Genes, Brains and Behaviour: Lecture 1

Karl-Friedrich Fischbach, Neurogenetics, Freiburg

The following slides are for teaching only

It is not allowed to use any of the slides for other purposes than learning

Sources used:

Duda Kvitsiania and Barry J. Dickson (2006). Shared neural circuitry for female and male sexual behaviours in Drosophila. Current Biology 16, R355-R356

Demir E, Dickson BJ. fruitless splicing specifies male courtship behavior in Drosophila. Cell. 2005 Jun 3;121(5): 785-94.

Stockinger P, Kvitsiani D, Rotkopf S, Tirián L, Dickson BJ. Neural circuitry that governs Drosophila male courtship behavior. Cell. 2005 Jun 3;121(5):795-807.

Manoli DS, Foss M, Villella A, Taylor BJ, Hall JC, Baker BS. Male-specific fruitless specifies the neural substrates of Drosophila courtship behaviour. Nature. 2005 Jul 21;436(7049):395-400. Epub 2005 Jun 15.

Kimura K, Ote M, Tazawa T, Yamamoto D. Fruitless specifies sexually dimorphic neural circuitry in the Drosophila brain. Nature. 2005 Nov 10;438(7065):229-33

- What is „inborn behaviour“,
- how is „heritability“ defined?

Are „inborn“ and „heritable“ really synonyms?

The colloquial use of these words often leads to the wrong interpretation of scientific data

„inborn“ is a term from developmental biology

inborn characteristics can hardly be altered by the environment

Examples:

eye colour
number of legs and fingers
Grip reflex of babies

this is opposed to aquired traits

Examples:

morphology of plants depend on light
your mother tongue

„Heritability“ (H „Erblichkeit“ in German) is a term of population genetics

= the fraction of the variability of a trait due to genetic variability

$$H = V_{genome} / V_{total}$$

$$V_{total} = V_{genome} + V_{env} + V_{interactive}$$

An inborn trait can have a very low heritability, e. g. the number of your fingers. Genetic variants are extremely rare.

Interactions between Genome - Environment

Example: Genetically programmed „Gestalt“ can affect rearing conditions of babies and development of personality including intelligence.

scheme of childlike characteristics (Kindchenschema) is inborn

Consequences from the scientific definition of „heritability“

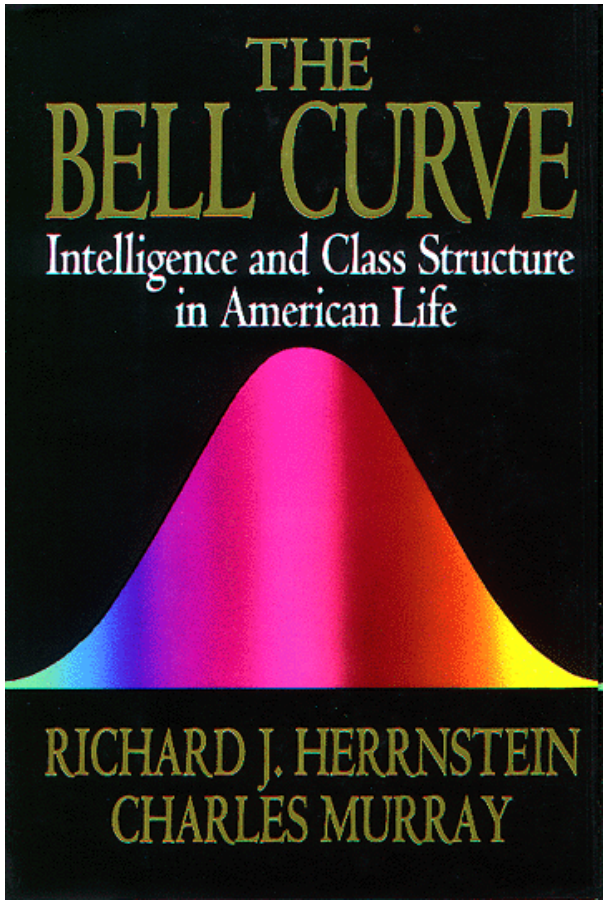
- Heritability (Erblichkeit) is not a natural constant, but dependent on environmental conditions and upon the population considered.
- Heritability has nothing to do with genetic determinism!
- Optimal Environment for all (it does not contribute to the trait variability) would result in 100% heritability.
- On the other hand, heritability would be 0% in a genetic clone.
- An important example: The heritabilty of the IQ <100% means, that their are environmental deficits for some of us.

An „intellectual“ desaster

twin studies:

60% „heritability“ of IQ

“intervention efforts are largely a waste of time and money”



Themes of the neurogenetics lecture in summer term 2010

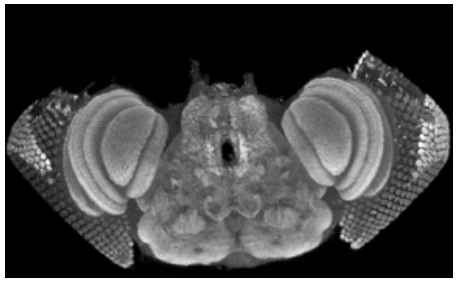
- Genetic programming of inborn behavior
  (5 lectures)

- Developmental neurogenetics
  (6 lectures)

- Genetic basis of human neurological diseases
- (2 lectures)

Different model organisms will be used

Genetic programming of inborn behavior



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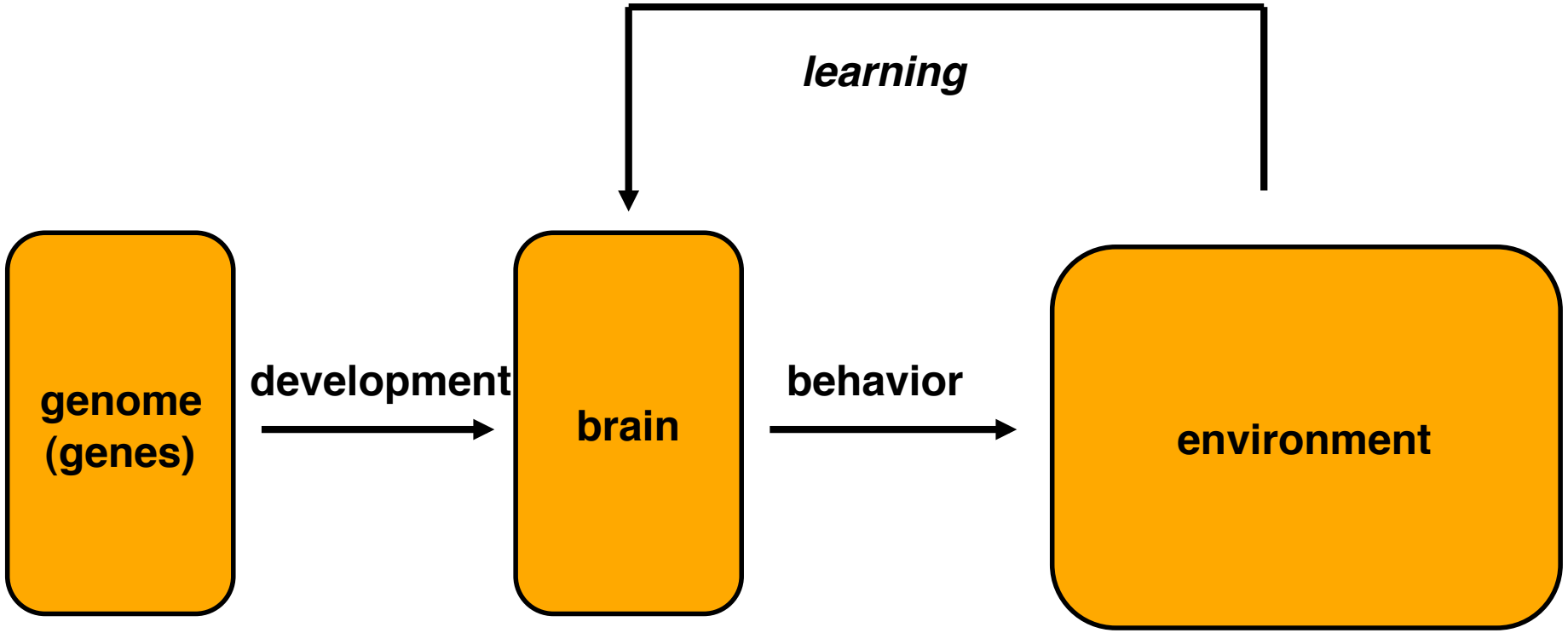
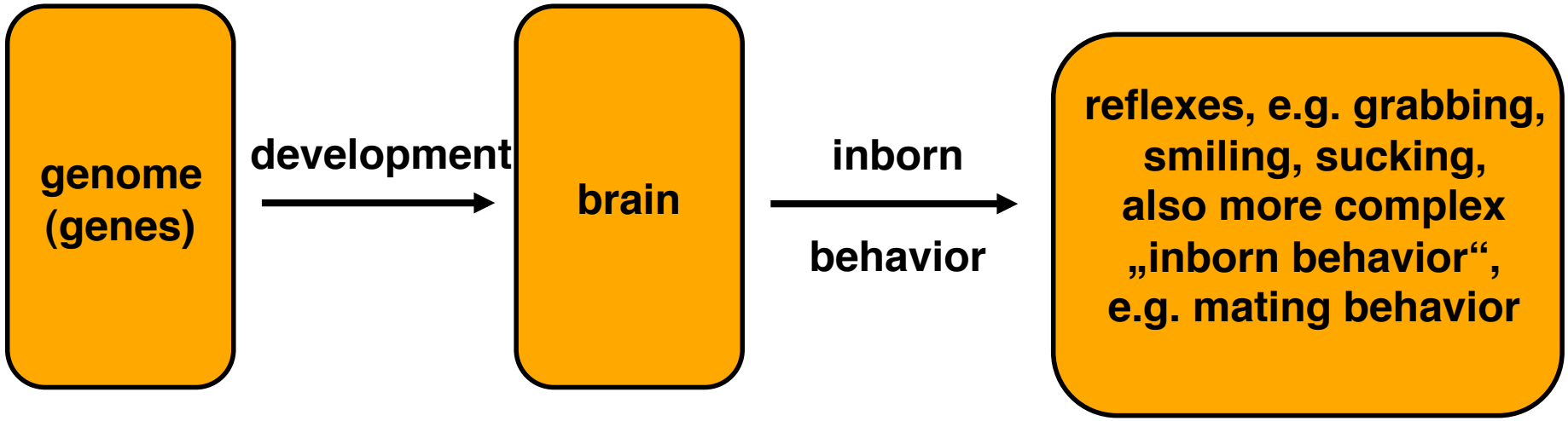
Main question of today‘s lecture

How do genes influence behavior?


learning
genome
(genes)
development
brain
behavior
environment

Simplification:
Focus on inborn behavioral patterns



The simplified question of our lecture:

„By what mechanisms do the behavioral differences between the sexes emerge during development and what is the role of genes in this process?“

Additional simplification:

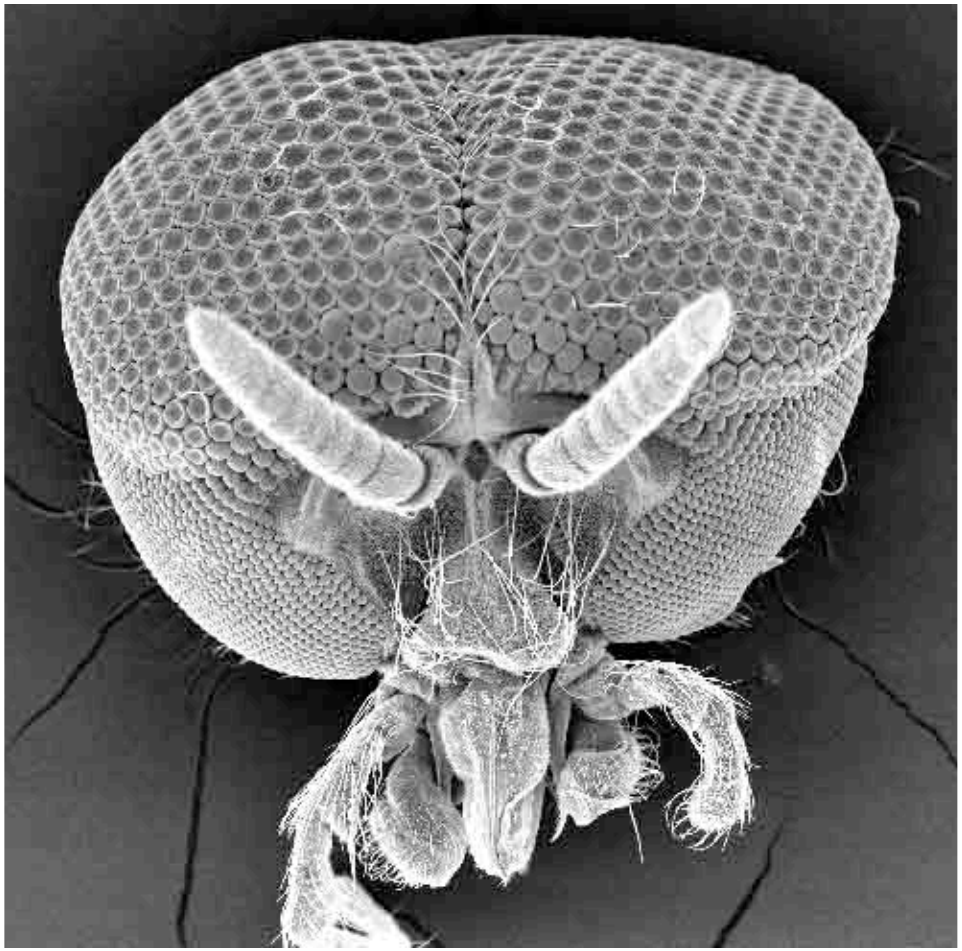
invertebrates as model systems especially Drosophila

Using sexual behavior of Drosophila as a model, the following questions can be asked:

- What are the epigenetic rules which direct the development of inborn behavior?
- For organs like eyes, brains, hearts etc. so called „master genes“ are known to exist. Do such master genes also exist for inborn behavior?
- Is development of sexual behavior coupled to sexual differentiation of the body?

sexual dimorphism of Simuliid flies (Kriebelmücken, Black Flies)

female



male

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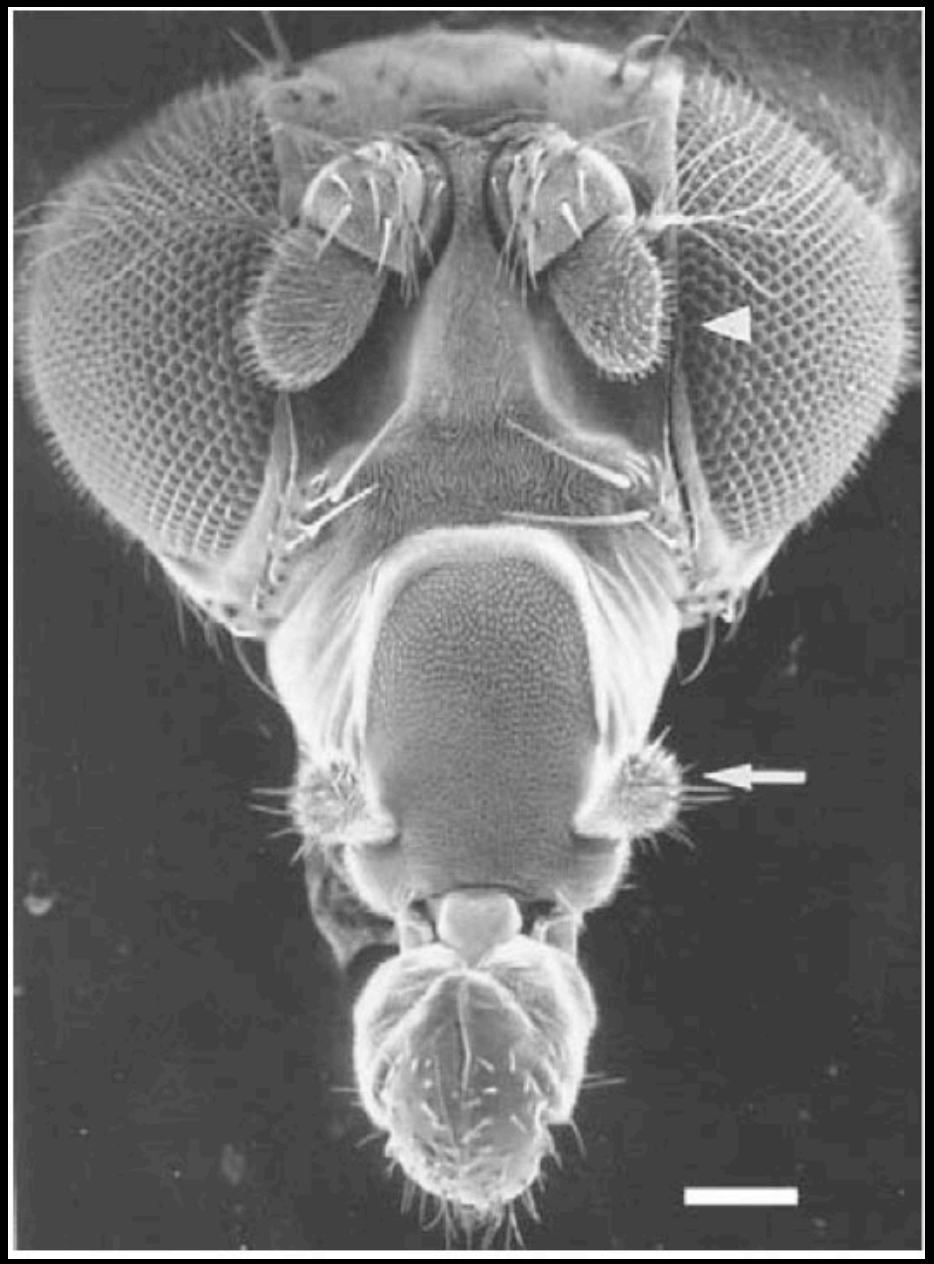
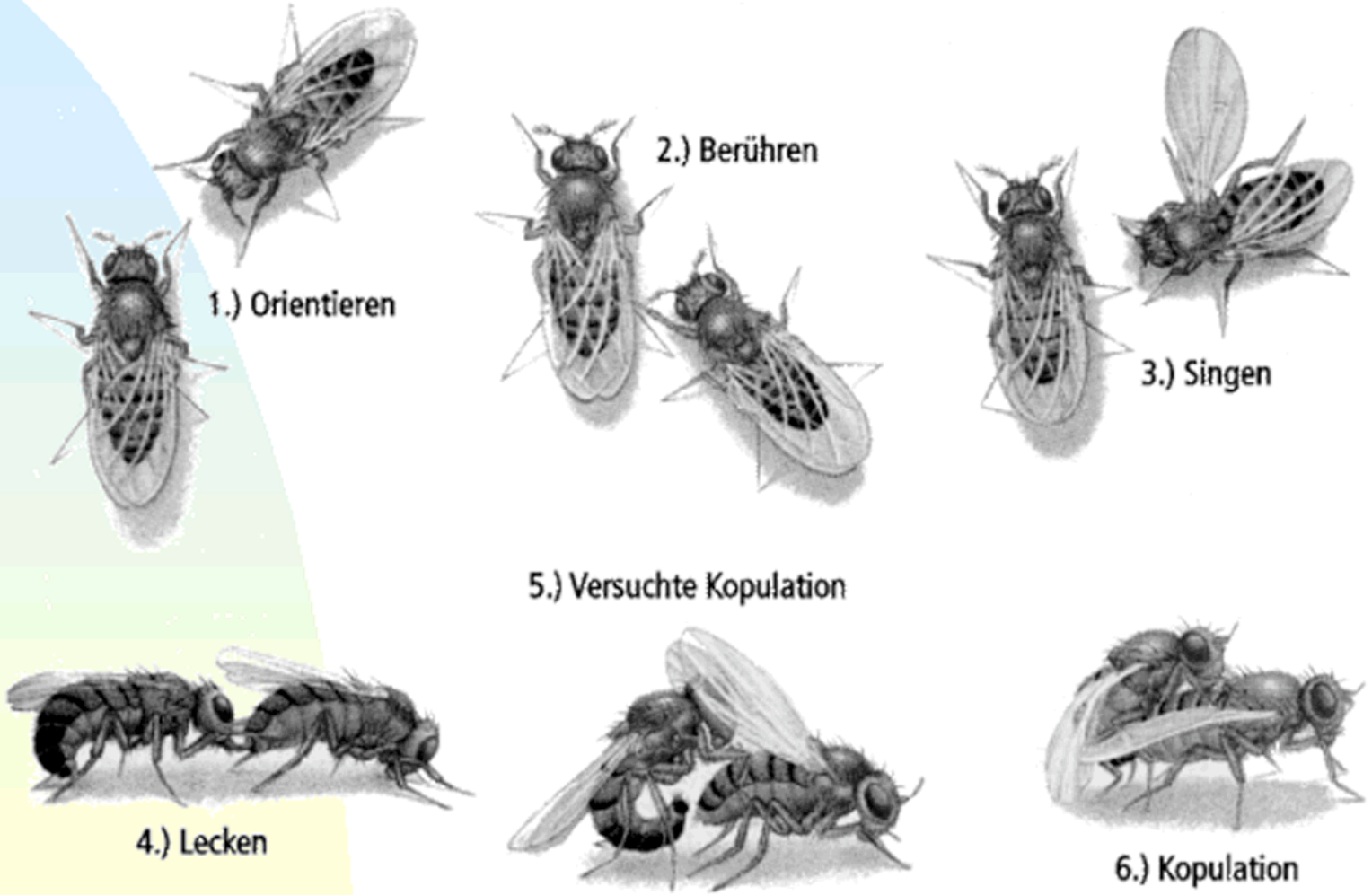
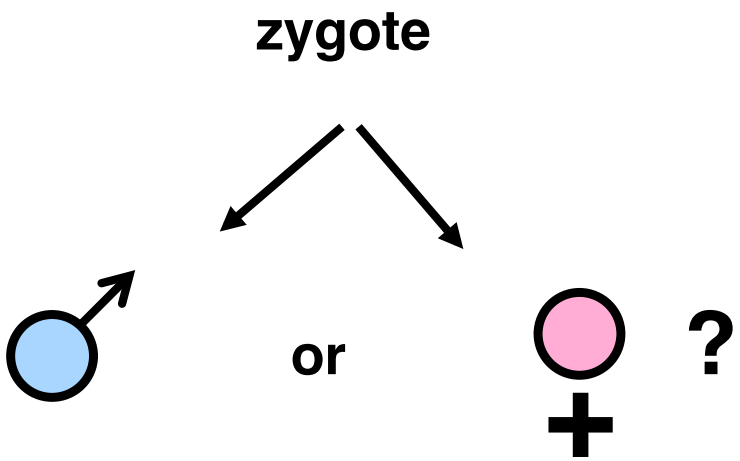
The head of Drosophila (male = female)



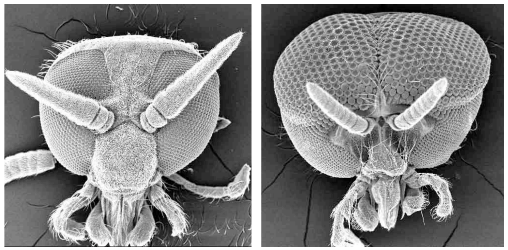
Inborn mating behavior of Drosophila (fixed action pattern)





1. step: **sexual determination**

2. step: **sexual differentiation**



a) somatic sex (sexual phenotype)

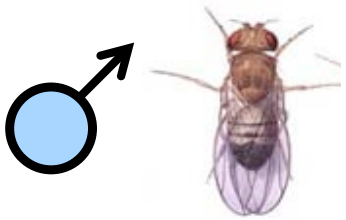
b) behavioral sex (sexual behavior)

successive environmental determination of sex in clownfish

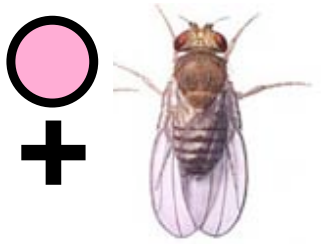
The largest clownfish of a colony is the female. The second largest fish is the male. All other clown fish of the colony are neutral. When the female dies, the male changes its sex and becomes the female. The next largest fish becomes the male.

genetic sex determination in Drosophila melanogaster

männlicher Karyotyp



weiblicher Karyotyp



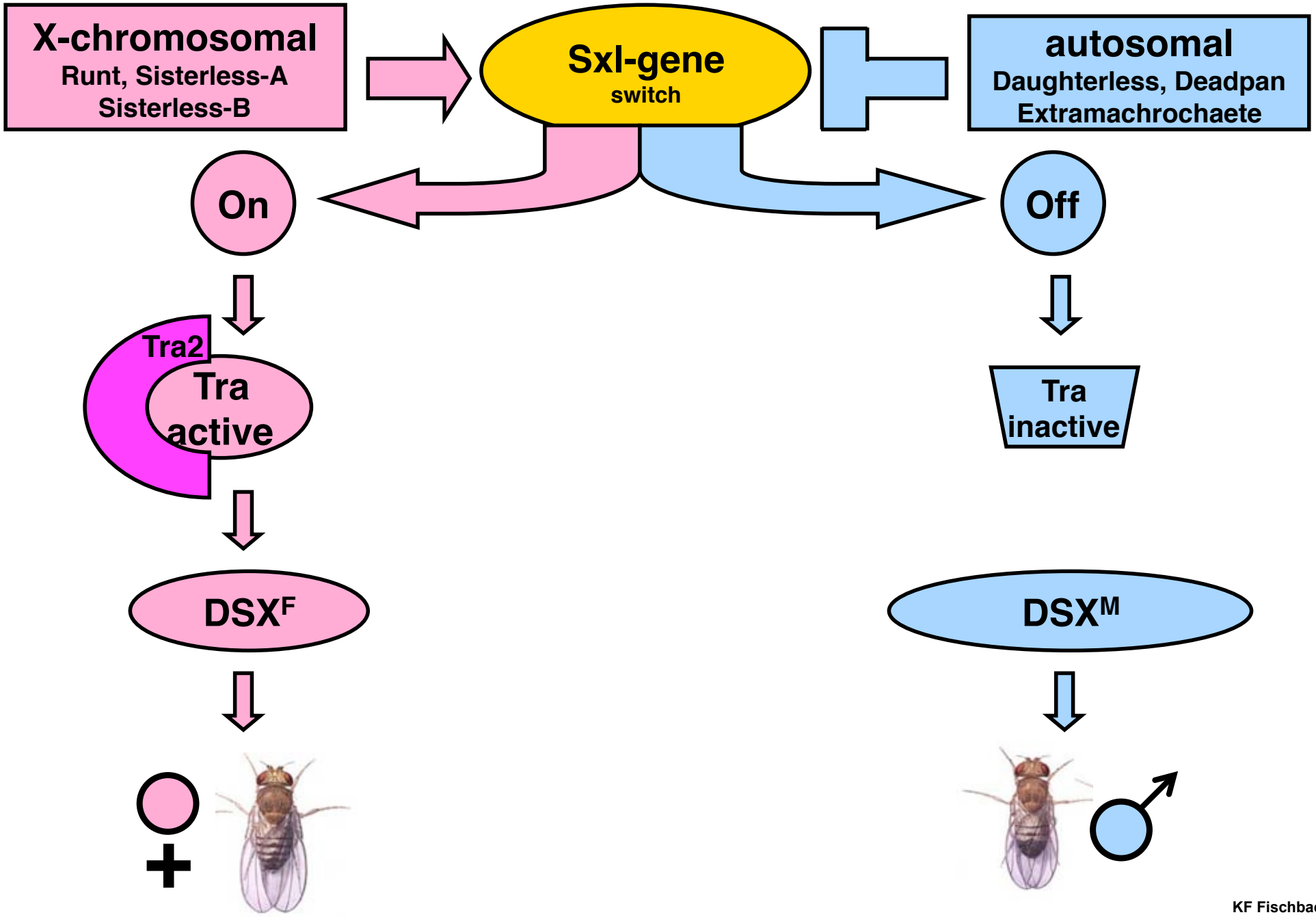
Sex determination in Drosophila

The numeric relationship of the number of X chromosomes to the autosomal chromosomes matters

- **XX → female**
- **XY → male**
- **XO → male** ←female (turner syndrom)
- **XXY → female** ←male (klinefelder s.)

In homo sapiens this is different: In humans presence or absence of the Y-chromosome matters.

Genetic sex determination in Drosophila



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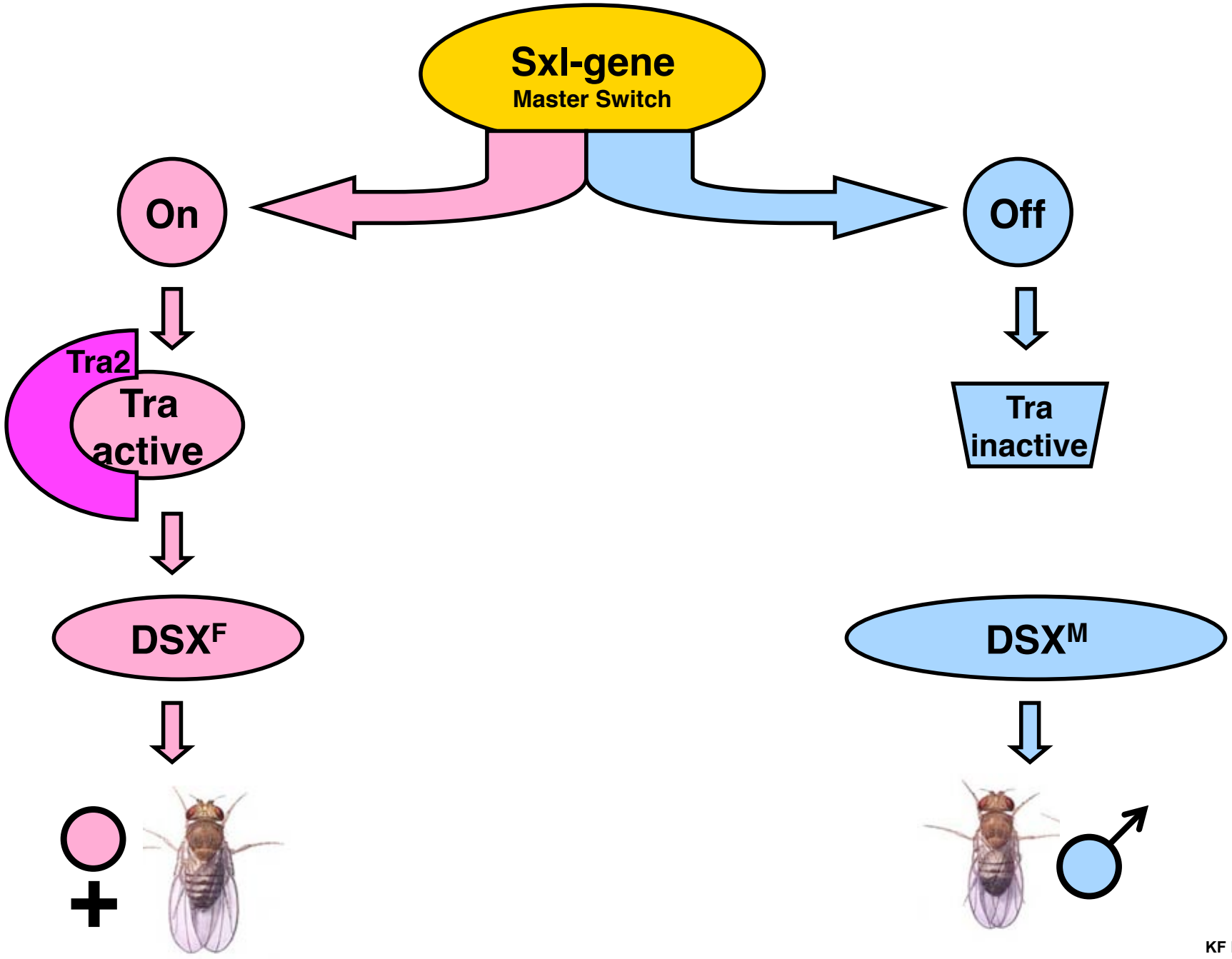
Somatic sex and sexual behavior



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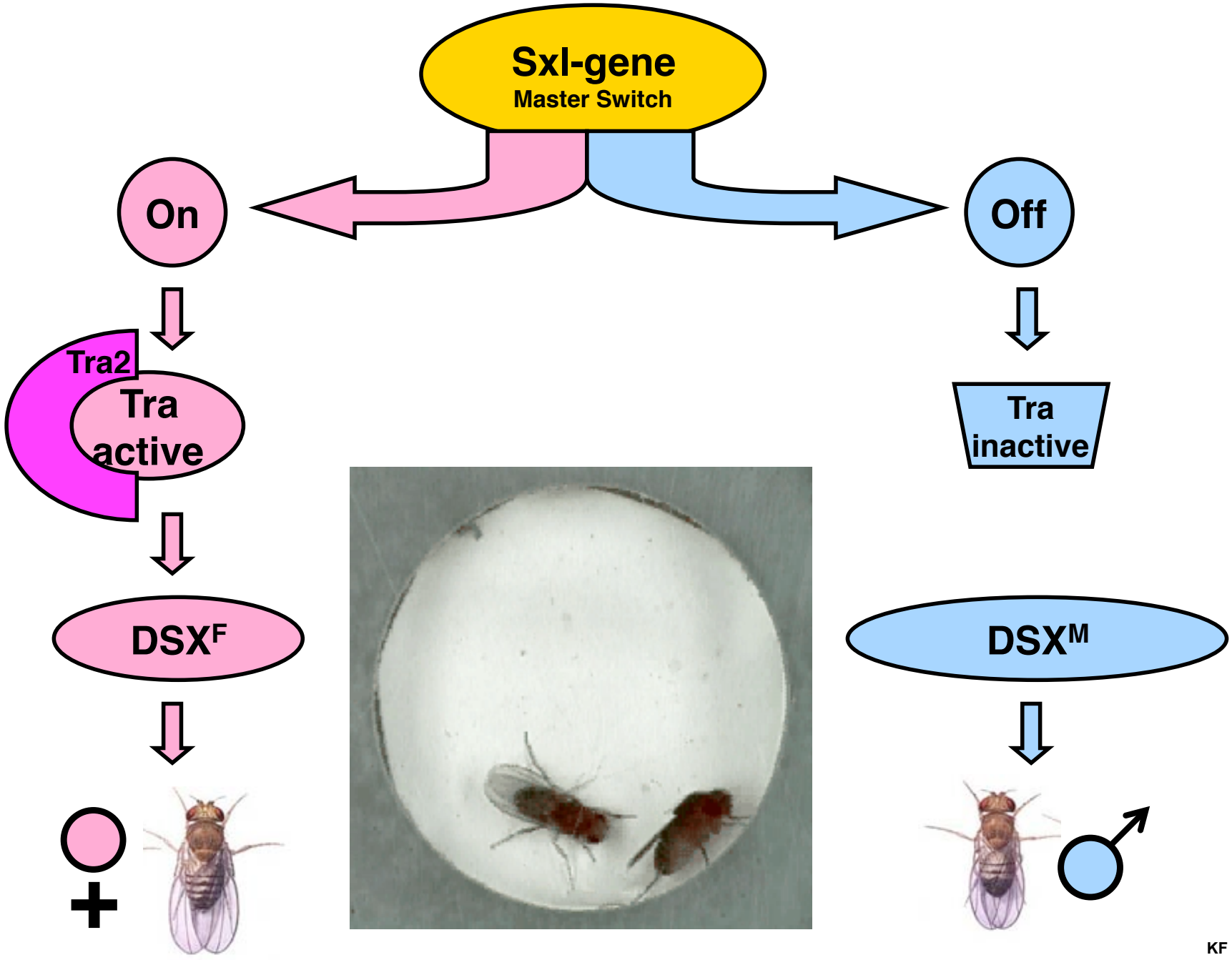
Somatic sex and sexual behavior



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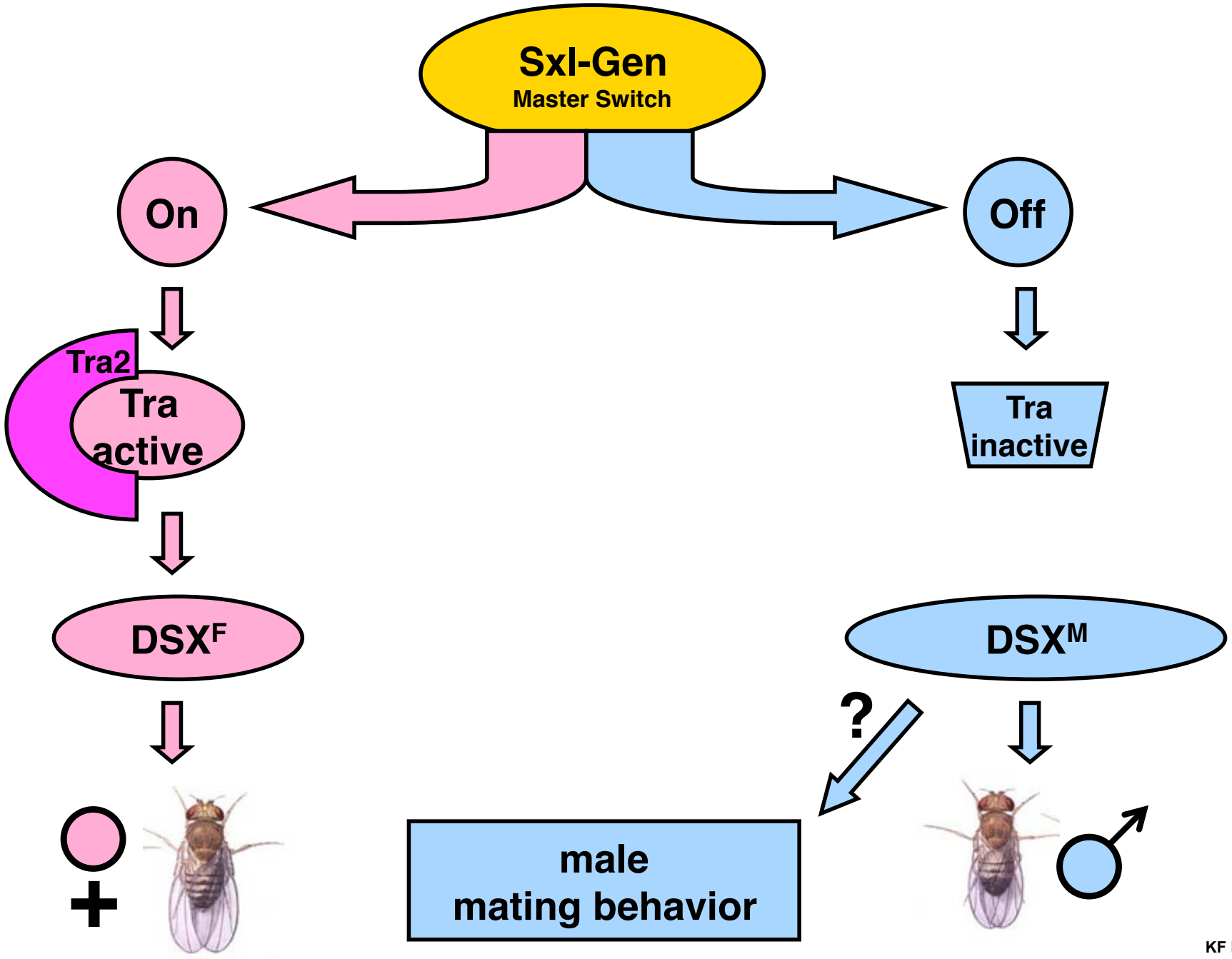
Somatic sex and sexual behavior



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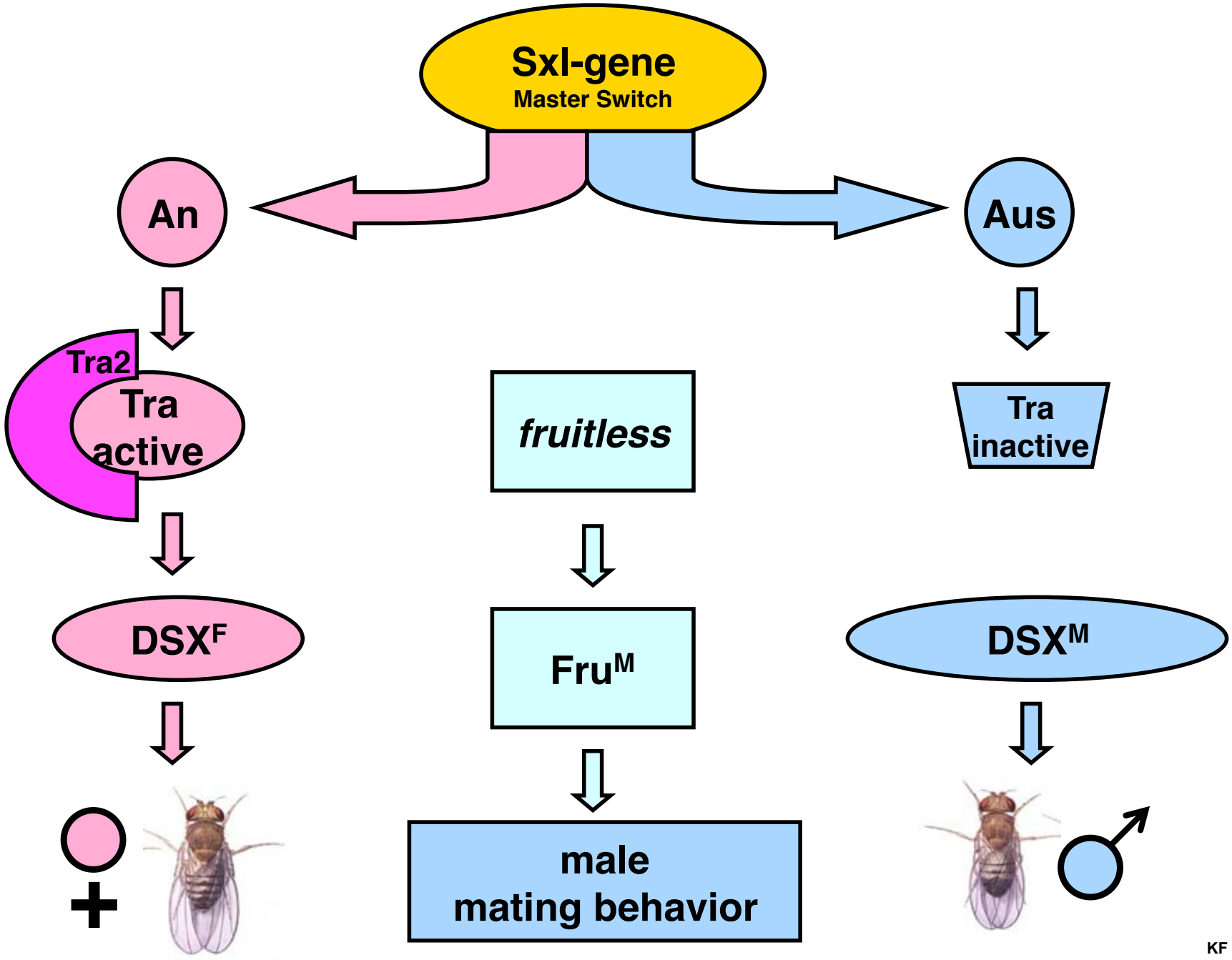
Somatic sex and sexual behavior



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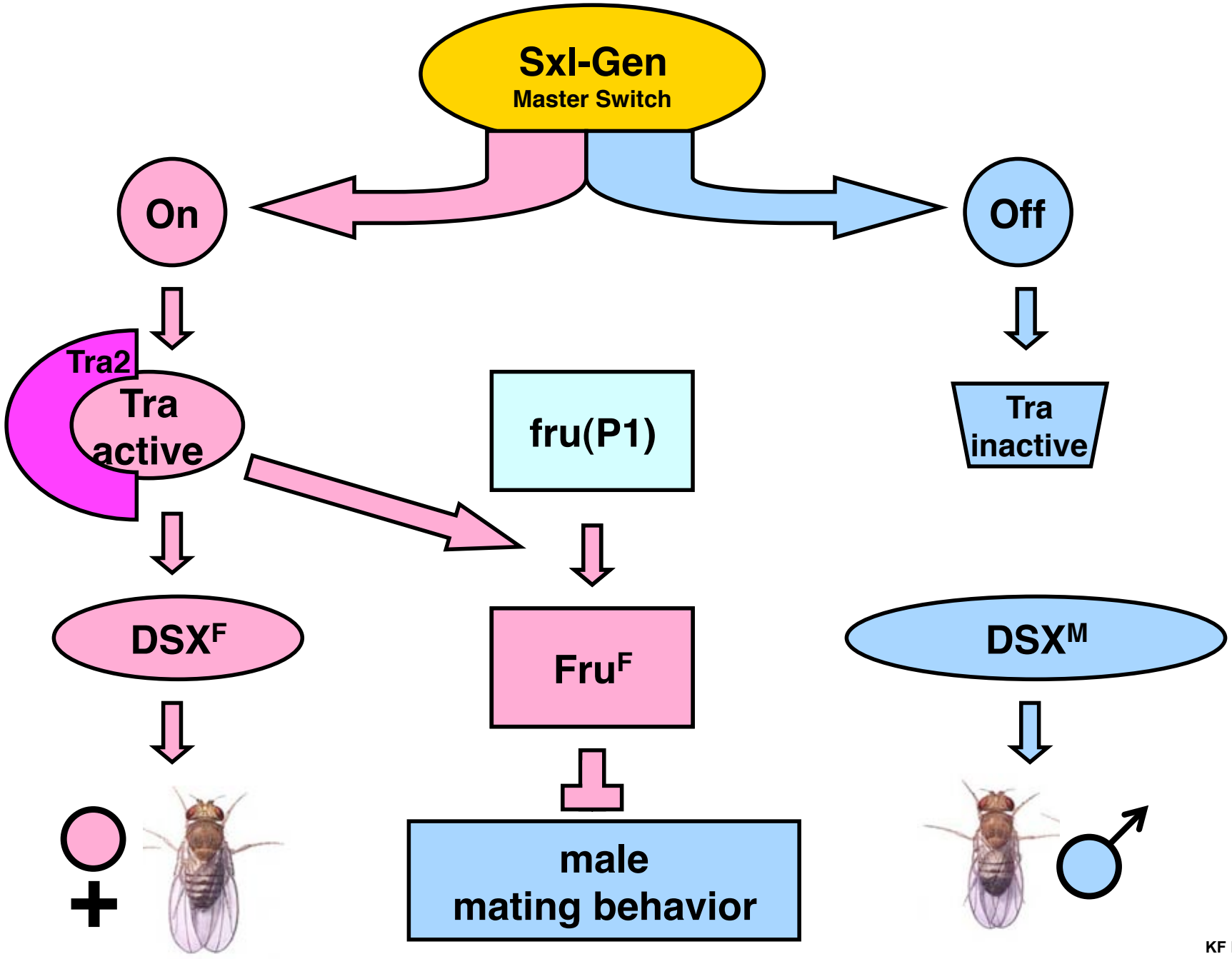
Somatic sex and sexual behavior



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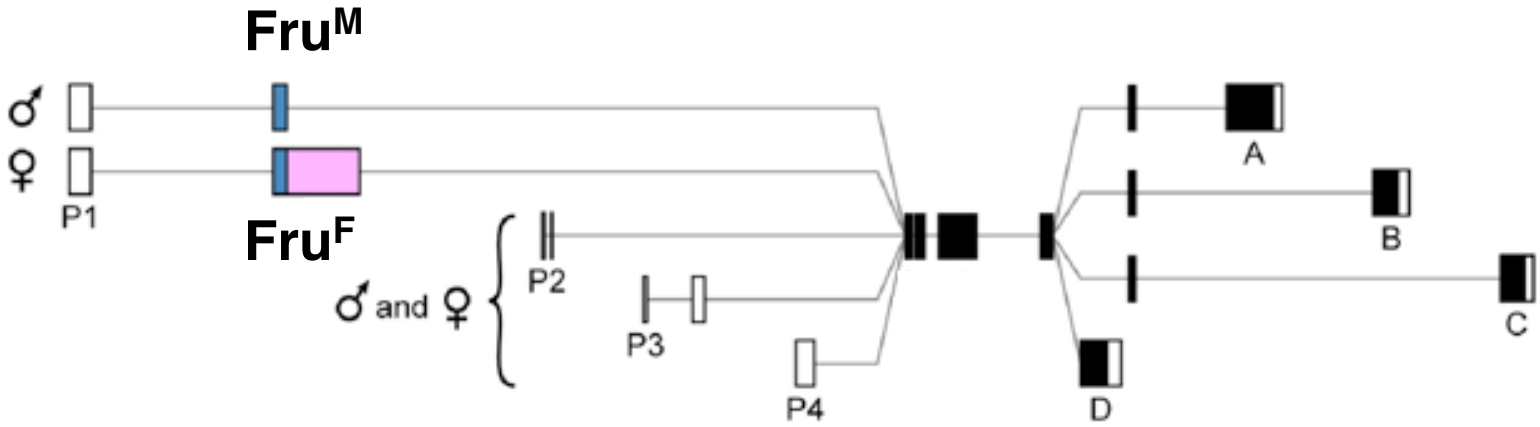
Is thus ***fruitless*** the master gene of sexual behavior?

The switch is even more subtle!

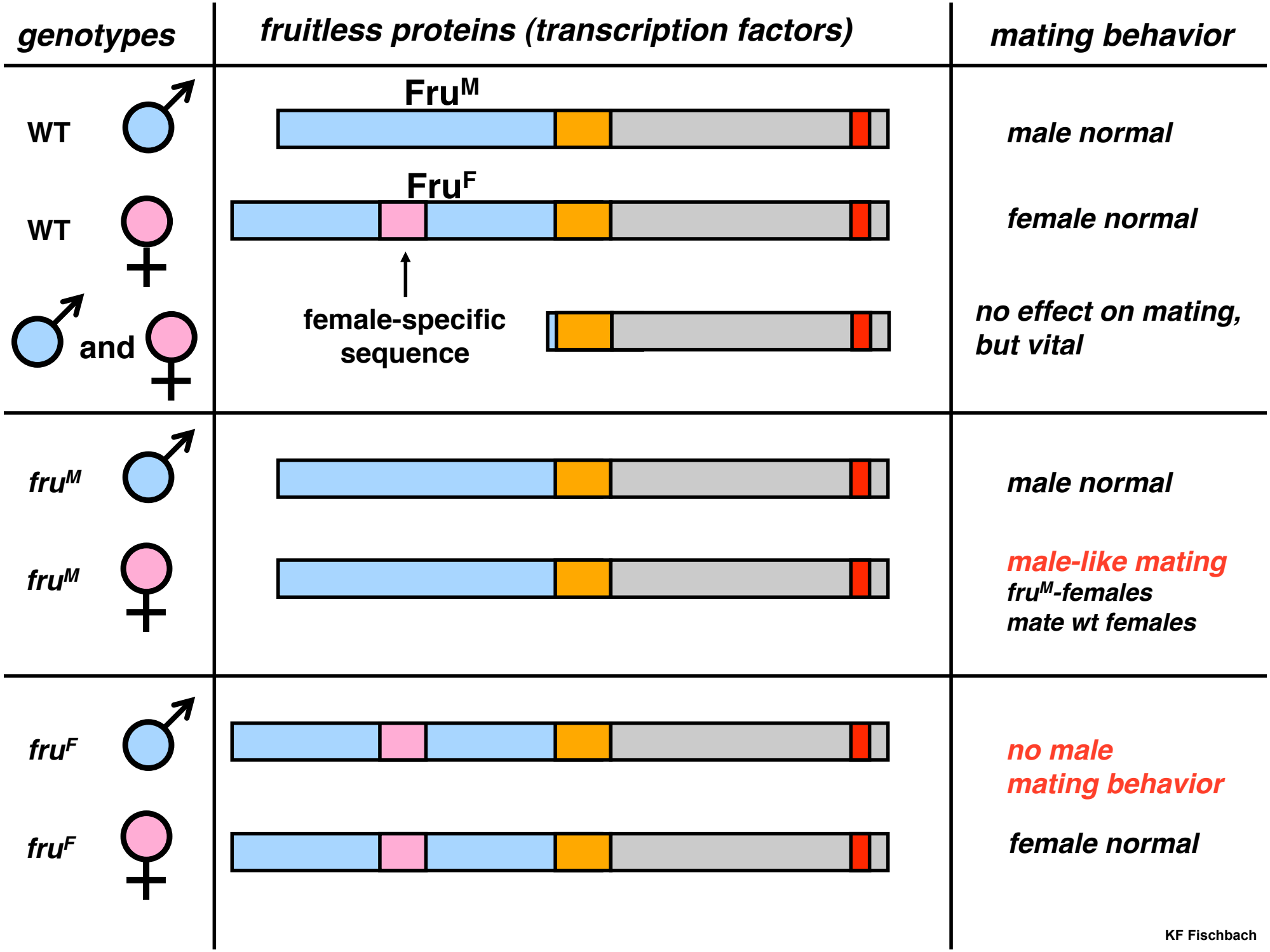
genomic organisation of the *fruitless*-gene

P1-P4 different promoters

mRNA-splicing variants



female P1-mRNAs express an additional exon, this makes the difference


genotypes
fruitless proteins (transcription factors)
mating behavior
WT
♂
Fru^M
male normal
WT
♀
Fru^F
female normal
♂ and ♀
female-specific sequence
no effect on mating, but vital
fru^M
♂
male normal
fru^M
♀
male-like mating
fru^M-females mate wt females
fru^F
♂
no male mating behavior
fru^F
♀
female normal
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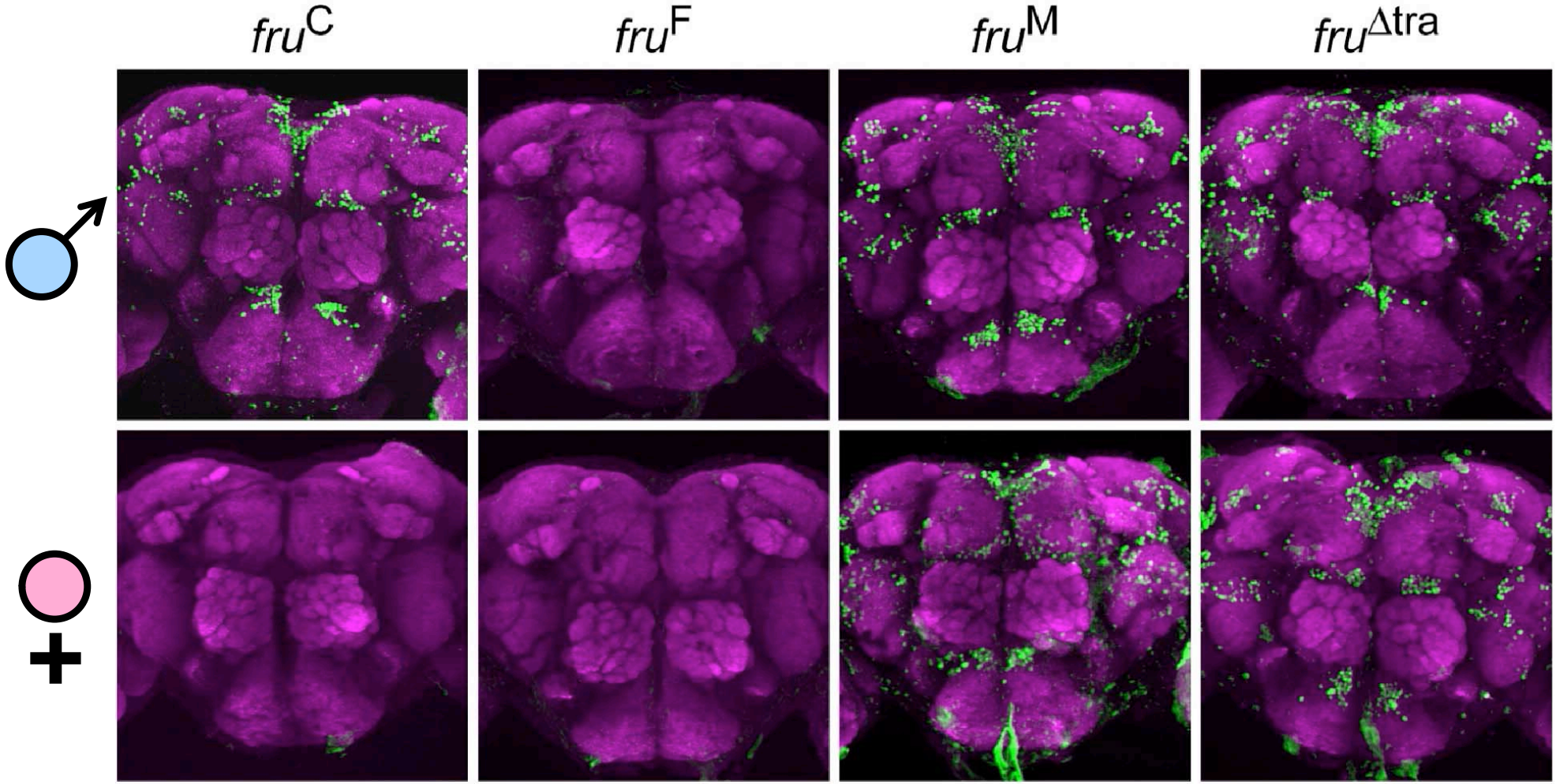
anti-Fru^{M} (green) positive neurons in brains of *fruitless* transformants



normal splicing	Fru^{M} can not be produced	only Fru^{M} can be produced	only Fru^{M} can be produced

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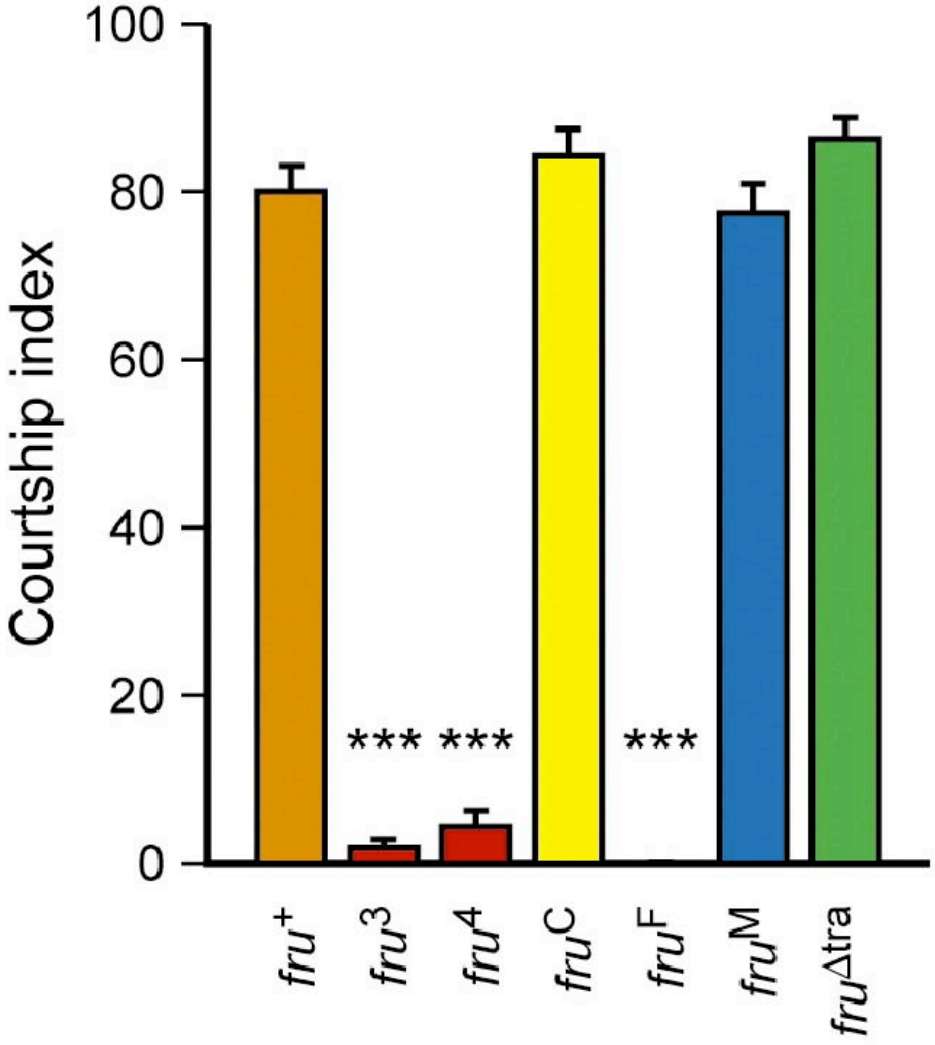
Fru^M is essential for male courtship: males without Fru^M do not mate



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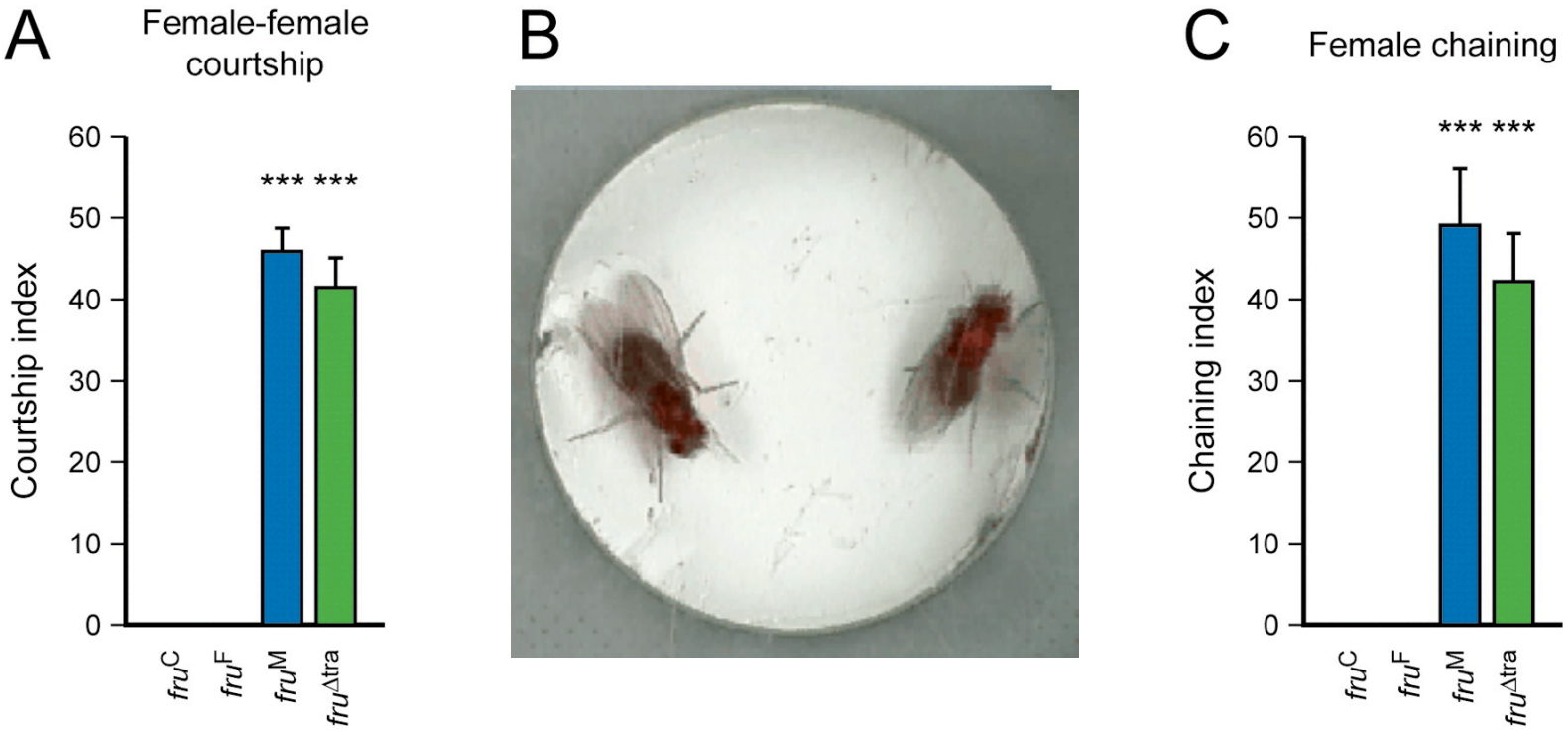
Fru^M is sufficient for male-like mating behavior



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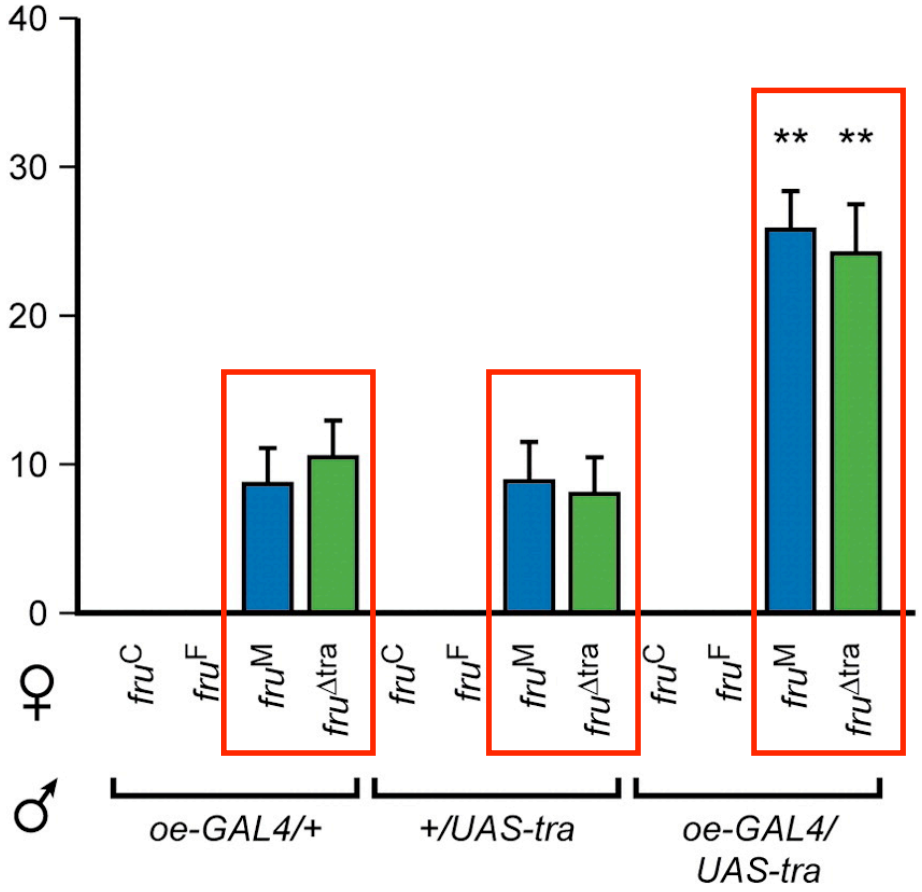
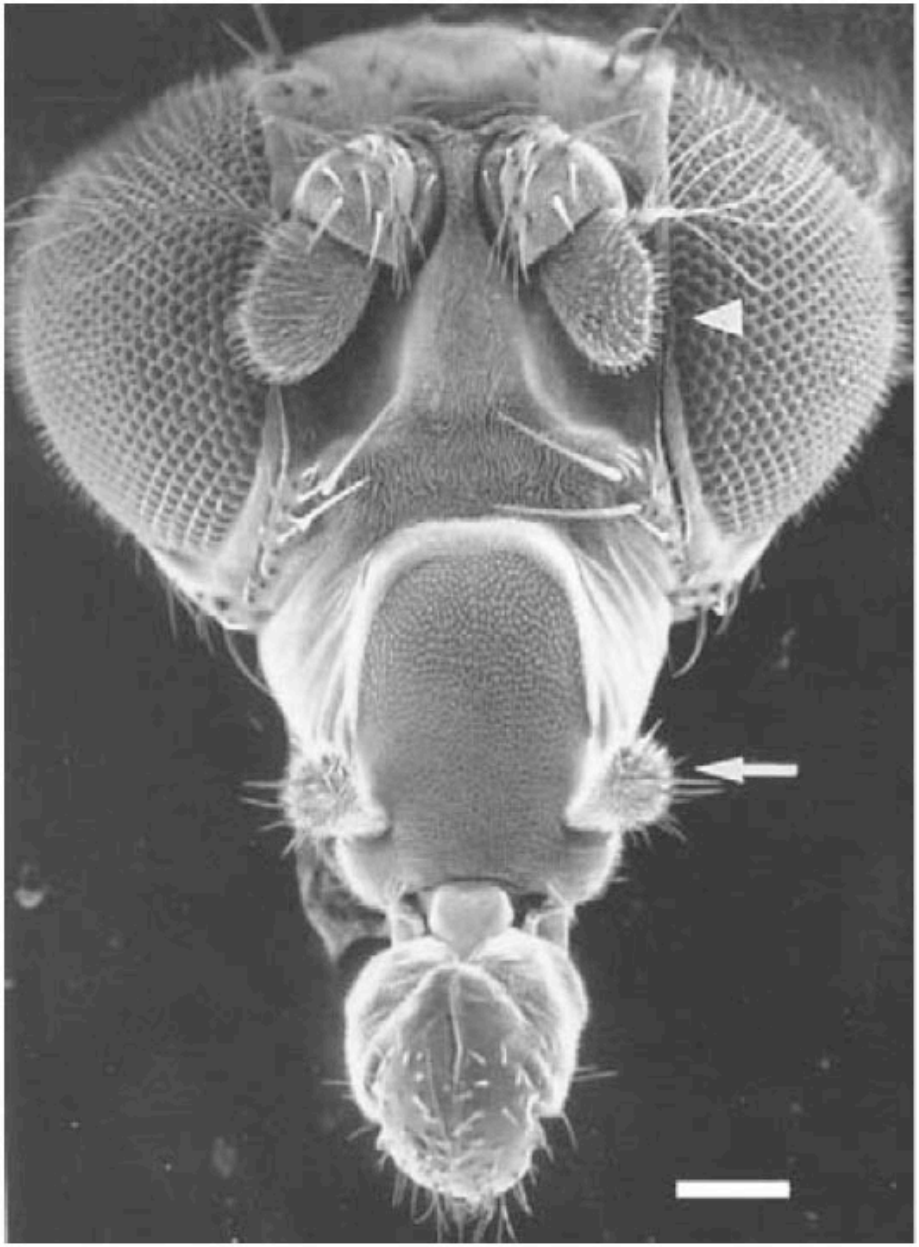
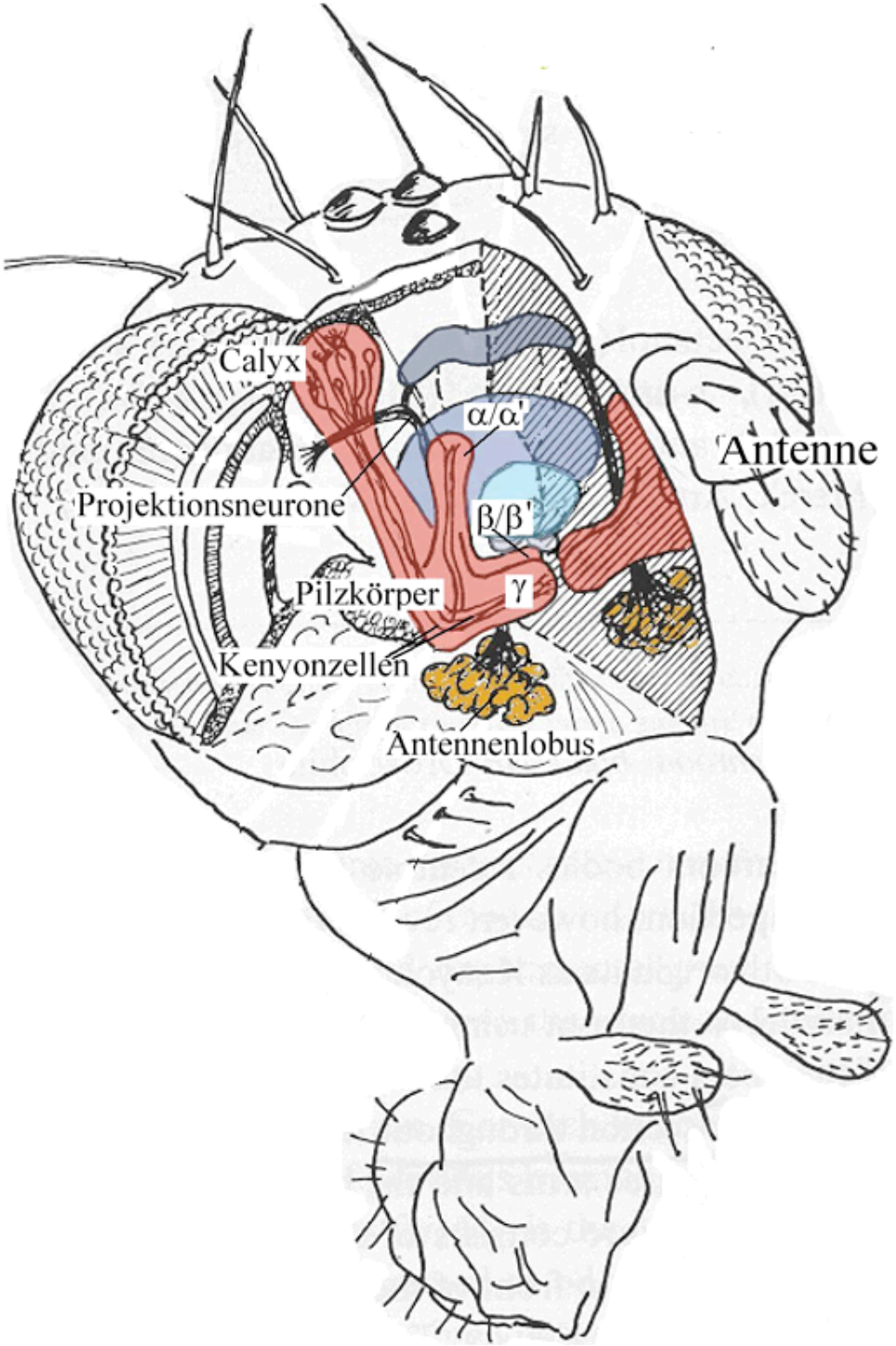
Reversal of roles in sexual behavior: females with Fru^M courtship males, which produce female pheromones



Any significance for humans?





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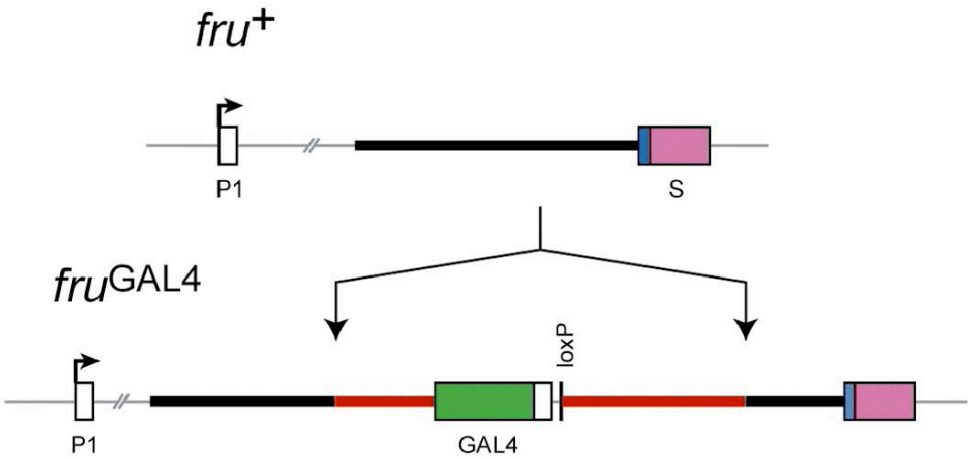
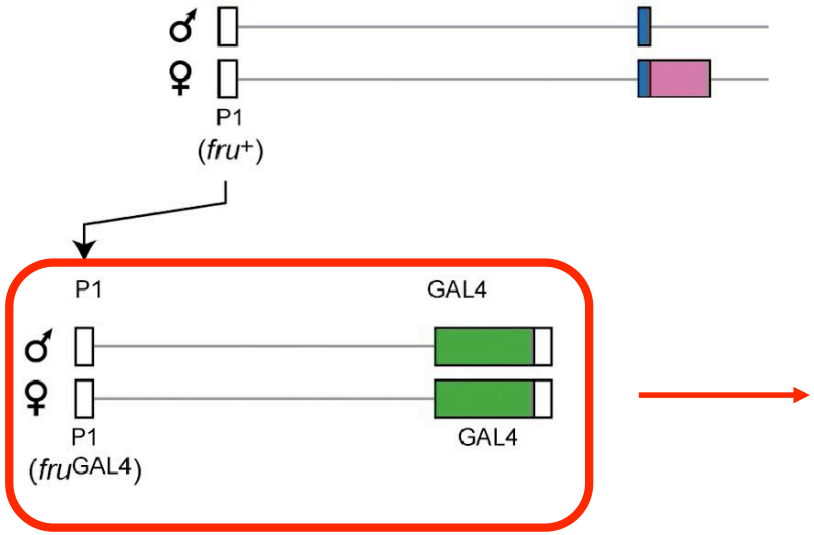
production of a P1-Gal4 reporter strain by homologous recombination



result at mRNA-level



This tool allows visualization or manipulation of neurons with active P1-promotors in males and females.

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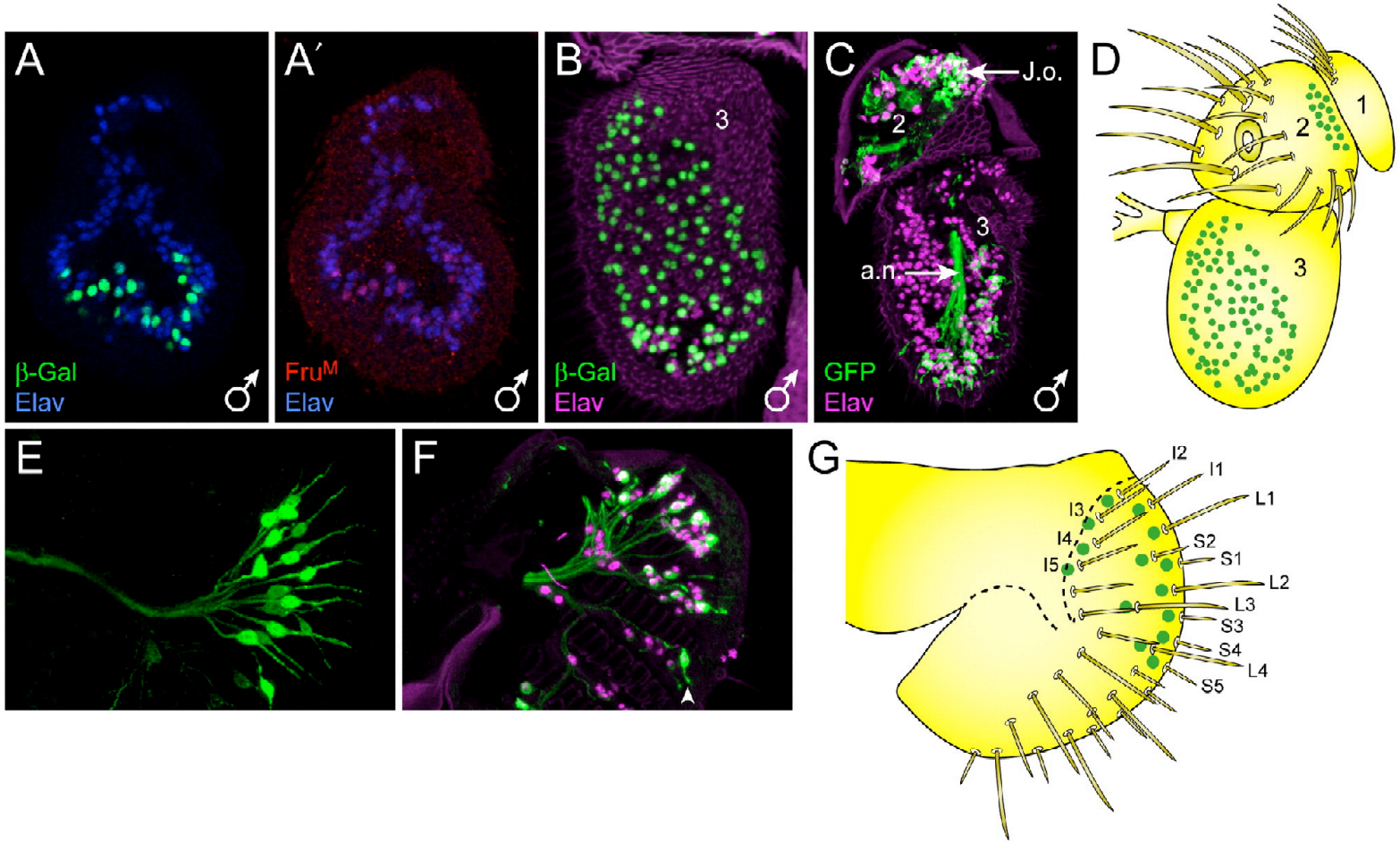
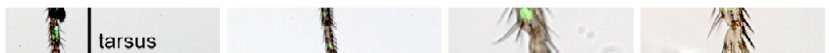
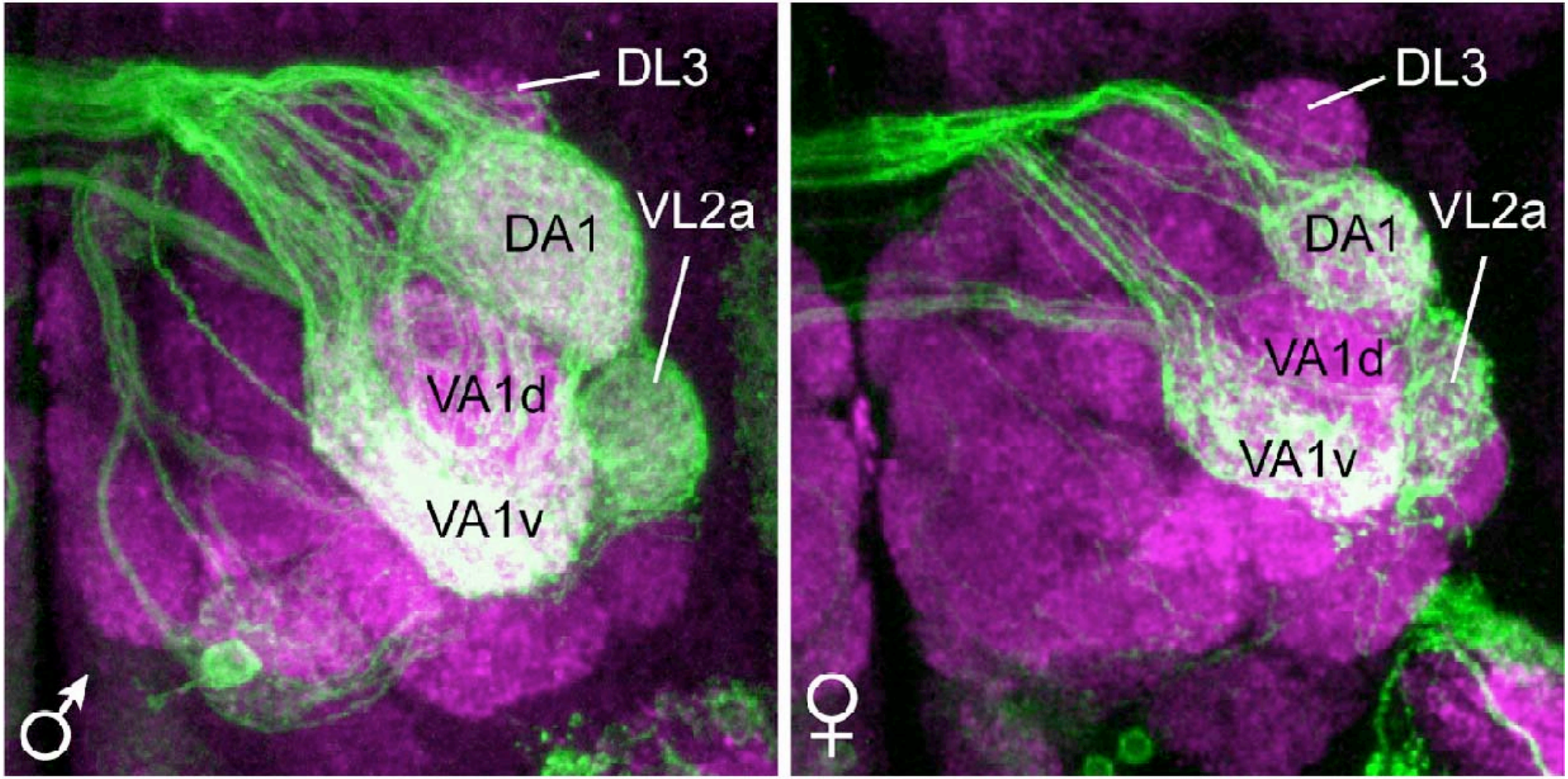
P1-aktive neurons in the pns





Axons of P1-Gal4 positive pheromone receptor neurons project in sexually dimorphic antennal glomeruli



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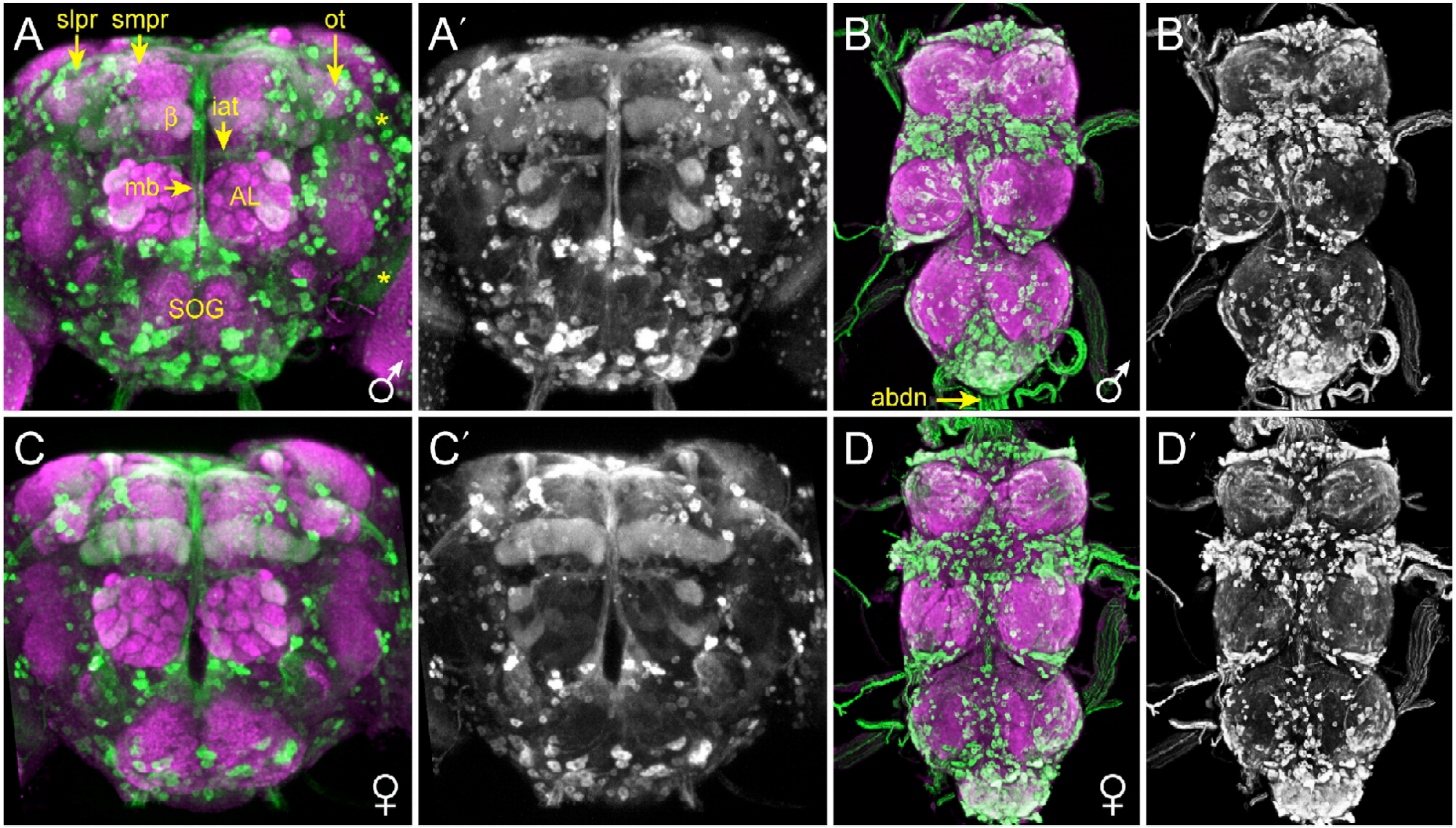
P1-Gal4 labelled fibre tracts:
In the brain there is no obvious sexually dimorphic structure



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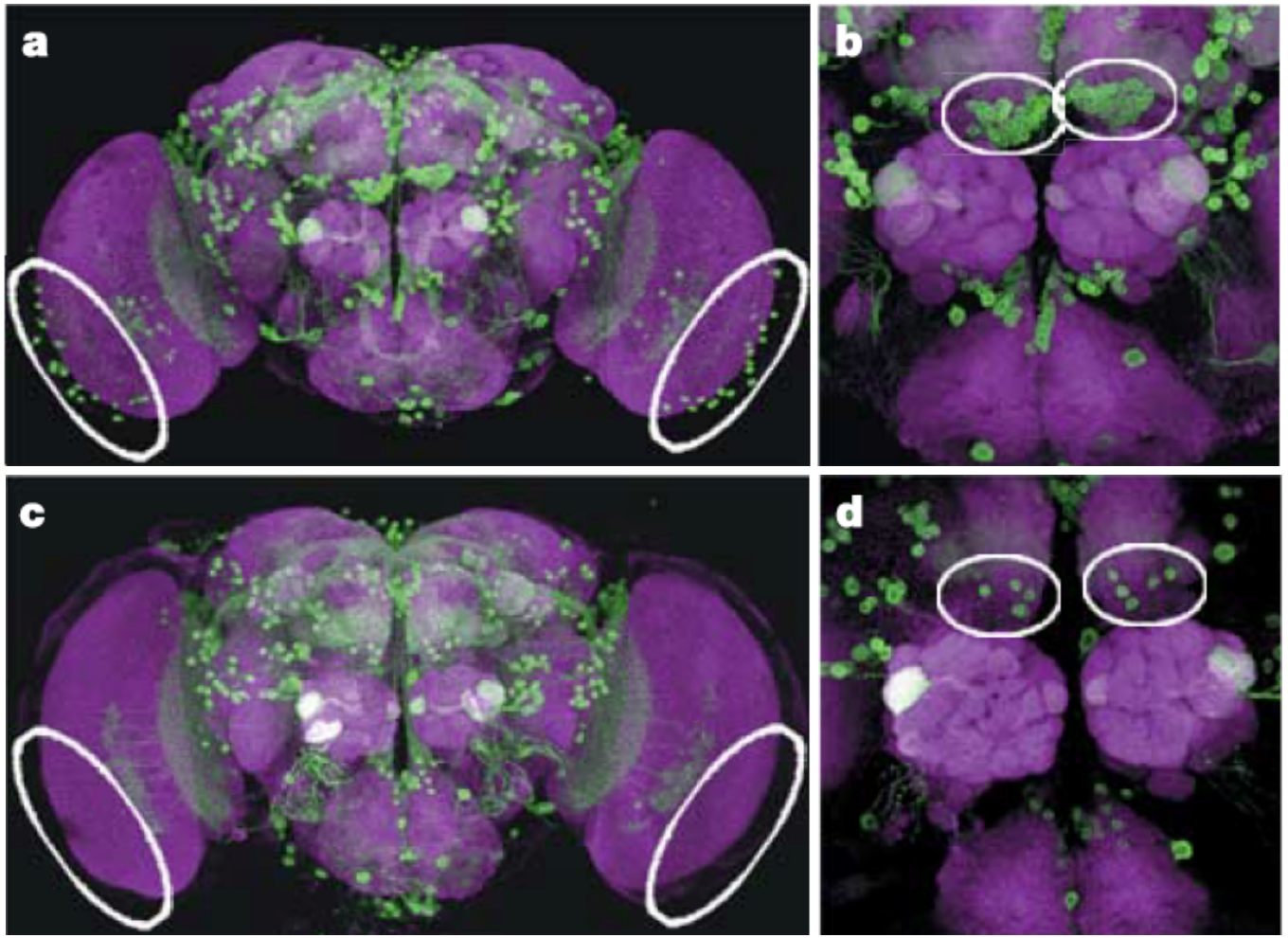
Sexual dimorphism in the Drosophila brain is hidden, but visible in enhancer trap line NP21

male

female



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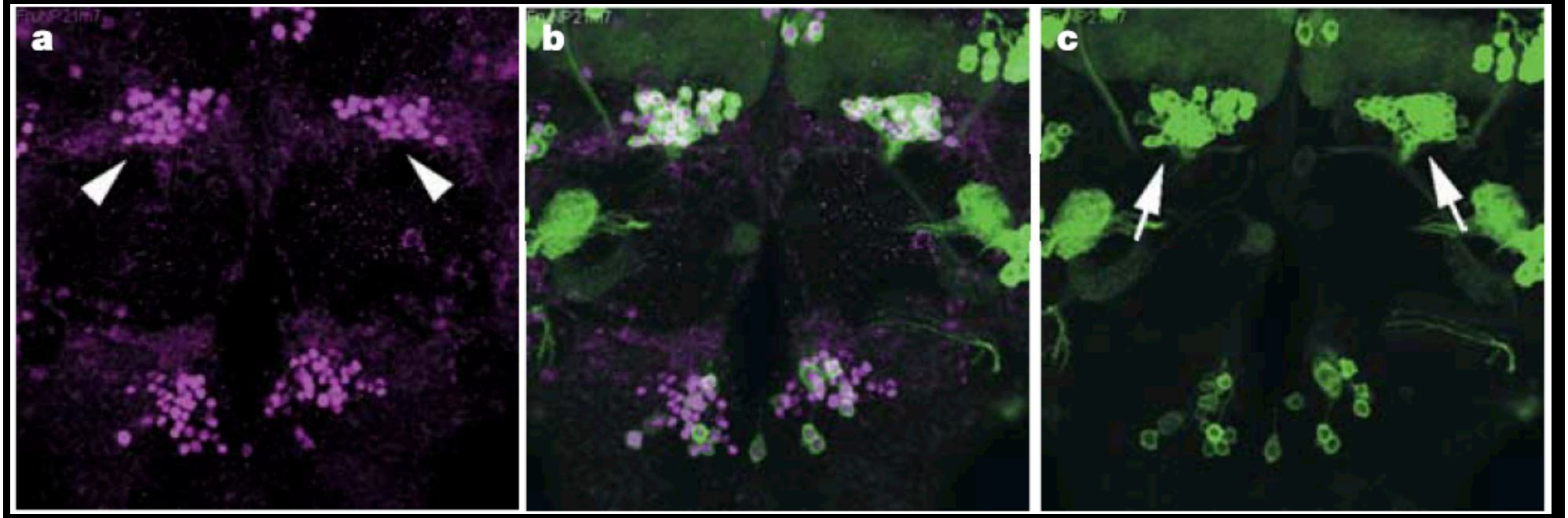
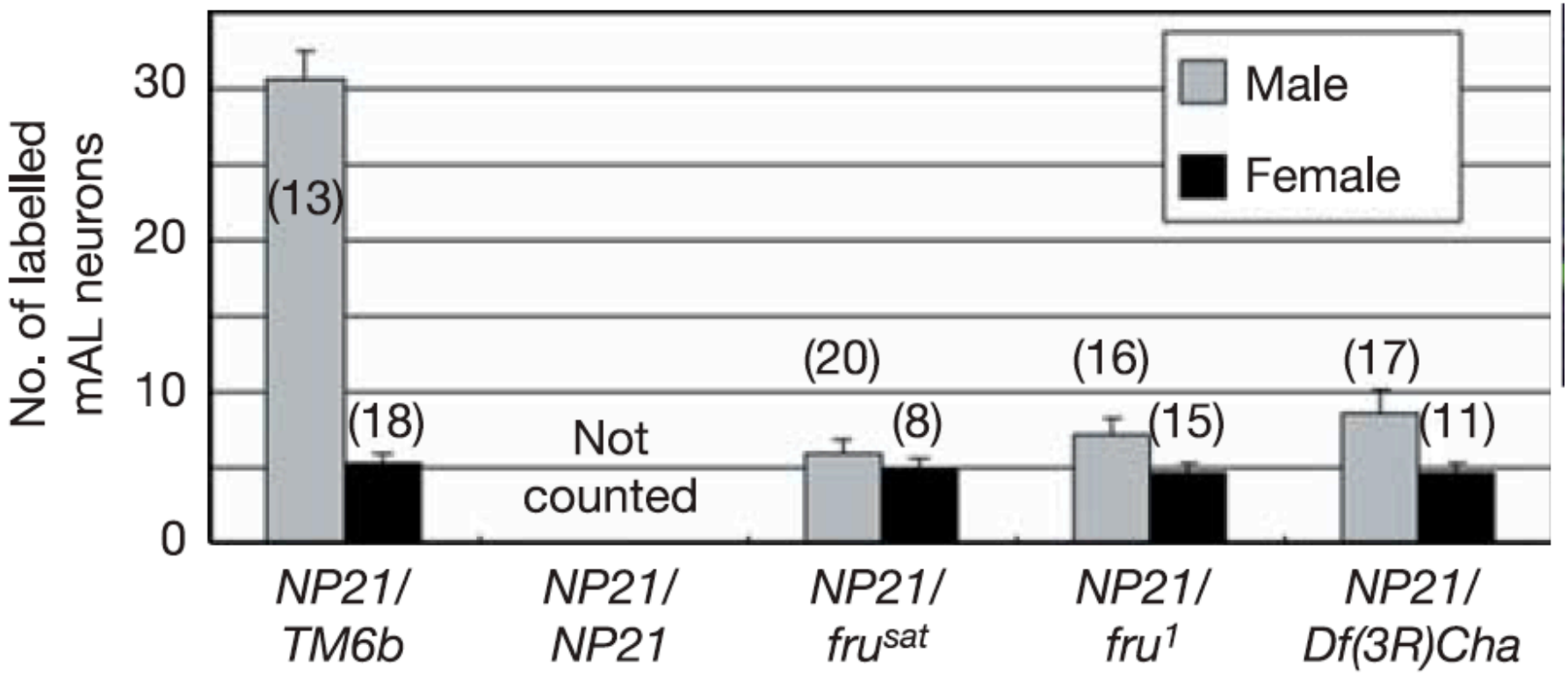
mAL neurons in NP21 males are Fru^{M} positive



Fruitless expression is essential for male brain phenotype to develop



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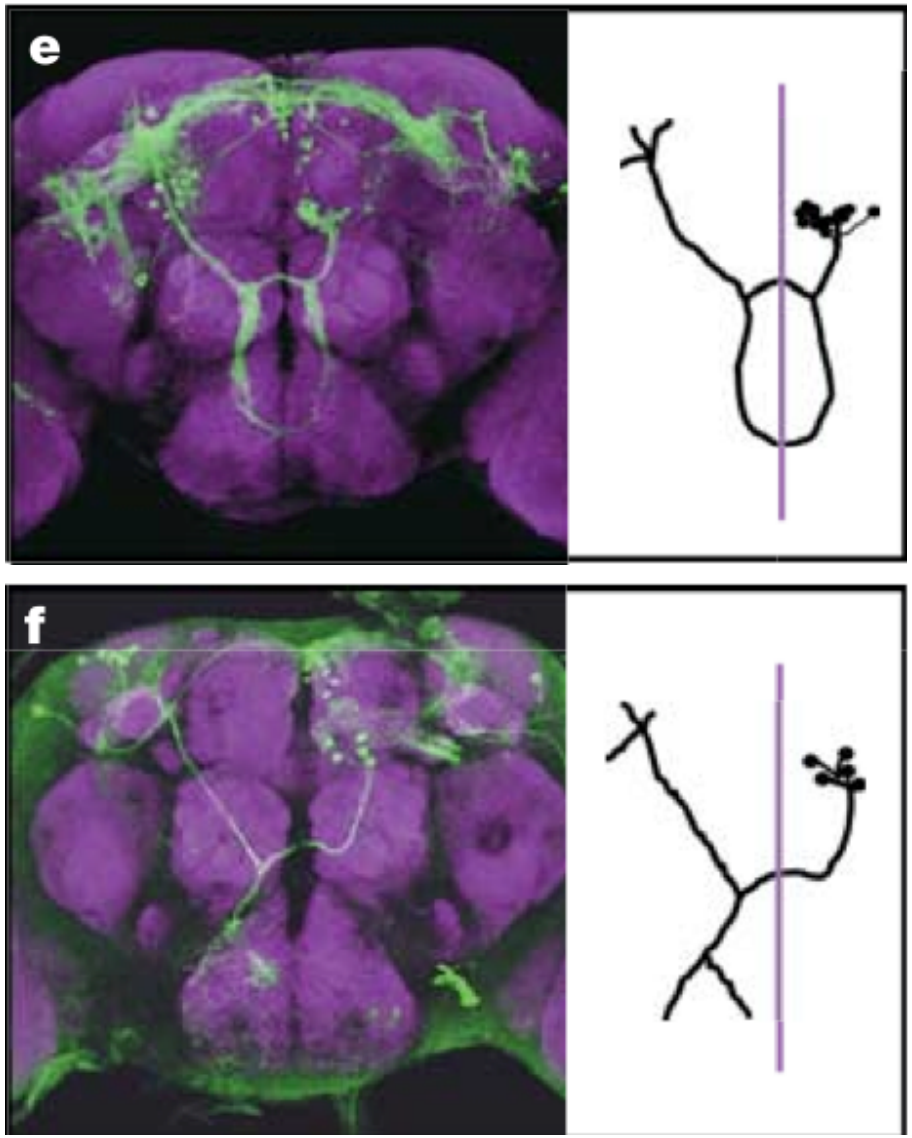
Sexual dimorphism in the Drosophila brain

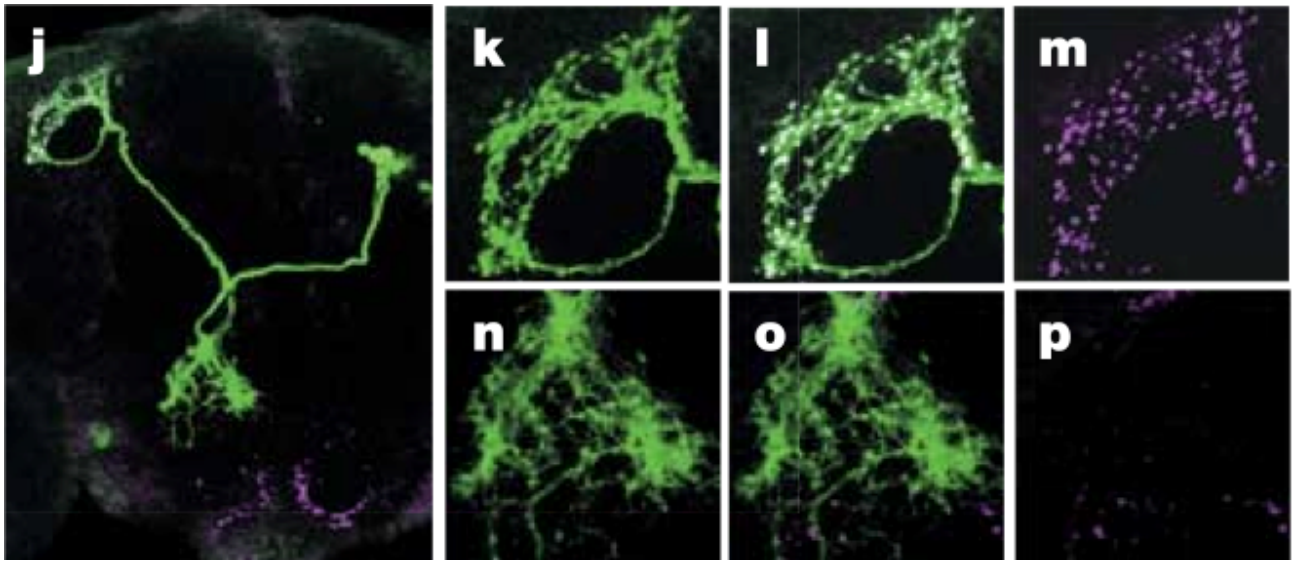
male

female



Sexual dimorphism in the Drosophila brain

Dendritic and axonal arborizations of sex specific neurones in a female



GFP

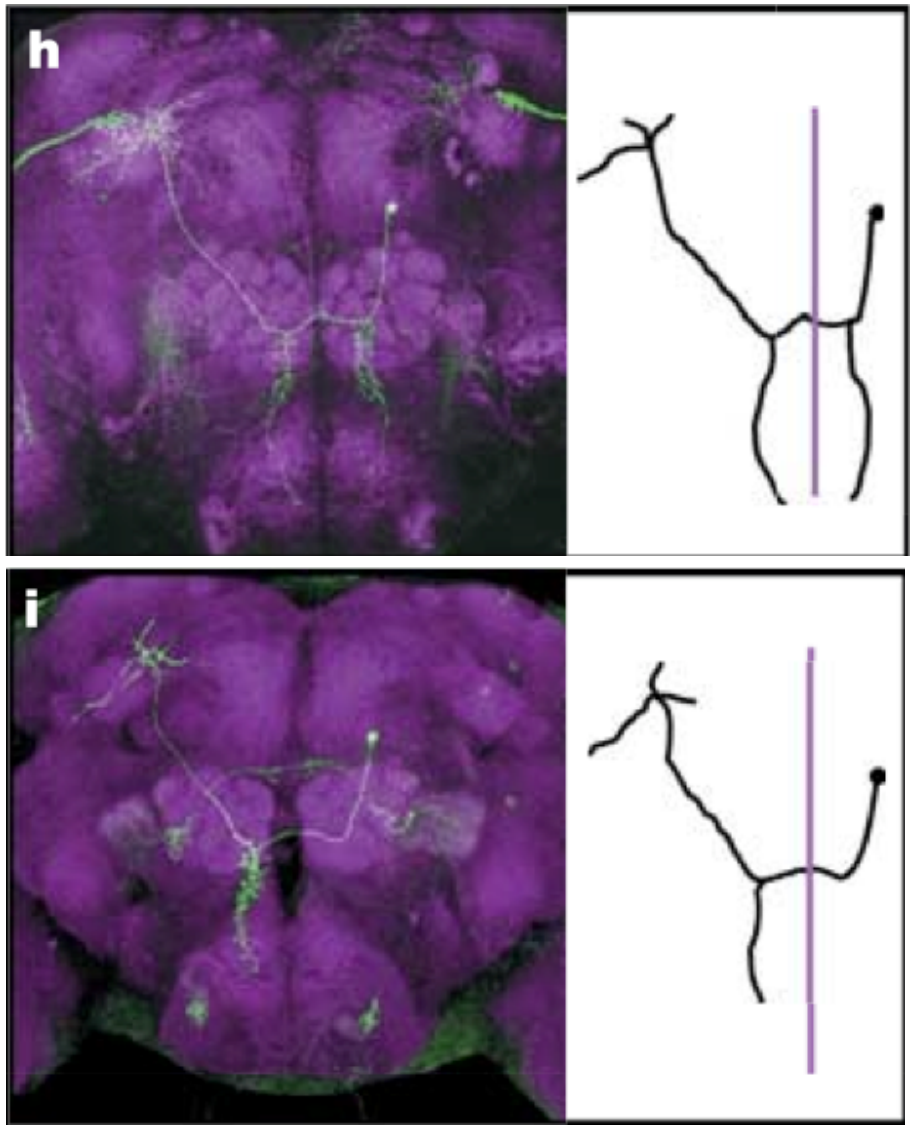
Synaptotagmin

Synaptotagmin marks axonal terminals (presynaptic protein)

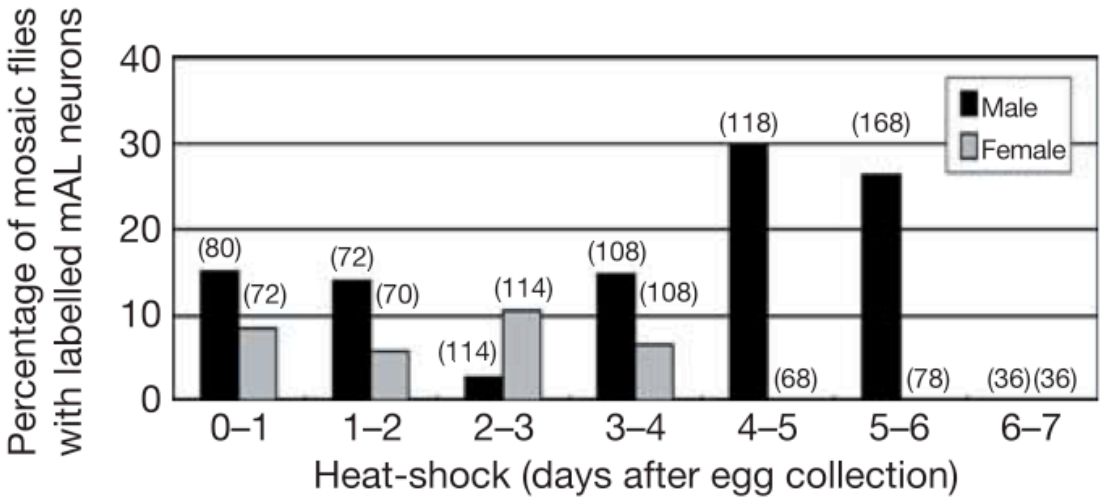
Two types of male specific neurons

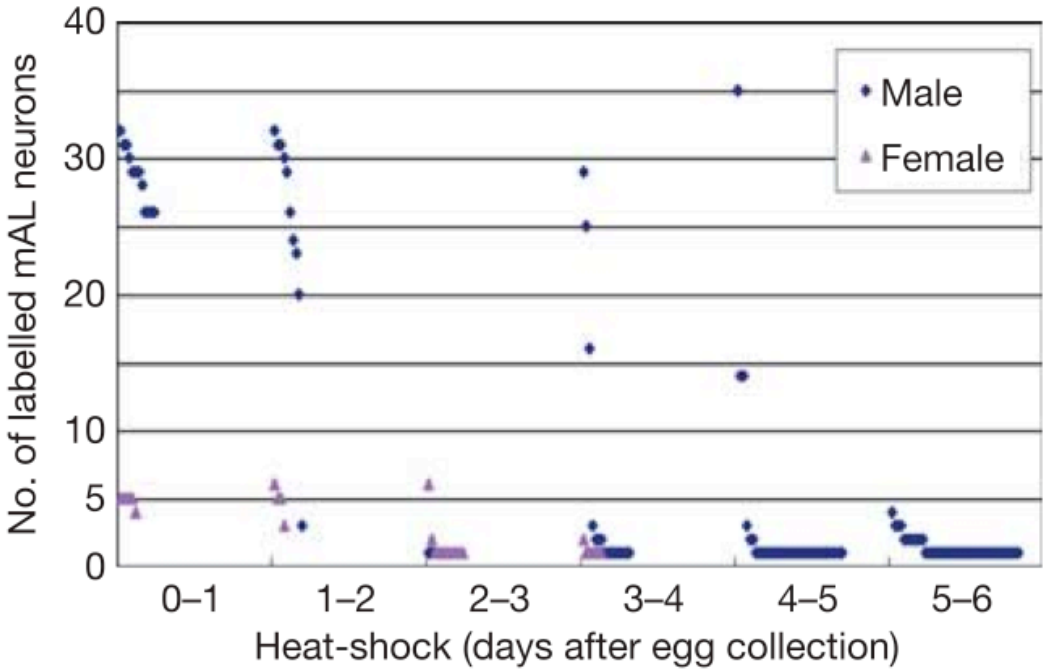
bilateral input

only contralateral input



Late heat shocks produce only male-specific clones: male specific clones are born late





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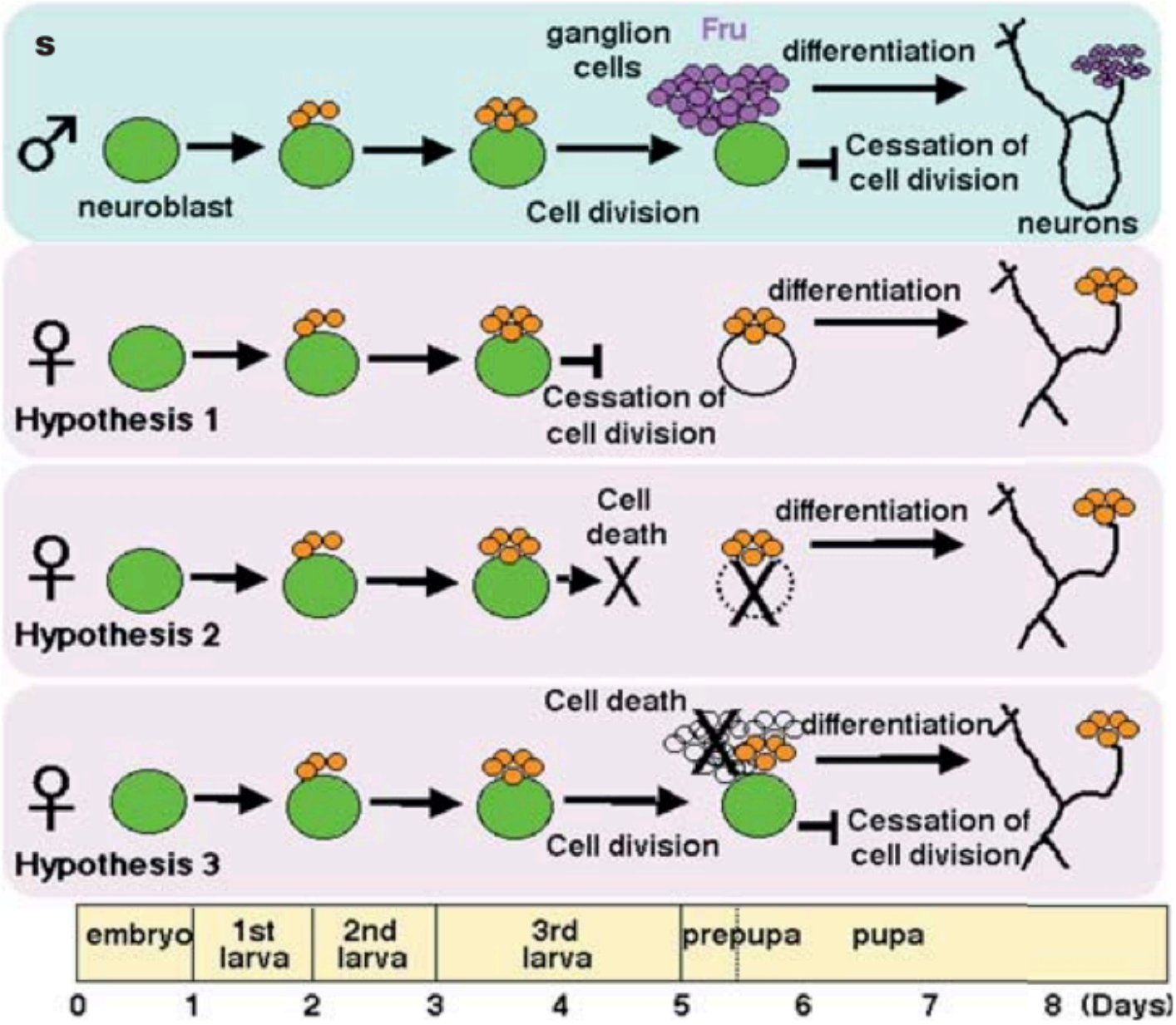
What process is influenced by fru^M?



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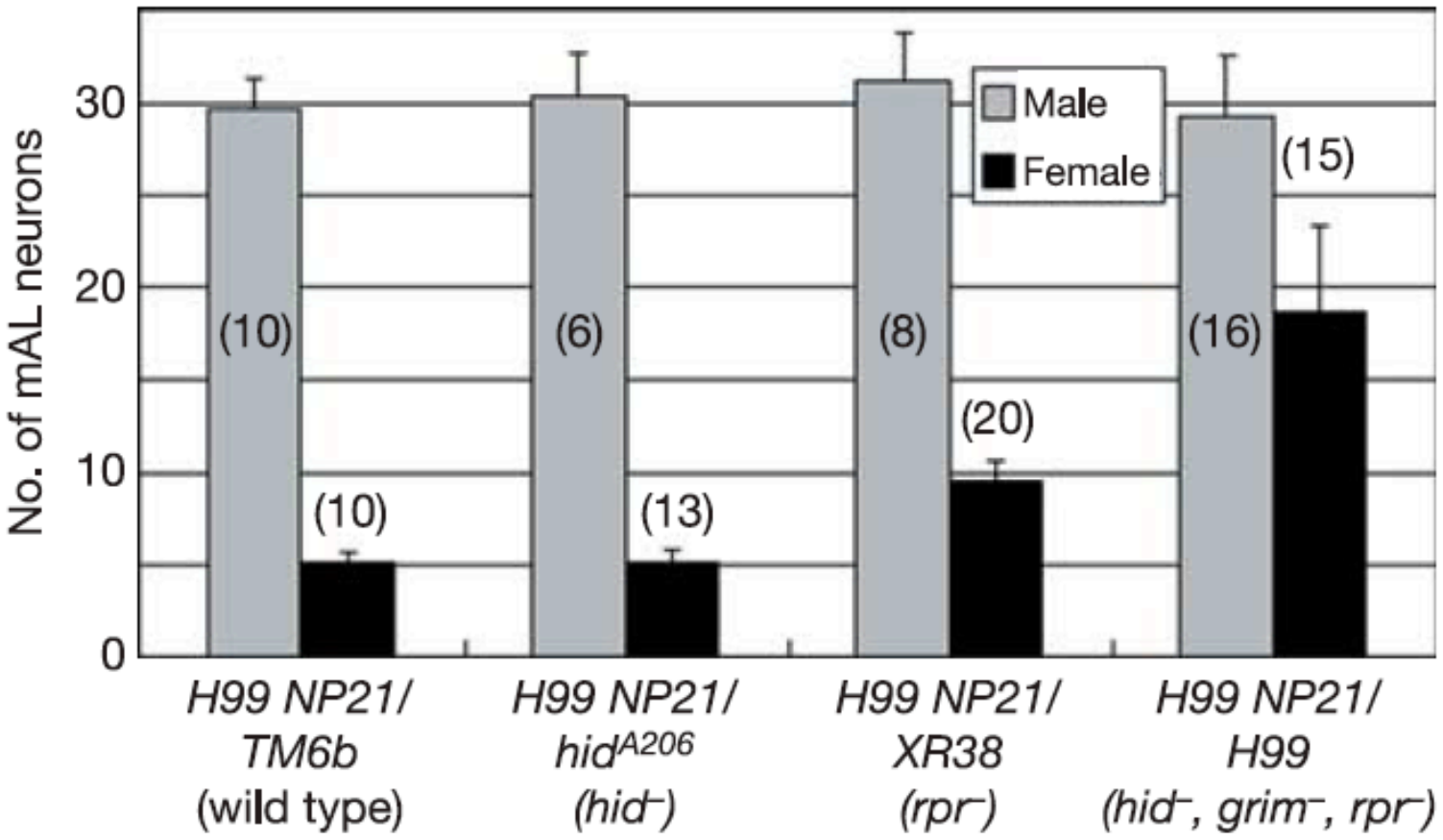
Effect of cell death on mAL sexual dimorphism



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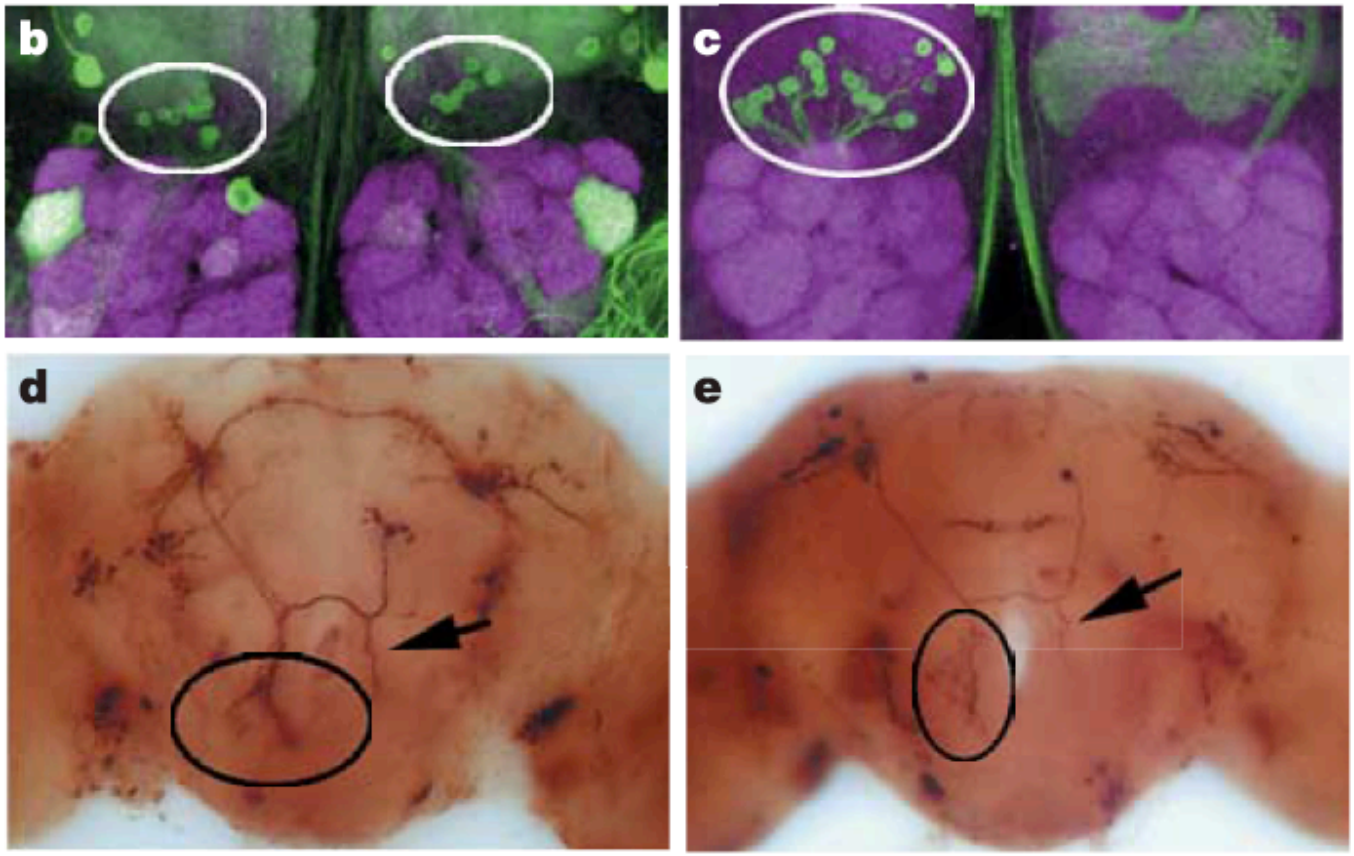
Effect of cell death on sexual dimorphism

Here: Shape of surviving mAL neurons
in late induced homozygous H99 clones in females

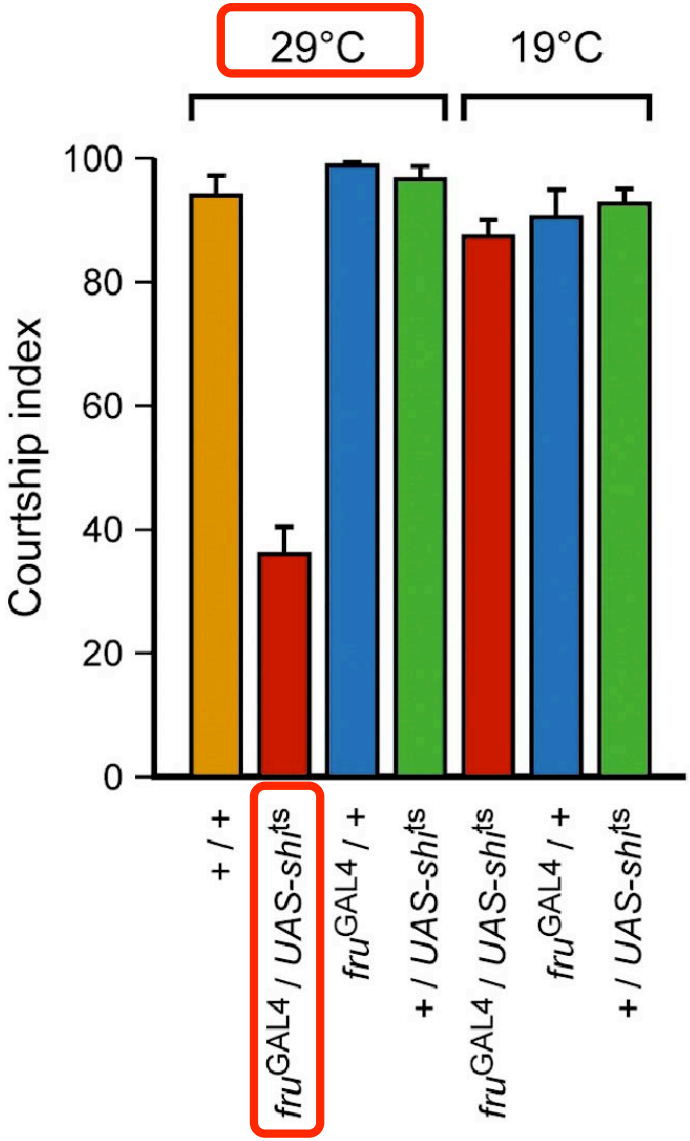


Fu^M protects neurons from cell death in males

In wild-type females, the cell death mechanism eliminates late-born neural progeny in the mAL population

Act the Fru^M positive neurones in the adult brain?

The reversible block of synaptic transmission in P1-aktive neurones inhibit male courtship



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Using sexual behavior of Drosophila as a model, we asked the following questions

- What are the epigenetic rules which direct the development of inborn behavior?
- For organs like eyes, brains, hearts etc. so called „master genes“ are known to exist. Do such master genes also exist for inborn behavior?
- Is development of sexual behavior coupled to sexual differentiation of the body?

Answers we found

- The sex-specific splice product Fru^M is **Master** of male mating behavior
- The expression is neuronal and can be observed in the pns and cns in about 2% of all neurones.
- Expression correlates with sexual dimorphisms. Fru^M protects late born neurons in males from degeneration.
- Genetic engineering makes it possible to exchange sexual behavior in the sexes, so that a female courts a male.

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Genetic and environmental factors influence sexual orientation in humans

A. homosexuality of brother pairs

if one, then also the other

source:
Archives of General Psychiatry (1991) 48, 1089-1096

monozygotic twins	**52%**
dizygotic twins	**22%**
one adopted	**11%**

A. homosexuality of sister pairs

if one, then also the other

source:
American Journal Psychiatry (1993)1508, 272-277

monozygotic twins	**48%**
dizygotic twins	**16%**
one adopted	**6%**

Thank you for your attention!