精神病蝇

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Drosophila the Psychopath

Why there are psychiatric disorders?

- Genetic defect
- Environment influence

Regular Research Process

Gene

↓

Gene’s Product/ Effect

↓

Neuron

↓

Circuit

↓

Behavior defect

- Relatively low homology with humans compared to rodents
- Lack of reliable tests to study more complex disease phenotypes in flies
- Difficult to translate disease symptoms into animal models

Depression

朱寰

Symptom of depression

- depressed mood
- lose interest
- significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt
- Recurrent thoughts of death

(dsm-5)

Psychological view

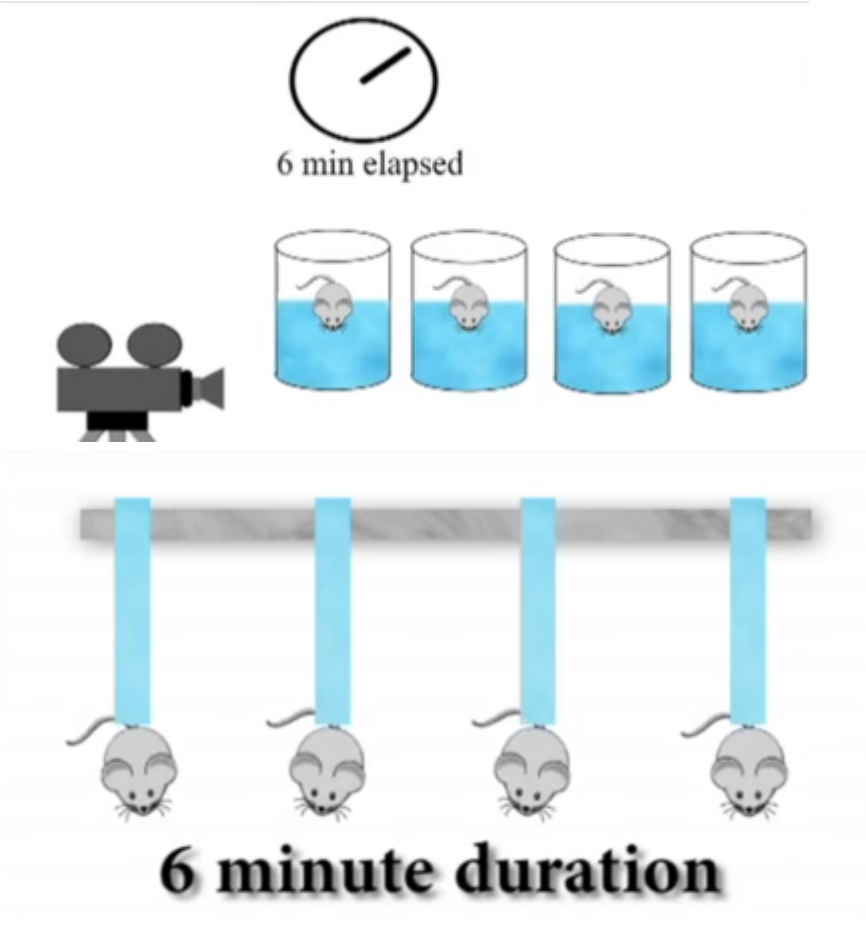
- **Learned helplessness** : strong sense of frustration and anxiety suppress motivation.
- **self-attack and self-denial** : animal always punish individual with anti-social characteristic , and one will punish himself if he has these traits.

Methods to induce depression in rodents

- chronic stress
- social isolation
- learned helplessness
- maternal deprivation

(psychiatric disorders: methods and protocols)

testing methods for rodents



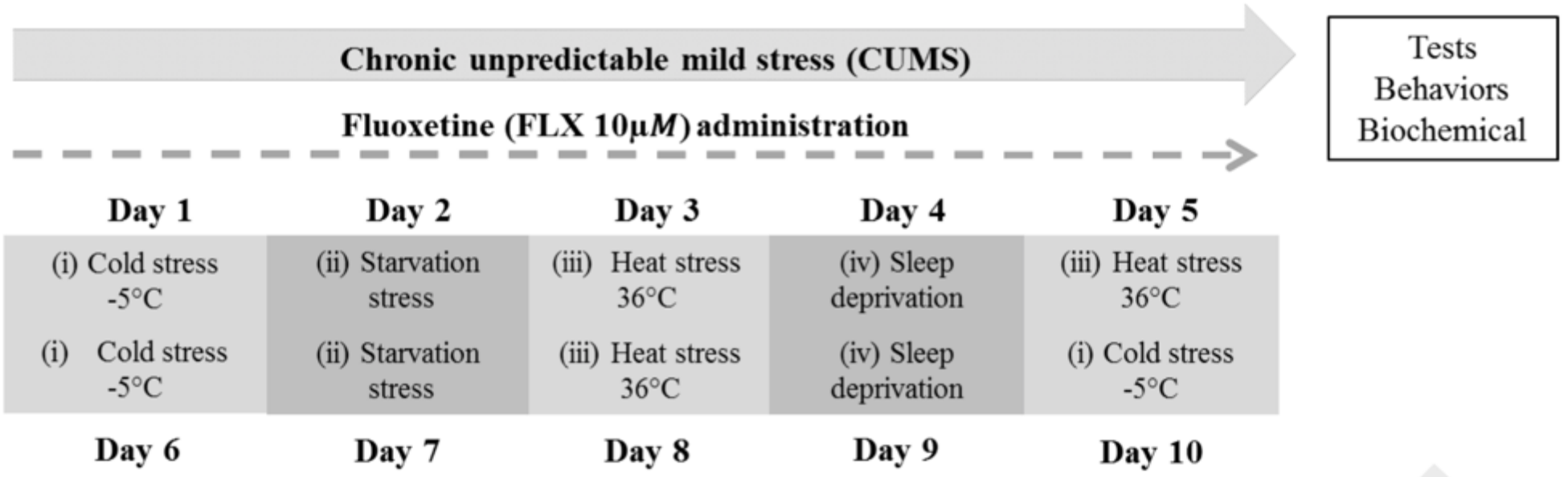
Adem Can . *et al*

- forced swimming test
- Tail Suspension Test
- sucrose preference test
- social interaction test

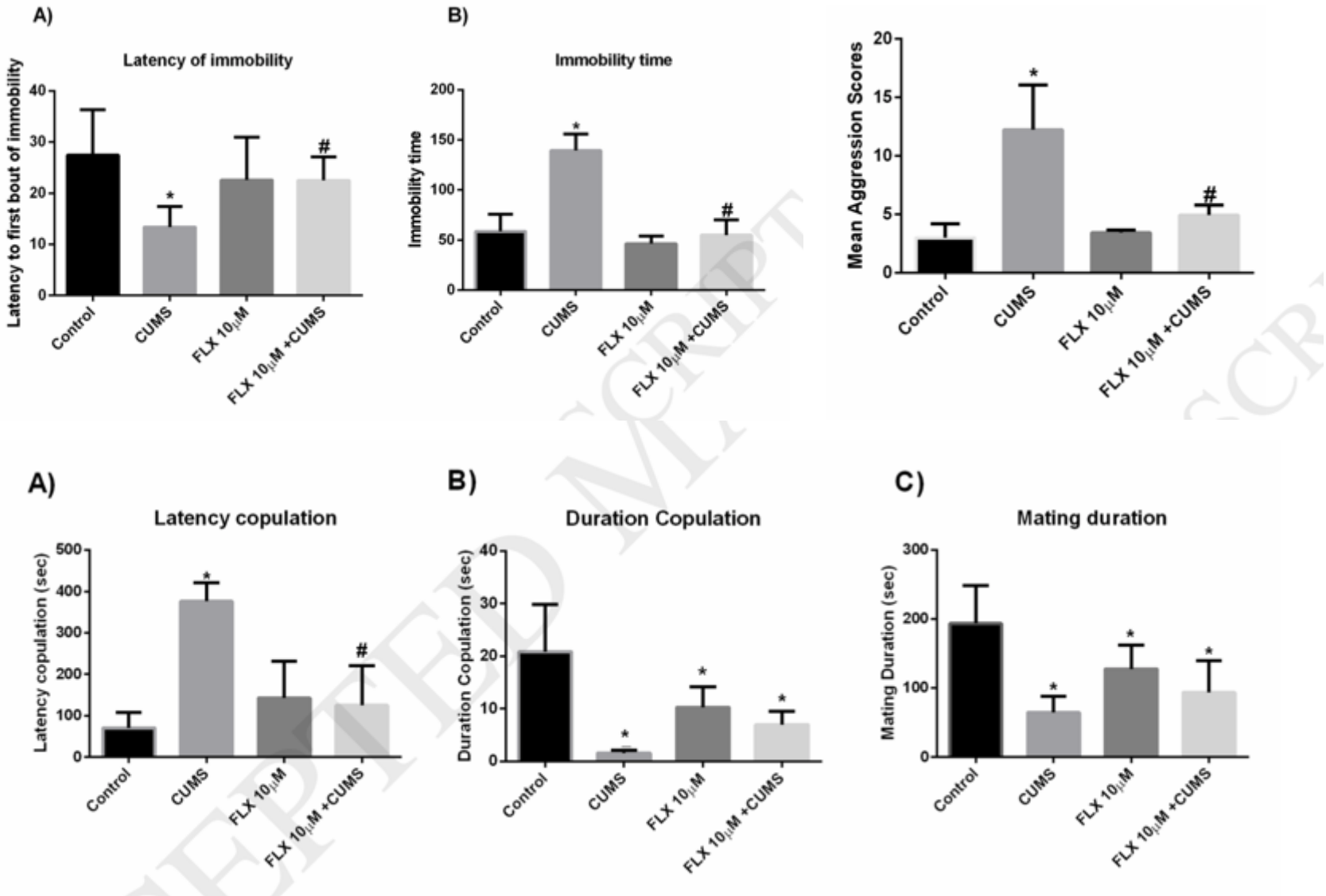
(psychiatric disorders: methods and protocols)

Depression in Drosophila

Chronic unpredictable mild stress induce depression-like state



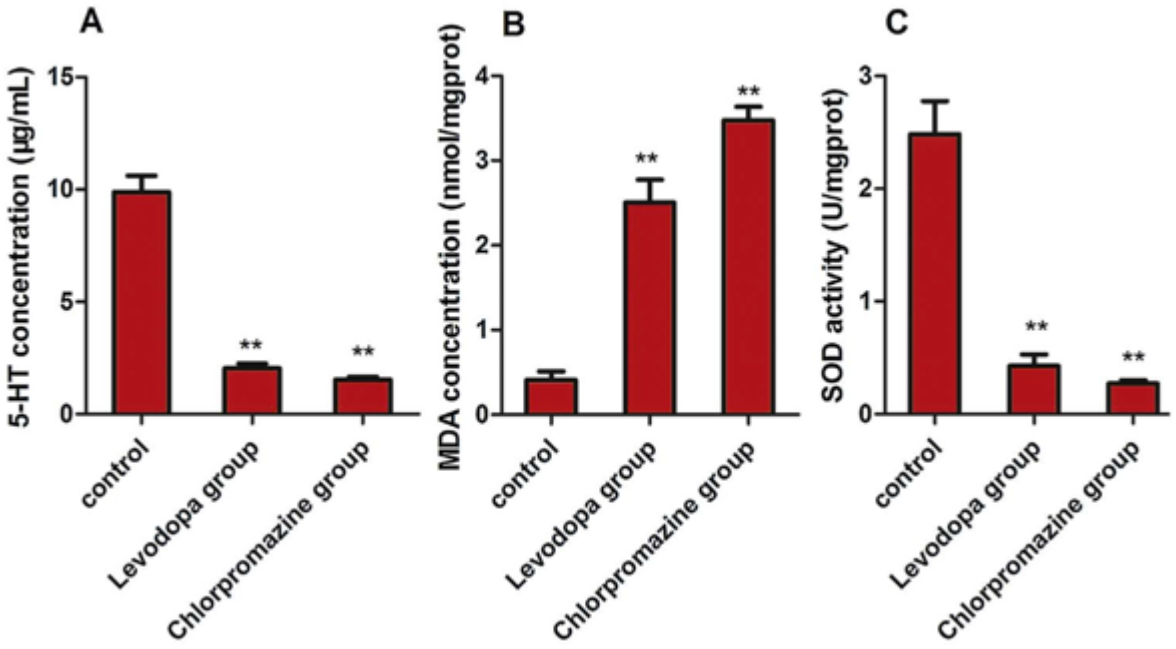
Stífani Machado *et al*



FLX，Fluoxetine (氟西汀，亦称百忧解)

Stífani Machado *et al*

Drug induces depression-like state



The influence of Levodopa and Chlorpromazine on flies' mating frequency.

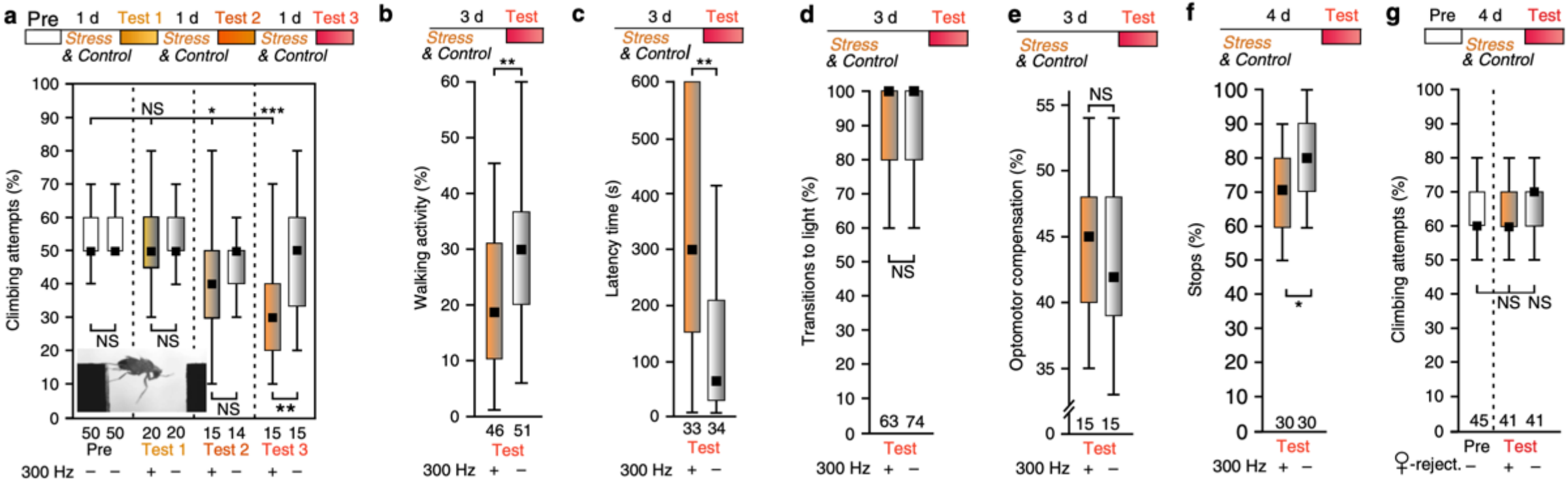
Drug concentration (mg/L)	Mating frequency (times)			
	Levodopa group		Chlorpromazine group	
	Male	Female	Male	Female
0 (Con)	2.20 ± 0.40	1.20 ± 0.20	2.20 ± 0.40	1.20 ± 0.20
2000	0.60 ± 0.20**	0.80 ± 0.10*	0.40 ± 0.10**	0.60 ± 0.20*

* $P < 0.05$.
** $P < 0.01$.

Chlorpromazine （氯丙嗪）

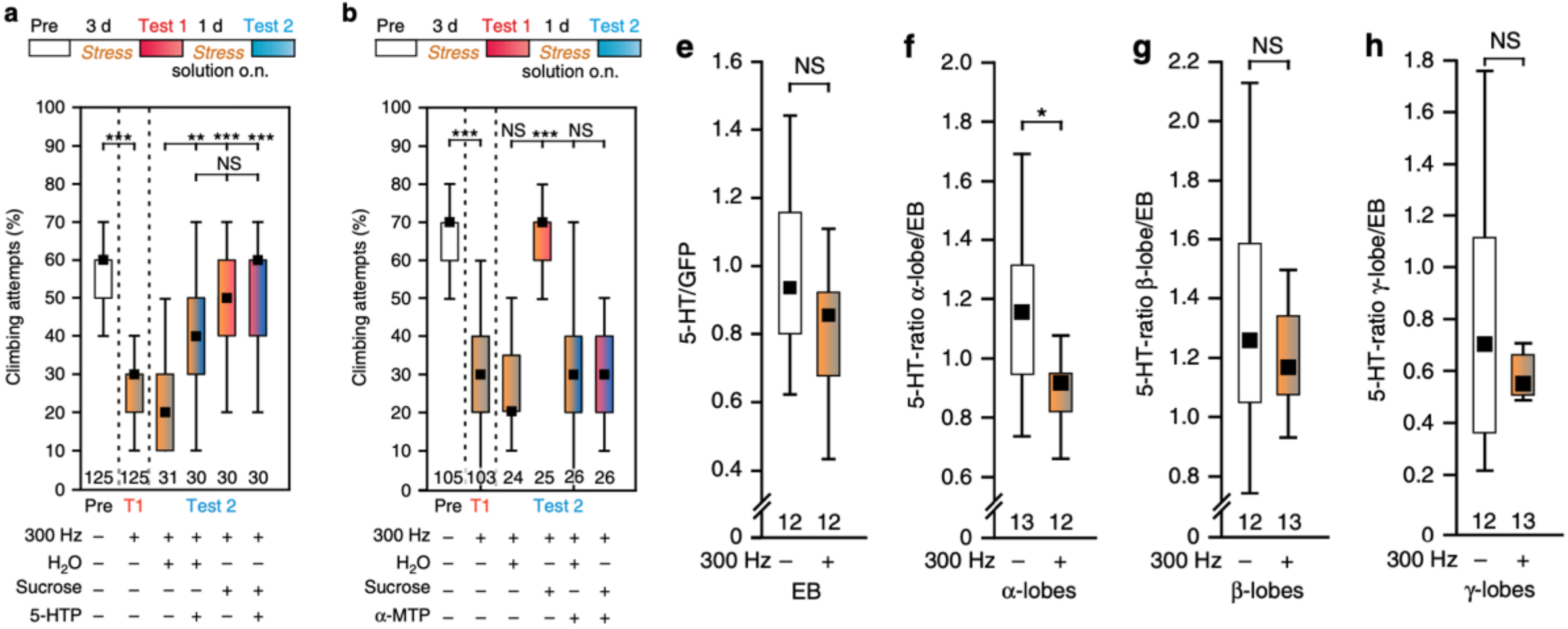
Ming-Di Jiang *et al*

Repeated inescapable vibrations induce depression-like state



Ariane-Saskia Ries .*et al*

Serotonin level in mushroom body a-lobes correlates with depression-like state

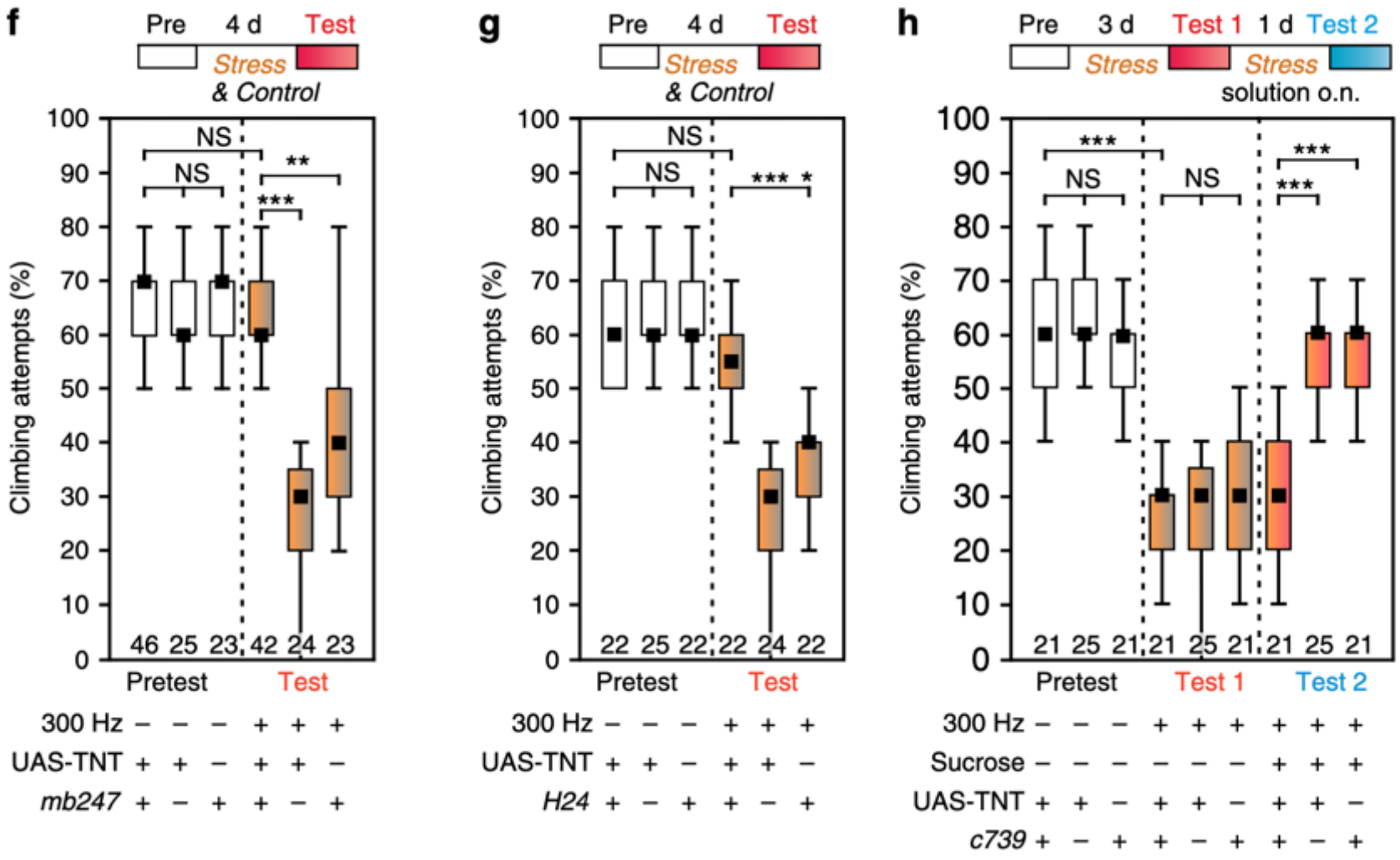


5-HTP, 5-hydroxy-L-tryptophan(5-羟基-L-色氨酸), serotonin precursor

a-MTP, a-methyl-DL-tryptophan (α-甲基-DL-色氨酸), a 5-HT-synthesis blocker

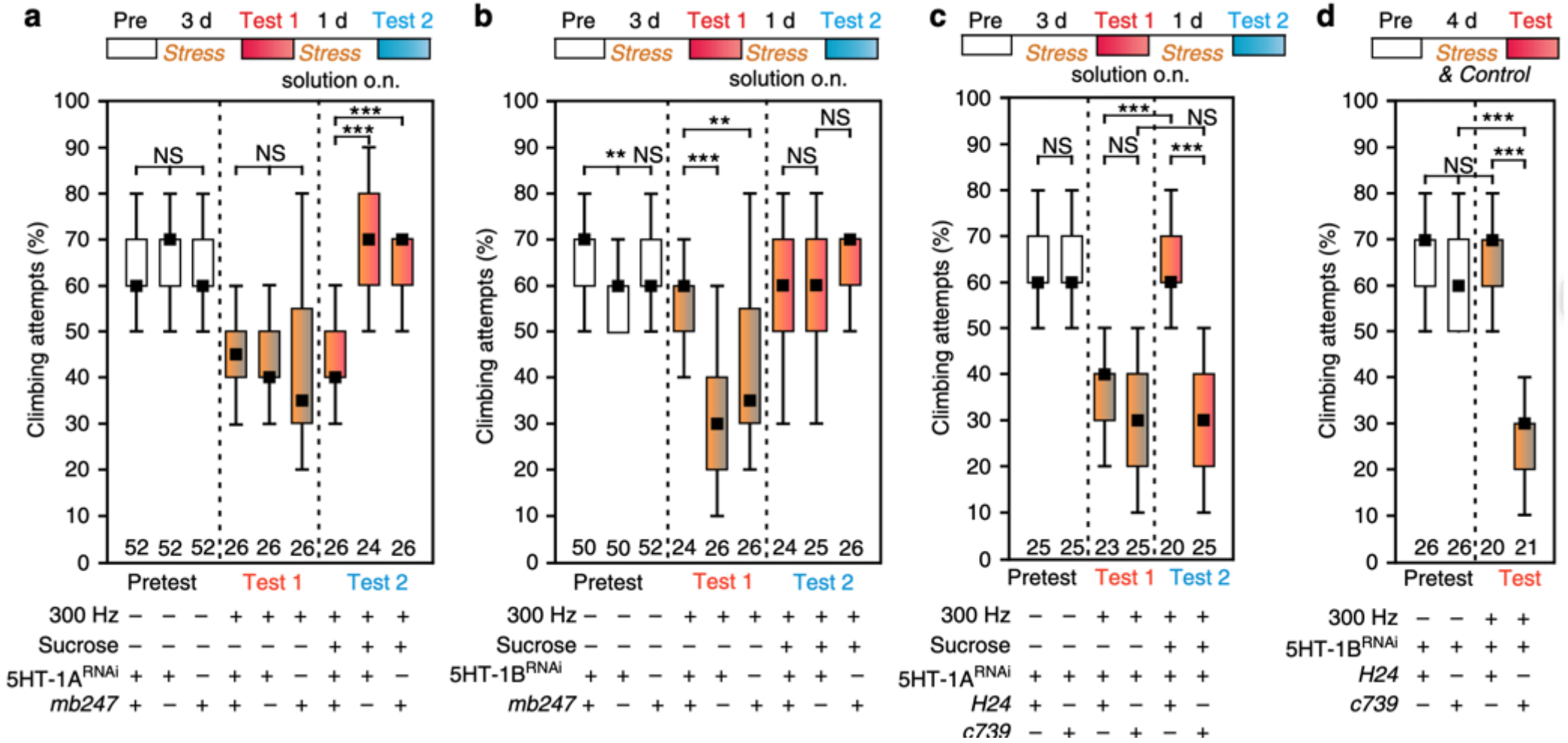
Ariane-Saskia Ries .*et al*

mushroom body α-,β- lobes play different role with γ-lobe in the modulation of depression-like state



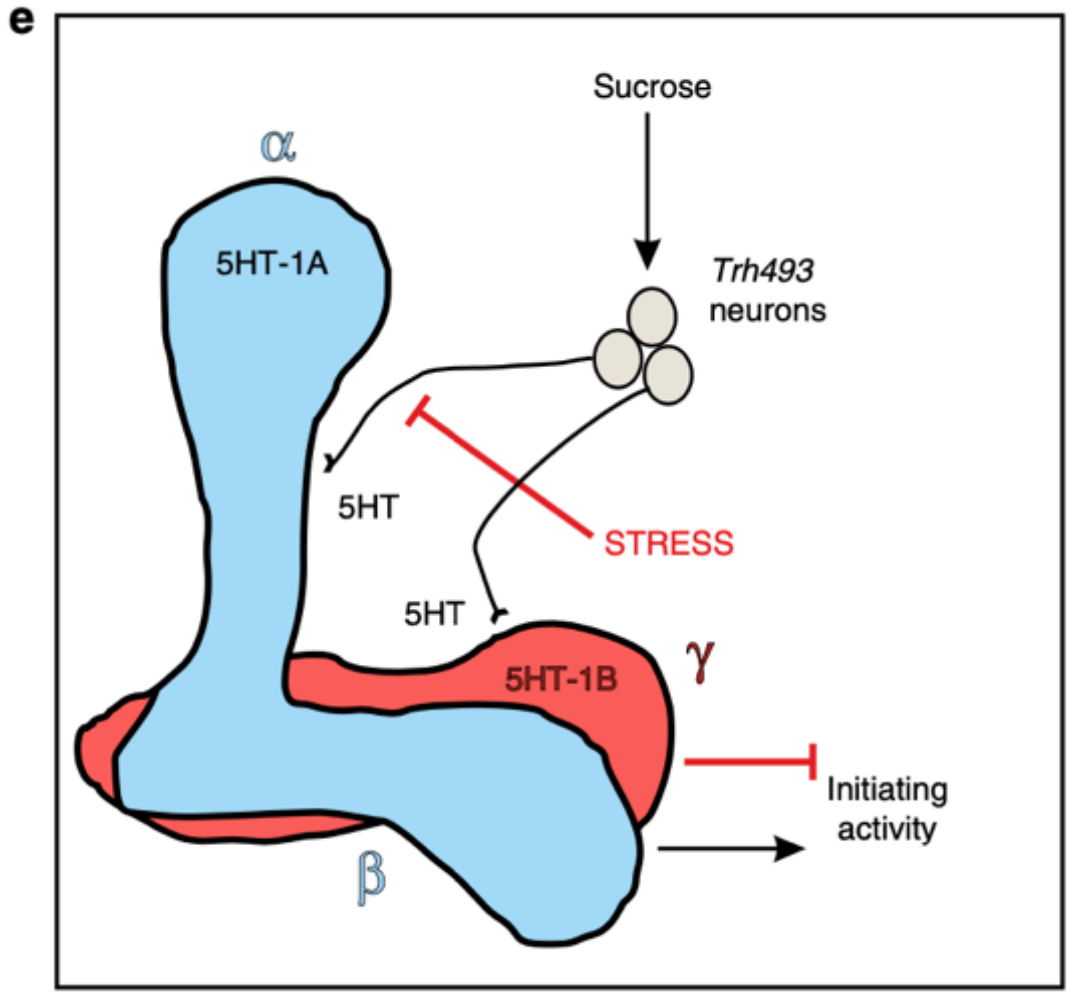
Ariane-Saskia Ries .*et al*

5-HT-1A effects in depression extinction
5-HT-1B effects in depression acquisition



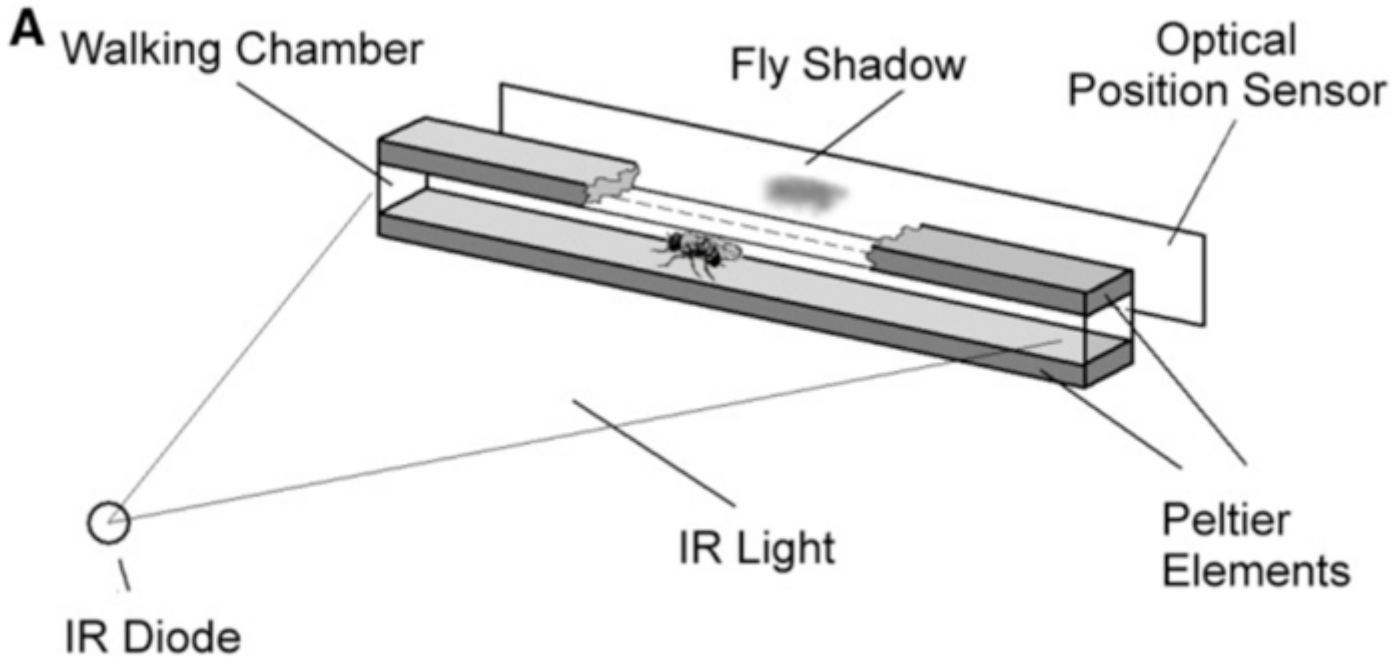
Ariane-Saskia Ries .*et al*

Model in depression regulation ?

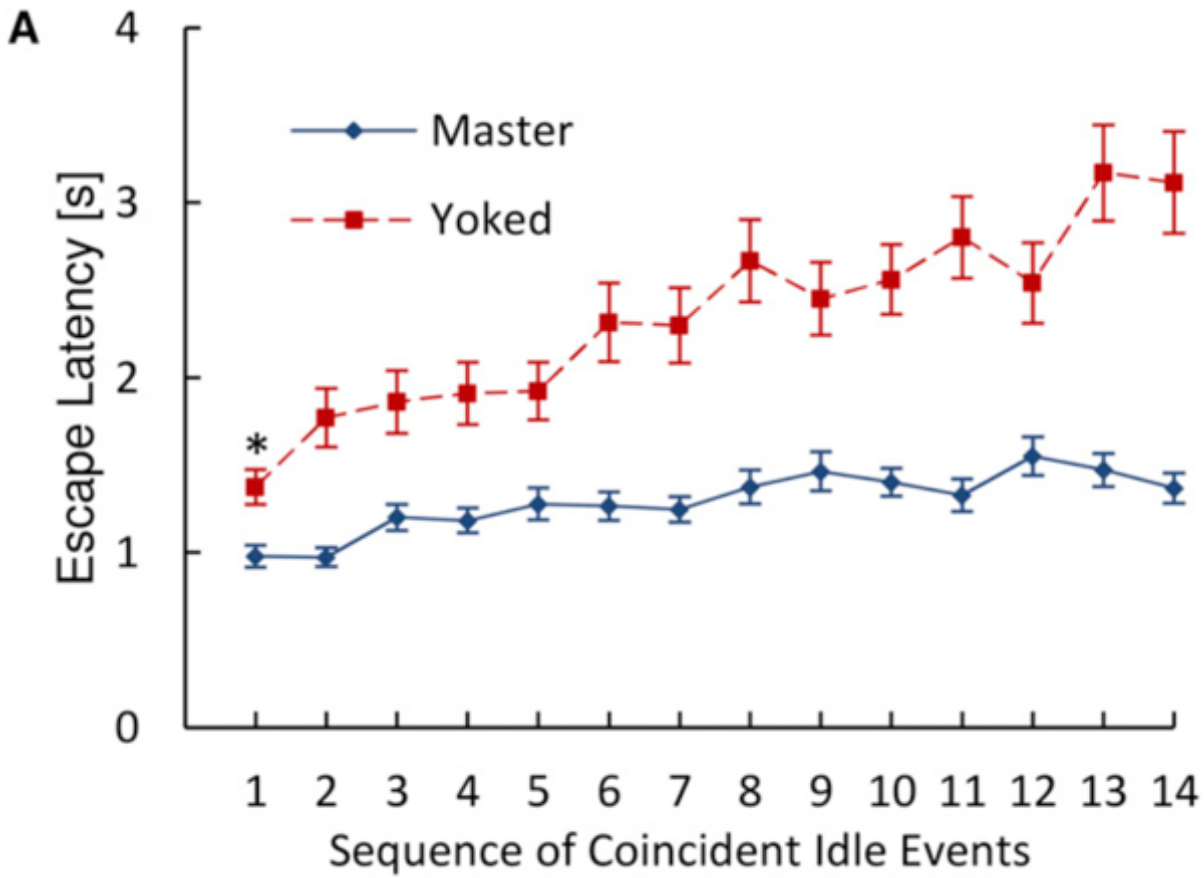


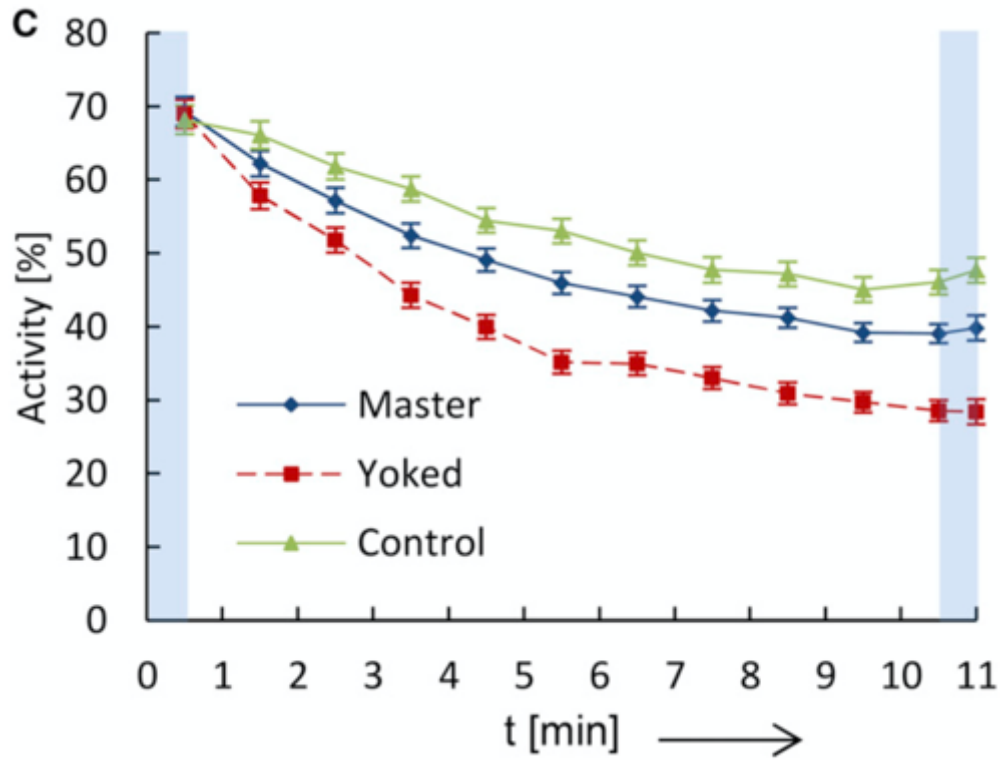
Ariane-Saskia Ries .*et al*

Learned helplessness in drosophila



Zhenghong Yang . *et al*





Zhenghong Yang . *et al*

Depression summary

- Inescapable stress（social/physical）inhibits escape behavior and motivation of other behavior .
- Reduced motivation can be recovered .
- 5-HT plays a very important role in depression. Depressed individual always has a low level of 5-HT . Higher 5-HT level can reduce depression.

Potential mechanism:

How behavior and motivation be inhibited?

How to inhibit behavior?

MOLECULAR VIEW

LTD?

LTP?

?

BEHAVIOR VIEW

Lack of motivation?

Classic conditioning?

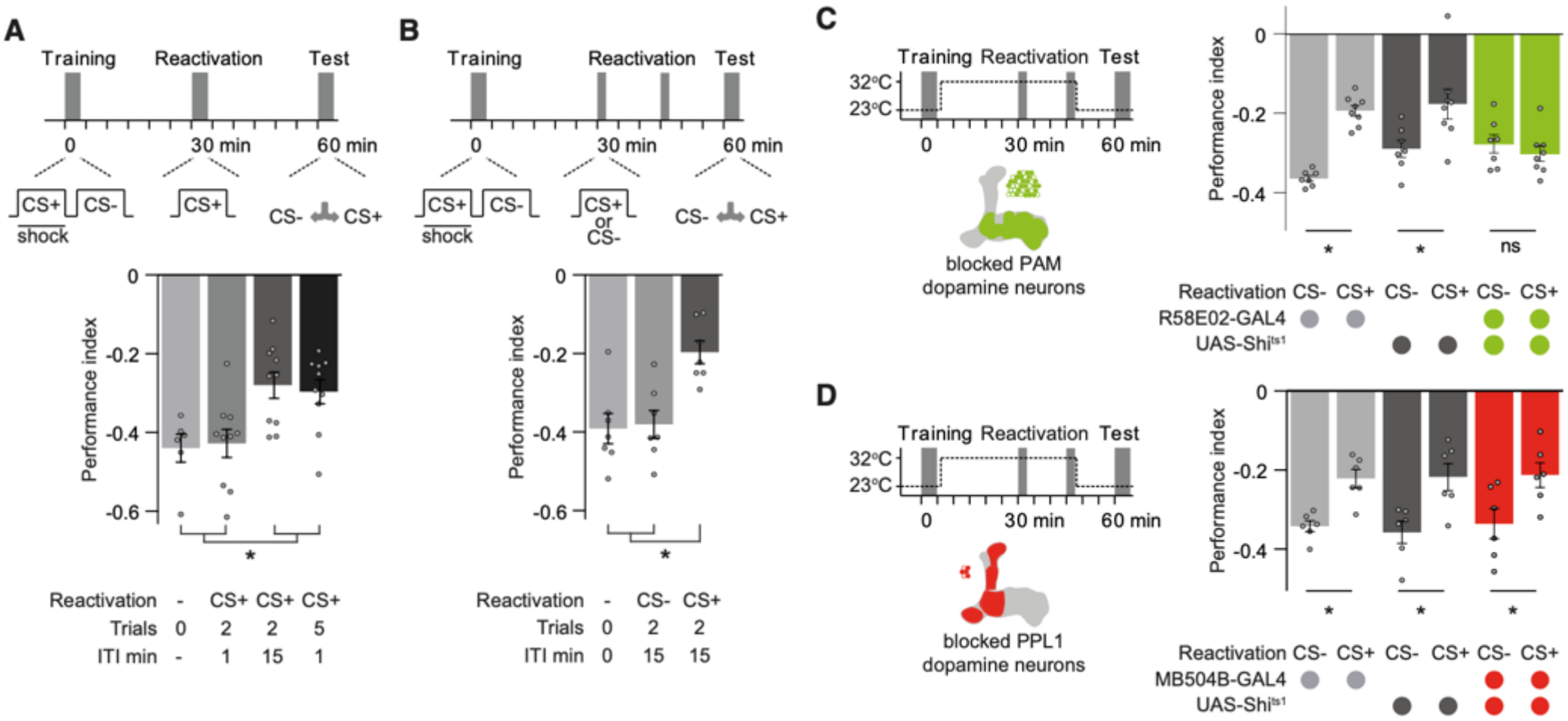
Operant conditioning?

Memory extinction?

Habituation ?

?

Extinction of Aversive Memory Requires PAM Dopamine Neurons



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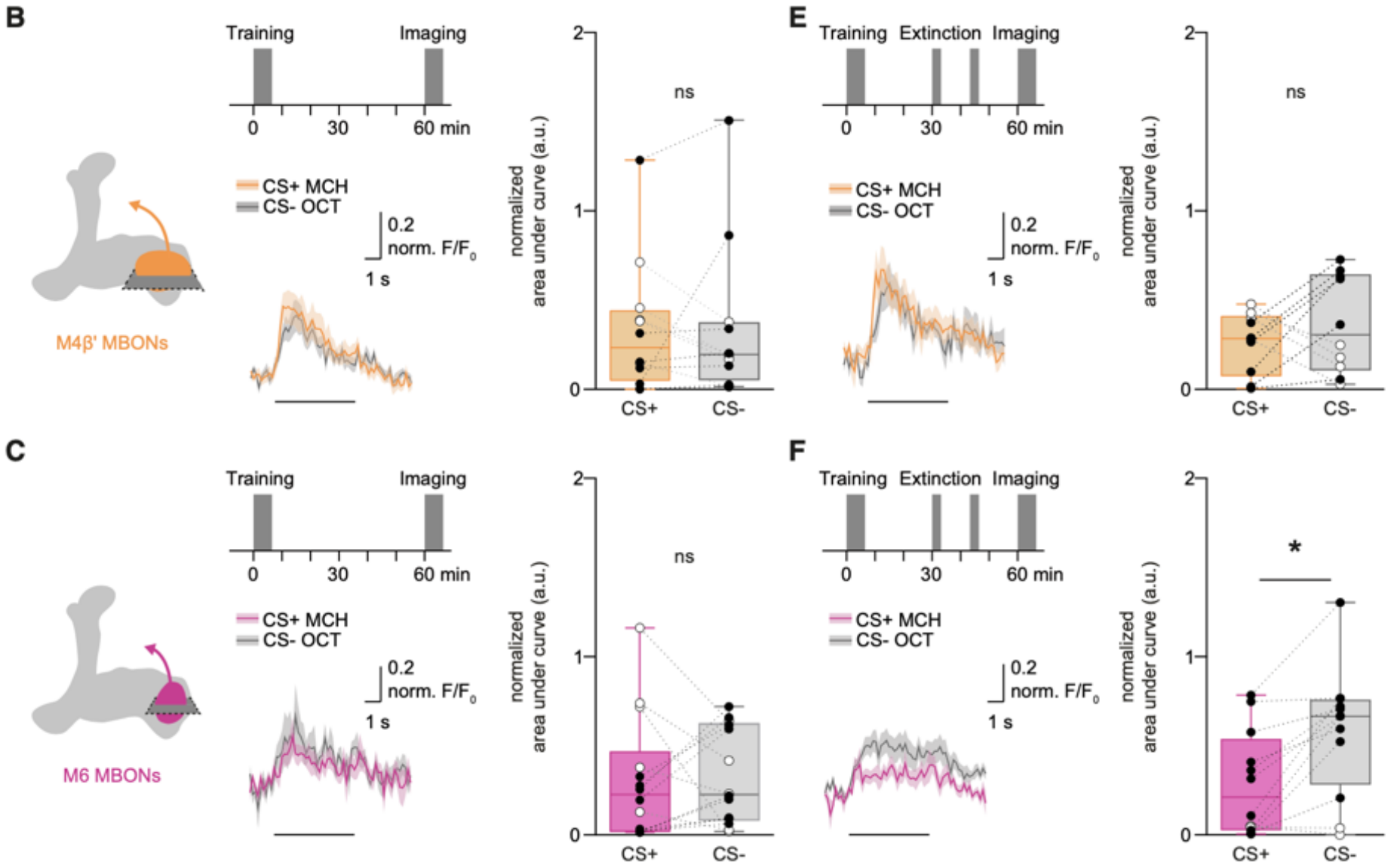
Memory traces can exist in parallel when aversive memory is extinguished



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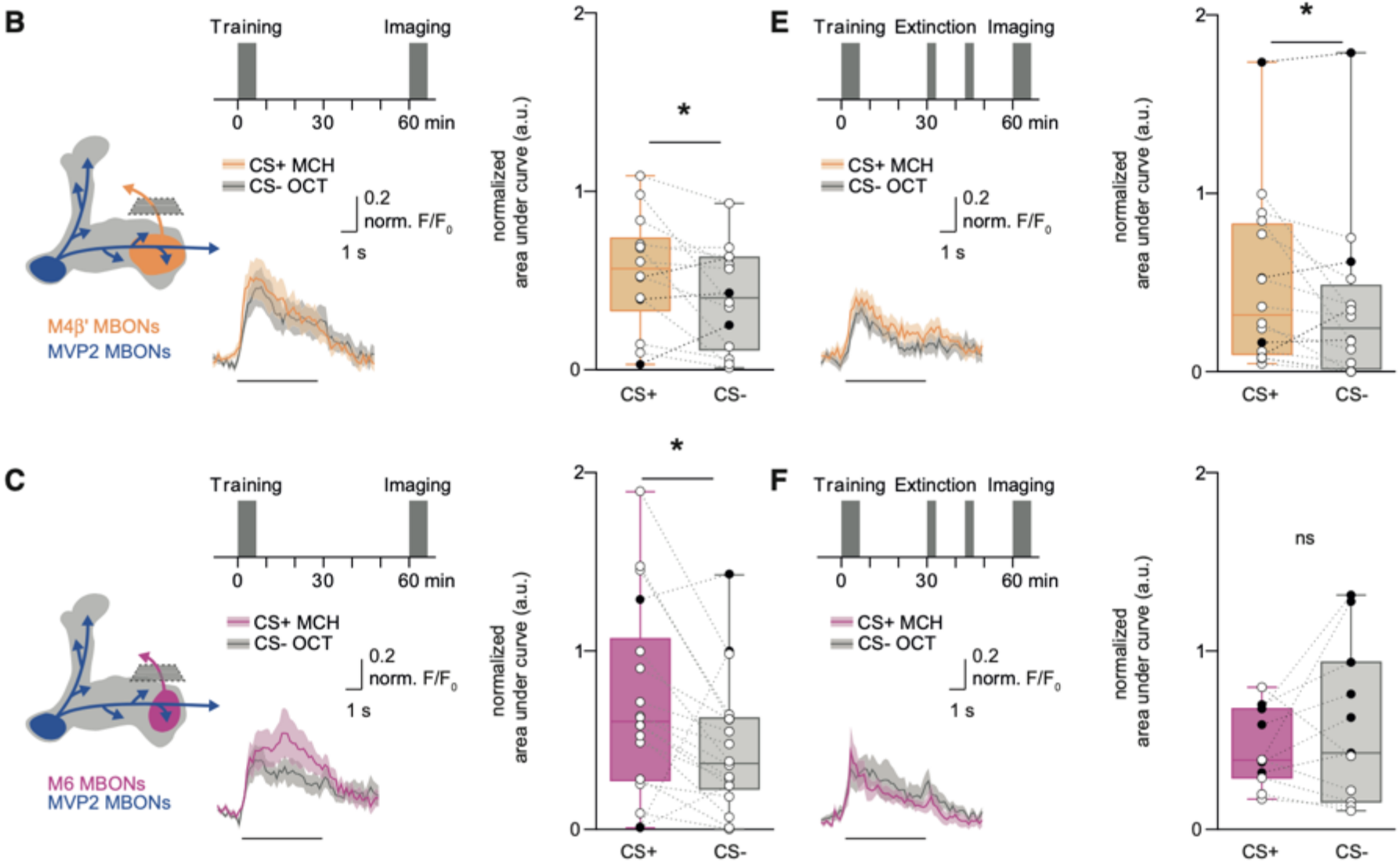
Aversive and Extinction Memories Are Integrated in M6 Neurons



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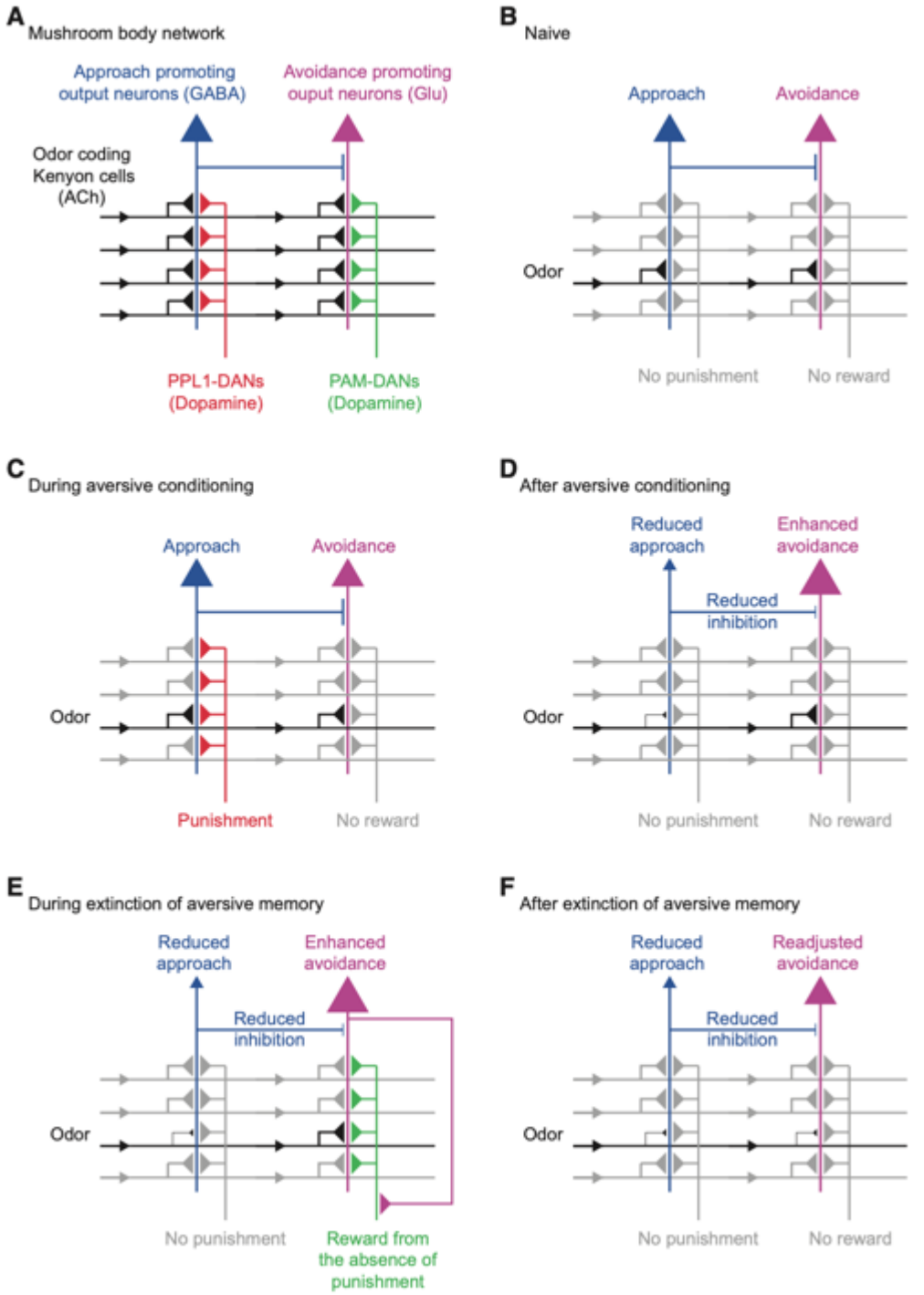
Model of memory acquaintance and extinct:



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Question

- Why serotonin? What does serotonin mean?Anything related with aggression?
- How does behavior(innate and learned) be inhabited?
- Where does behavior(innate and learned) be inhabited? Mushroom body or somewhere else?
- Can motivation be inhabited by frustration? How motivation be inhabited?
- Why individual can keep a rather long depression state even stress is removed?

Schizophrenia

“Mental cancer”

蒋昕钰

Research history of schizophrenia

Mid-19th century

Dementia praecox(早发性痴呆)
(Morel,1856)

Hebephrenia（青春痴呆）
(Hecker,1871)

Catatonia(紧张症)
(Kahlbaum,1874)

1896

Emil Kraepelin
the founder of modern scientific psychiatry

dementia praecox

sub-acute development of a peculiar simple condition of mental weakness occurring at a youthful age

1911

Eugen Bleuler

Schizophrenia

Schizein: Split *Phren*: Mind

Association, Apathy, Ambivalence, Autism

Clinical manifestations

Positive symptoms
- Delusions(妄想)
- Hallucinations(幻觉)

Negative symptoms
- Hypomnesia(记忆减弱)
- Blunted emotions
- Disordered expression
- Social withdrawal

Disorganization of thinking and behavior

Cognitive decline

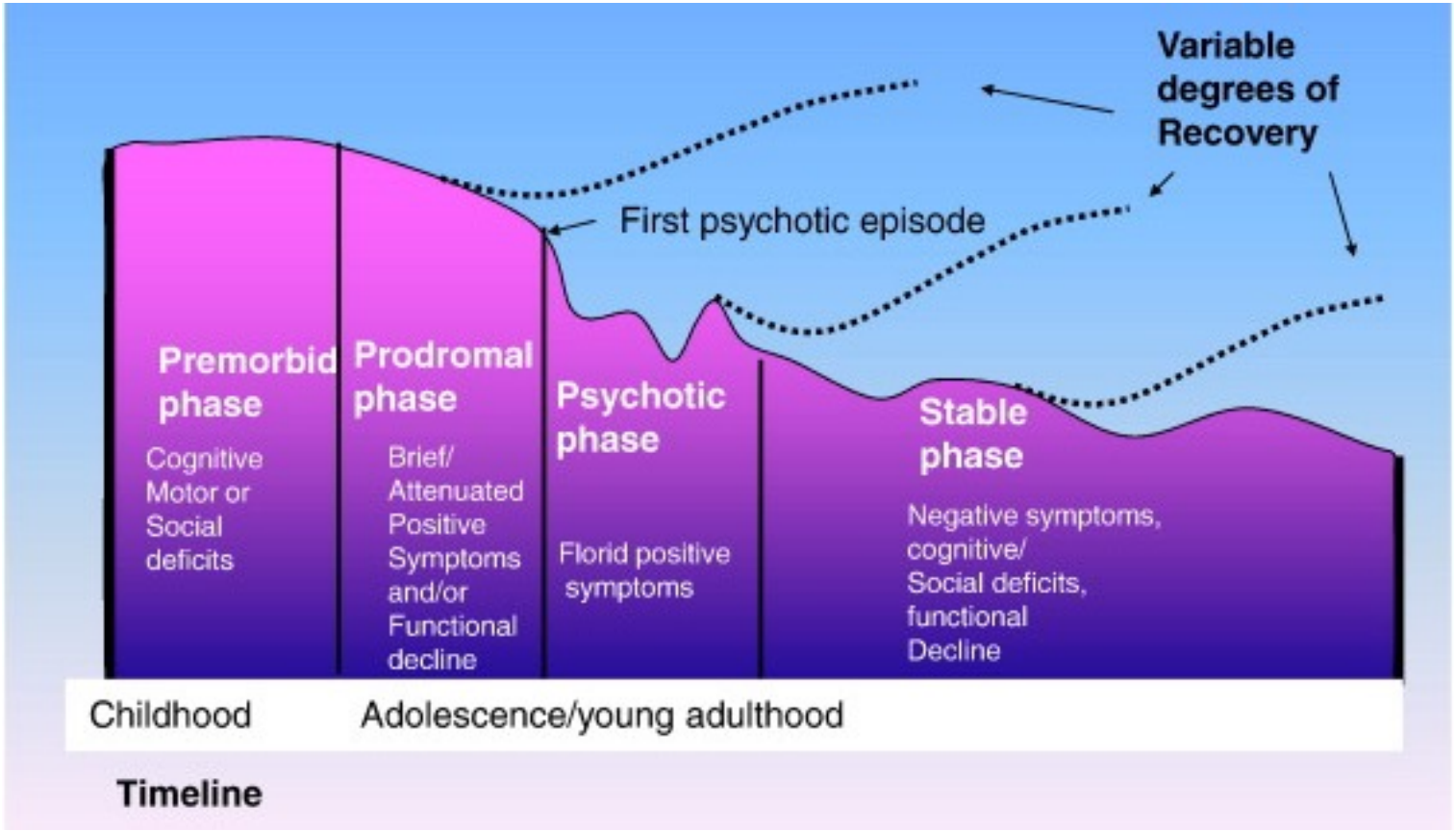
Mood symptoms

Motor symptoms and catatonia

Onset and course of schizophrenia

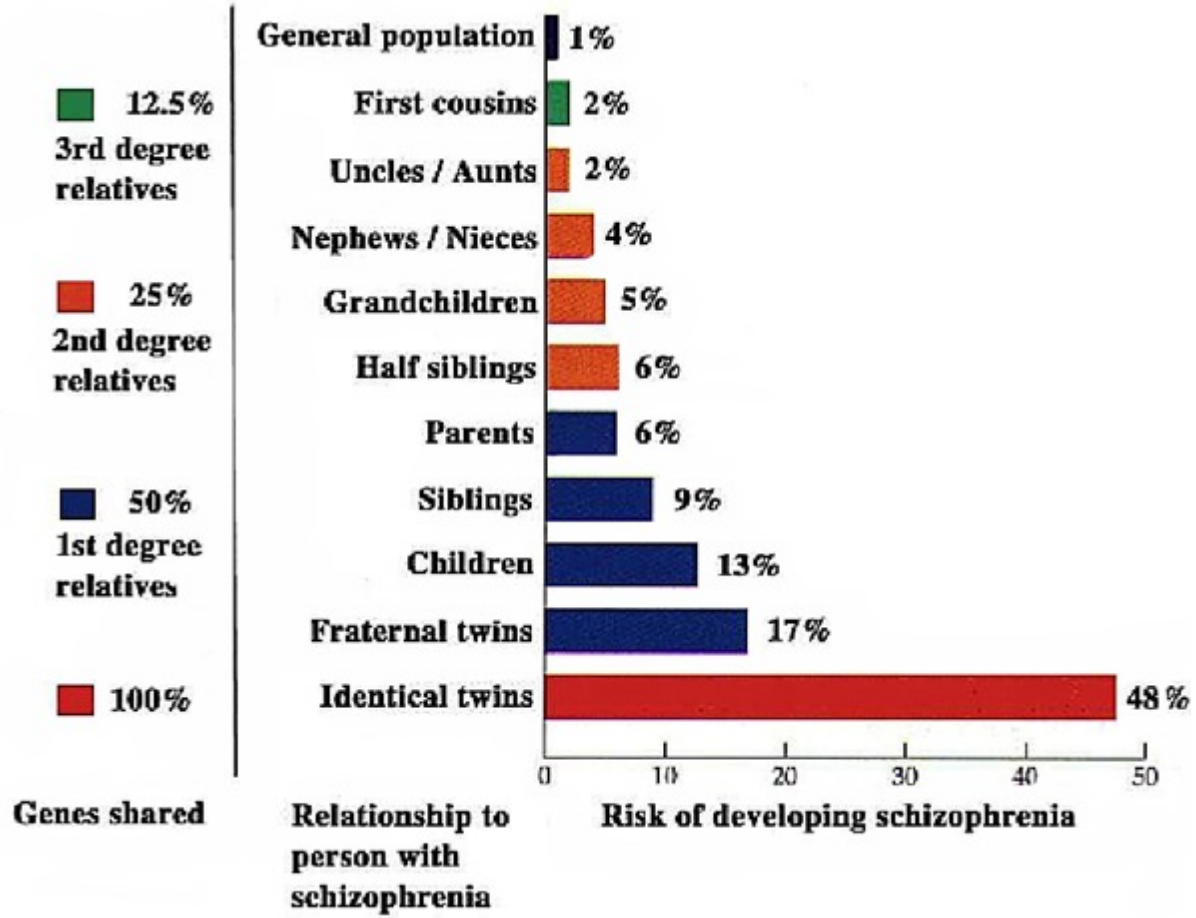
chronic and relapsing

The onset of schizophrenia typically occurs between the ages of 15 to 45 years



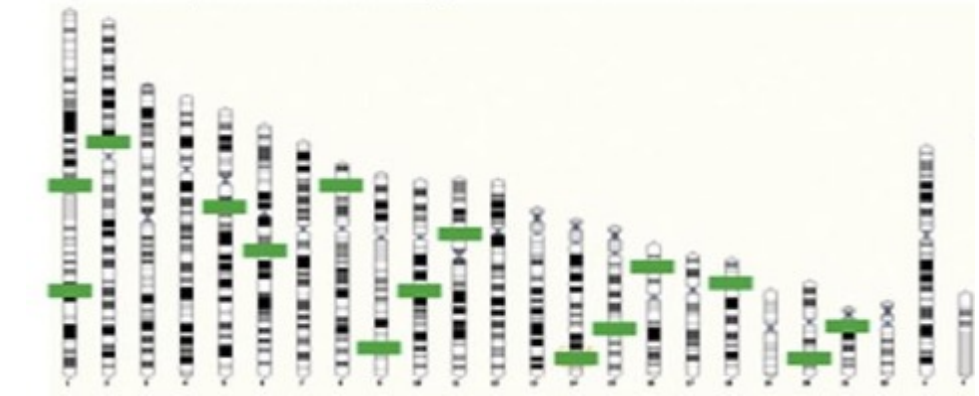
(Tandon, Nasrallah et al., Schizophr Res, 2009)

Genetic basis for schizophrenia



(Harrison, J Psychopharmacol, 2015)

Schizophrenia, high-risk variation



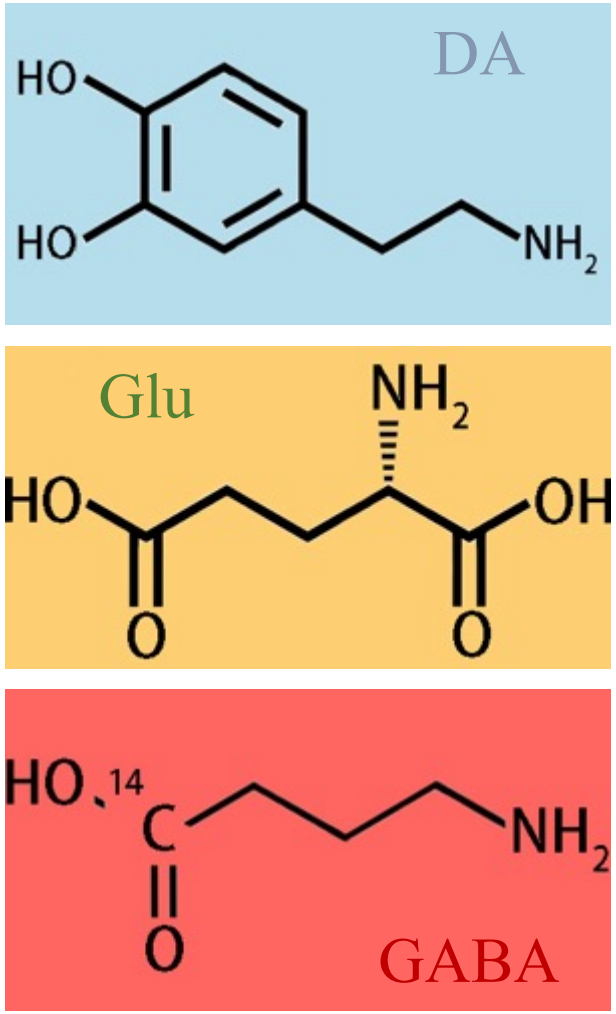
Implicated gene	Name of gene/product	Notes
CACNA1C	L-type calcium channel α subunit, type 1c ($Ca_v1.2$)	Important in neuronal function. Mutations cause Timothy syndrome and Brugada syndrome.
DISC1	Disrupted in schizophrenia-1	Identified in a large Scottish pedigree with a chromosome 1:11 translocation. A multifunctional scaffolding protein. Not GWAS significant.
DRD2	Dopamine D2 receptor	Long known to be the key target of antipsychotic drugs, GWAS data now indicate that the *DRD2* gene may play a role in schizophrenia.
MIR137	MicroRNA 137	Non-protein-coding gene. A microRNA, which regulates other genes by binding to the 3′ untranslated region of their transcripts.
NRG1	Neuregulin 1	Growth factor, involved in many aspects of nervous system development and plasticity. Not GWAS significant.
TCF4	Transcription factor 4	Basic helix-loop-helix transcription factor. Haploinsufficiency causes Pitt–Hopkins syndrome.

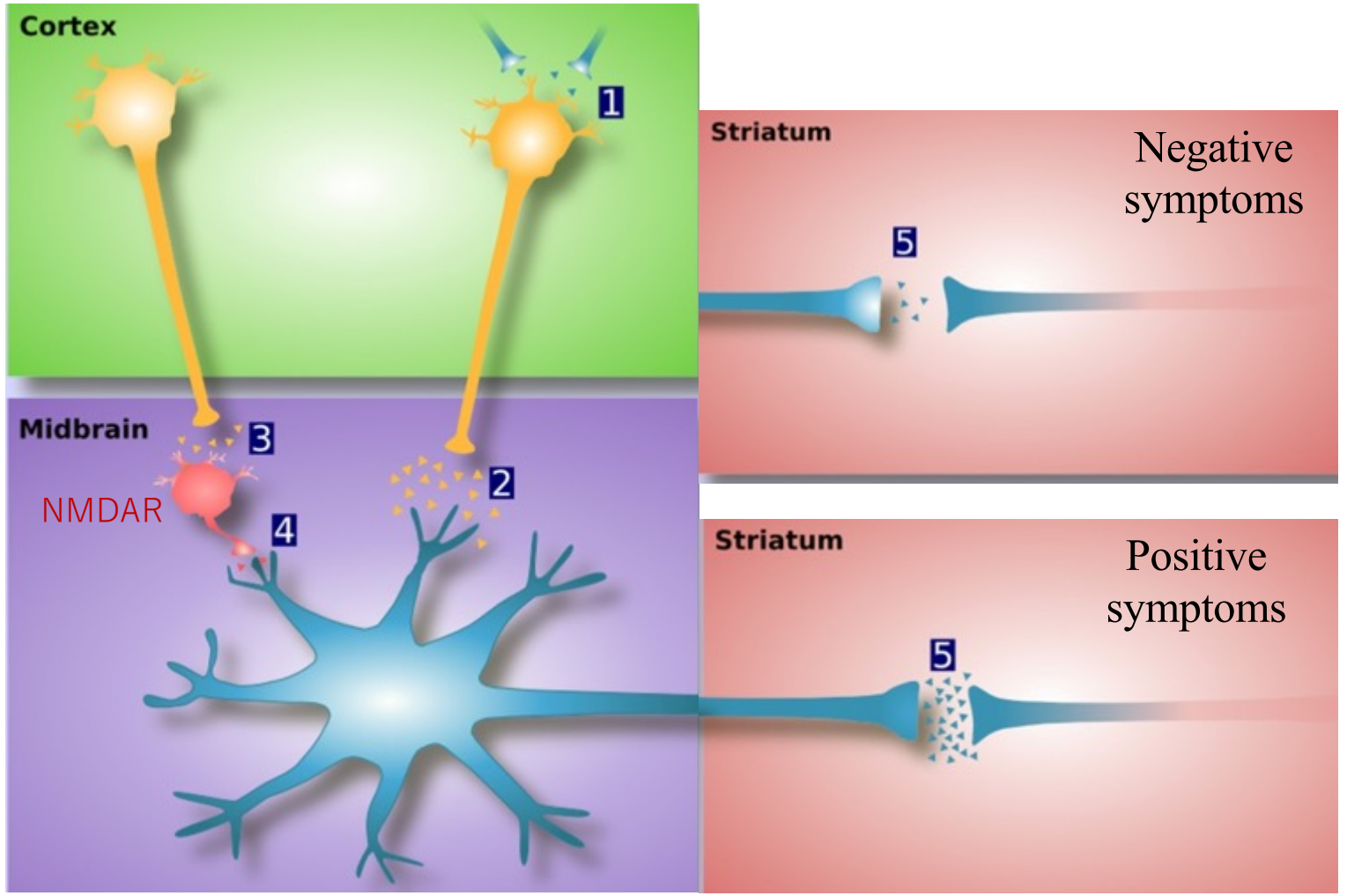
Environmental risk factors

Risk factor	Average relative risk of schizophrenia if risk factor present (approximate)
Family history of schizophrenia	2–70
Any specific single gene variant	1.1–1.5
Urbanicity	2–3
Migration	2–3
1^{st} or 2^{nd} trimester maternal infection or malnutrition	2–3
Winter birth	1.1
Obstetric and perinatal complications	2–3
Cannabis or stimulant use	2–3
Paternal age >35 years	1.5–3
Male gender	1.4

(Tandon, Keshavan et al., Schizophr Res, 2008)

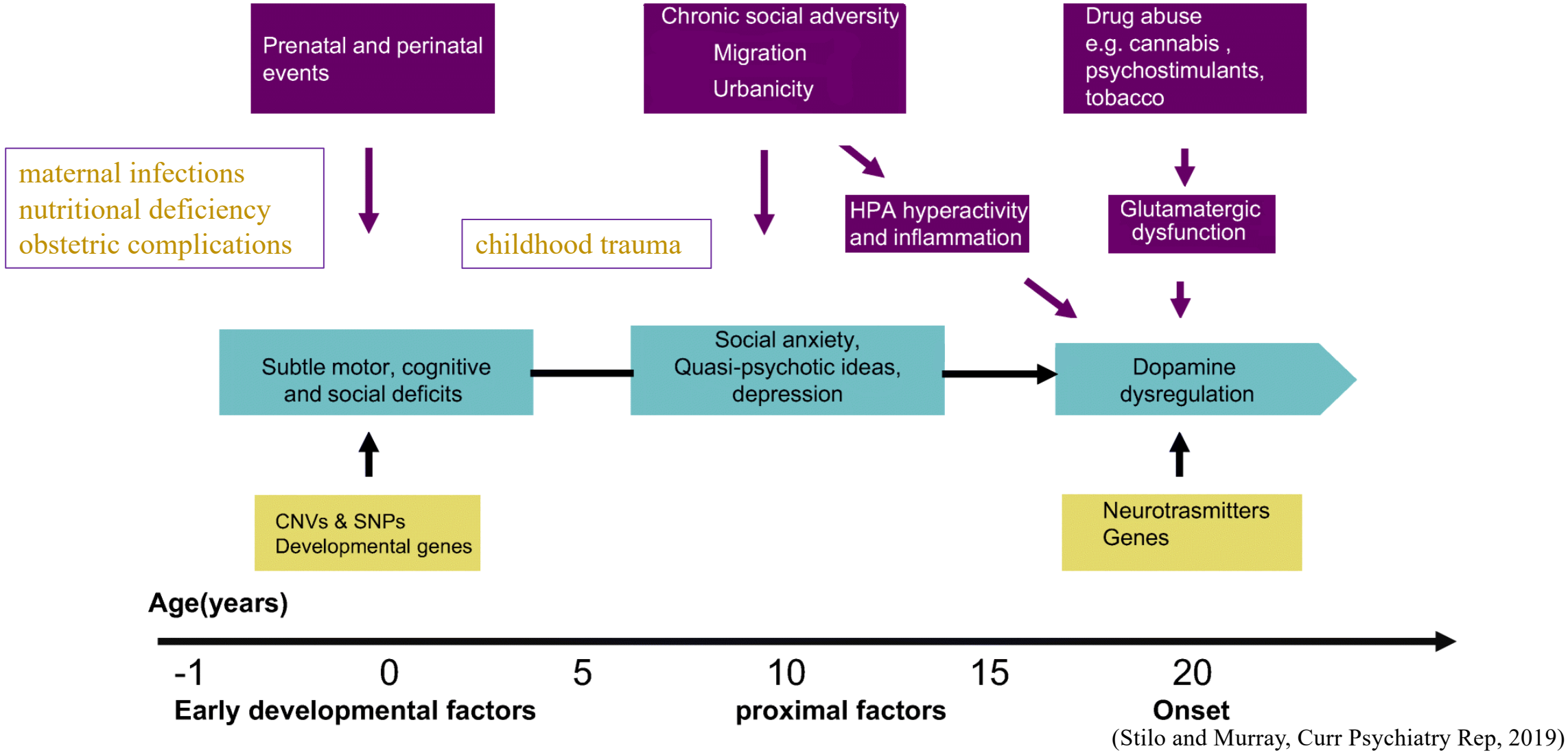
Neurotransmitter abnormality hypothesis





(Howes, McCutcheon et al., Biol Psychiatry, 2017)

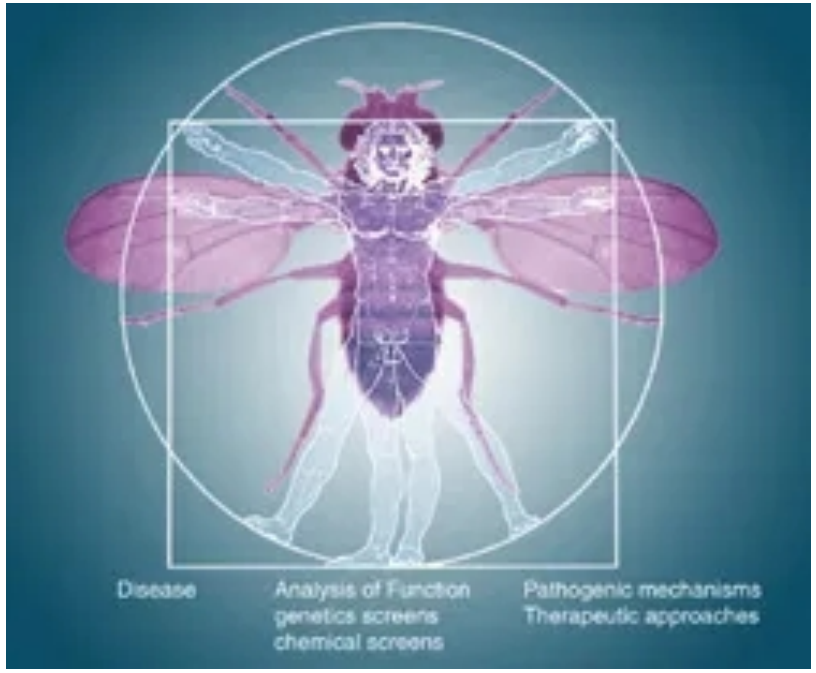
Gene–Environment Interaction

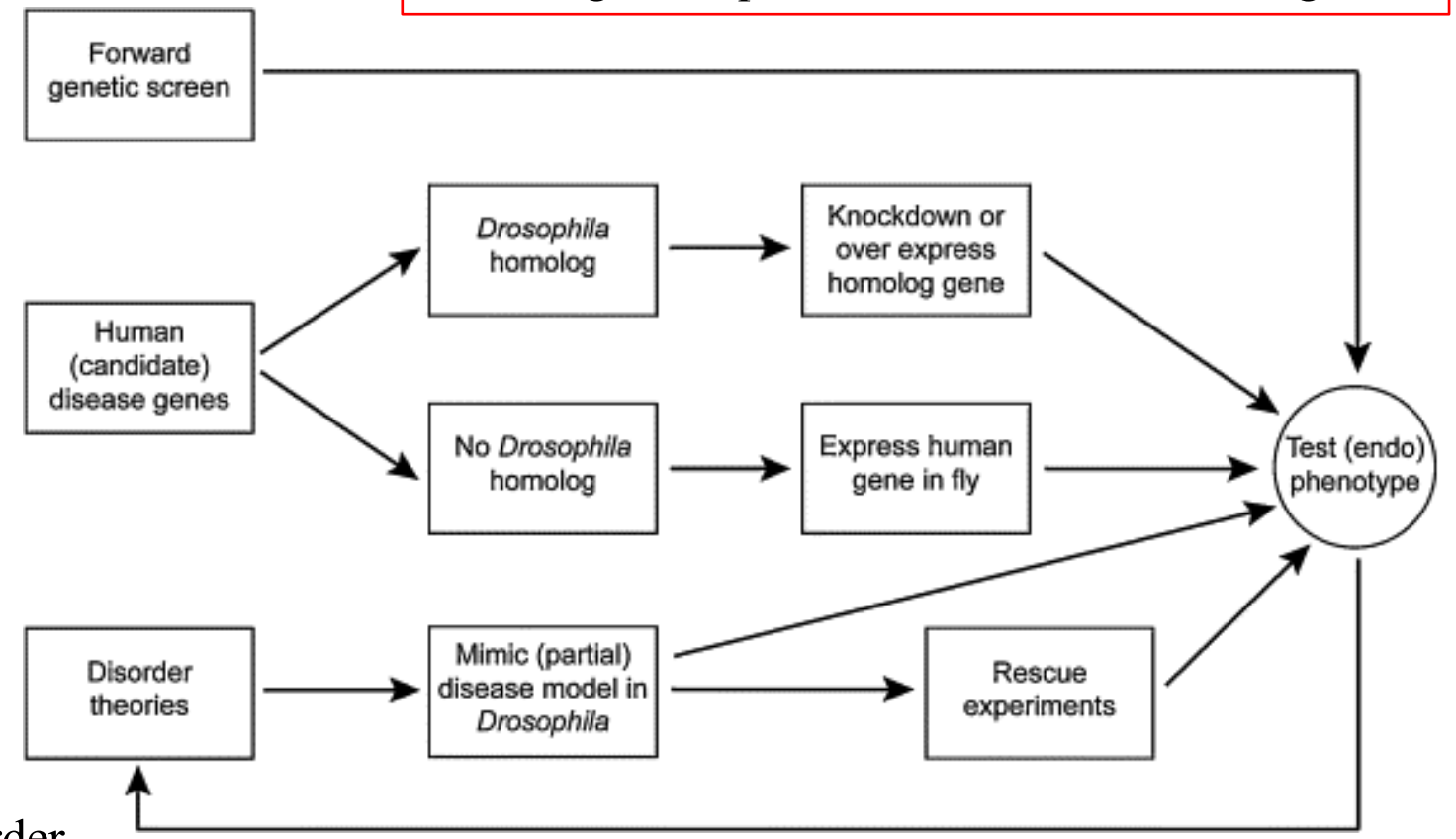


(Stilo and Murray, Curr Psychiatry Rep, 2019)

Drosophila strategies to study schizophrenia

What exactly should we measure when screening *Drosophila* mutants for candidate genes





Schizophrenia is not a single gene disorder

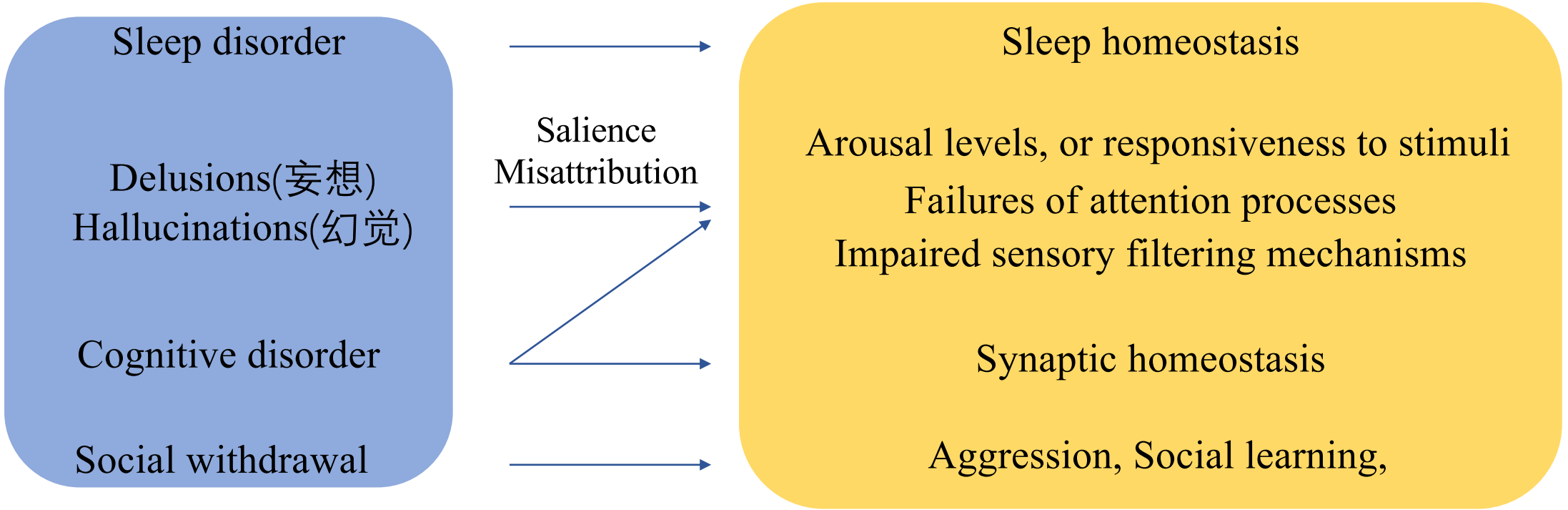
Schizophrenia is heterogeneity and anthropocentrism

(van Alphen and van Swinderen, Brain Res Bull, 2013)

Drosophila models of schizophrenia

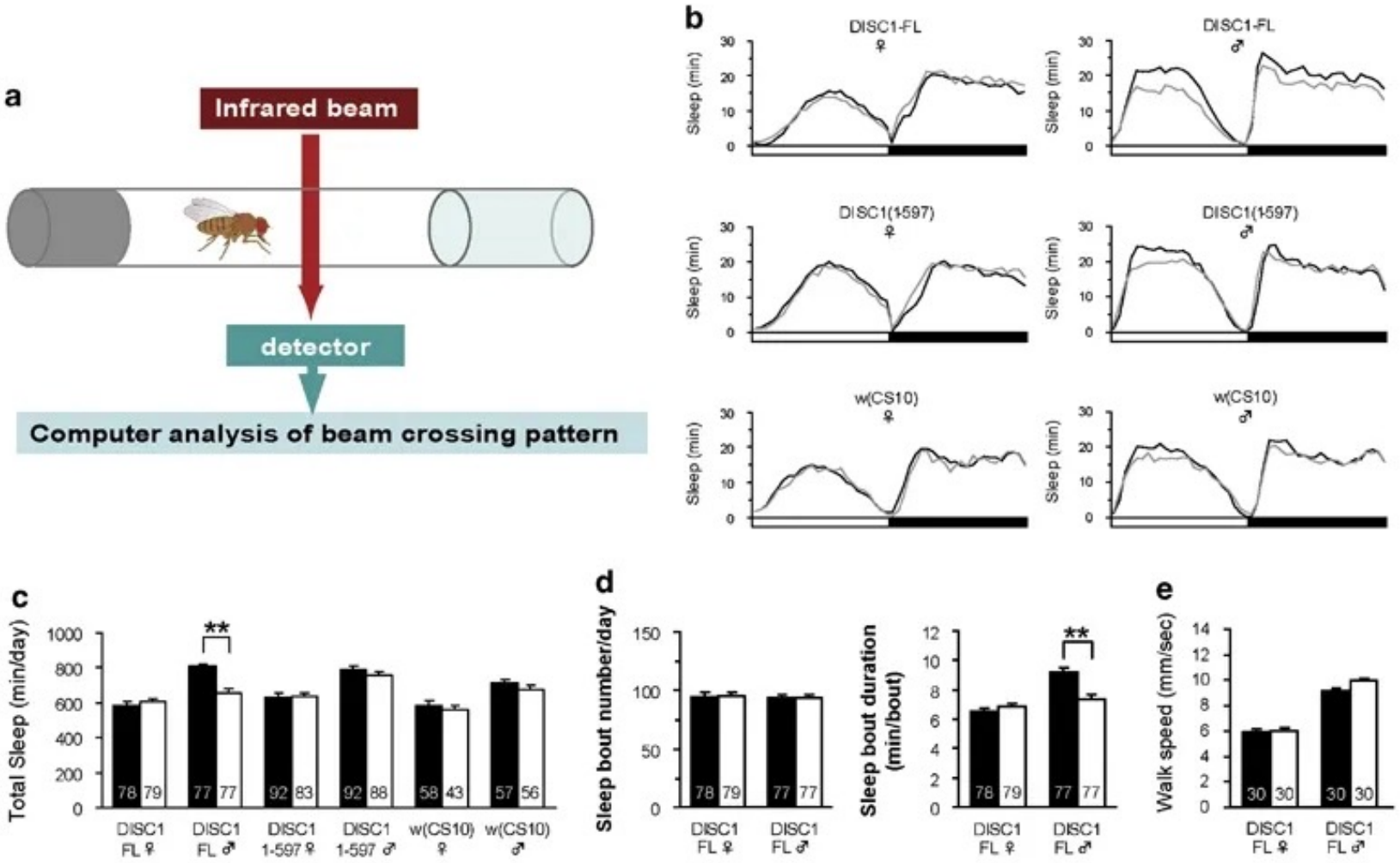
Break down illnesses into fundamental symptom clusters that are more closely linked to single gene

→ Endophenotypes - characteristic observable behaviors



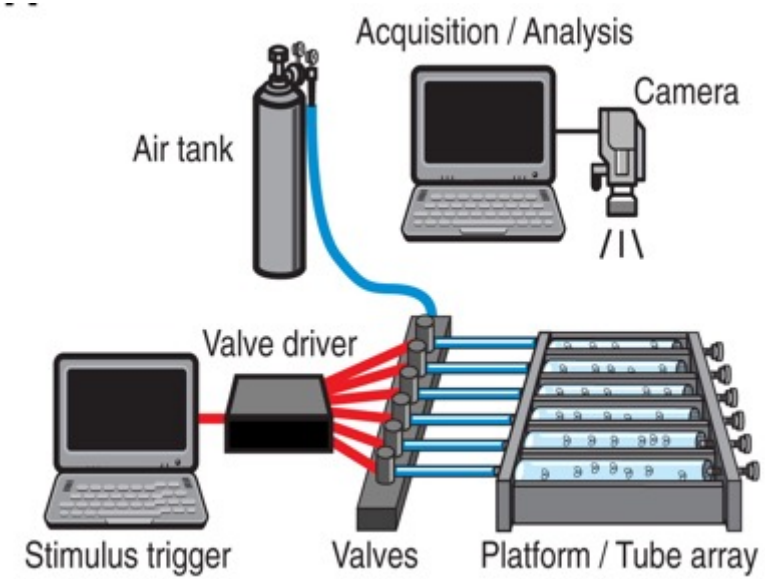
Aberrant Salience Allocation：a patient tries to make sense of aberrant salience attributed to random events in the environment

DISC1 flies with accumulation of exogenous human DISC1 display disturbance in sleep homeostasis

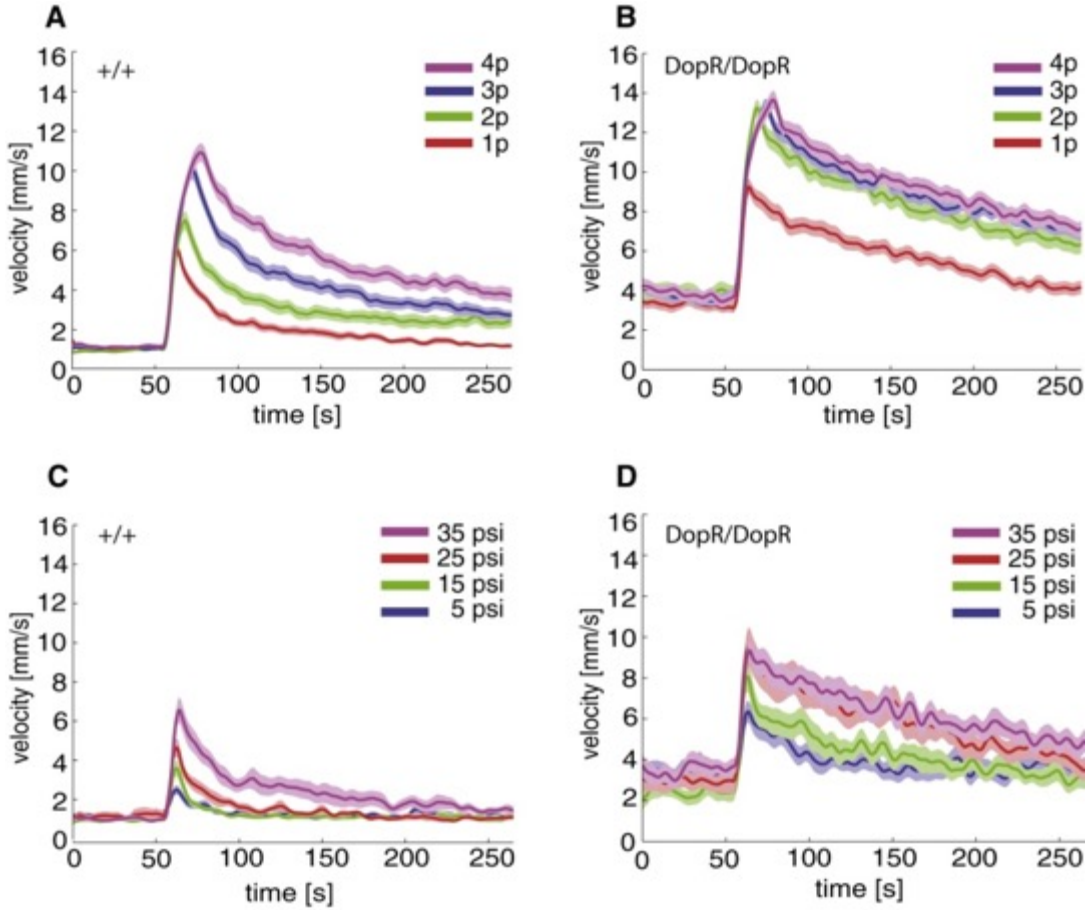


(Sawamura, Ando et al., Mol Psychiatry, 2008)

Loss-of-function mutations in *DopR* enhance repetitive startle-induced arousal

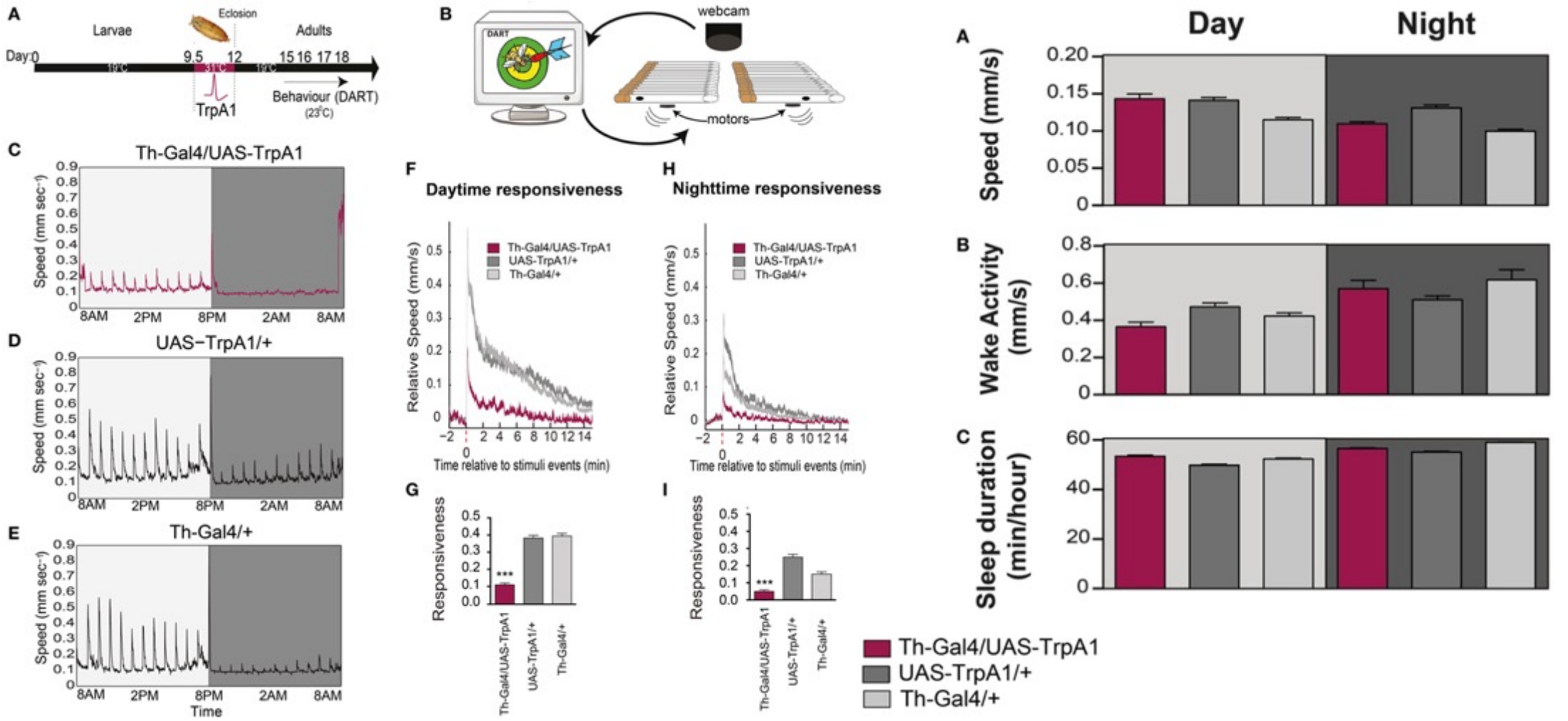


Environmentally Stimulated Arousal
repetitive mechanical startle



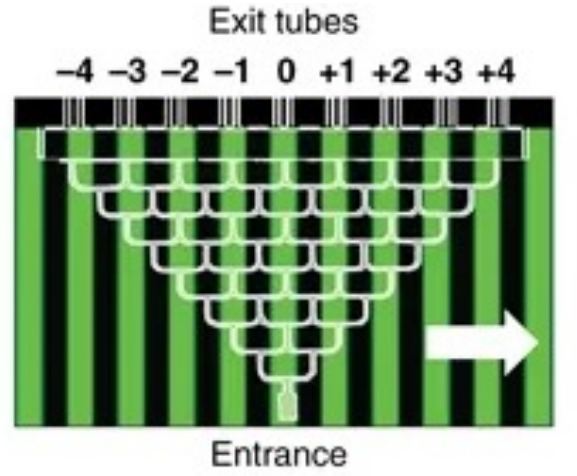
(Lebestky, Chang et al., Neuron, 2009)

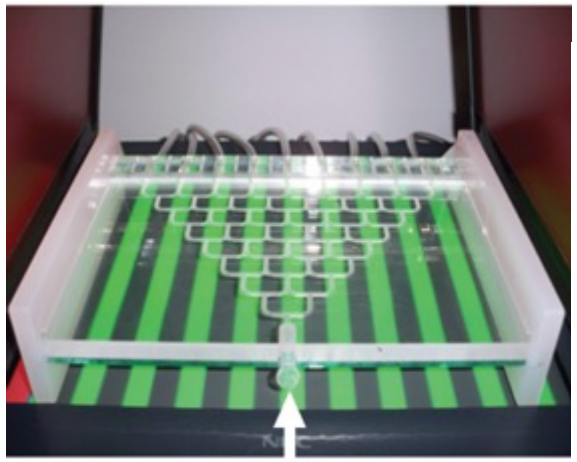
Transient activation of DA during development decreases behavioral responsiveness to mechanical stimuli regardless of sleep-wake



(Ferguson, Petty et al., Front Psychiatry, 2017)

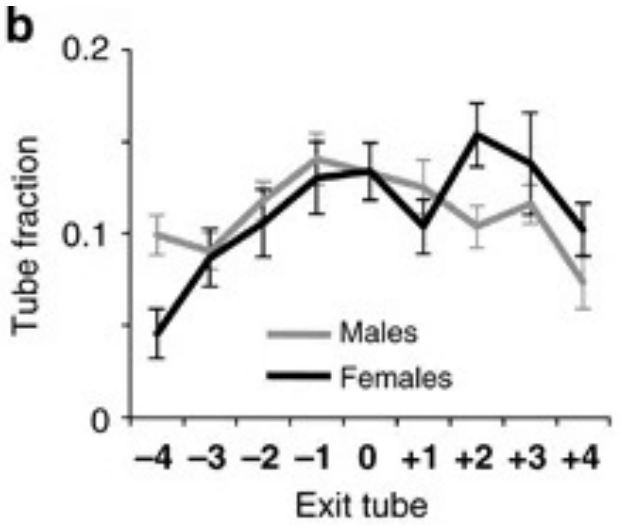
Increasing DA activity during later stages of development increases visual responsiveness in adult

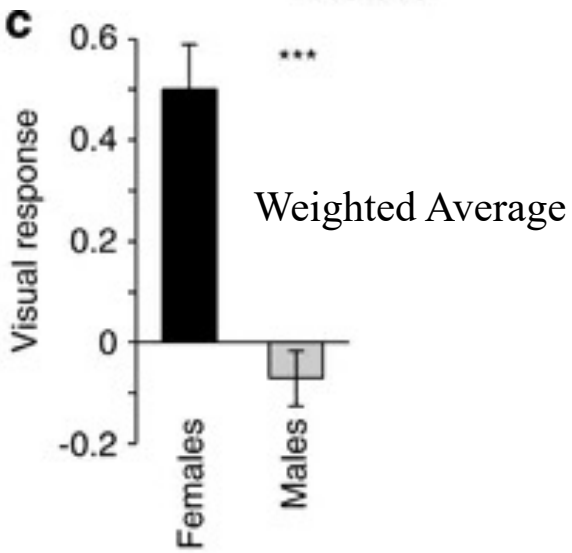




Optomotor Maze

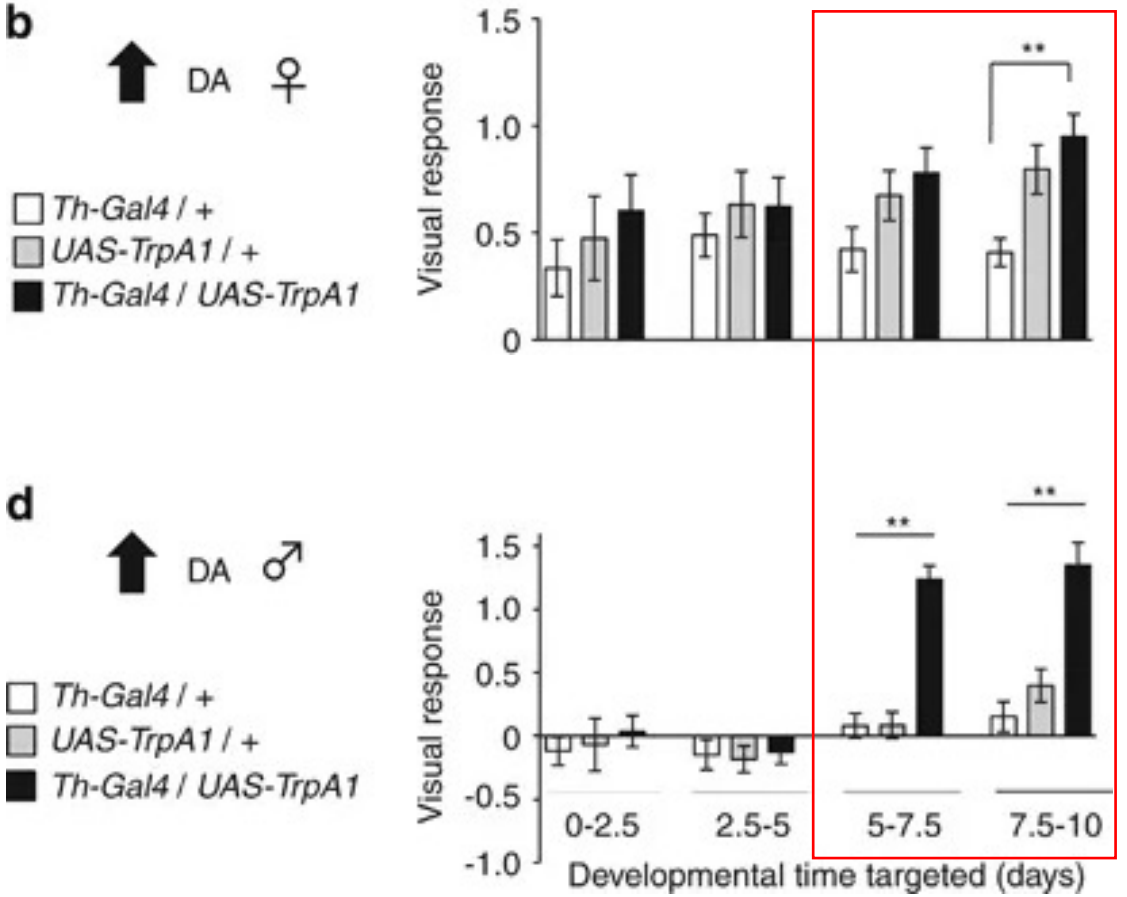
28×19×1 cm





Weighted Average

Pupa Stage



(Calcagno, Eyles et al., Transl Psychiatry, 2013)

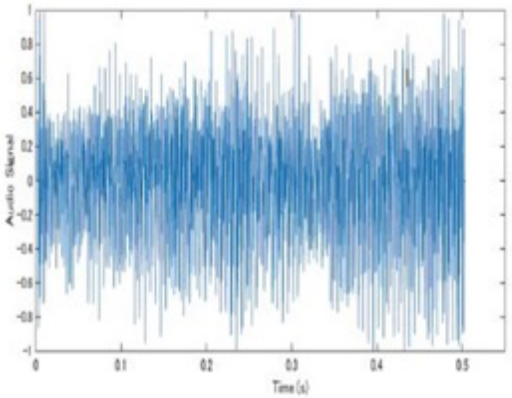
Prepulse Inhibition

Drosophila melanogaster larvae can exhibit prepulse inhibition

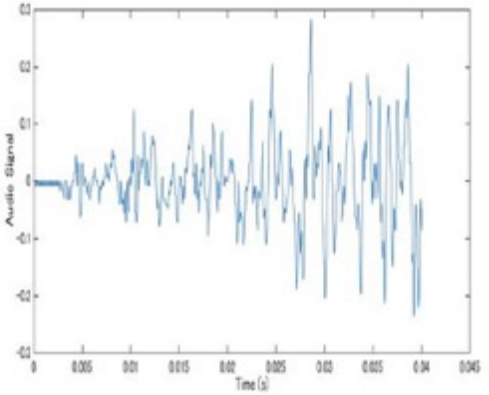
Startle Stimulus → Startle Response

Weaker Non-startle Stimulus → Startle Stimulus → Startle Response ↓

Pulse



Prepulse

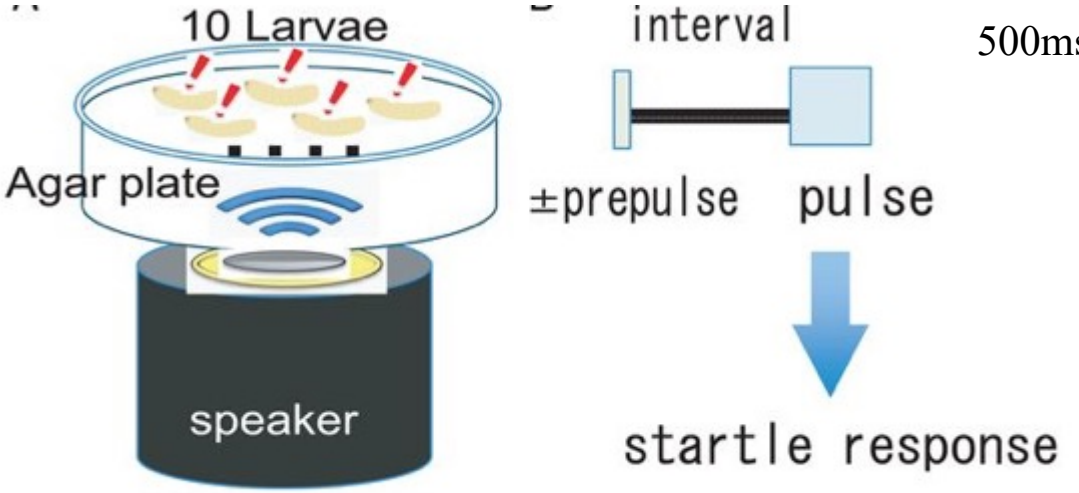


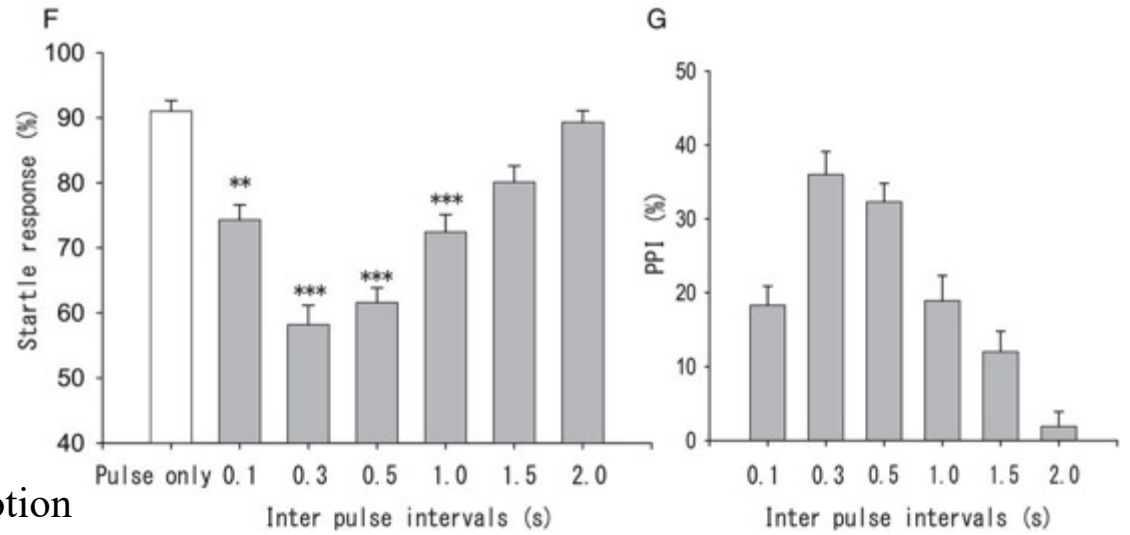
500ms, 70dB

40ms

Startle response value:
Total Score / Full Score

PPI:
(startle response value – startle response value without the prepulse) / startle response value without the prepulse

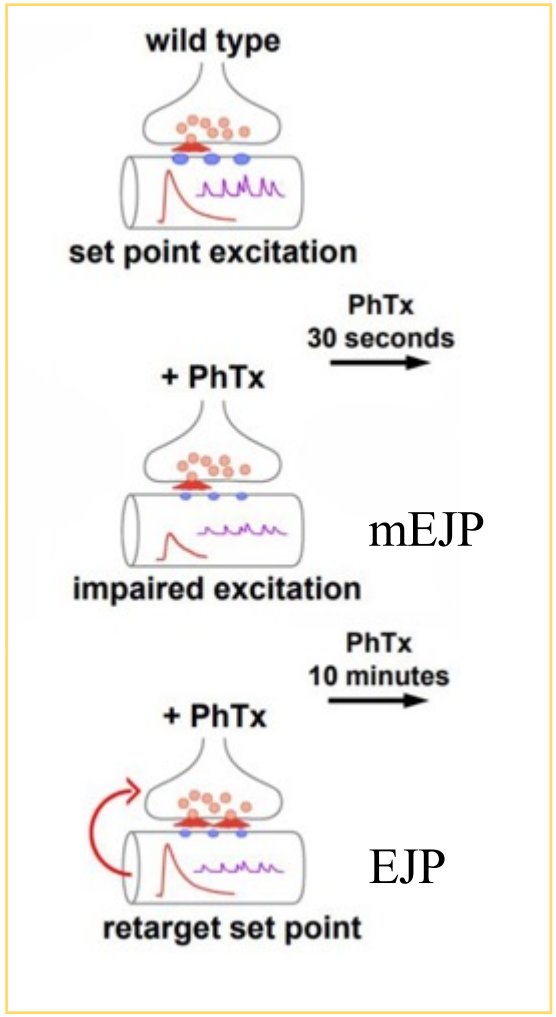


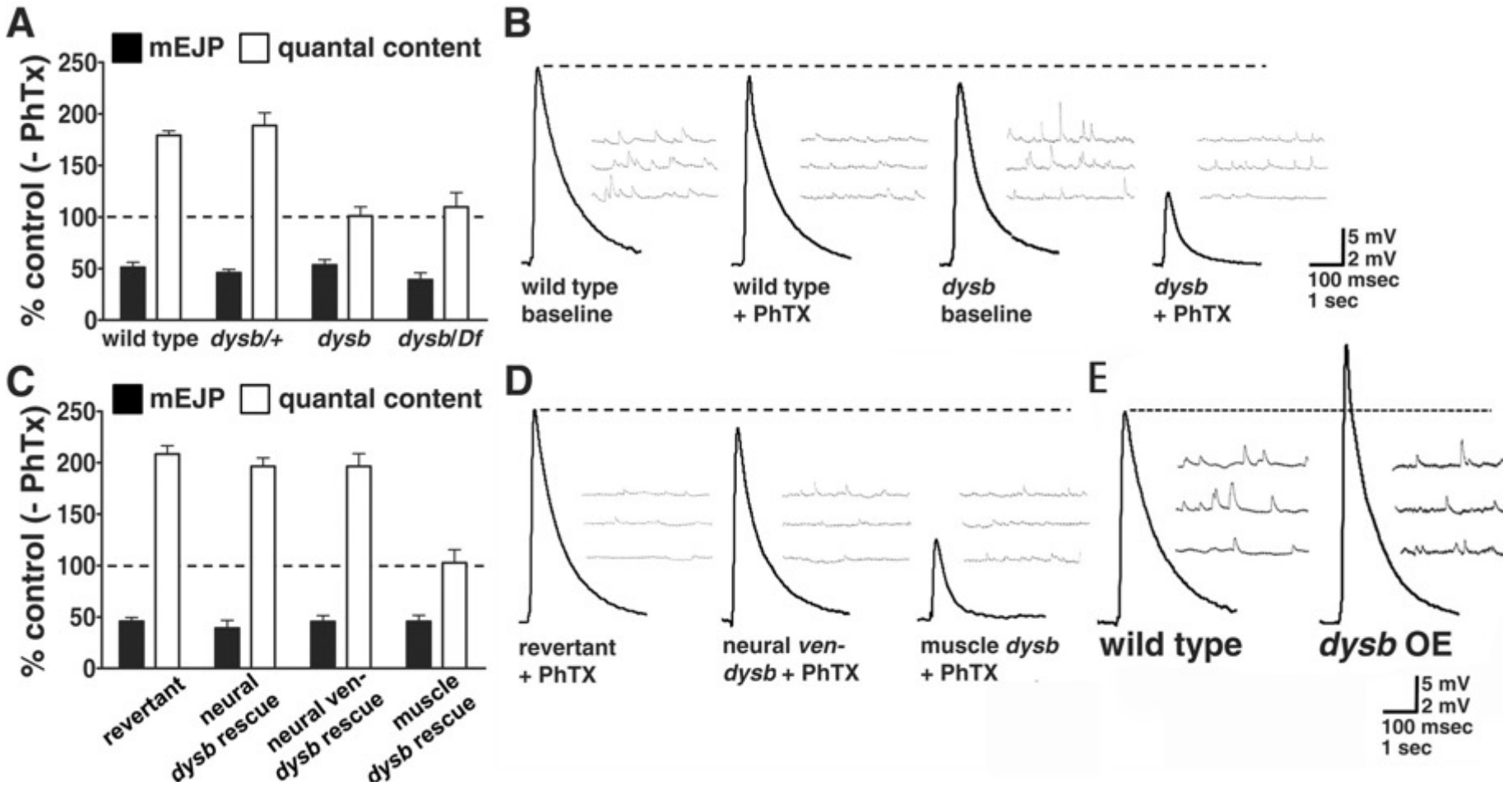


mouth-hook retraction, excessive turning, backward locomotion

(Matsumoto, Shimizu et al., Biol Open, 2018)

dysbindin is an essential presynaptic component in a homeostatic signaling system





% control = value (+PhTx) / value (-PhTx)
Quantal content = average EJP/average mEJP

(Dickman, Science, 2009)

Questions:

To what extent can psychiatrists use fly behaviors to study what their human patients are experiencing?

How to model high brain functions, probably more specific to primates in *Drosophila*?

Is schizophrenia a side effect in the evolution of the brain?

Why do some mental illnesses such as autism and schizophrenia have certain special talents?

Autism

赵环

Diagnostic criteria of autism spectrum disorder

Autism spectrum disorder (ASD):孤独症谱系障碍

- Persistent deficits in social communication and social interaction across multiple contexts
- Restricted, repetitive patterns of behavior, interests, or activities
- Symptoms must be present in the early developmental period
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

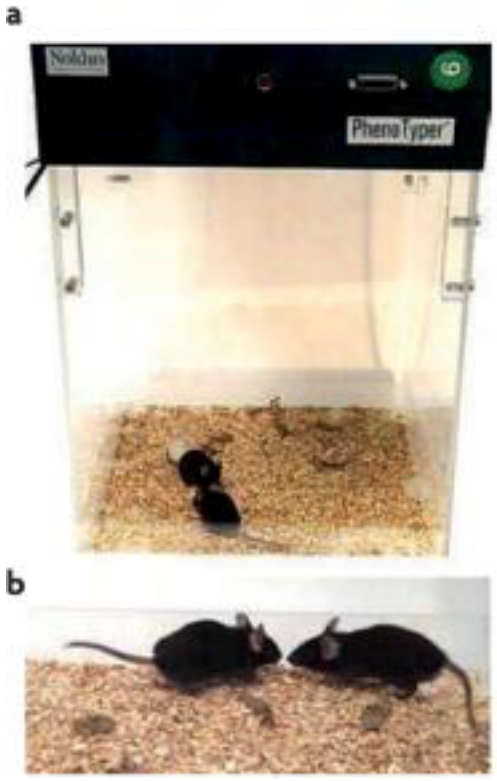
Cause of autism spectrum disorder

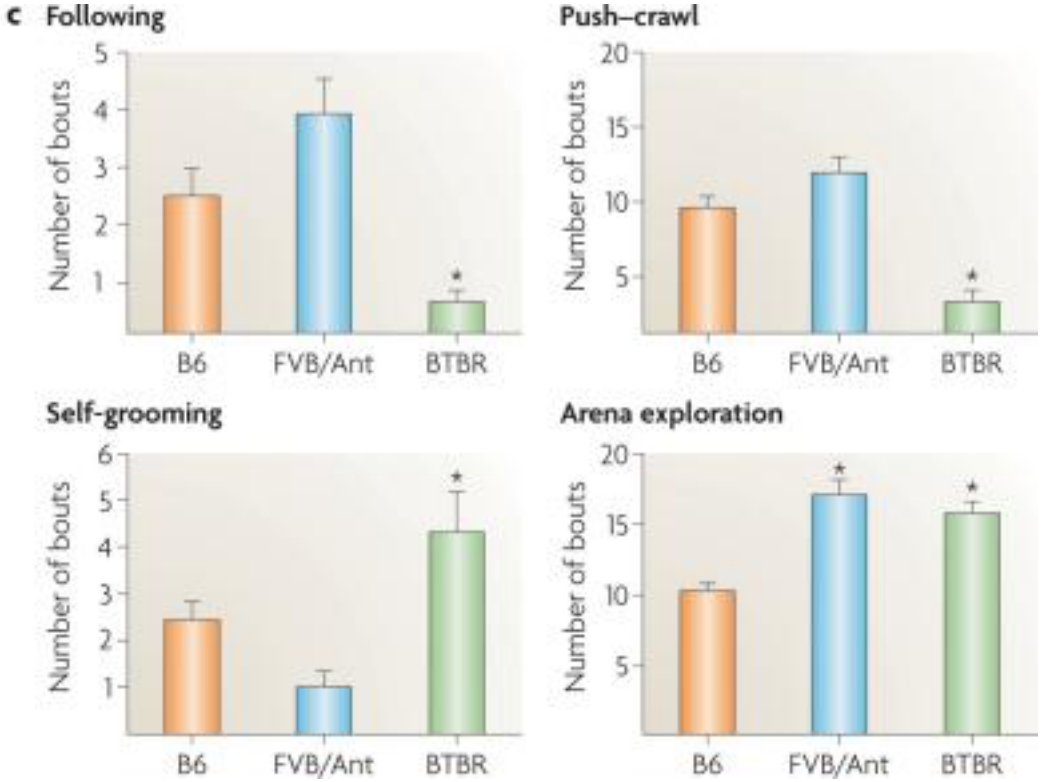
- Genetic factors
  - Inheritance
  - Neuroendocrine disorder
- Environmental factors
  - Infection and immunity
  - Physical and chemical stimulation during pregnancy

Autism spectrum disorder-related syndromes test: modeling with rodents and Drosophila

Rodents：

- Sociability Test
- Open Field Behavior Test
- Learning and Memory Test

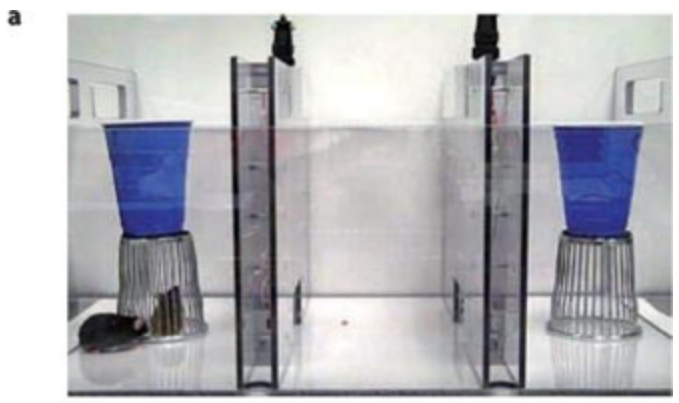


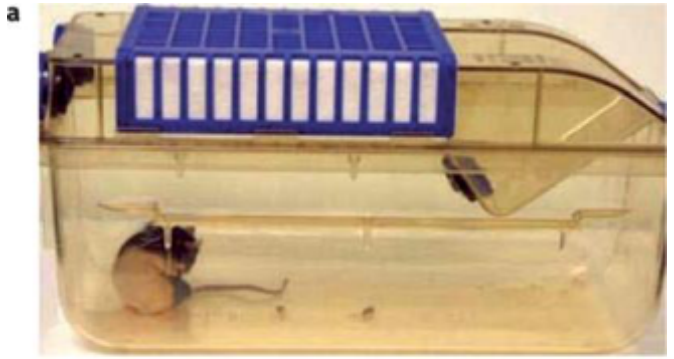


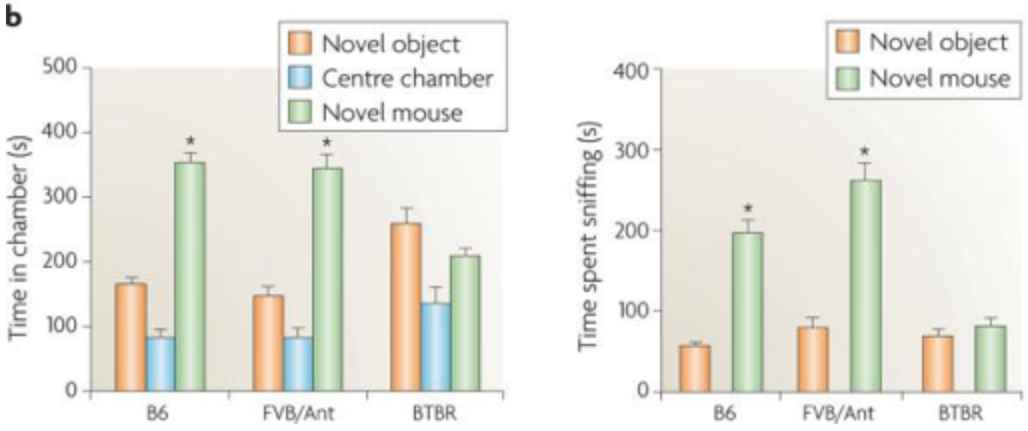
Silverman JL. Nature Reviews Neuroscience. 2010

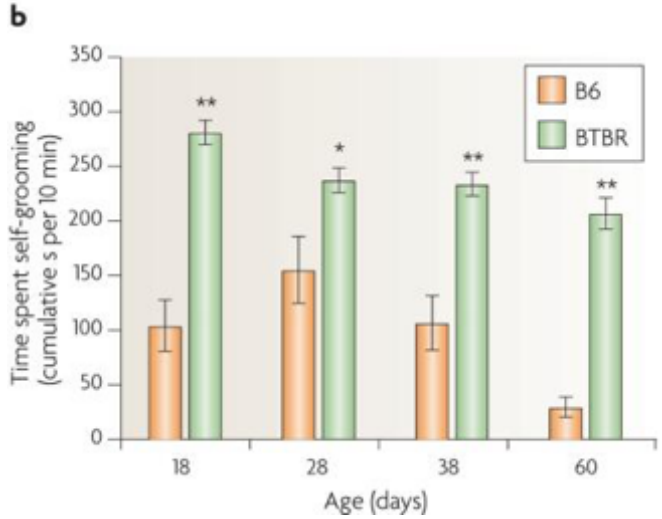
ASD-related syndromes tested in rodents

Automated three-chambered social approach





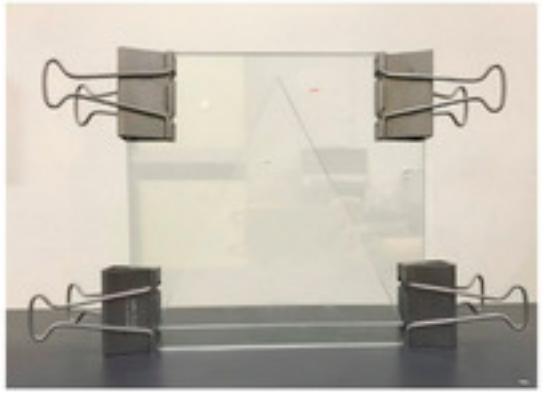


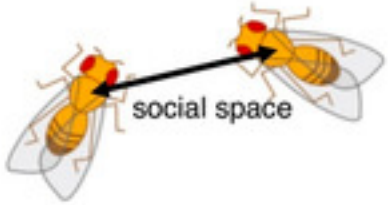


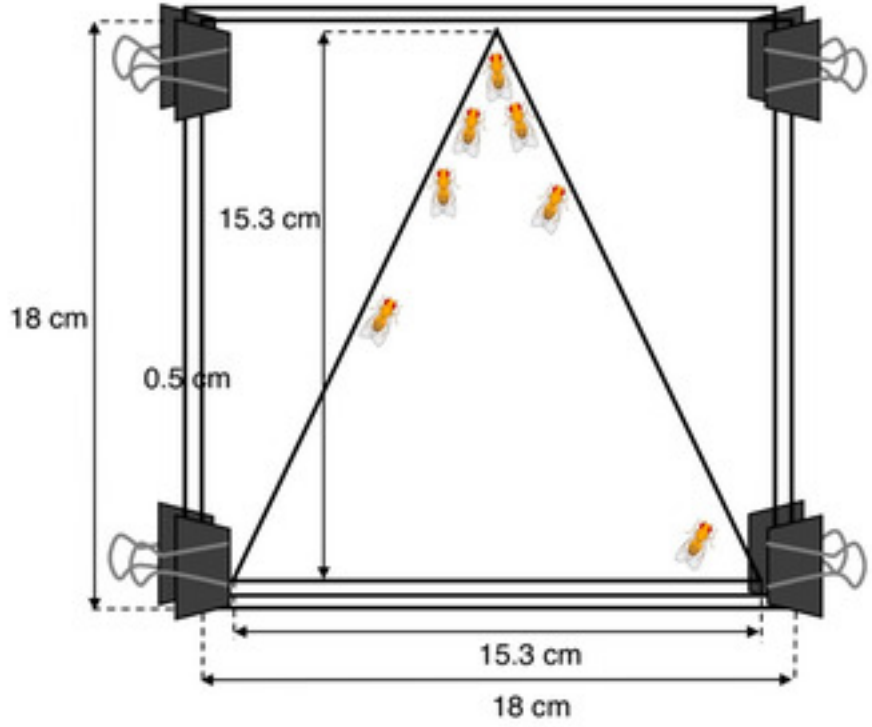
Silverman JL. Nature Reviews Neuroscience. 2010

ASD-related syndromes tested in Drosophila

- Social Space Assay



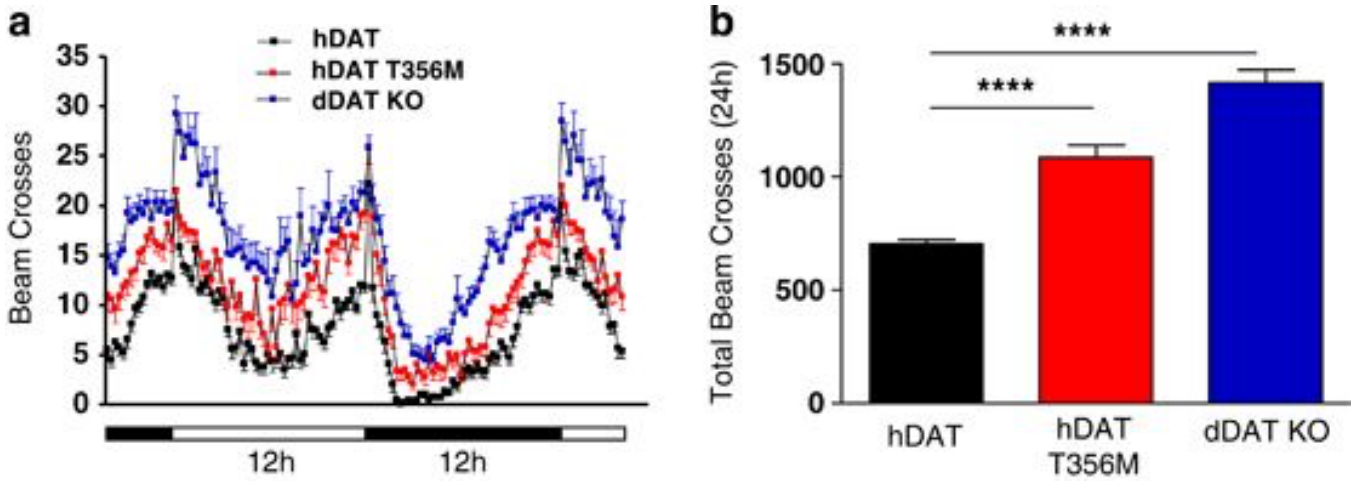


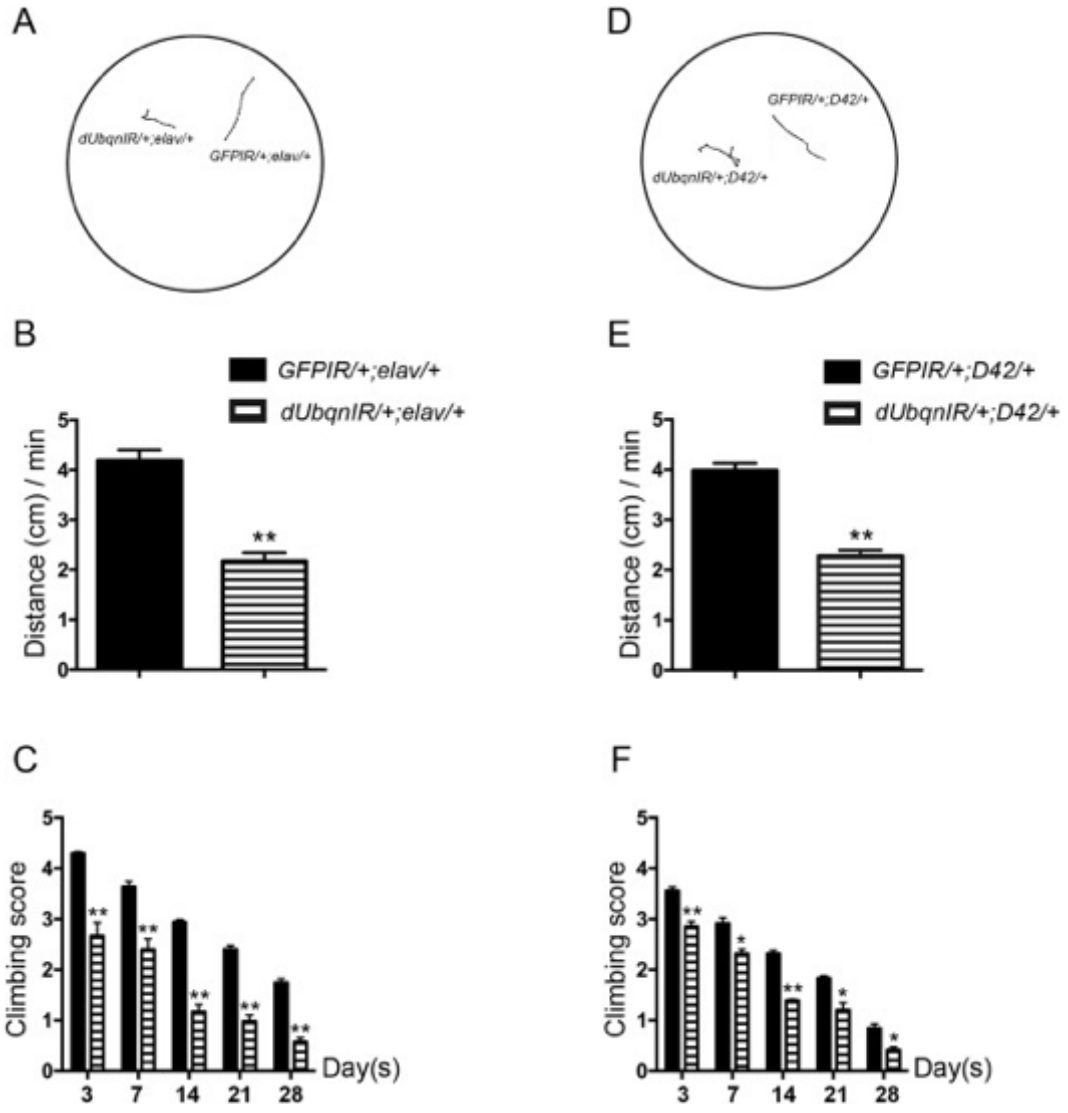


Ibuki Ueoka et al. Molecular Science. 2019

ASD-related syndromes tested in Drosophila

- *Drosophila* Activity Assay

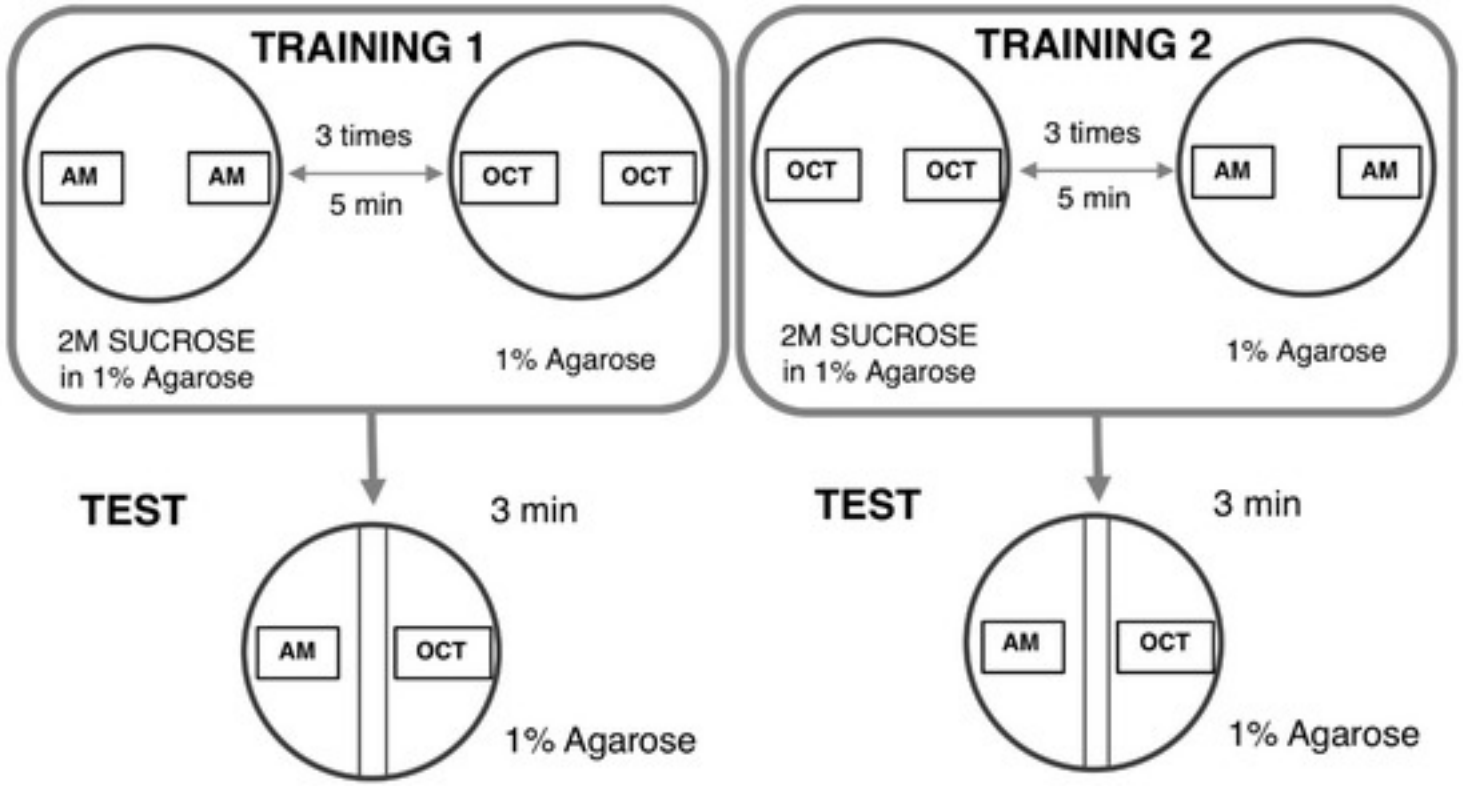




P J Hamilton et al. Molecular Psychiatry. 2013

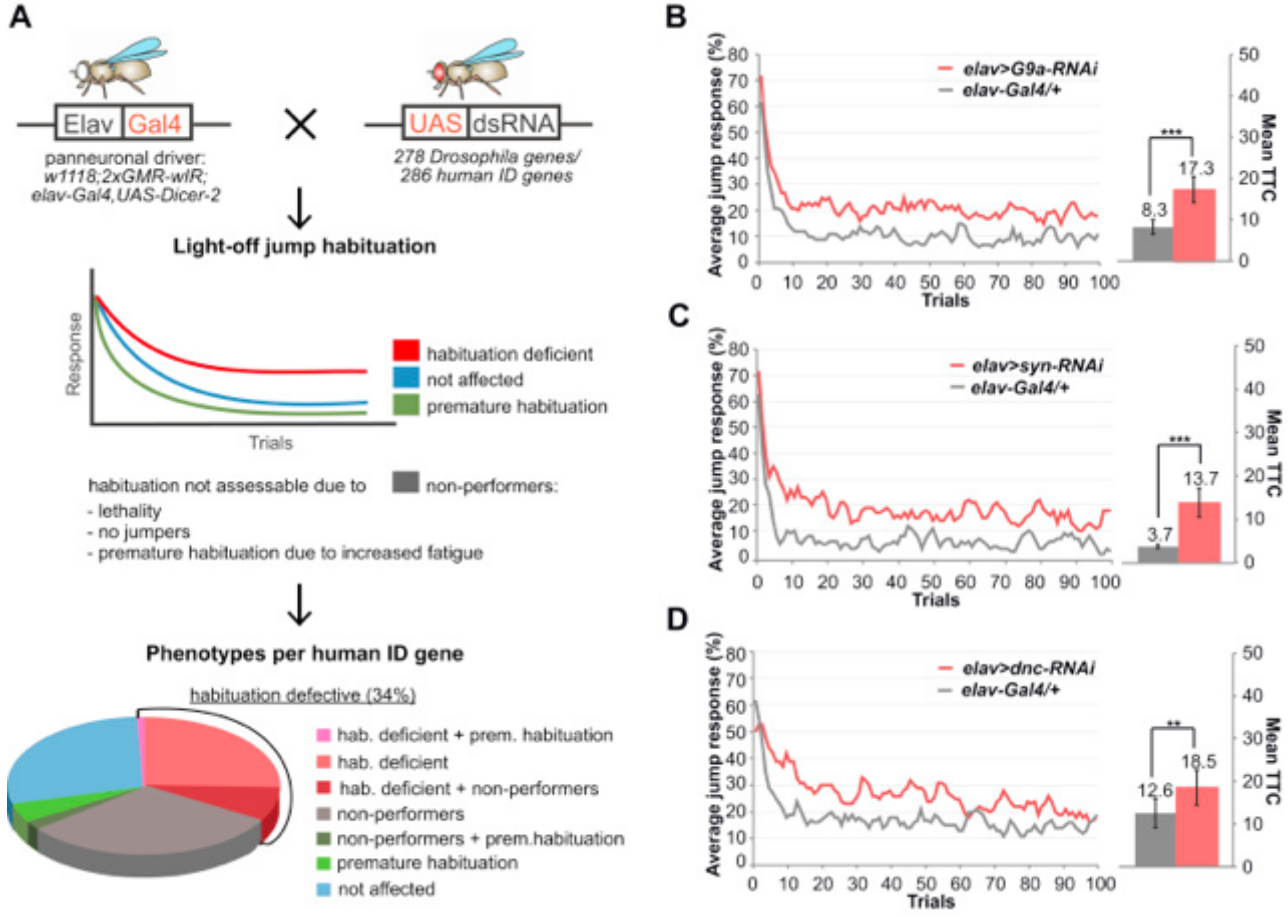
ASD-related syndromes tested in Drosophila

- Odor–Taste Learning Assay in Larvae



Ibuki Ueoka et al. Molecular Science. 2019

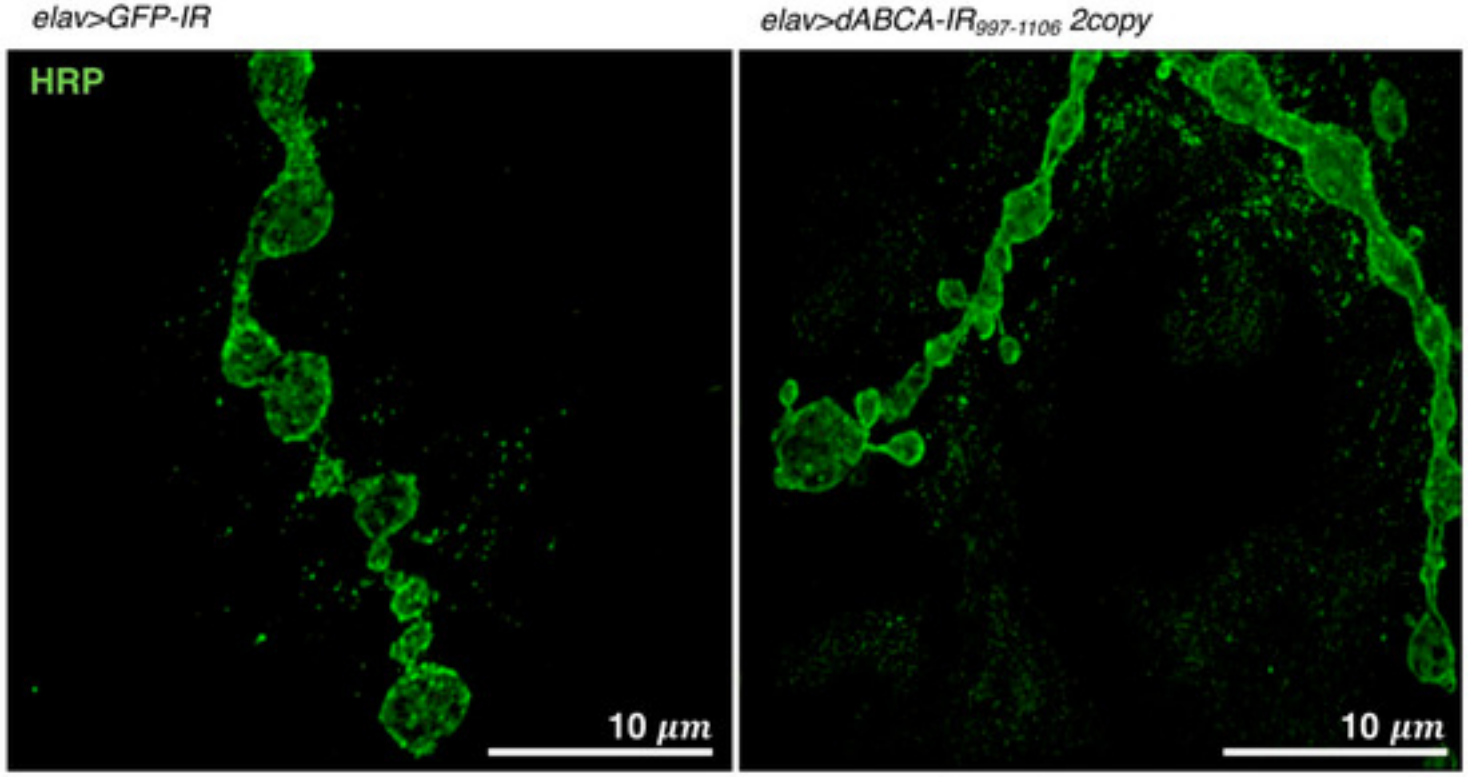
Habituation Learning



Machaela Fenckova et al. Biological Psychiatry. 2019

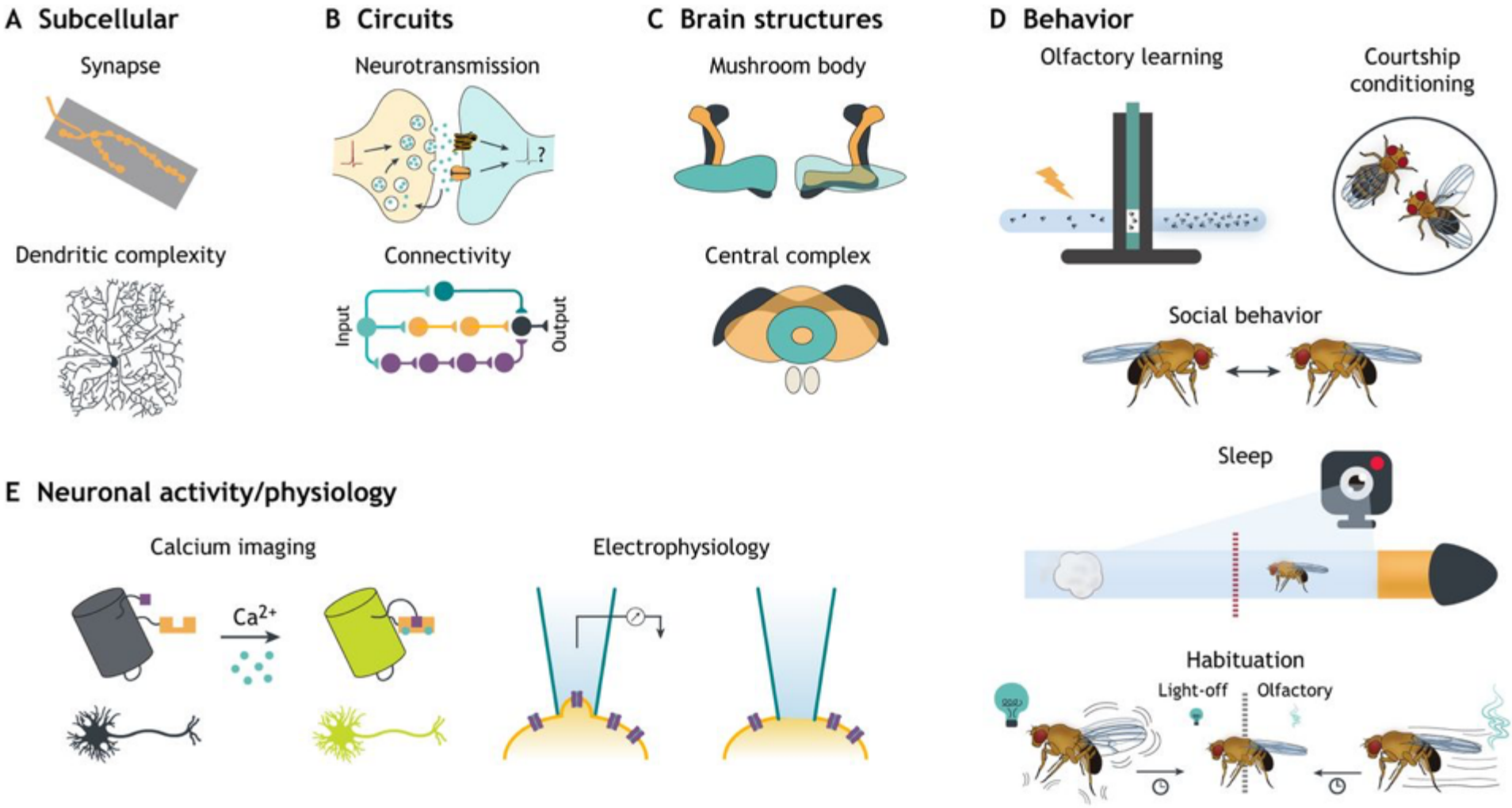
ASD-related syndromes tested in Drosophila

- Visualization of NMJs by Super Resolution Microscopy



Ibuki Ueoka et al. Molecular Science. 2019

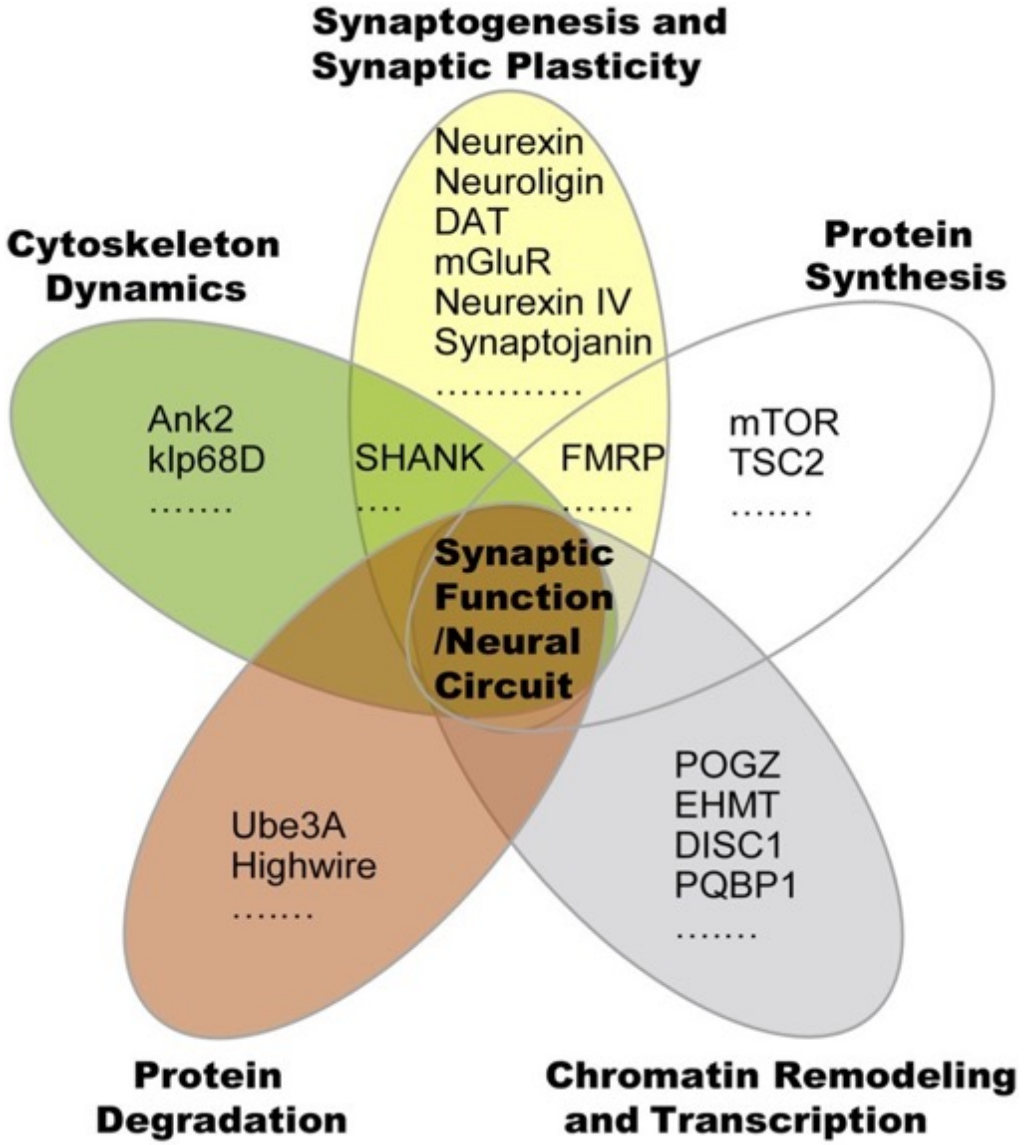
Drosophila as a model in ASD investigation



Mireia Coll-Tané et al. Science. 2019

Genes and neurotransmitters in ASD

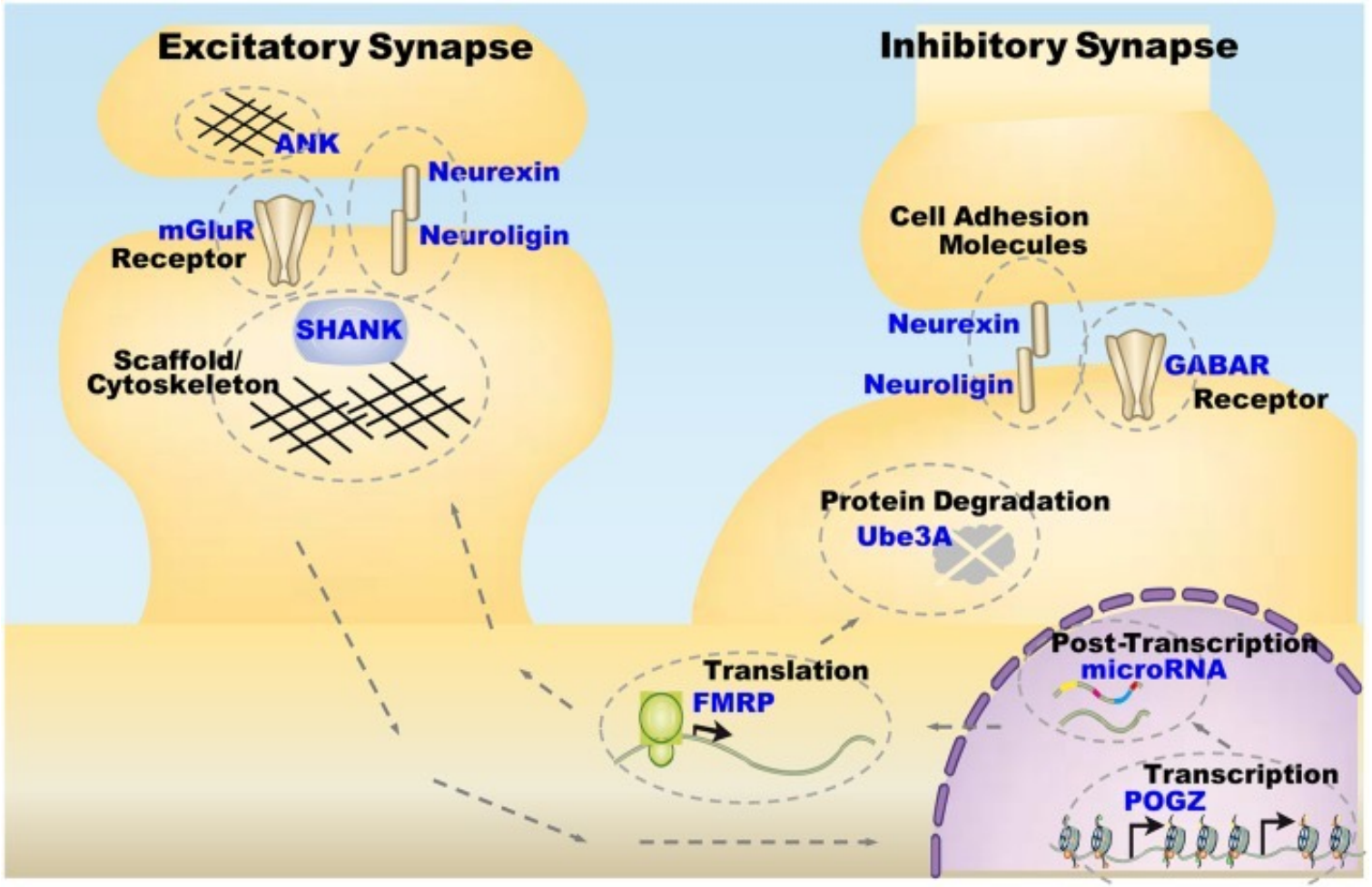
- ASD-associated genes regulate synaptic function and neural circuits through various cellular events.



Yao Tian et al. Neuroscience Bulletin. 2017

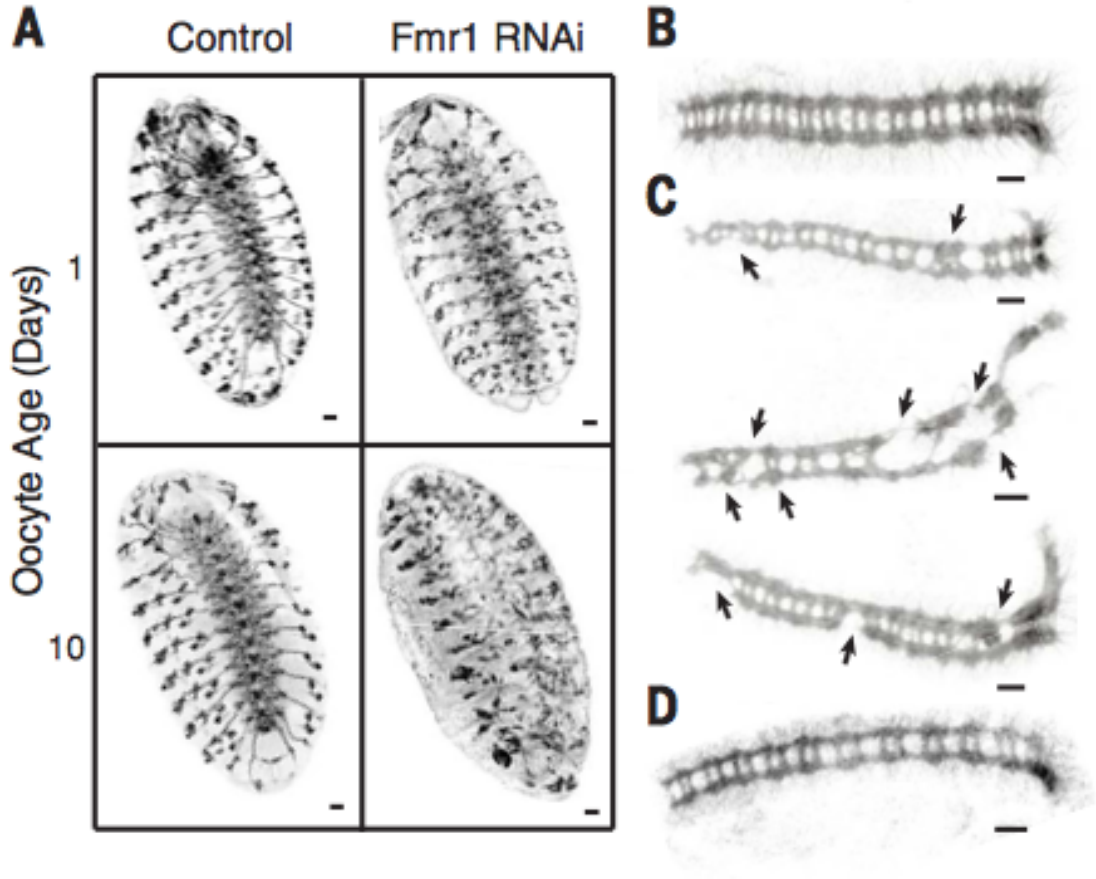
Genes and neurotransmitters in ASD

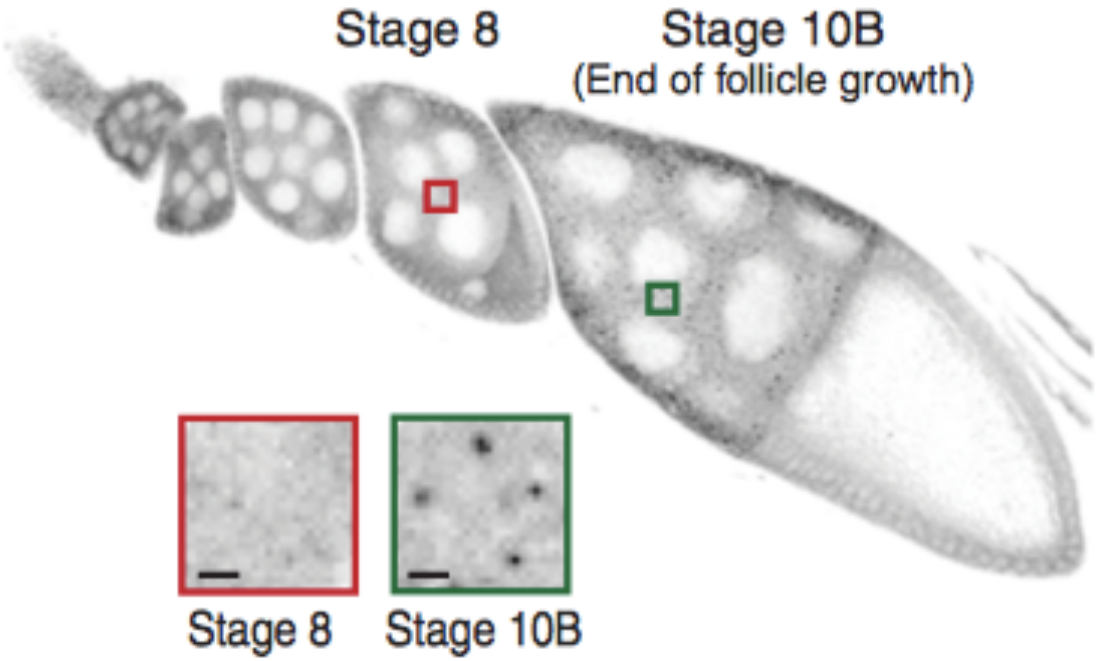
- Functions of ASD-associated genes in different cellular processes.



Yao Tian et al. Neuroscience Bulletin. 2017

FMR1 cause the most common inherited human autism spectrum disorder.





Ethan J. Greenblatt and Allan C. Spradling. Science. 2018

Animal models of ASD and ASD-related syndromes

- **Models based on single ASD genes:**

Neuroligins (NLGNs) , Neurexins (NRXNs), SHANK3, MECP2, FMR1 ……

- **Environmental models:**

Prenatal sodium valproate (VPA) exposure

Maternal autoantibodies

Maternal immune activation

Treatment of ASD

- （1）Therapy based on interpersonal relationships
- （2）Skill-based intervention therapy
- （3）physiologically oriented intervention
- （4）Comprehensive therapy