	7	5	6	18	
Loss	1	0	0	5	6	3	5	6	6	20	7	4	0	11	
Draw	0	0	1	4	5	2	5	1	6	14	11	4	6	21	
Total	2	5	7	13	27	8	10	7	12	37	25	13	12	50	

Counts of wins, losses, and draws by experienced winner, experienced loser, and socially naive flies paired with experienced and naive opponents.

Prior experiences induces submissive or aggressive behavior and drives short-term effect formation in loser and winner

in loser flies

in winner flies



Both winners and losers show short-term memory of the results of previous bouts.

Trannoy, S., et al. (2016).

Repeated defeats lead to long-lasting consequences and the 24-h loser effect requires de novo protein synthesis.



Trannoy, S., et al. (2016).

Only losers demonstrate a longer-term memory that requires protein synthesis.

The winning is perceived as rewarding, while losing is perceived as aversive



The activities of the PPL1- γ 1pedc dopaminergic neuron and the MBON- γ 1pedc> α/β mushroom body output neuron are required for aversion to an olfactory cue associated with losing fights.

How to reverse the loser effect?



Multiple neurotransmitters and neuropeptides, including octopamine, dopamine, 5-HT, dsk, neuropeptide F, and tachykinin (Tk), are involved in aggression in *Drosophila*.

The winners show increased calcium activity in Dsk- expressing neurons



Conditional overexpression of DSK promotes winner effect and winner show increased calcium activity of DSK Neurons.

Wu, F., et al. <u>Elife</u> (2020).

Activation of 5-HT Neurons Promotes Losers to Re-engage in a Fight



Activation of 5-HT Neurons Promotes Fighting of Losers Against Winners





Serotonin is necessary and sufficient for overcoming the loser effect



5-HT1B receptors are responsible for restoring aggression in losers



R2/R4m neurons in the Ellipsoid Body are responsible for overcoming the loser effect



P1 neurons act upstream of 5-HT signaling



Suppressive loser mentality is effectively removed by increasing serotonin signaling

Article

Servetion Signals Overcome Loser Mentality in 2020 Drosophila

HIGHLIGHTS

Activating a small subset of serotonin neurons promotes losers to fight.

Serotonin is necessary and sufficient for modulating aggression in losers.

The neural circuit for motivating losers includes P1, 5-HT, and 5-HT1B neurons.

Elevating 5-HT signaling overcomes the depressive behavioral state in losers.

No strong dominance relationships were formed in fights between females

Behavioral patterns and transitions seen in fights between pairs of male and pairs of female *D. melanogaster*.

High-posture fencing with a wing threat Hold Boxing & Hightussling Shove/ Thrust with a win threat Walking posture Lunge retreat fencing Lunge ++ Low-Low posture posture Approach fencing fencing Head Walking Wing flicking retreat butt FEMALE MALE е

The Absence of Dominance Relationships in Female Fights.

fru plays a critical role in establishing dominance relationships of males.

Consecutive wins

Take home message

- Encounters between flies were frequent during the first 10 min of pairing and then dropped significantly.
- Both winners and losers show short-term memory of the results of previous bouts and only losers demonstrate a longer-term memory that requires protein synthesis.
- The winning is perceived as rewarding, while losing is perceived as aversive.
- The activities of the dopaminergic neuron and mushroom body output neuron are required for aversion to an olfactory cue associated with losing fights.
- Serotonin is necessary and sufficient for modulating aggression in losers and the neural circuit for motivating losers includes P1, 5-HT, and 5-HT1B neurons.
- Female have no dominance relationships were formed in fighting.

question

- An increasing aggression is not identical to reversal of the loser effect, the neural mechanisms of overcoming the loser effect is unclear.
- The underlying neural mechanisms of negative social experiences (sexual rejection and fighting loser) modulate multiple behaviors.
- Whether aggression in flies, like most complex behaviors in most organisms, comprises both innate and learned components.

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