Sexual dimorphism in brain and behavior: Organization and activation

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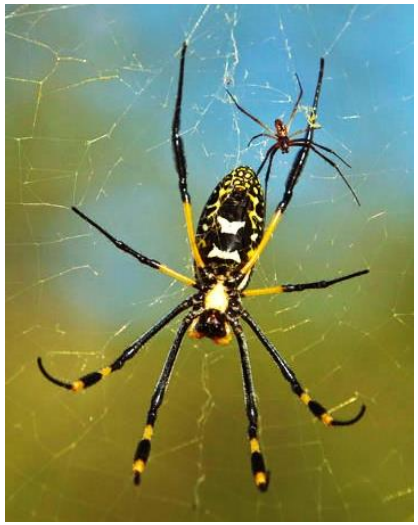
May, 2024

Sexual dimorphism

Sexual dimorphism is the difference in form between male and female members of the same species

Sexual dimorphism: in morphology



Sexual dimorphism in social and reproductive behaviors

Territoriality (aggressive) Behavior

Pup Nursing and Maternal aggression

Innate Behavioral Repertoires

Courtship Behavior

Sexual Behavior

Behavioral Neuroendocrinology

Arnold A. Berthold
(1803-1861)

Hypothesis: Intact testes are necessary for the development of male-typical characteristics

Research question tested: Are the effects of prepubertal castration in males, dependent on neural connections to the testes?

Castration

Castration +
Transplantation
in the same body

Castration +
Transplantation
in another body

Berthold's experiment- summary

Findings:

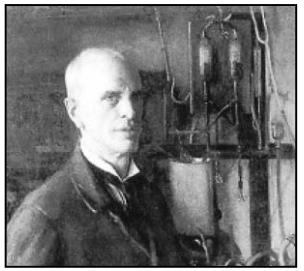
-Males that were castrated as juveniles later showed deficits as adults, in male-typical morphology and behaviors.

-All of these effects could be reversed if the subject's testes, or the testes of another male, were implanted into the body cavity.

Conclusion:

Testes influence the development of male-typical morphology, and male-typical behavior, NOT through nerves, but by secreting a substance into the bloodstream (i.e. hormones).

Hormone (hormoa; to excite) was first assigned by Dr. Starling in 1905



Ernest Henry Starling
(1866-1922)

"The chemical messengers which, speeding from cell to cell along the blood stream, may coordinate the activities and growth of different parts of the body"

William C. Young
(1899-1965)

Suggested that the same kind of relationship between embryonic and adult effects of hormones might hold in the brain.

Endocrinology, 1959

ORGANIZING ACTION OF PRENATALLY ADMINISTERED TESTOSTERONE PROPIONATE ON THE TISSUES MEDIATING MATING BEHAVIOR IN THE FEMALE GUINEA PIG[1]

CHARLES H. PHOENIX, ROBERT W. GOY, ARNOLD A. GERALL AND WILLIAM C. YOUNG

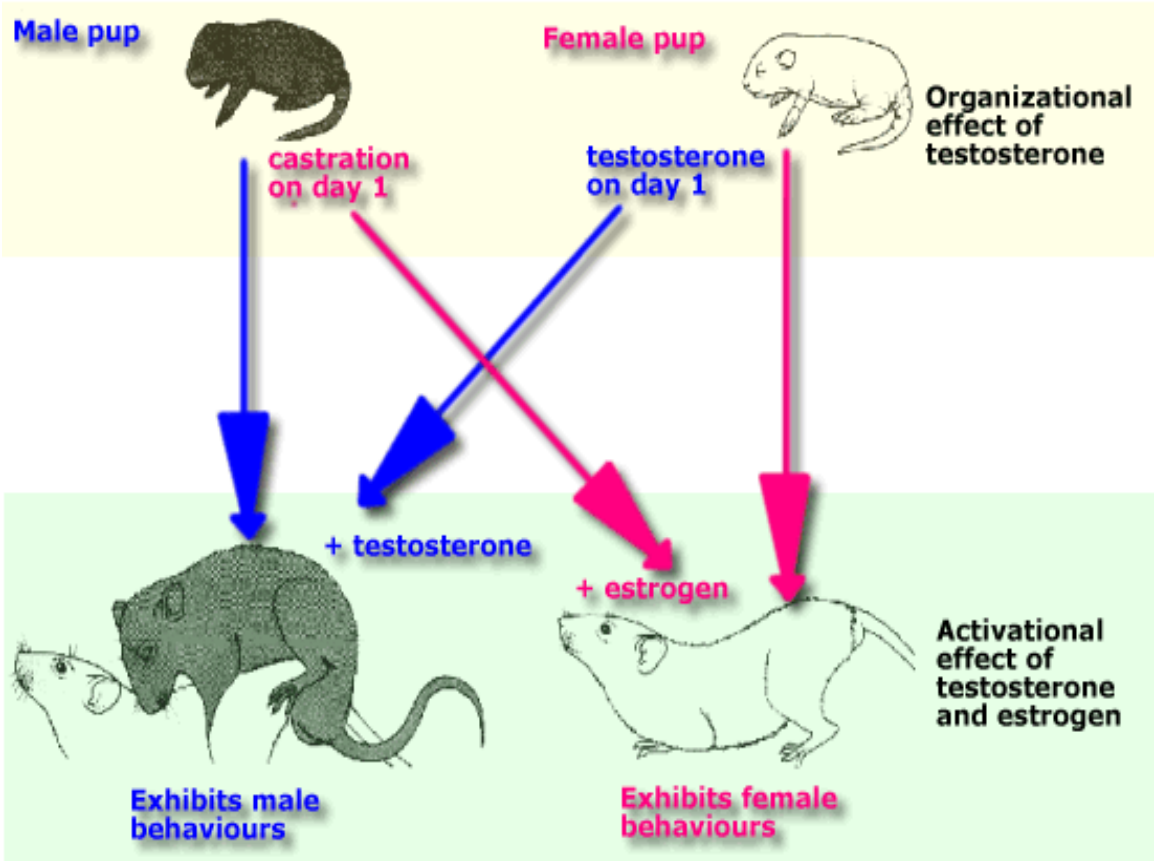
Department of Anatomy, University of Kansas, Lawrence, Kansas

William C. Young
(1899-1965)

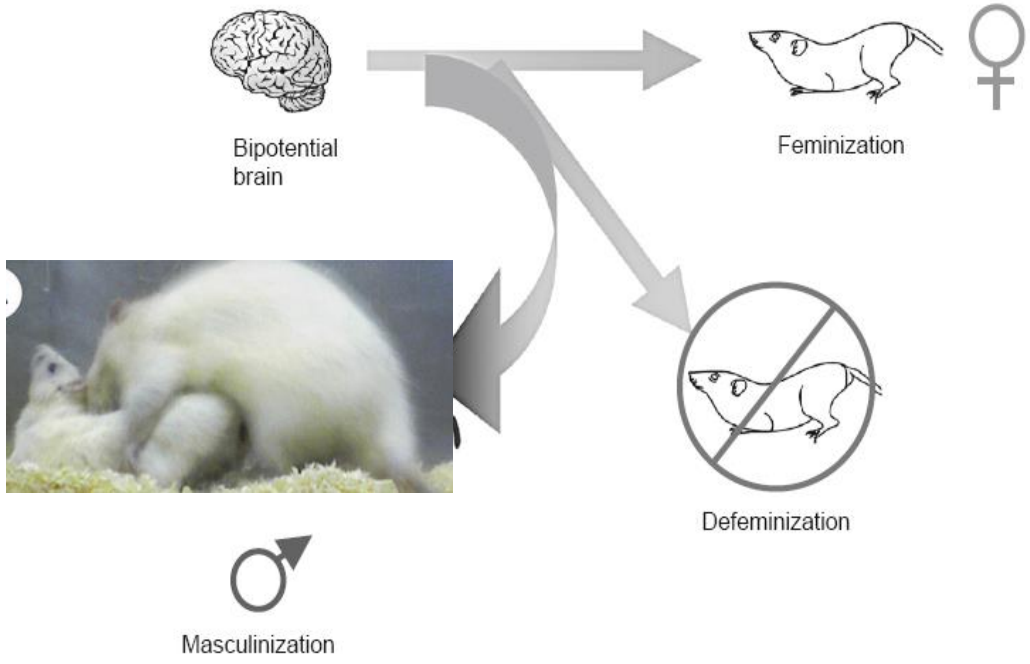
Female guinea pigs that had been exposed to androgens *in utero* were much more likely to express male-like copulatory behavior when exposed to androgens as adults, and they were also less likely to express female-typical receptive behavior when treated with estrogen and progesterone.

Endocrinology, 1959

Effects of male castration and female testosterone treatment



The organization and activation model

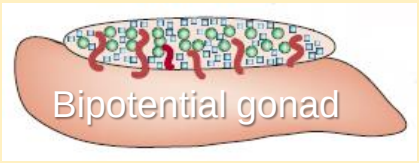


• Sex hormones act during the prenatal stage to irreversibly organize the nervous system in a sex-specific manner.
• During adult life, the same hormones possess activation effects, causing it to function in a sex-typical manner

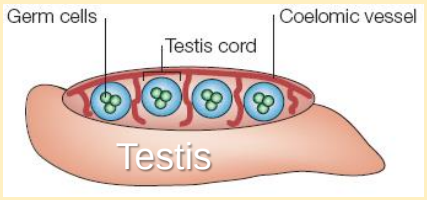
The classic model of brain sexual differentiation

Embryonic

XY ♂

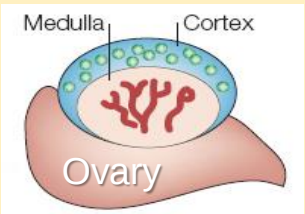


♀ XX



SRY gene

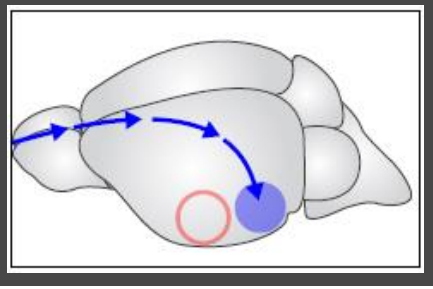
\+ -

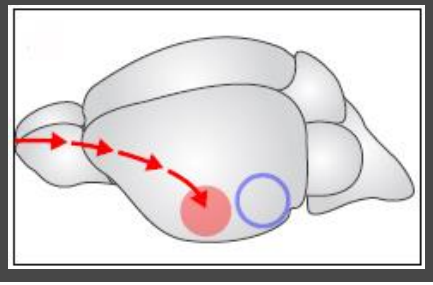


Perinatal

Testosterone/
Estradiol

Organization
(permanent changes)





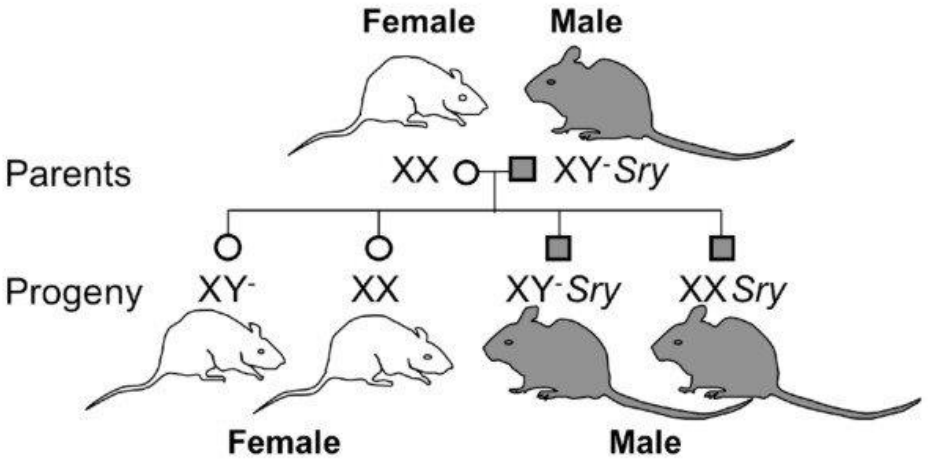
Adult

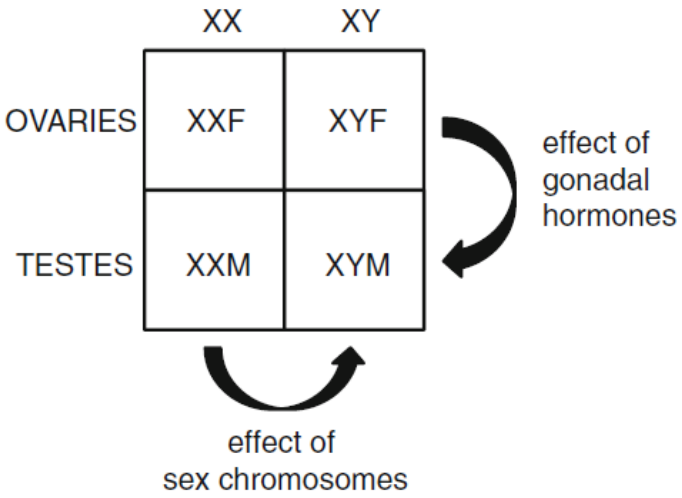
Testosterone

Activation

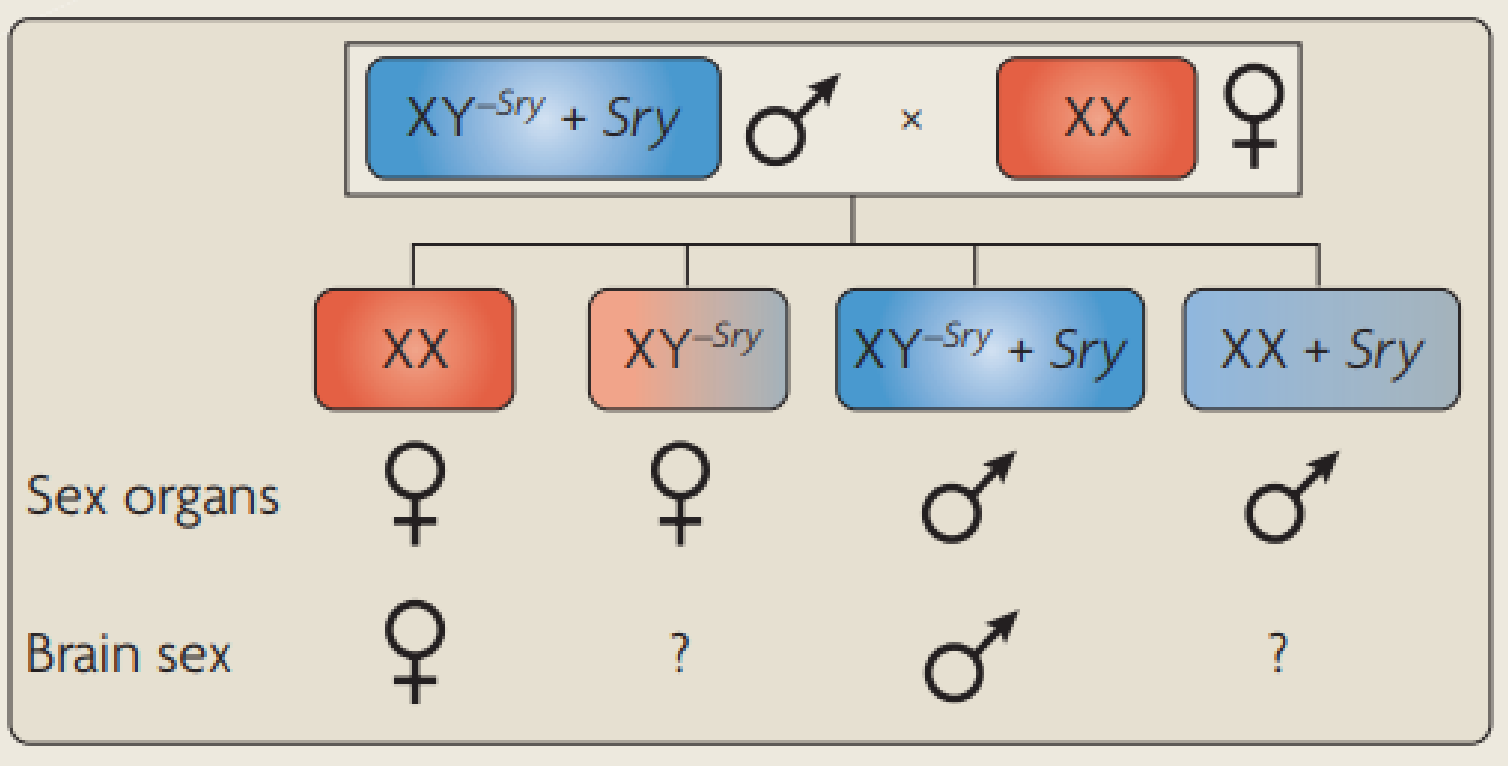
Estradiol &
Progesterone

Genetic manipulation of Y chromosome and SRY gene in mice (Four Core Genotypes)



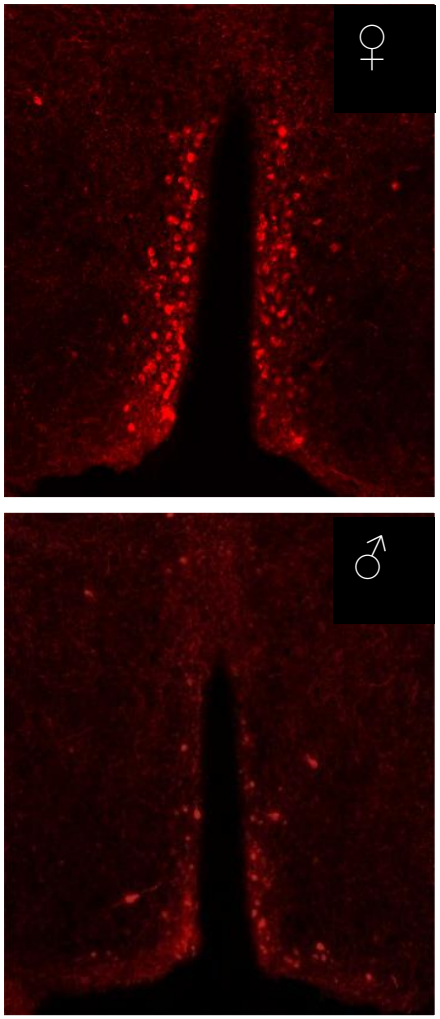


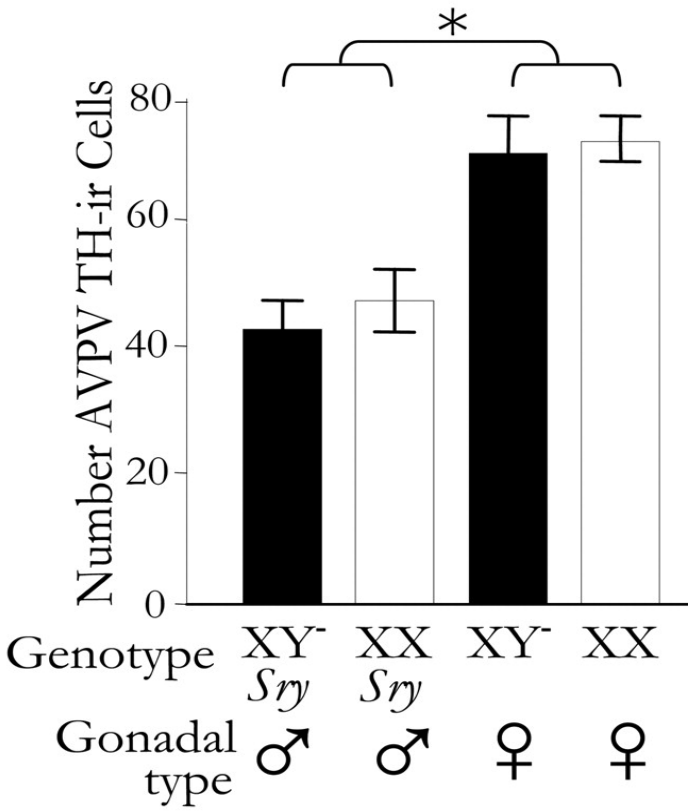
Burgoyne and Arnold, 2016;
Burgoyne et al., 1998;
De Vries et al., 2002


XY−Sry + Sry
×
XX
XX
XY−Sry
XY−Sry + Sry
XX + Sry
Sex organs
Brain sex
?
?

Example: *Sry* gene control the expression of sexually dimorphic gene in the brain

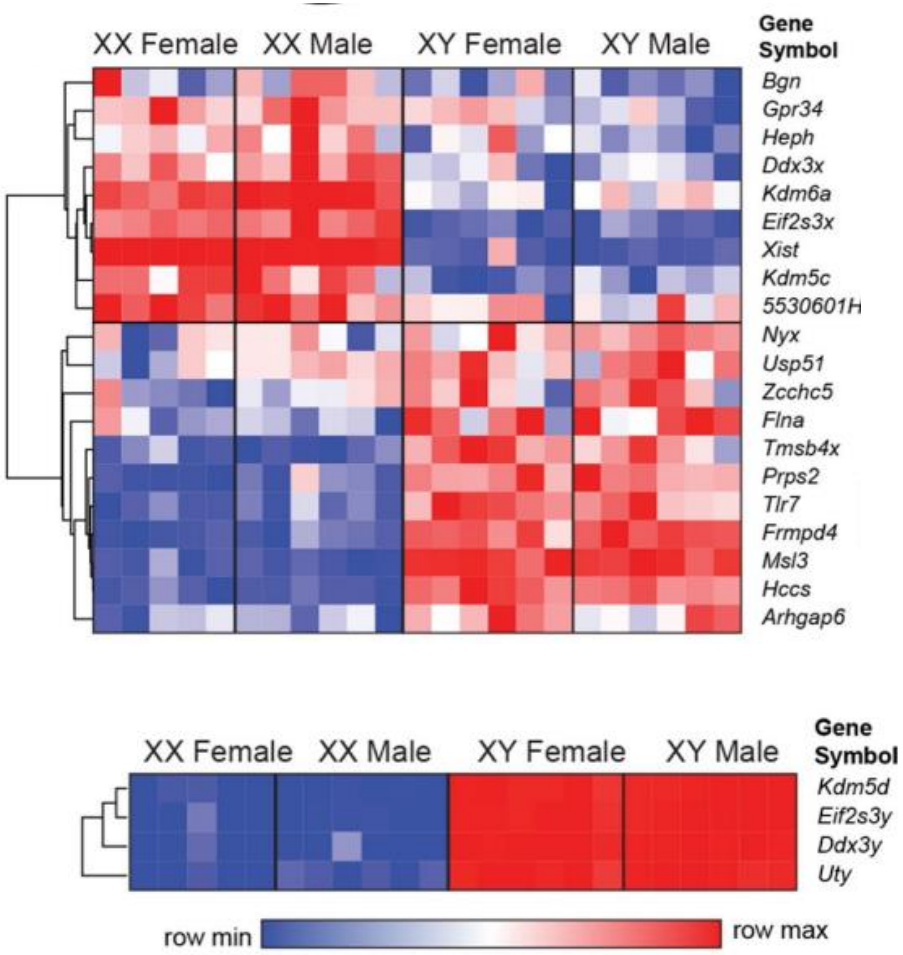
Tyrosine Hydroxylase (TH)-expressing neurons in the hypothalamus



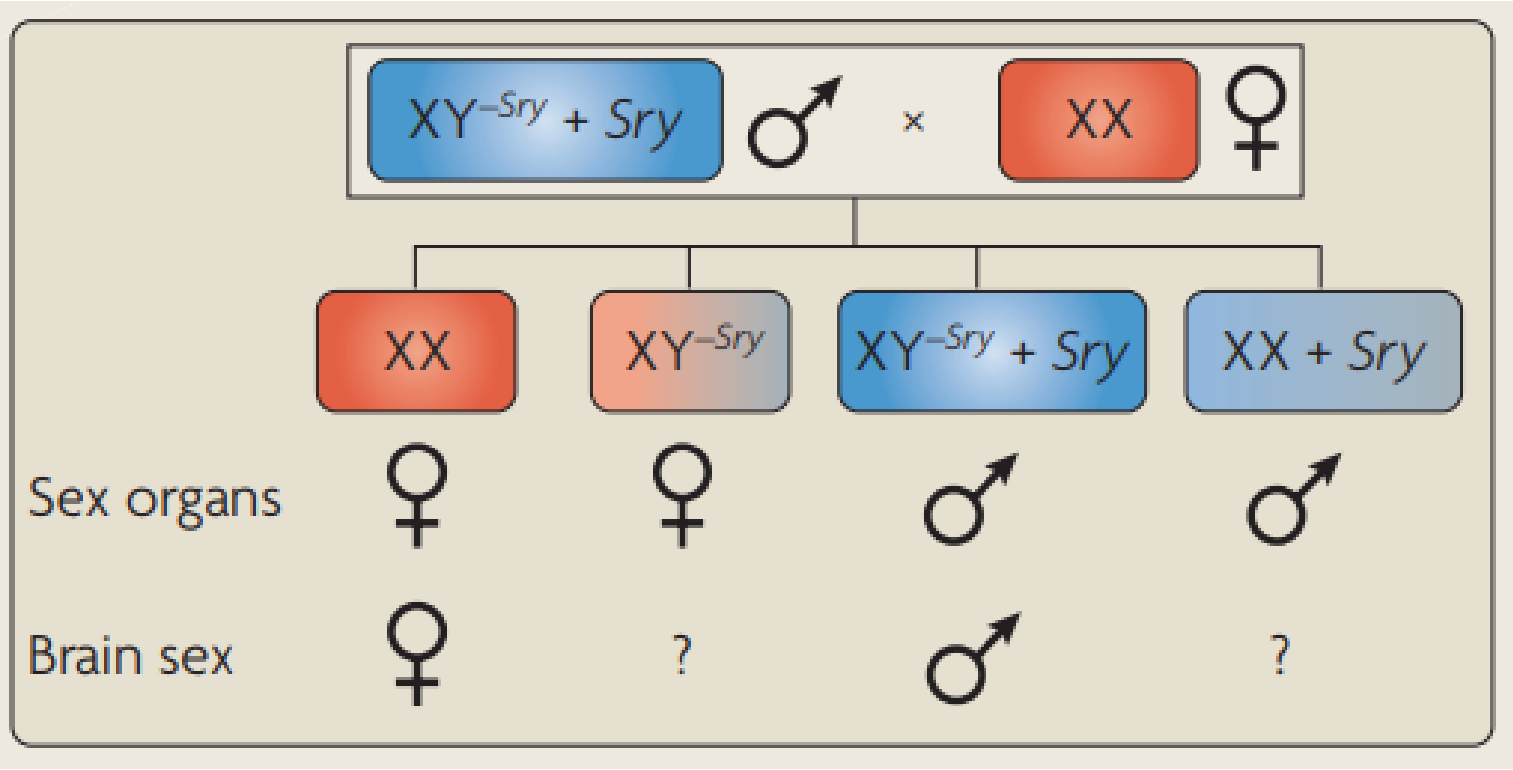


Arnold et al 2004, Endocrinology

Examples: Genes that are differentially expressed by sex chromosome in the hippocampus



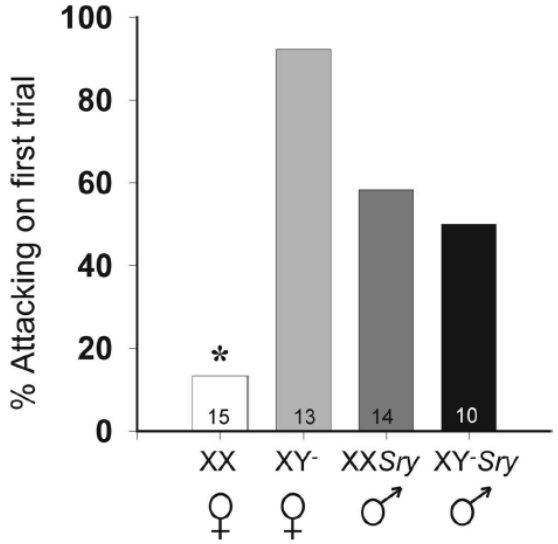
Ocañas et al 2022



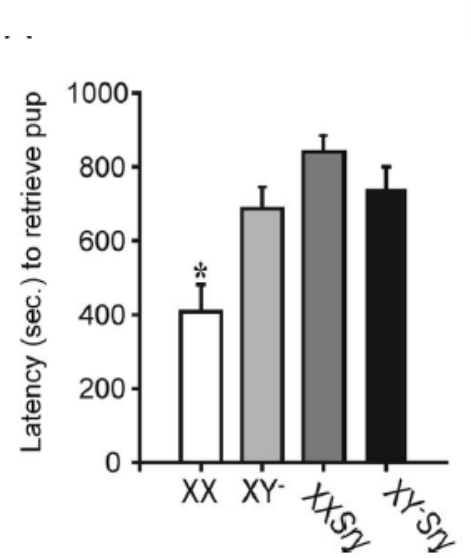
Behavior **?** **?**

The *Sry* gene and sex chromosomes genes regulate sexual dimorphism in social behaviors

Aggressive behavior

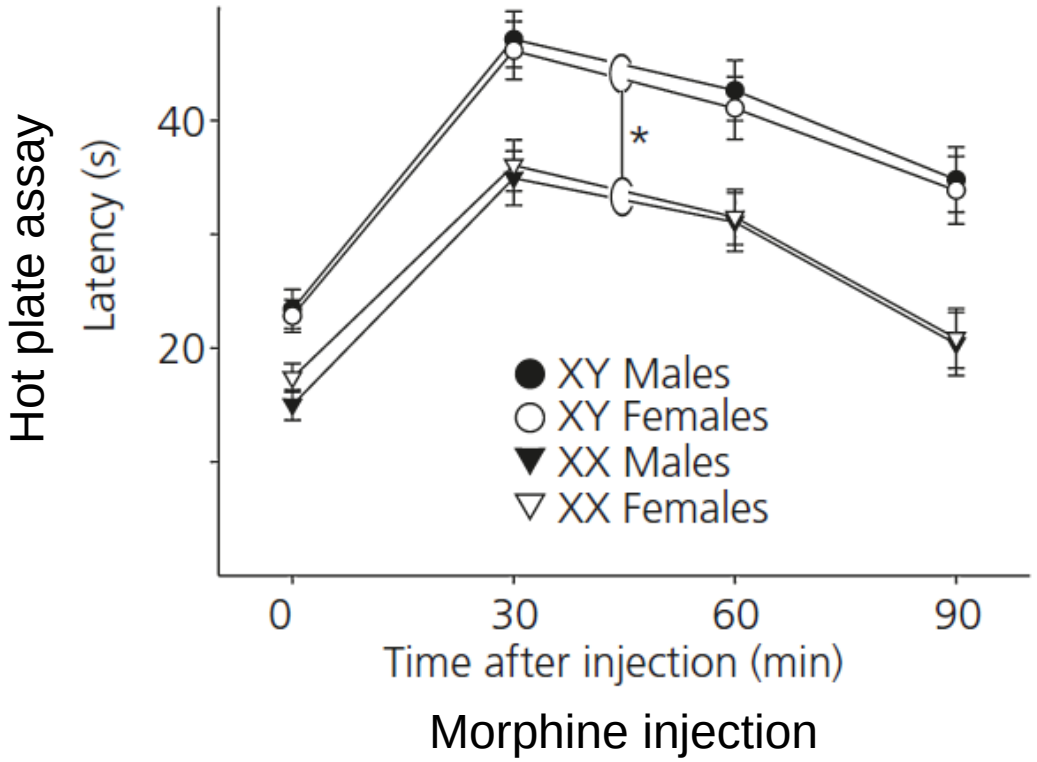


Maternal behavior



Gatewood et al 2006

Effect of sex chromosomes on nociception



Gioiosa et al 2008

The Klinefelter syndrome, also known as the **XXY genetic disorder**

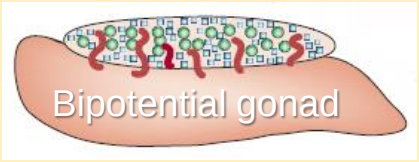
symptoms include:

1. Reduced fertility or full infertility
2. Female-typical body characteristics

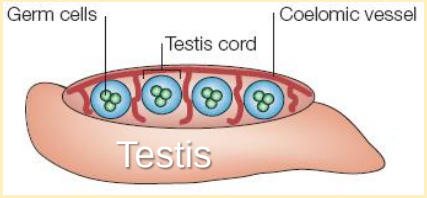
The classic model of brain sexual differentiation

Embryonic

XY ♂



♀ XX



SRY gene

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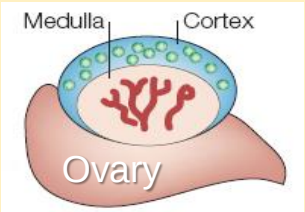
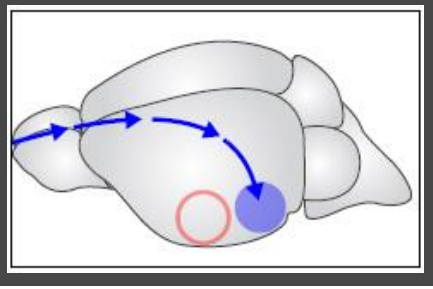
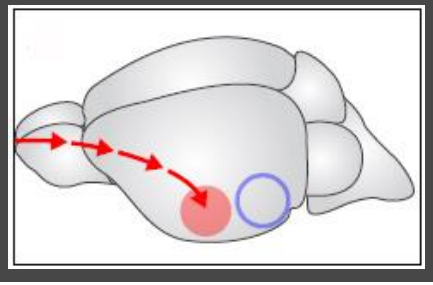


Perinatal

Testosterone/
Estradiol

Organization
(permanent changes)





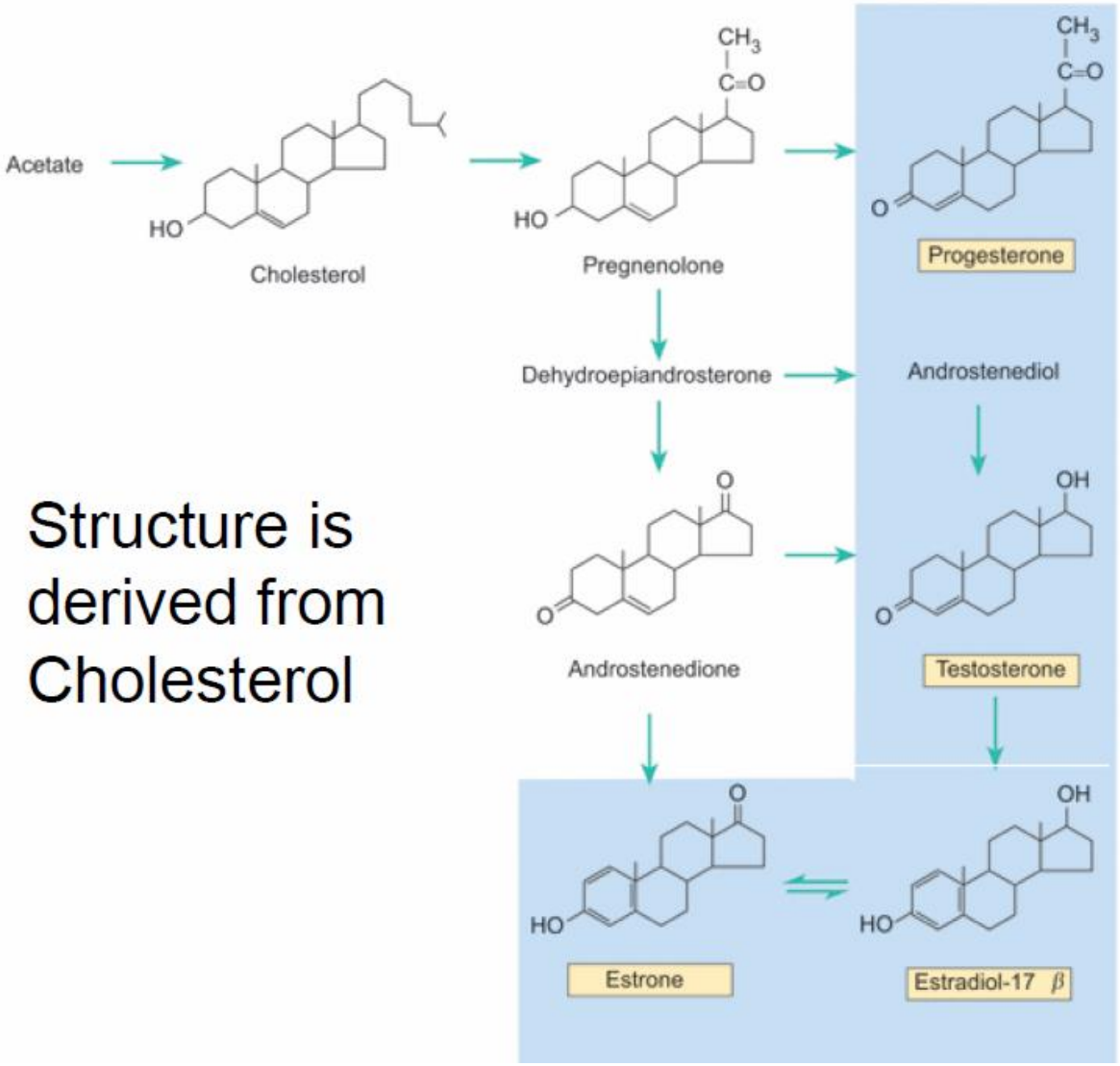
Adult

Testosterone

Activation

Estradiol &
Progesterone

The sex hormones



Structure is derived from Cholesterol

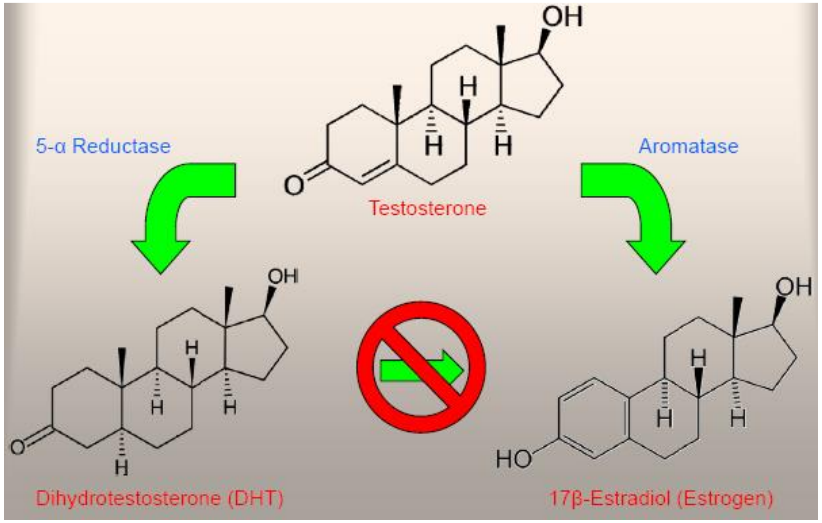
"Male" (androgenic) sex hormone

-Also secreted by the adrenal gland

"Female" (estrogenic) sex hormone

* Both are steroid hormones and secreted in both sexes

Testosterone, Estradiol or DHT masculinizes the brain ?



• Testosterone treatment in neonatal rats is blocked by prior administration of specific estrogen receptor antagonist

• DHT does not mimic the effect of testosterone

• Radio-labeled testosterone is recovered from the brain as radio-labeled estradiol

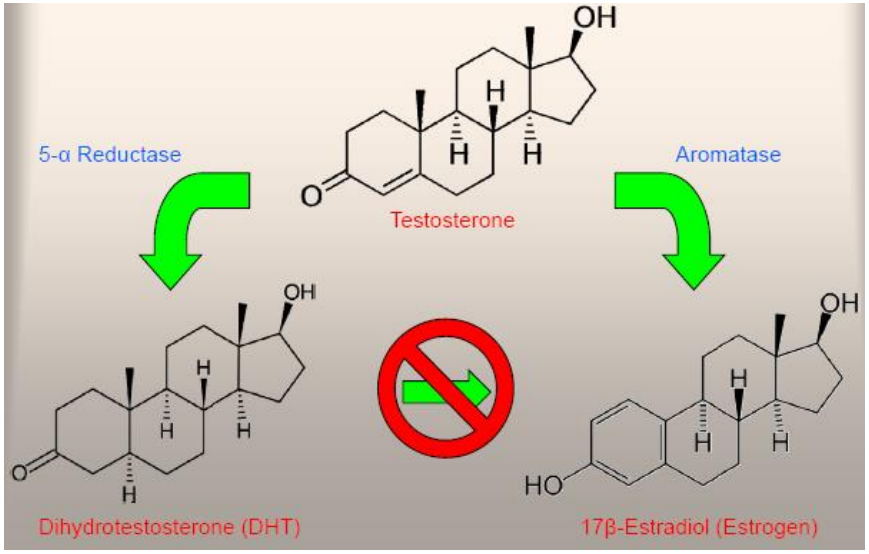
• Aromatase inhibitors counteract the effect of testosterone administration

Estradiol masculinizes the brain

Why isn’t the female brain masculinized by estrogen?

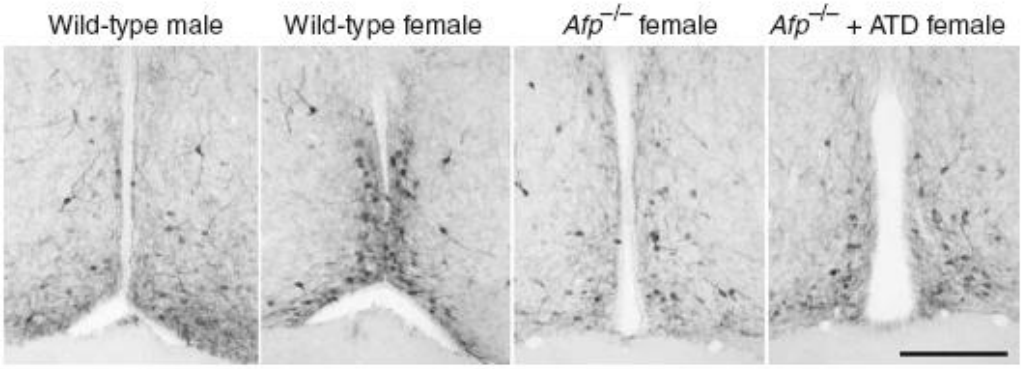
- Estradiol production by the fetal ovaries is minimal
- High levels of circulating α-fetoprotein (AFP) in embryos

AFP = Fetal plasma protein that binds estrogens with high affinity and prevents it’s passage through the placenta.

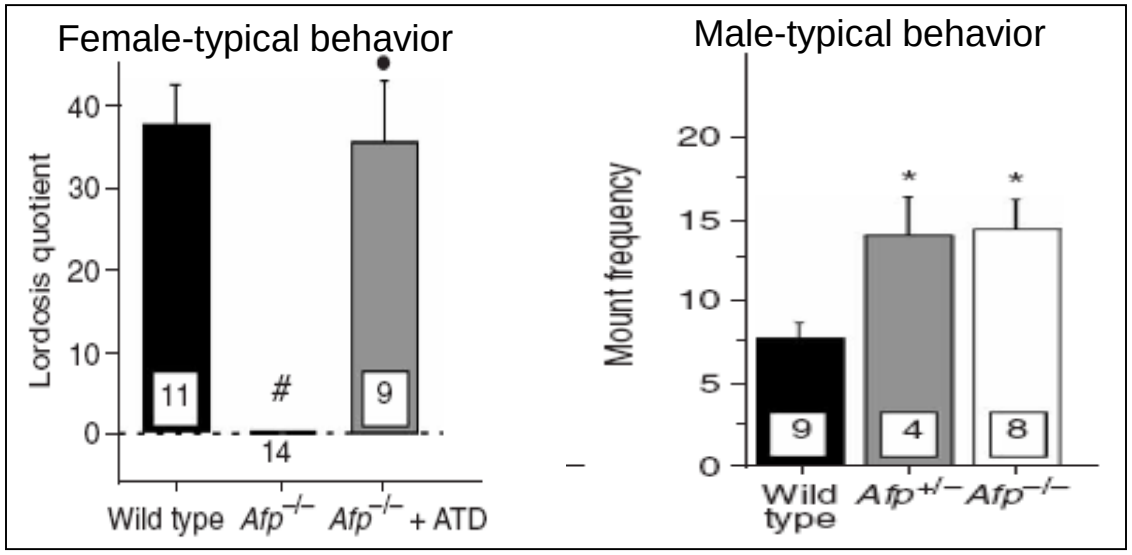


Role of Alpha-fetoprotein (AFP) in female brain development

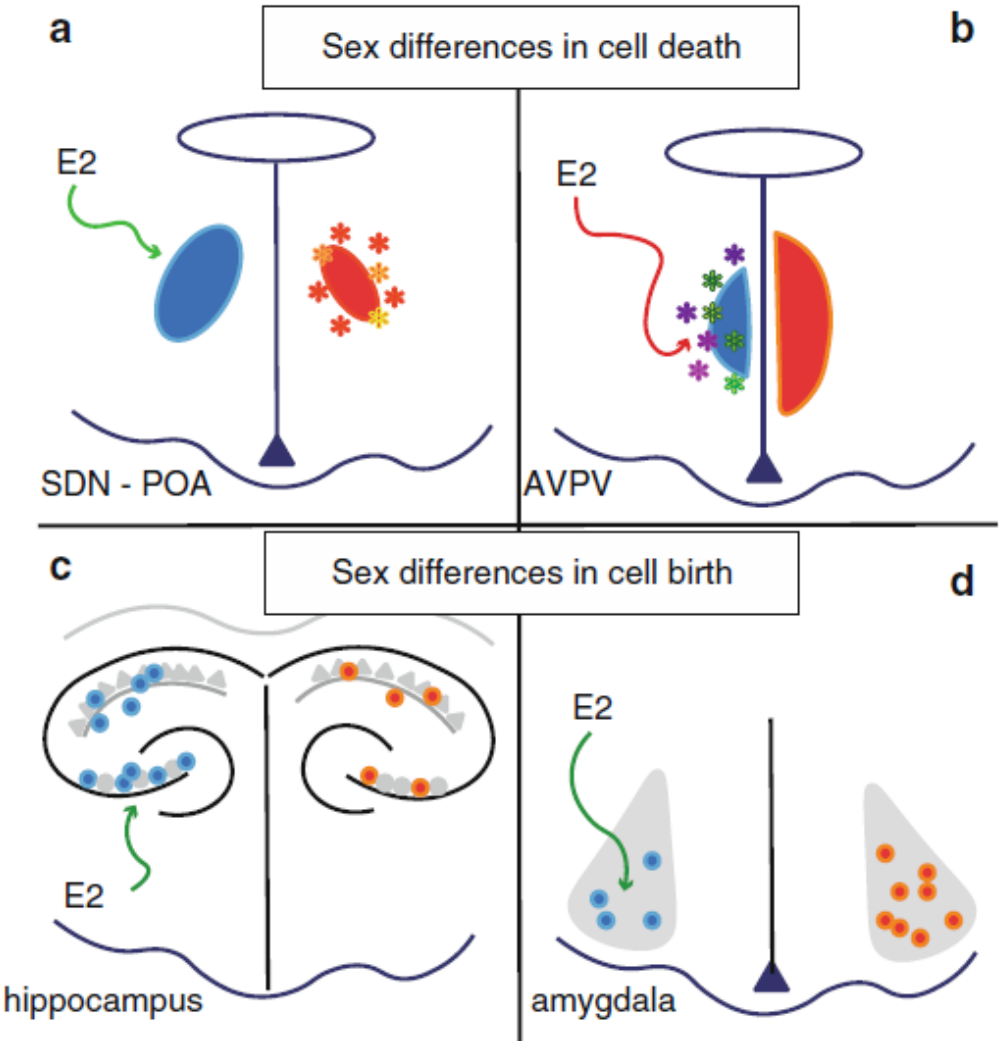
Expression of the TH gene in the hypothalamus (AVPV)



ATD=
Aromatase inhibitor



Baker et al 2005



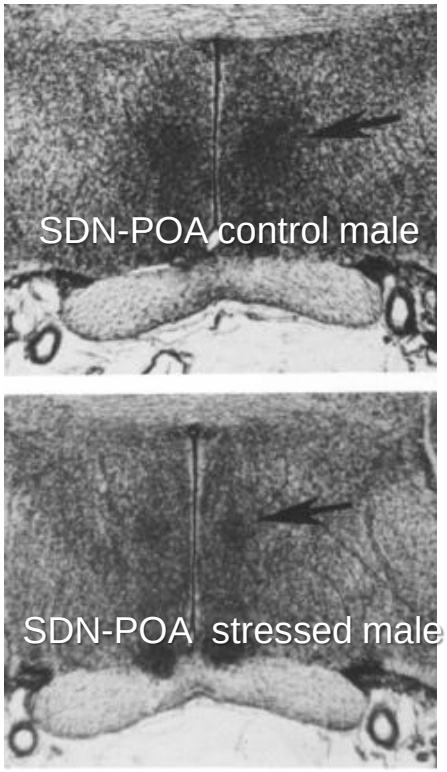
Arnold and McCarthy, 2016

Epigenetic mechanisms underlying the development of sex-typical brain and behavior

Effect of prenatal stress on sexual dimorphism in the rat brain

SDN measurements

Treatment	*Days postnatally*		
	Birth	*20 Days*	*60 Days*
Males			
Control	0.259 ± 0.015	**0.858 ± 0.083	**0.643 ± 0.035
ES	*0.471 ± 0.034	*0.419 ± 0.049	*0.345 ± 0.034
NS	*0.447 ± 0.027	*0.553 = 0.086	*0.278 ± 0.039
Females			
Control	0.261 ± 0.021	0.369 ± 0.027	0.378 ± 0.025
ES	0.324 ± 0.034	0.440 ± 0.076	0.258 ± 0.023
NS	0.363 ± 0.033	0.502 ± 0.066	0.339 ± 0.036

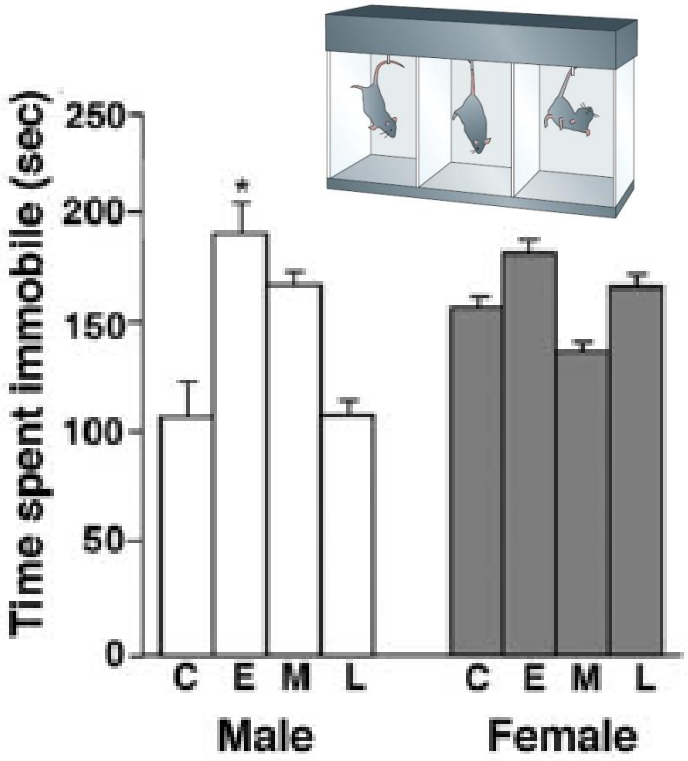


ES: Environment stress (change in lighting/ temperature)
NS: nutritional stress (50% of total food of control males)

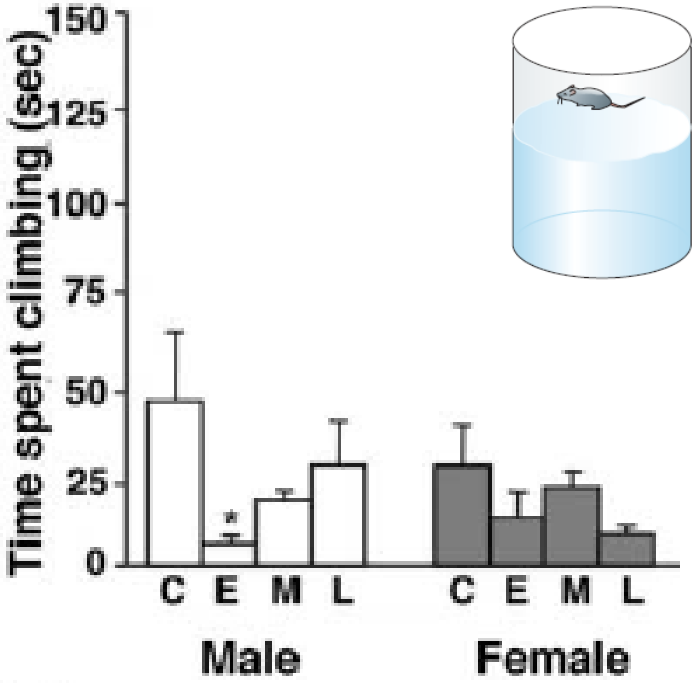
Anderson et al 1985

Sex-specific programing of offspring behavior after stress early in pregnancy

Tail suspension assay



Forced swim test



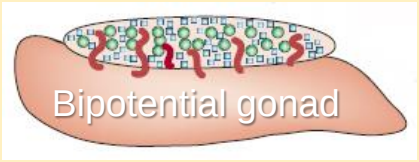
C: control;
Prenatal stress during (E) early, (M) mid or (L) late gestation

Mueller and Bale 2008

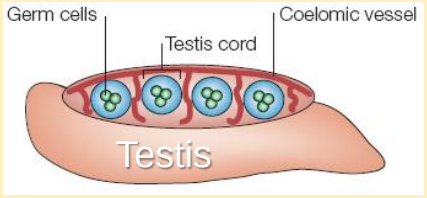
The classic model of brain sexual differentiation

Embryonic

XY ♂



♀ XX



SRY gene

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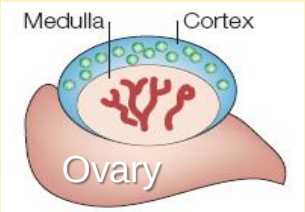

Perinatal

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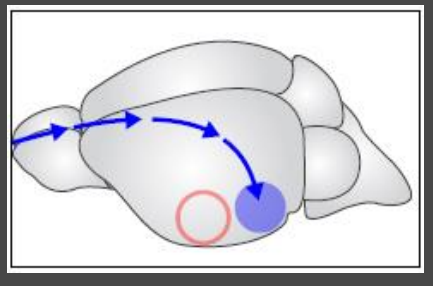

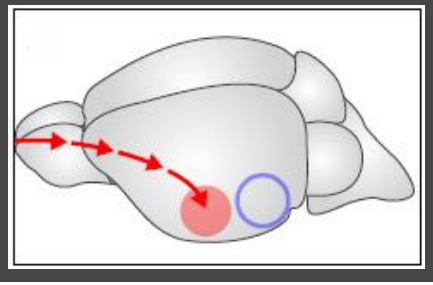

Adult

Testosterone

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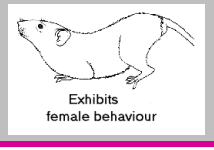


Hormonal regulation of social behavior during adulthood

Aggressive behavior

Sexual behavior

Maternal behavior

Maternal behavior in postpartum female rats

Pup-directed behavior in virgin and postpartum female

Virgins

Infanticide

Postpartum

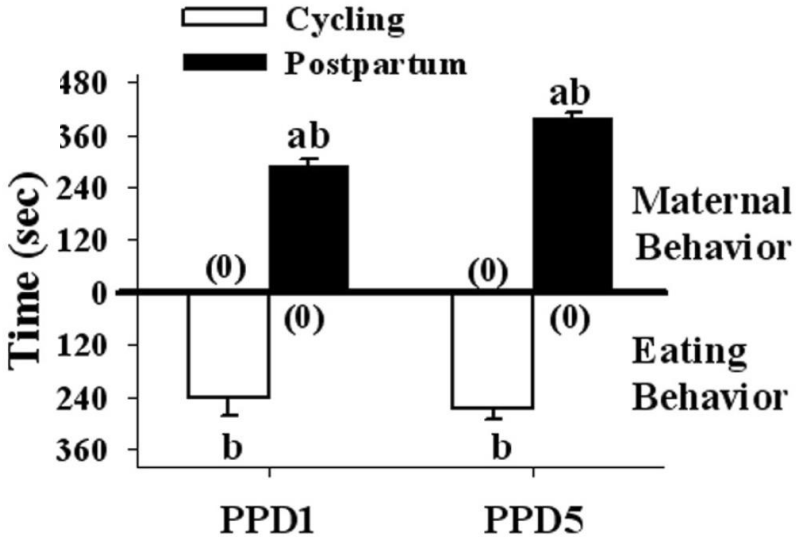
Maternal

Measuring parental behaviors in mice

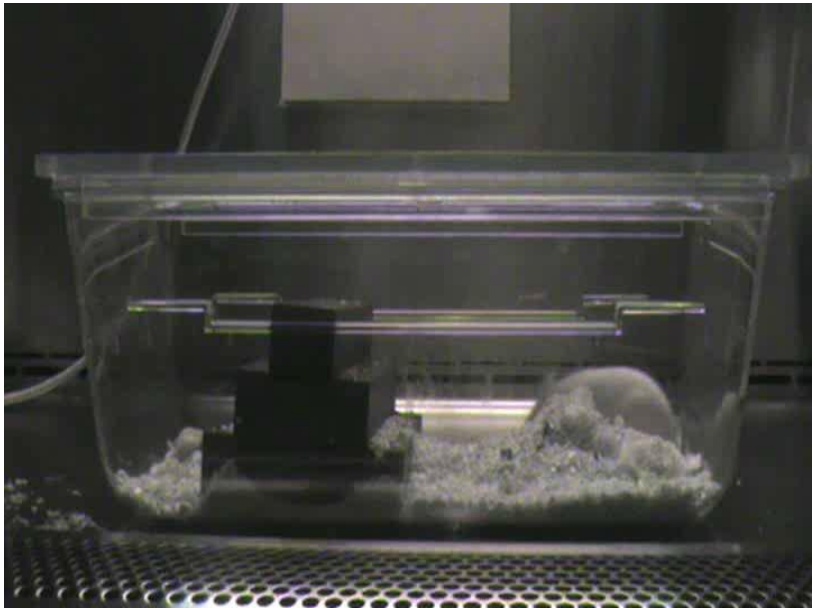
Pup nursing behavior (retrieval) by females

Pup-directed behavior (ignoring) by males

Pups are highly motivated stimuli for dams



Afonso et al 2009



Scott et al 2015

Comparison of Two Positive Reinforcing Stimuli: Pups and Cocaine Throughout the Postpartum Period

B. J. Mattson, S. Williams, J. S. Rosenblatt, and J. I. Morrell
Rutgers, The State University of New Jersey

Behav. Neurosci. 2001

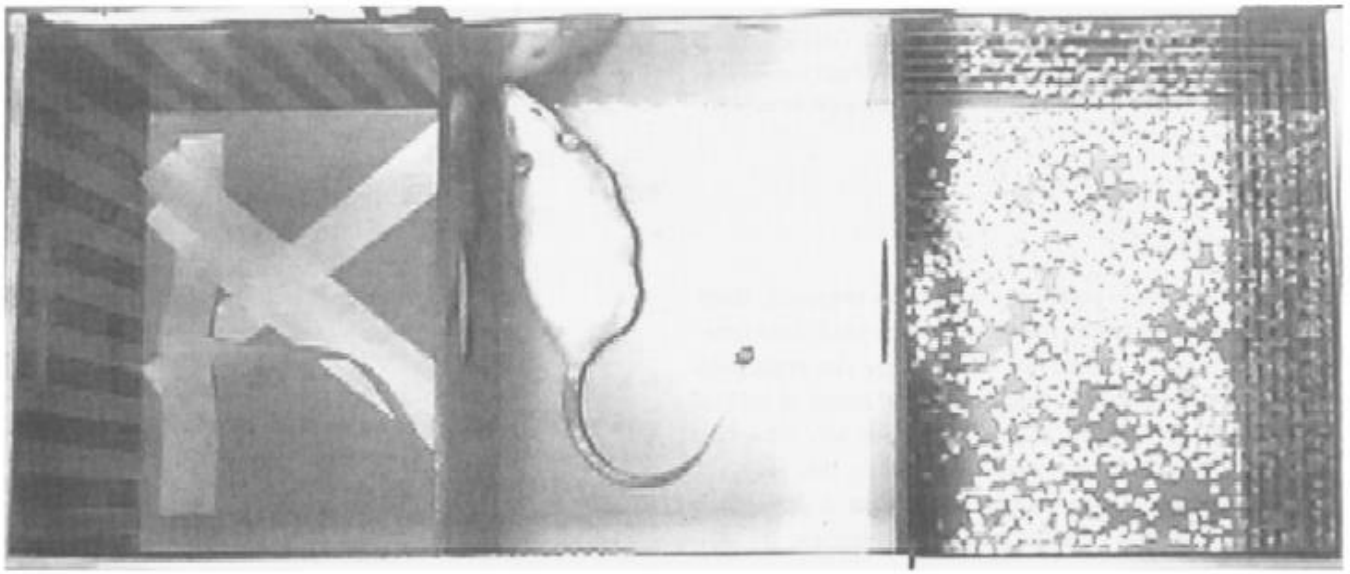


Figure 1. Place preference paradigm apparatus as prepared for a typical testing session. The tactile (strips and squares) and visual (vertical and horizontal) contextual cues in the outer chambers are visible. Inner walls are red, with a 10.1-cm hole, which enabled the dam to travel throughout the apparatus.

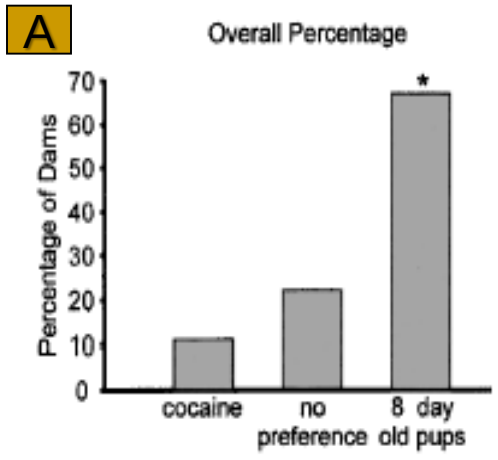
Studying maternal behavior motivation using conditioned place preference (CPP) test

- The CPP procedure assesses the preference for or the motivation to seek a reinforcing stimulus, including a variety of natural reinforces.
- Animals are given pairings of an unconditioned reinforcing stimulus with a set of unique environmental cues that serve as the conditioned stimulus.

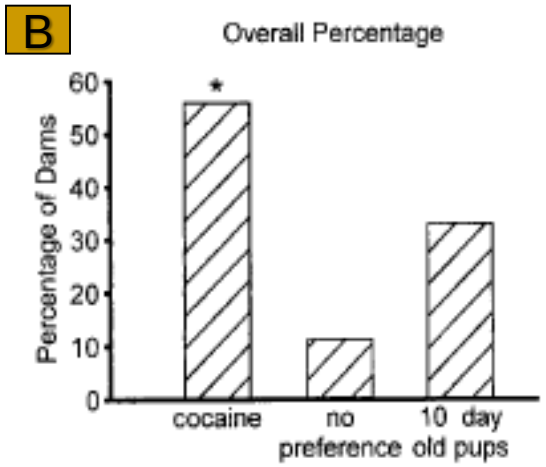
The reward value of pup stimuli to mothers

- Females were exposed to unconditioned stimuli (pups or cocaine) in the presence of conditioned stimuli cues.
- On postpartum day 8 (**A**), 10 (**B**) or 16 (**C**), the time the dams spent in each chamber and their behavior were recorded.

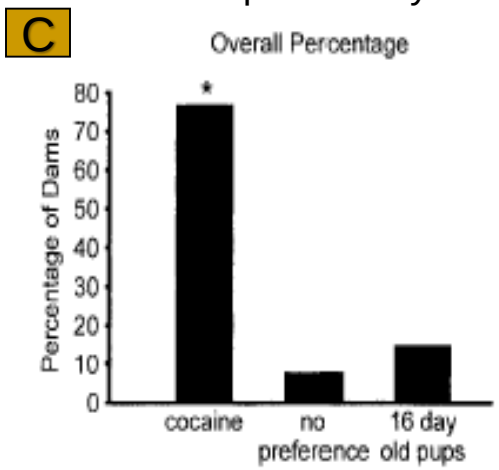
Postpartum day 8



Postpartum day 10



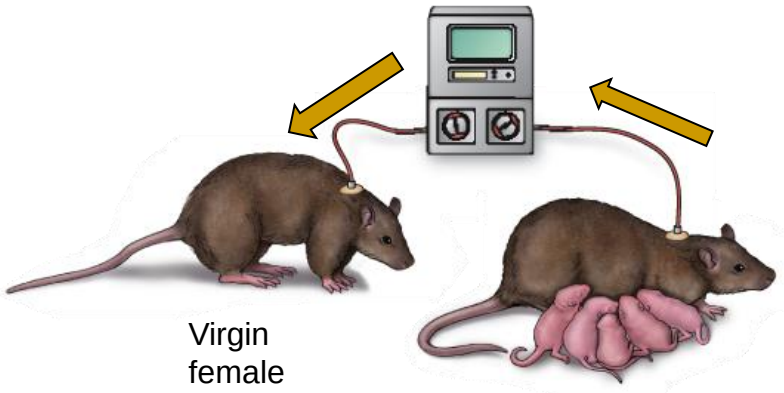
Postpartum day 16



Mattson et al. 2001

Maternal behavior induced by maternal blood plasma

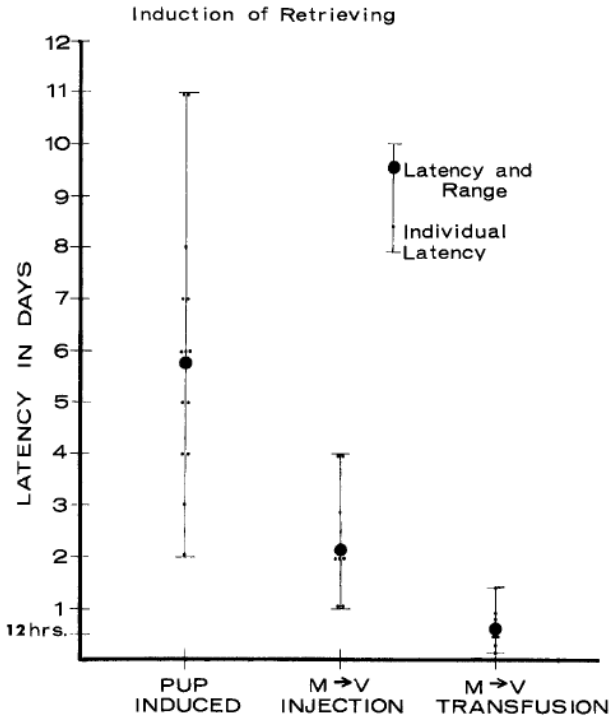
Joseph Terkel



Blood was transfused from a parturient female (one that had given birth within 30 min prior to the onset of the transfusion) into a virgin female.

Terkel and Rosenblatt, 1968

Hormonal factors underlying maternal behavior

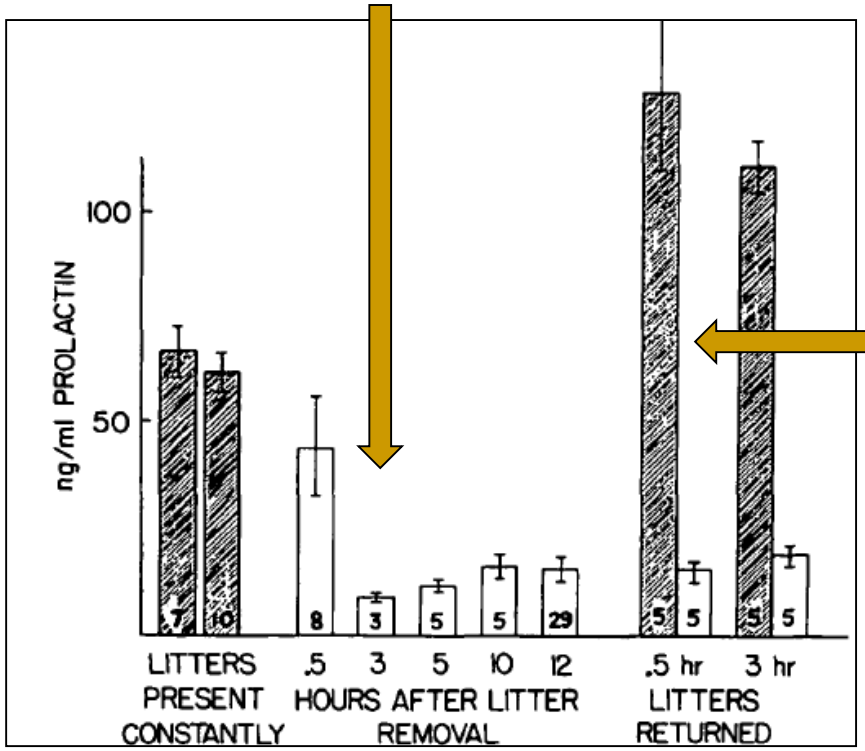


Maternal behavior of virgin females toward newborn (unfamiliar) pups is facilitated following blood transfusion from maternal females (lactating)

Terkel and Rosenblatt, 1972

Prolactin in serum and maternal care in rats

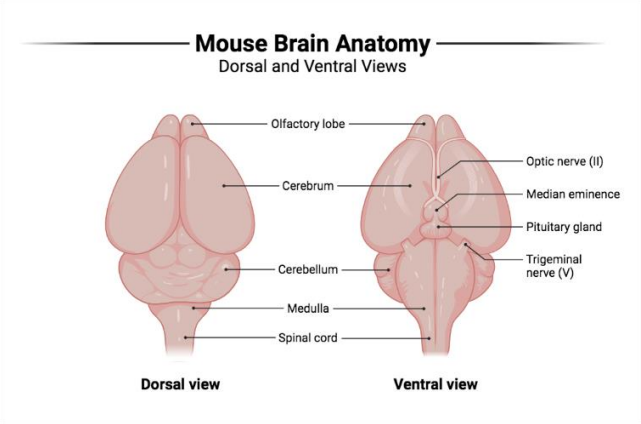
• Removal of litters from mother rats resulted in a rapid decline of serum prolactin levels, reaching pregnancy levels 3 hr later

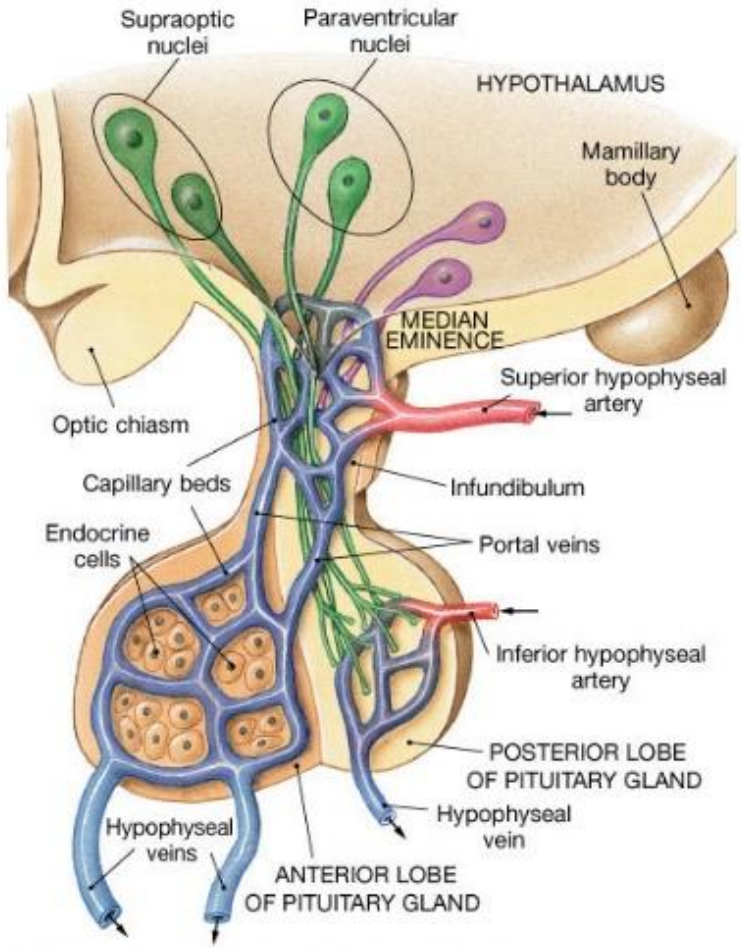


• When litters were returned to their mothers for 0.5-3 hr serum prolactin increased sharply

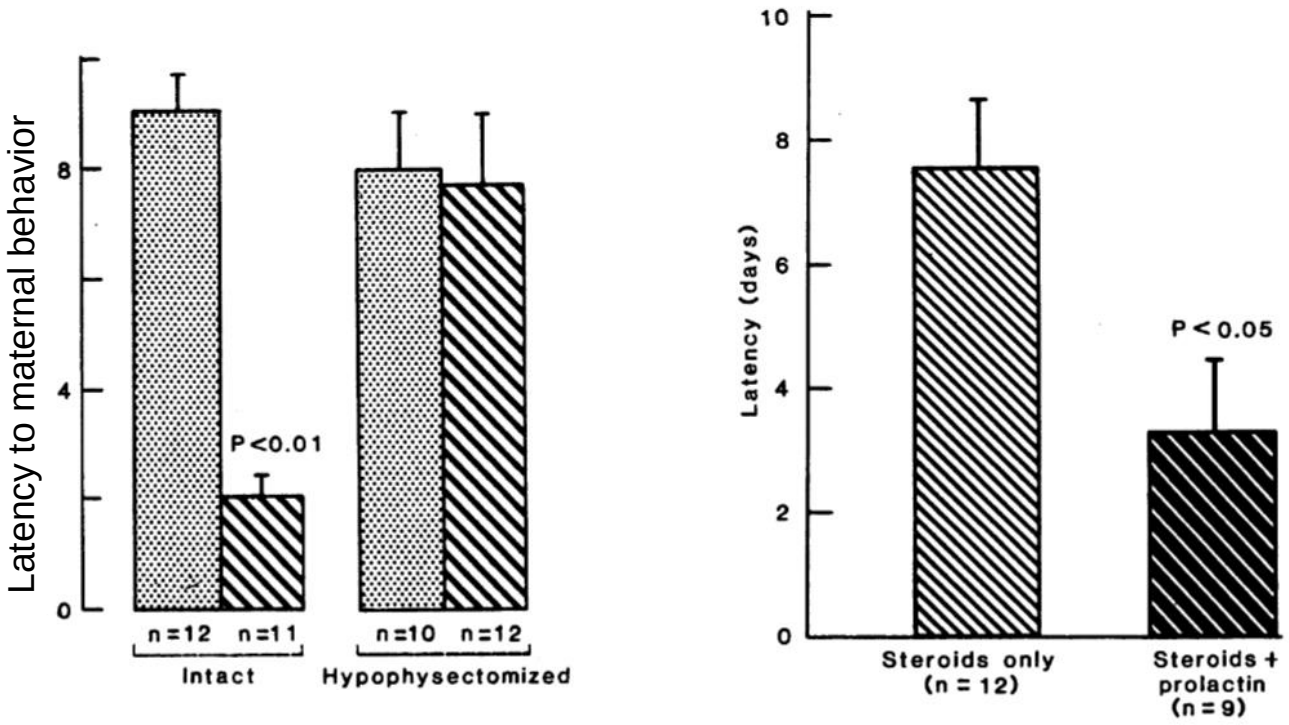
Amenomori et al 1970

Prolactin is released from the pituitary gland and required for maternal care



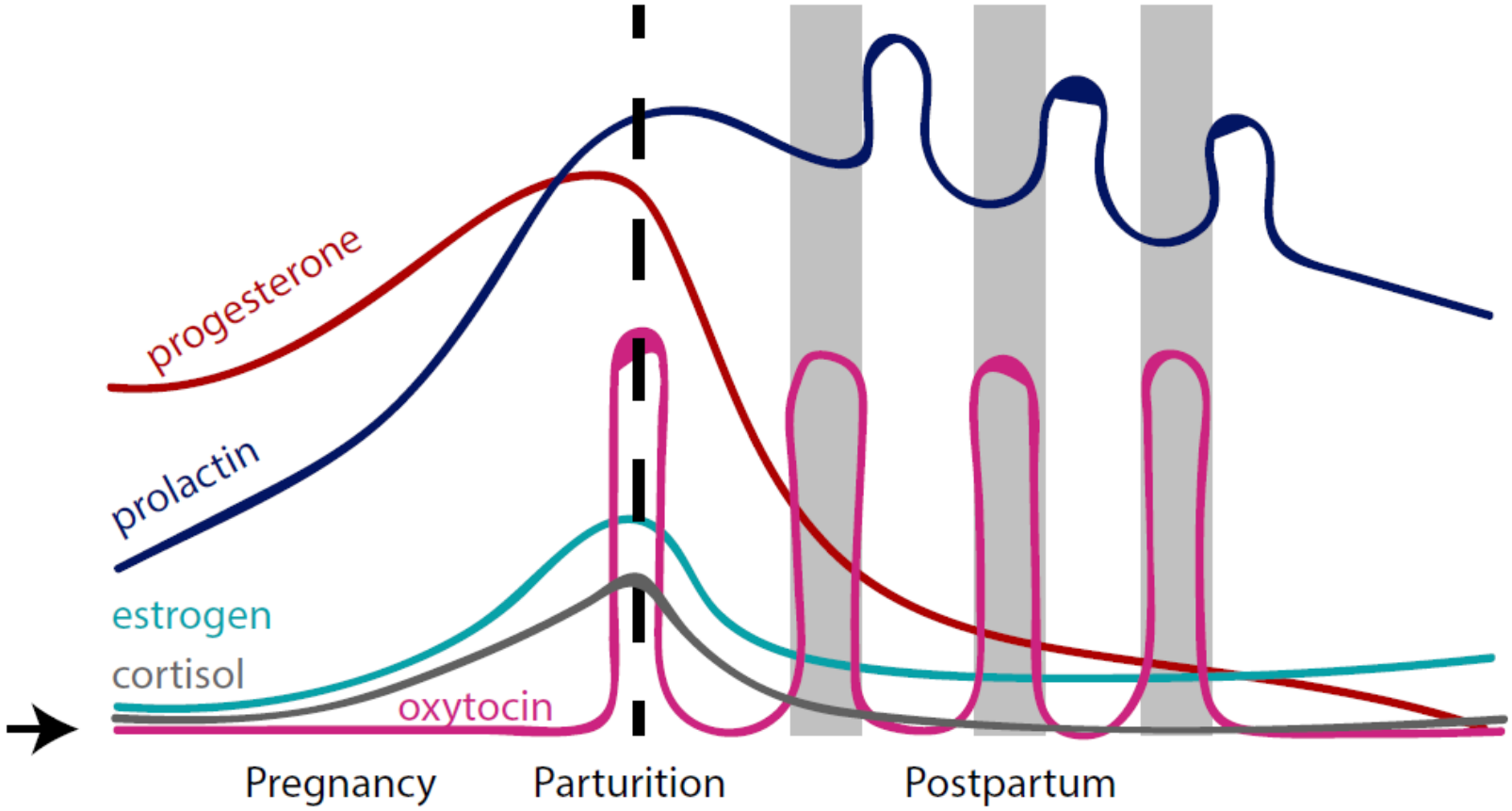


Prolactin is released from the pituitary gland and required for maternal care

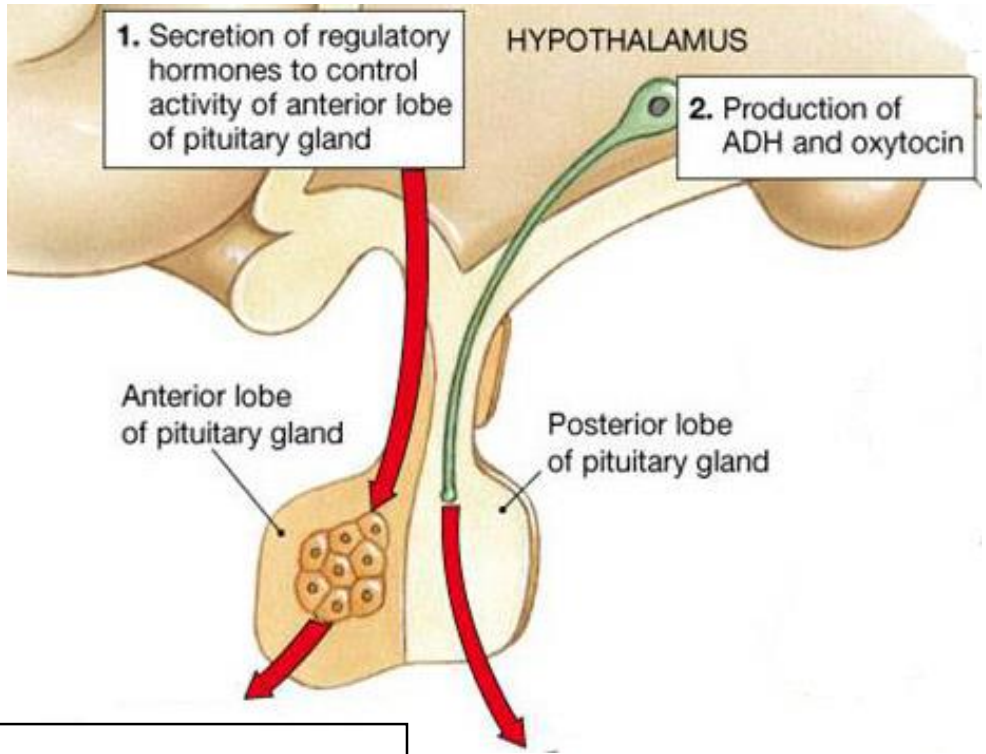


*Naïve rats ovariectomized treated
with steroids (estradiol+progesterone)

Bridges et al. 1984


progesterone
prolactin
estrogen
cortisol
oxytocin
Pregnancy
Parturition
Postpartum

The Hypothalamus-Pituitary-Gonadal Axis

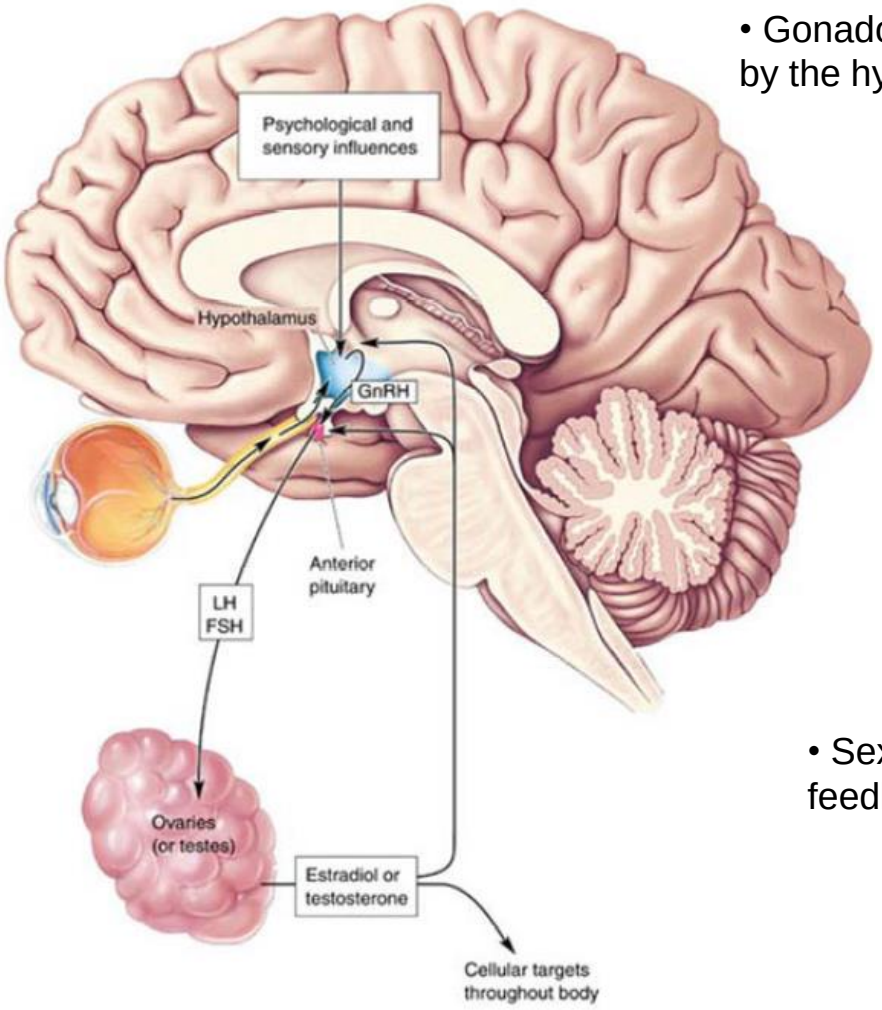


Prolactin (PRL)
Growth Hormone (GH)
Adrenocorticotropic hormone (ACTH)
Thyroid-stimulating hormone (TSH)
Follicle-stimulating hormone (FSH)
Luteinizing hormone (LH)

Vasopression
Oxytocin

Hormonal regulation on sexual behavior

The Hypothalamus-Pituitary-Gonadal Axis



• Gonadotropin Releasing Hormone (GNRH) is released by the hypothalamus to stimulate anterior pituitary

↓

• Gonadotroph cells in anterior pituitary release Luteinizing Hormone (LH) & Follicle-Stimulating Hormone (FSH).

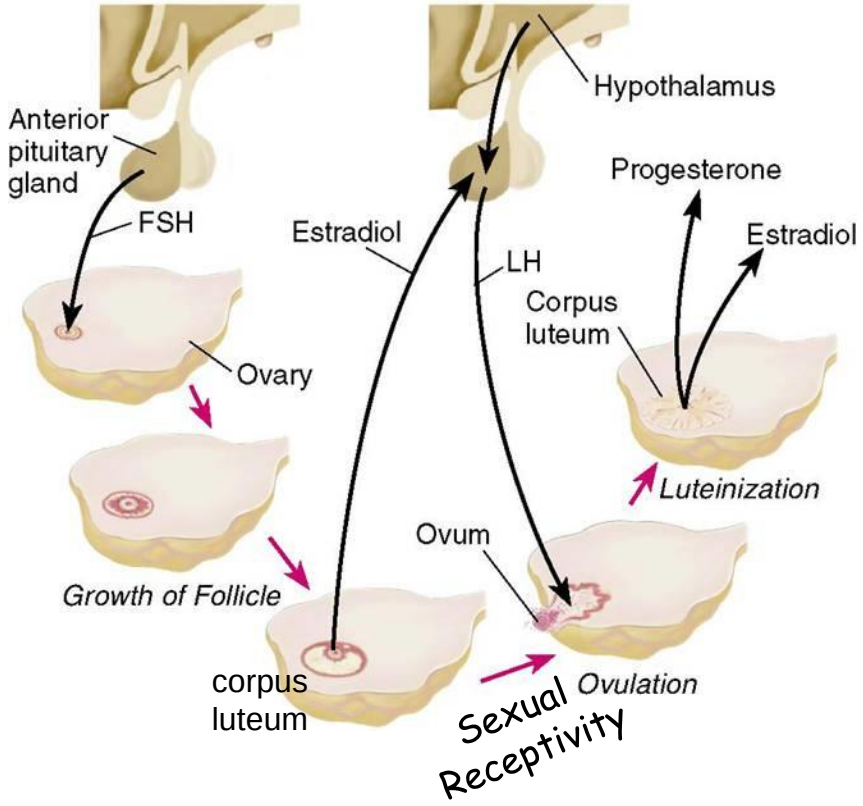
↓

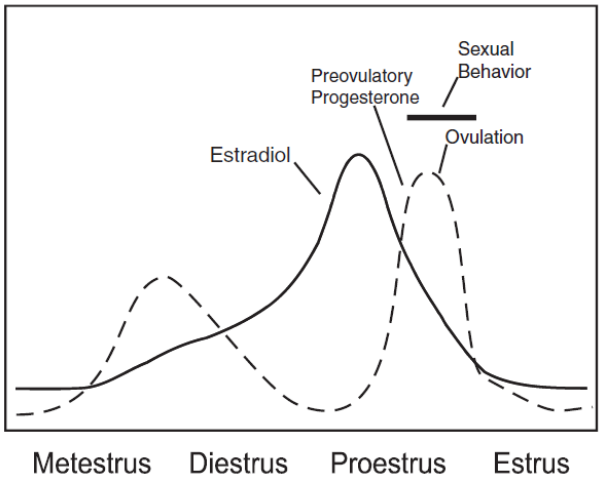
• LH and FSH stimulates the gonads (Testes and Ovaries).

↓

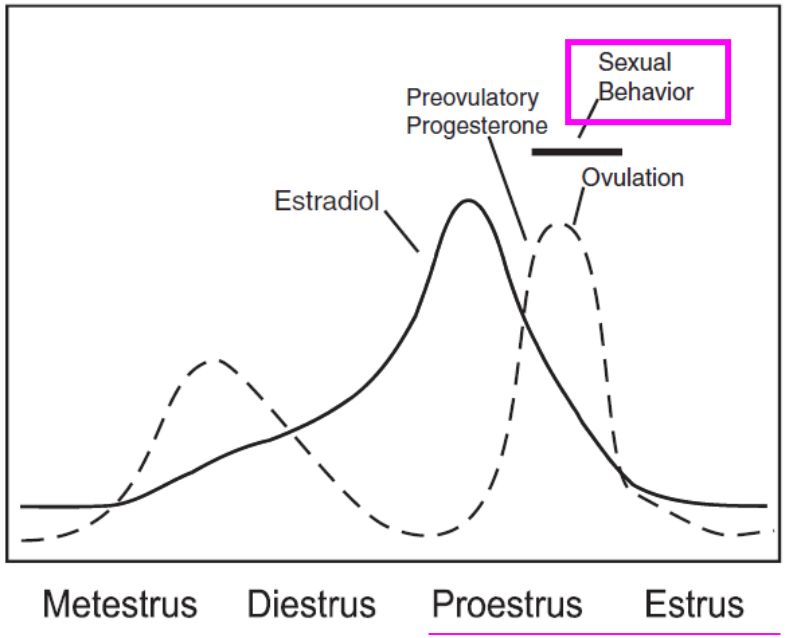
• Sex hormones released from the gonads feedback to influence brain functions

The Hypothalamus-Pituitary-Gonadal Axis and estrous cycle of female rats





Hormonal activation of female-typical sexual behavior

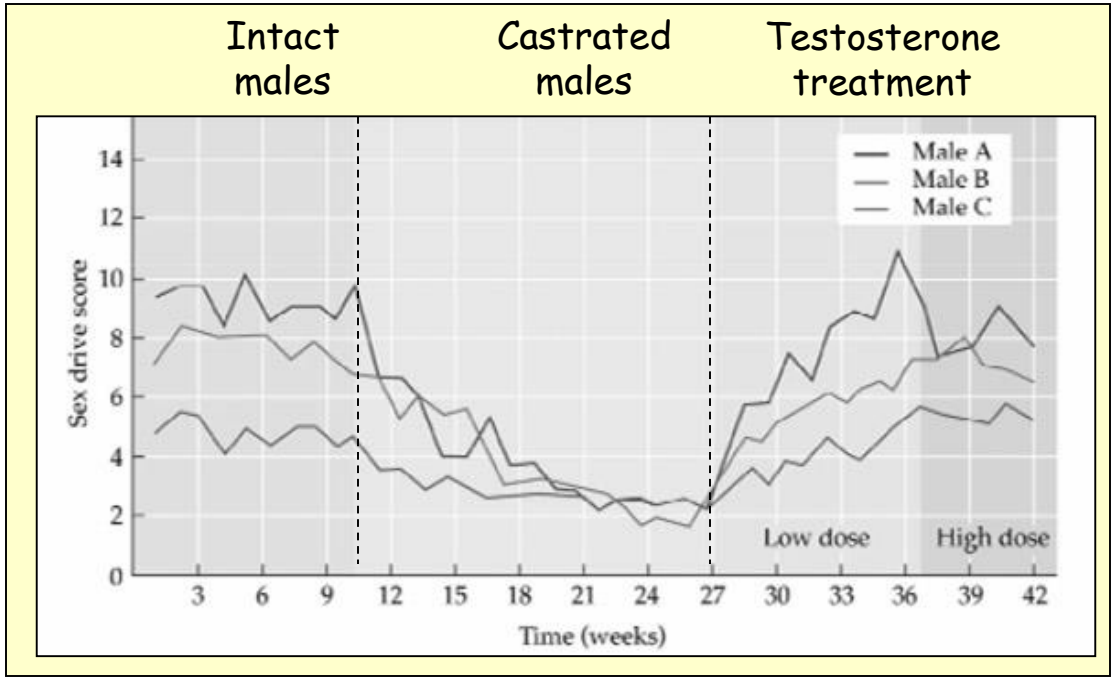


0 hours	42 hours	Lordosis?[1]
Oil	Oil	No
Estradiol (low dose)	Oil	Usually low
Oil	Progesterone	No
Estradiol	Progesterone	High

- In all rodents, gonadectomy decreases (abolishes) female sexual receptivity

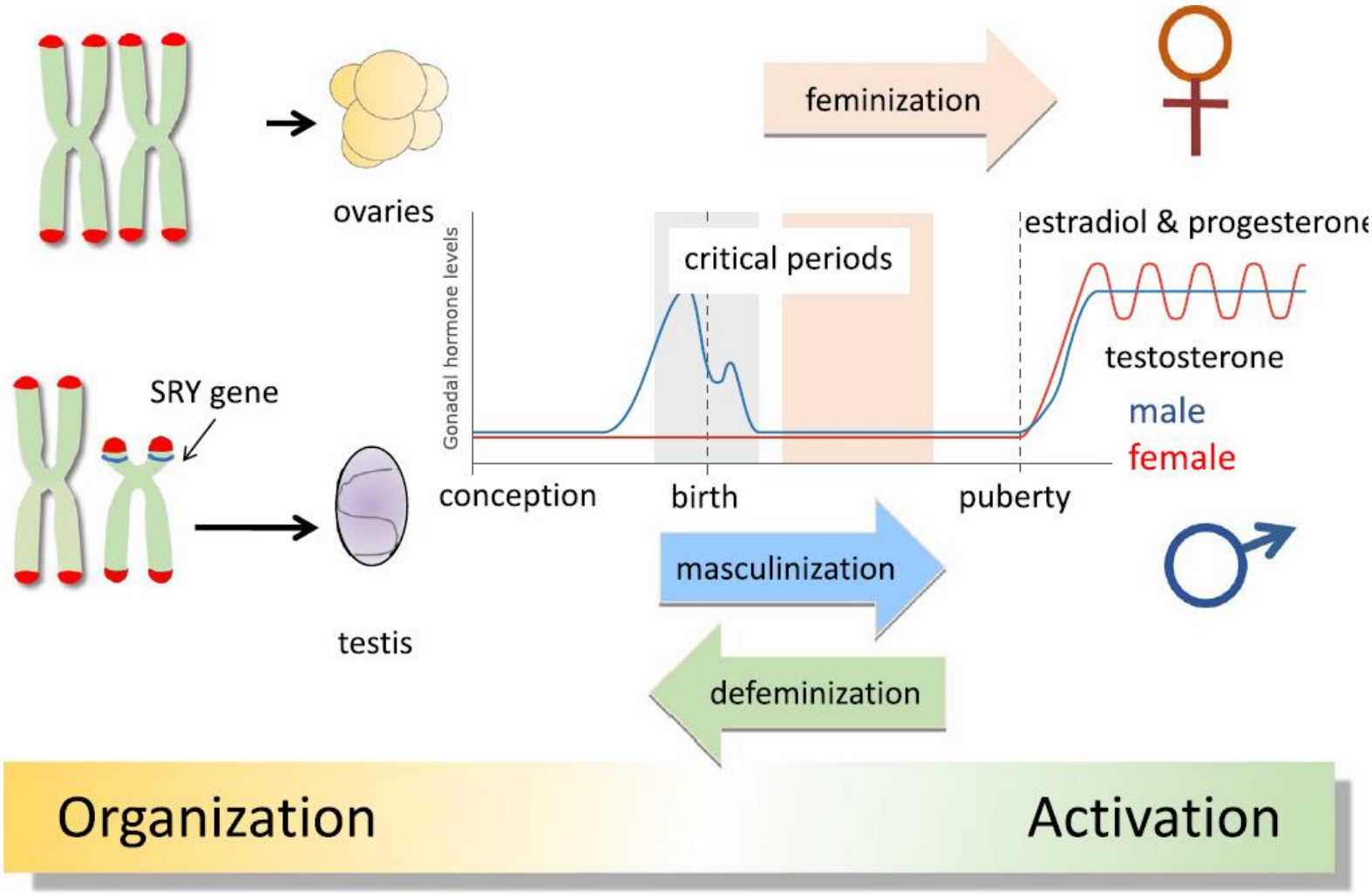
- Estrogen and progesterone replacement reinstates sexual behavior of females

Effects of castration & testosterone treatment on males



•In all rodents, gonadectomy decreases (abolishes) male courtship and sexual behavior

•Testosterone replacement reinstates sexual behavior in males



McCarthy 2020

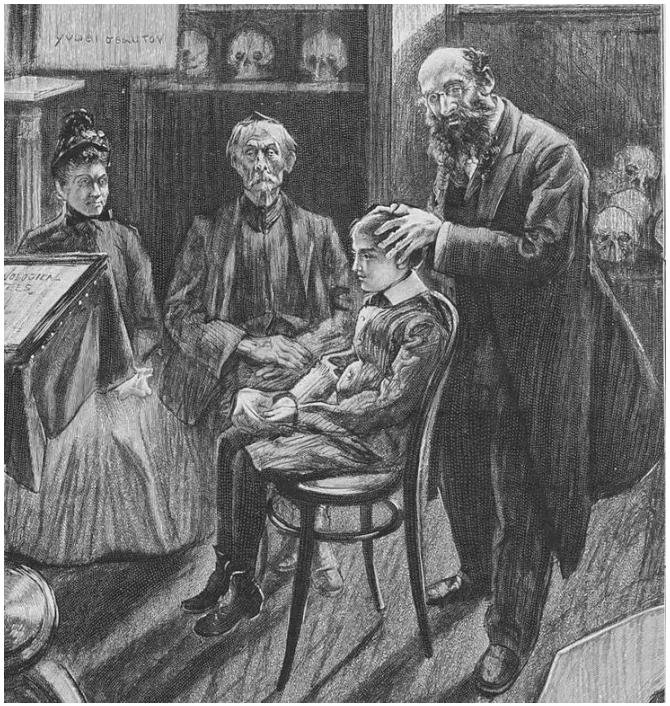
The relationship between organization of the brain and behavioral function in adulthood

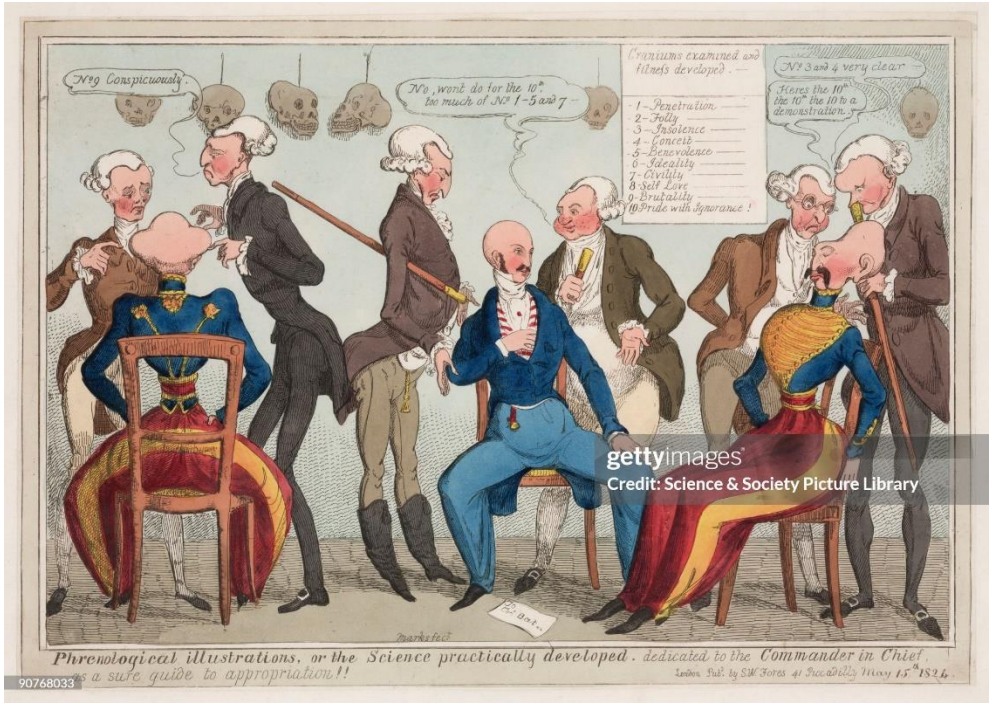
Phenology and Localization

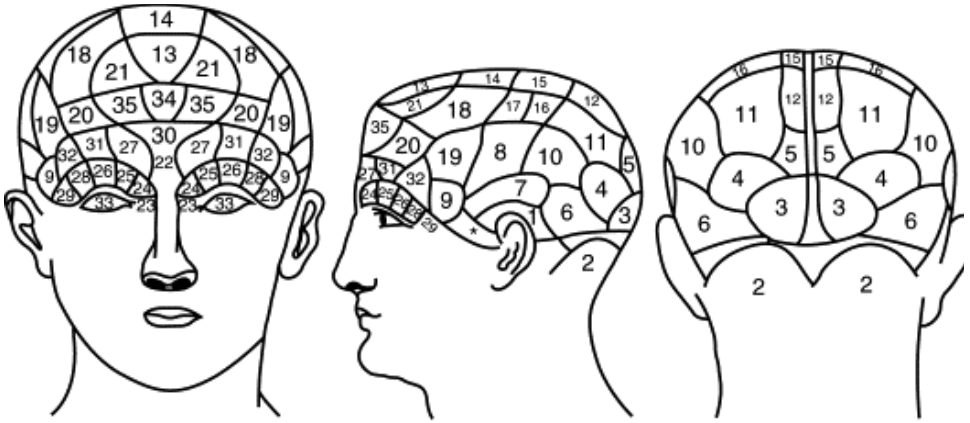
Franz Joseph Gall (1758-1828)

Person's personality and mental functions/diseases could be determined by the shape of their skull

Based on the concept that the brain is the organ of the mind, and that certain brain areas have localized, specific functions or modules.







Affective faculties

Propensities	Sentiments
Desire to live	10 Cautiousness
* Alimentiveness	11 Approbativeness
1 Destructiveness	12 Self-esteem
2 Amativeness	13 Benevolence
3 Philoprogenitiveness	14 Reverence
4 Adhesiveness	15 Firmness
5 Inhabitiveness	16 Conscientiousness
6 Combativeness	17 Hope
7 Secretiveness	18 Marvelousness
8 Acquisitiveness	19 Ideality
9 Constructiveness	20 Mirthfulness
	21 Imitation

Intellectual faculties

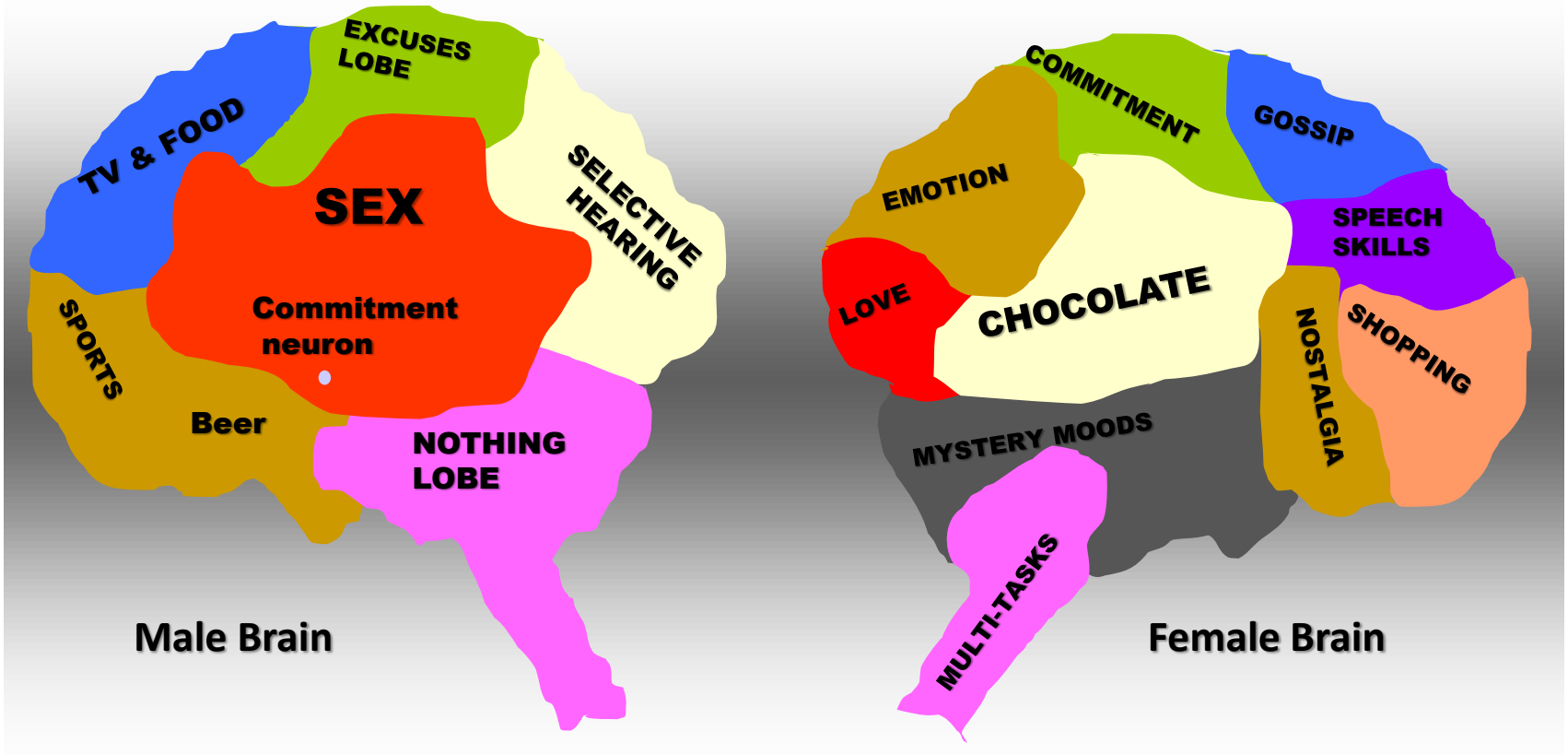
Perceptive	Reflective
22 Individuality	34 Comparison
23 Configuration	35 Causality
24 Size	
25 Weight and resistance	
26 Coloring	
27 Locality	
28 Order	
29 Calculation	
30 Eventuality	
31 Time	
32 Tune	
33 Language	

“The study of the organization of the brain should march side by side with that of its functions.”

How can the female and male brains explain why females and males are so different?

Dimorphic brain functions/structures → Dimorphic social behaviors ?

How can the female and male brains explain why females and males are so different?



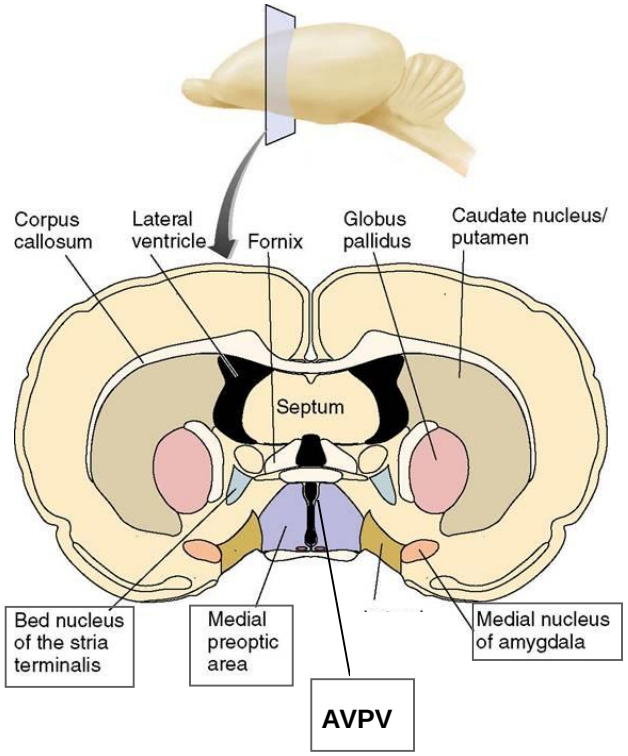
Sexually dimorphic brain nuclei in rodents

Bed Nucleus of the Stria Terminalis (BNST)
Sexually Dimorphic-Nucleus of Preoptic Area (SDN-POA)
Posterodorsal Medial Amygdala (MePD)

} Larger in male

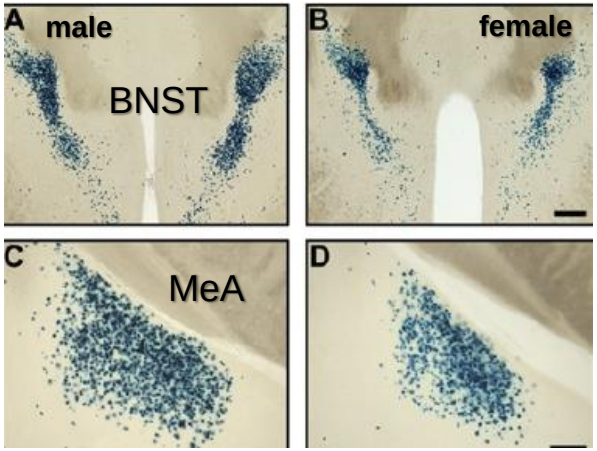
Anteroventral Periventricular Nucleus (AVPV)

} Larger in Female



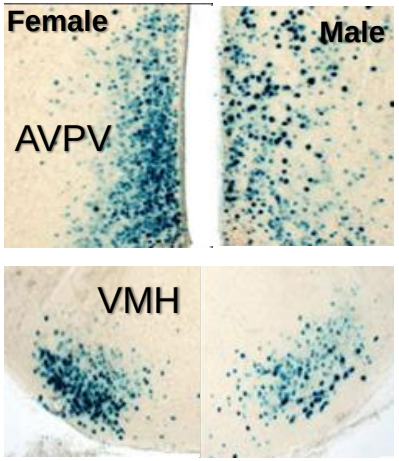
Sexual dimorphism: Gene expression

Androgen receptor



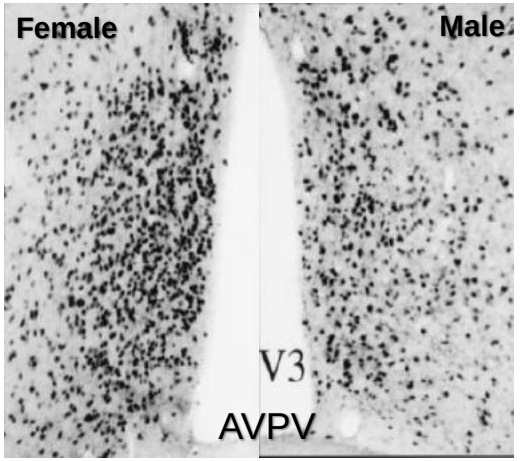
Juntti et al 2010, *Neuron*

Progesterone receptor



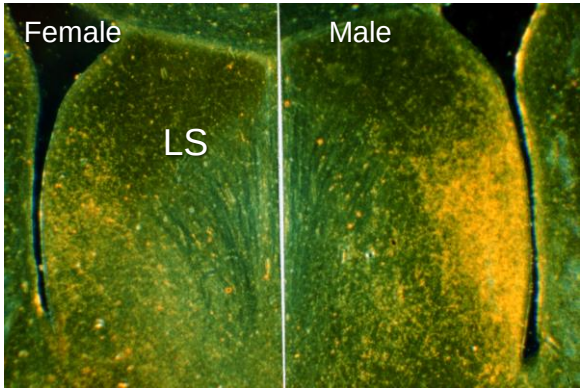
Yang et al 2013, *Cell*

Estrogen receptor α



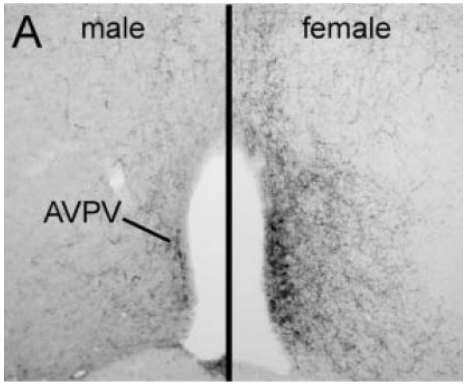
Simerly et al 1997, *PNAS*

Vasopressin fibers



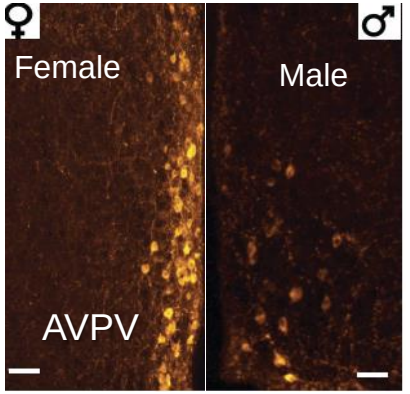
(Curtesy Geert de Vries)

Kisspeptin



Clarkson & Herbison 2006, *Endocrinology*

Tyrosine Hydroxylase

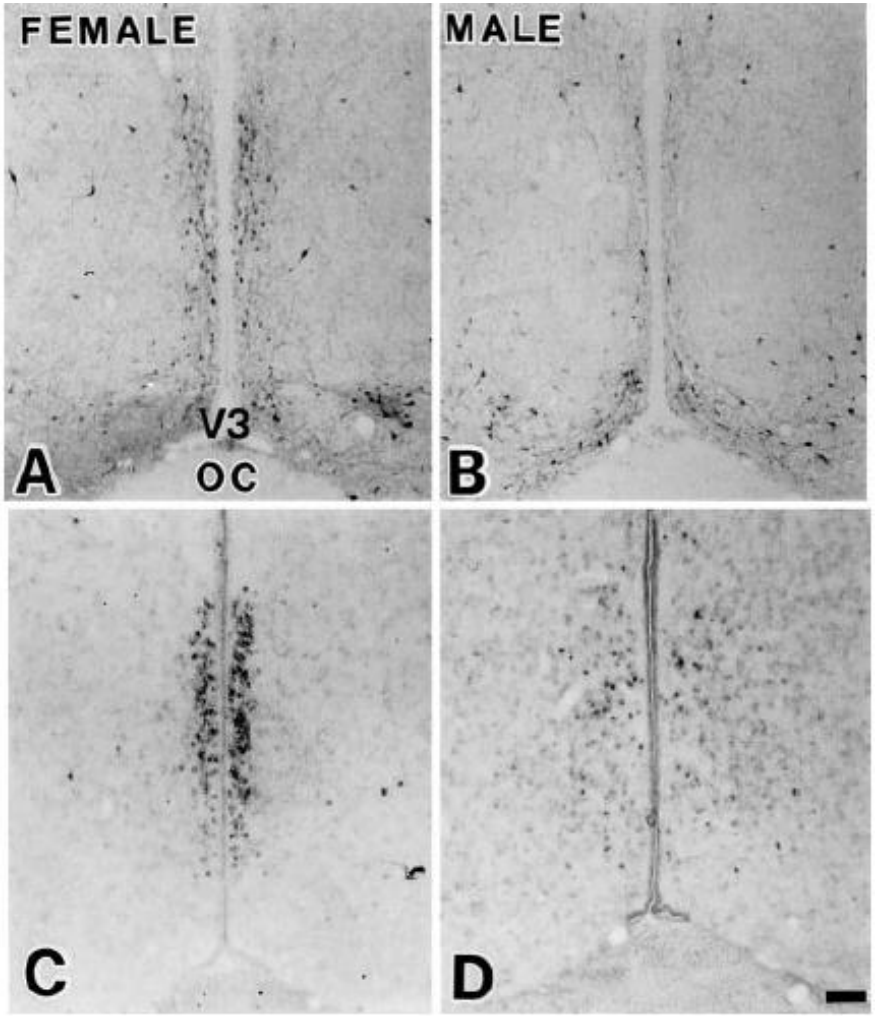


Scott et al 2015, *Nature*

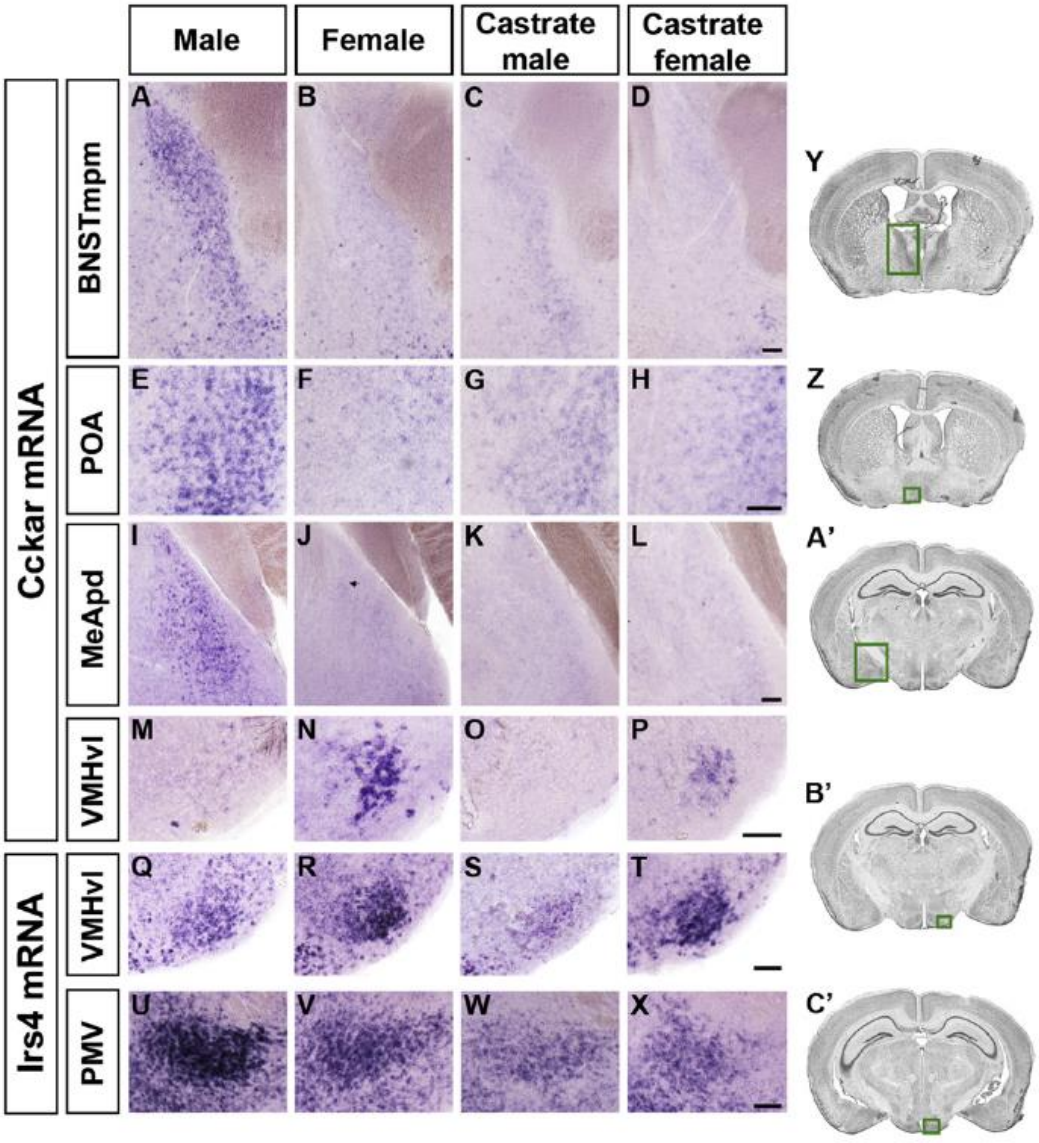
Sex differences in esrtogen-receptor-beta in the AVPV of rats can be altered by hormonal manipulation

Adult-intact

Prenatally hormone-manipulated

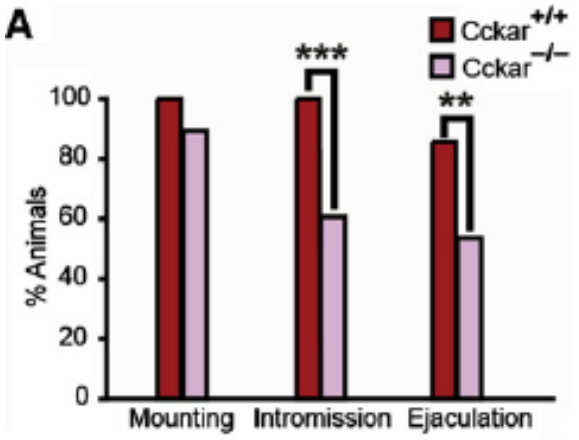


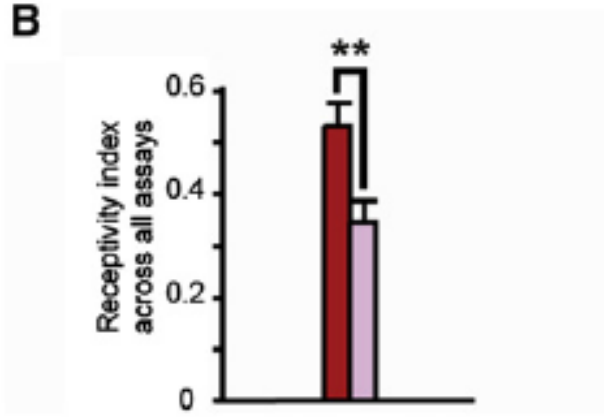
Orikasa et al 2001


Male
Female
Castrate male
Castrate female
Cckar mRNA
Irs4 mRNA
BNSTmpm
POA
MeApd
VMHvl
VMHvl
PMV
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
Q
R
S
T
U
V
W
X
Y
Z
A'
B'
C'

Xu et al 2012

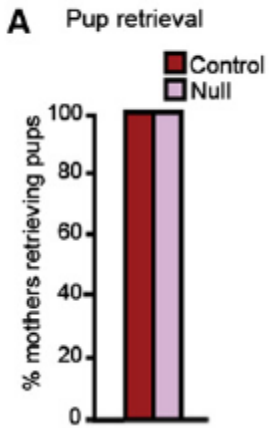
Control of female sexual behavior by *Cckar*

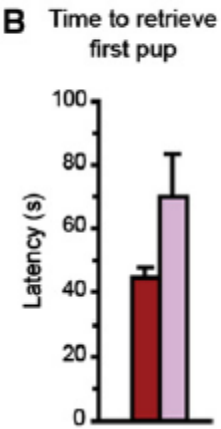


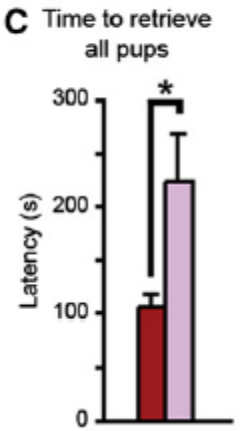


Control of maternal behaviors by *Irs4*

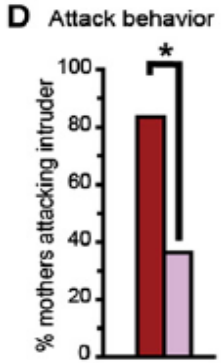
Maternal care

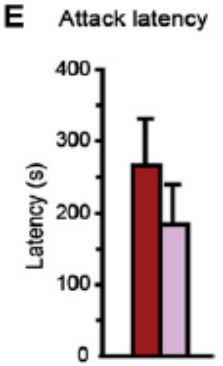


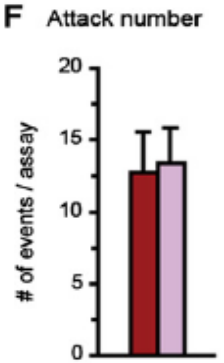


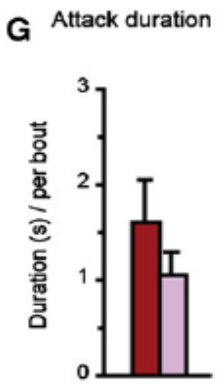


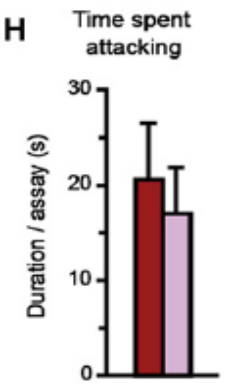
Maternal aggression

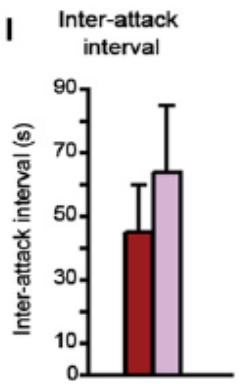








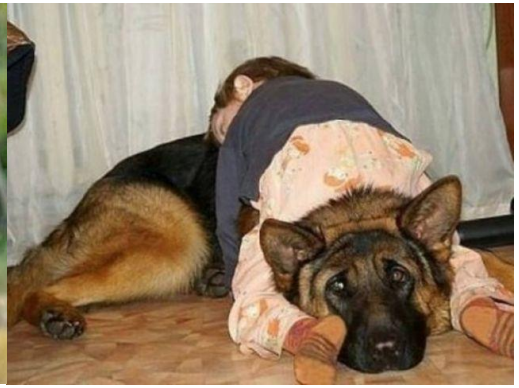




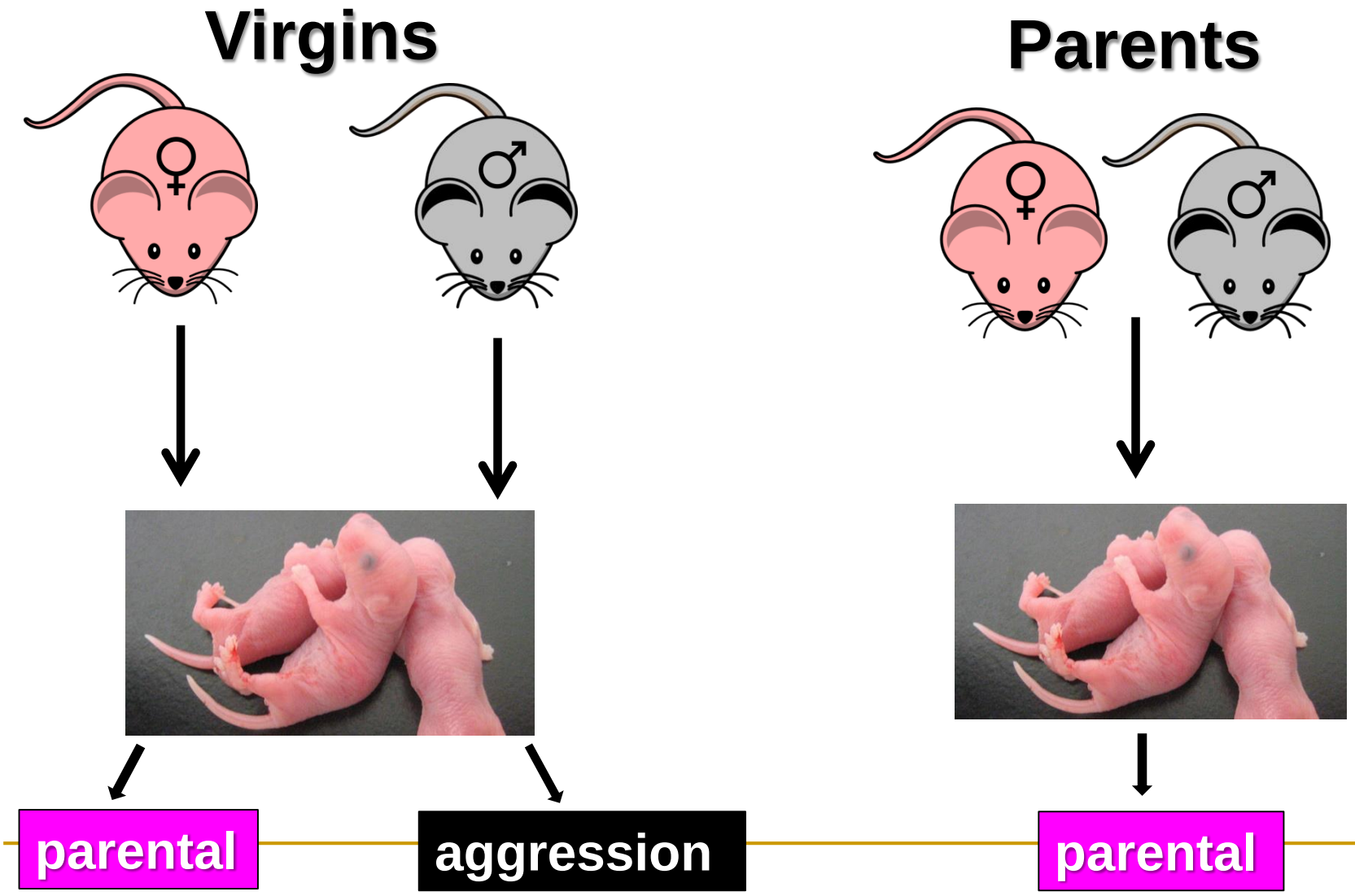
How are sexually dimorphic reproductive behaviors encoded by the male and female brain?

Dimorphic brain functions/structures ⇨ **Dimorphic social behaviors ?**

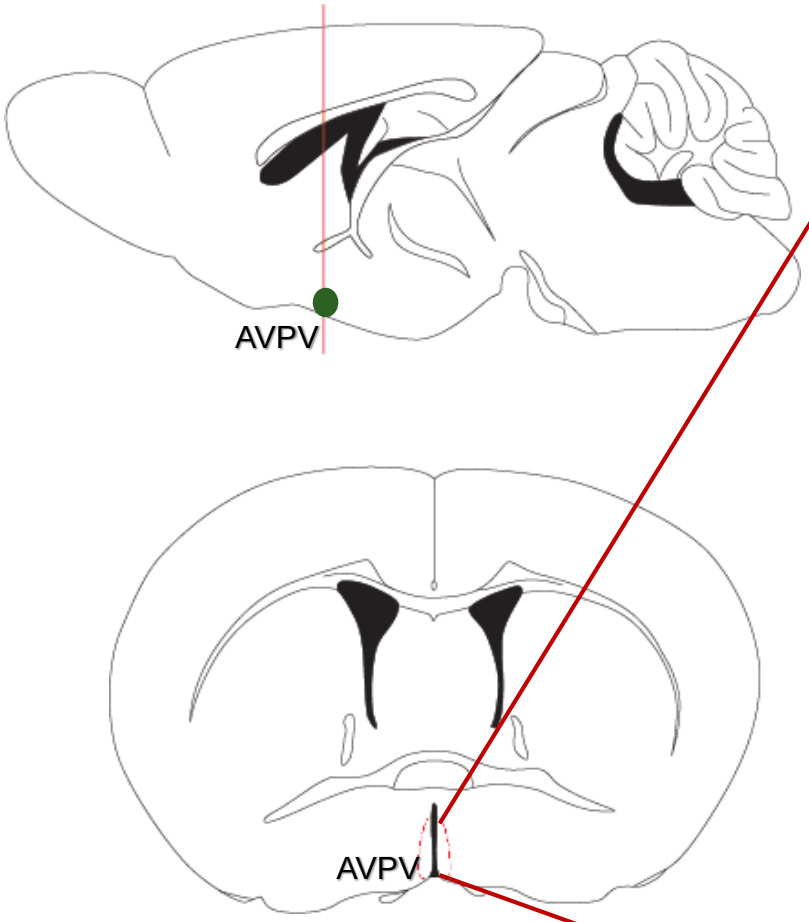
Parental care- evolutionary conserved behavior

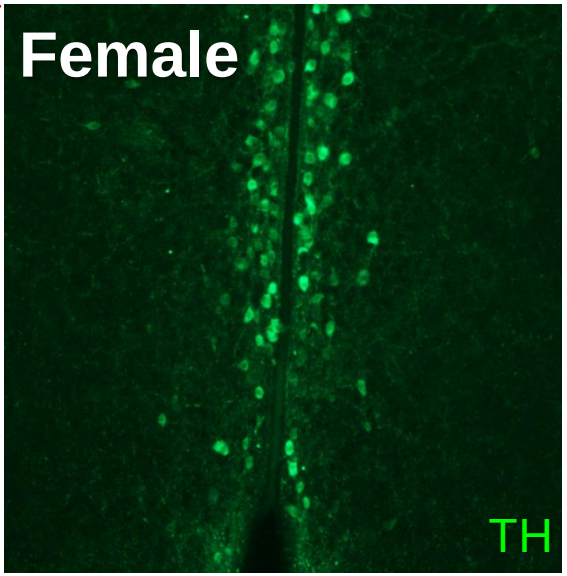


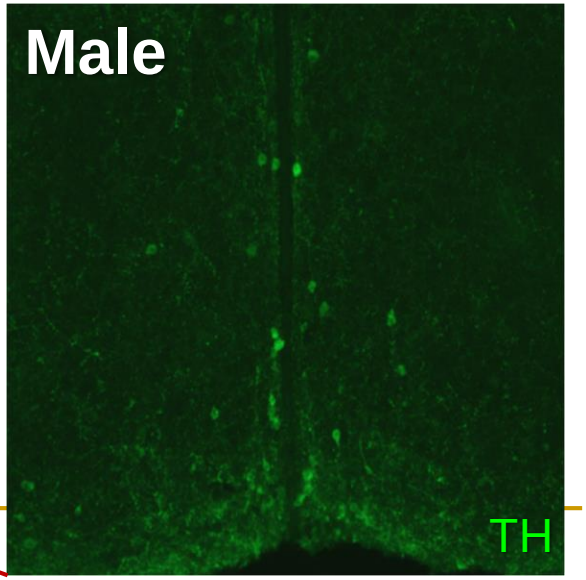
Sexual dimorphism in pup-directed behaviors



Sexual dimorphism in tyrosine hydroxylase-positive neurons in the Anteroventral Periventricular Nucleus (AVPV)







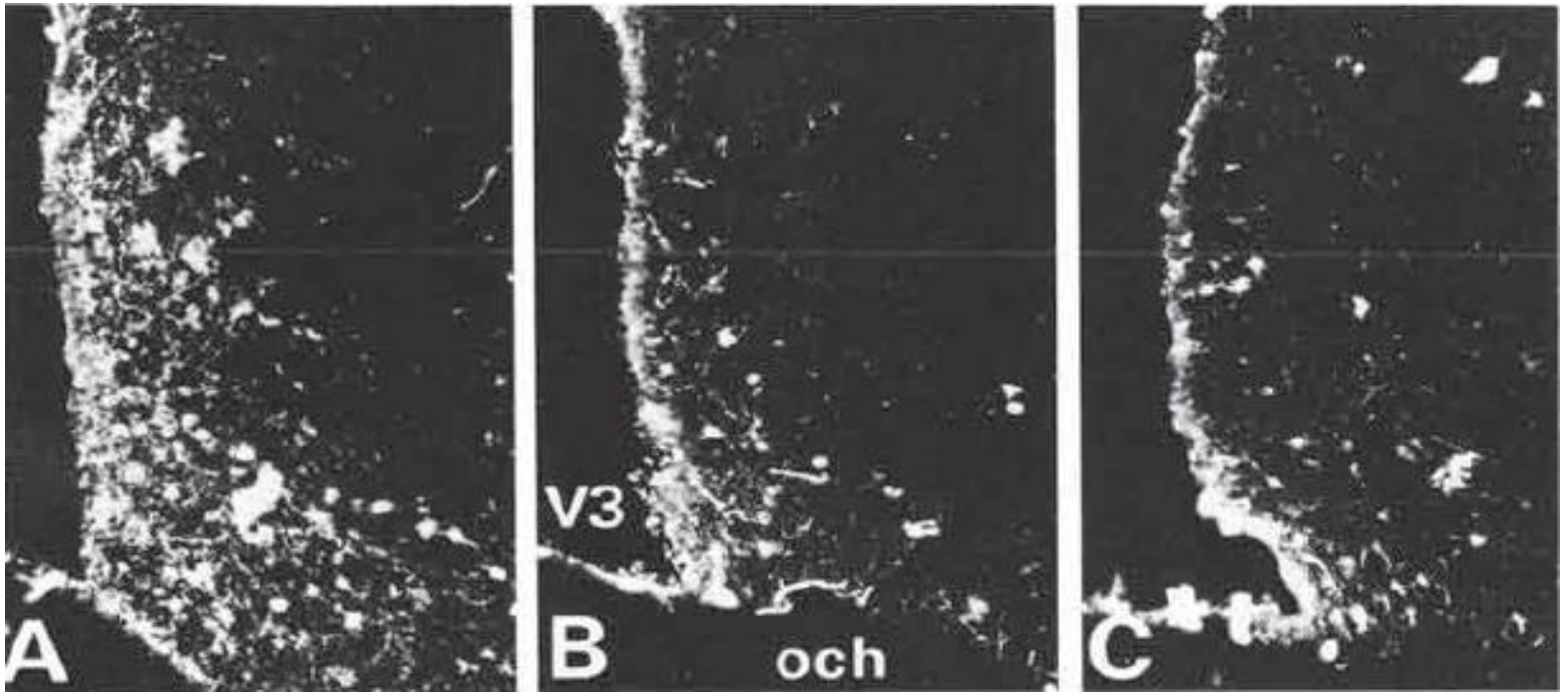
TH= Tyrosine hydroxylase

TH-immunoreactive fibers and cells in the AVPV

Female

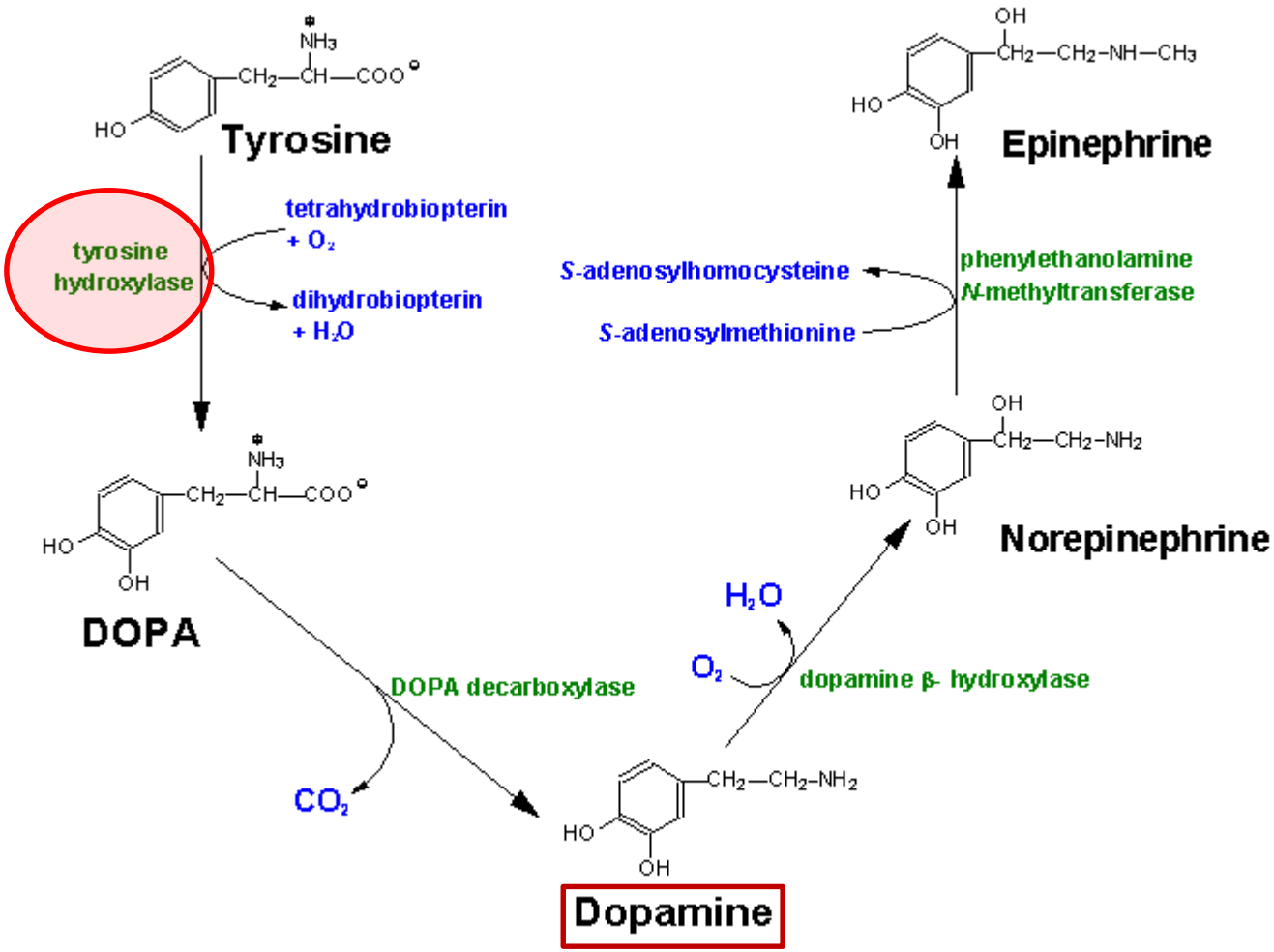
Male

Female+
testosterone (prenatally)



Simerly et al 1985

TH-expressing neurons in the AVPV can produce dopamine

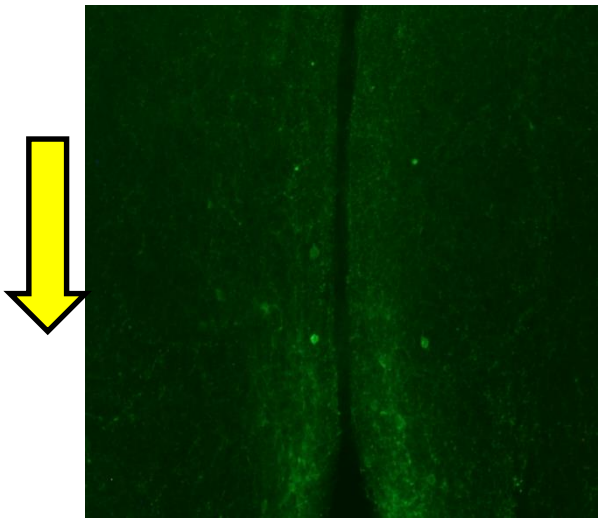


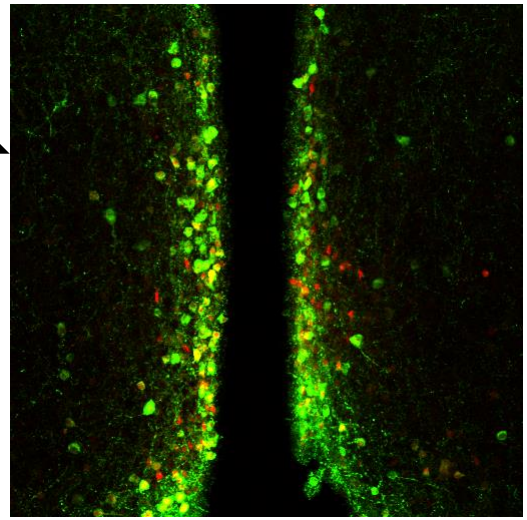
Selective manipulations of TH^{+} AVPV neurons in adult males and females

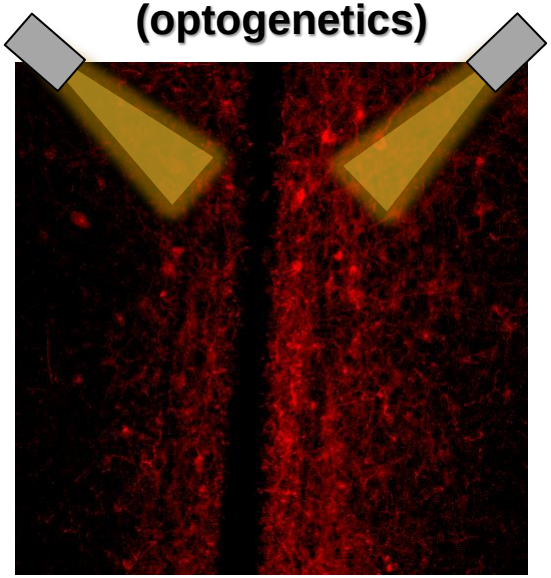
Neuronal ablation

Neuronal over-expression

Neuronal activation using light stimulation (optogenetics)







TH-ablation

TH-overexpression

TH-ChR2

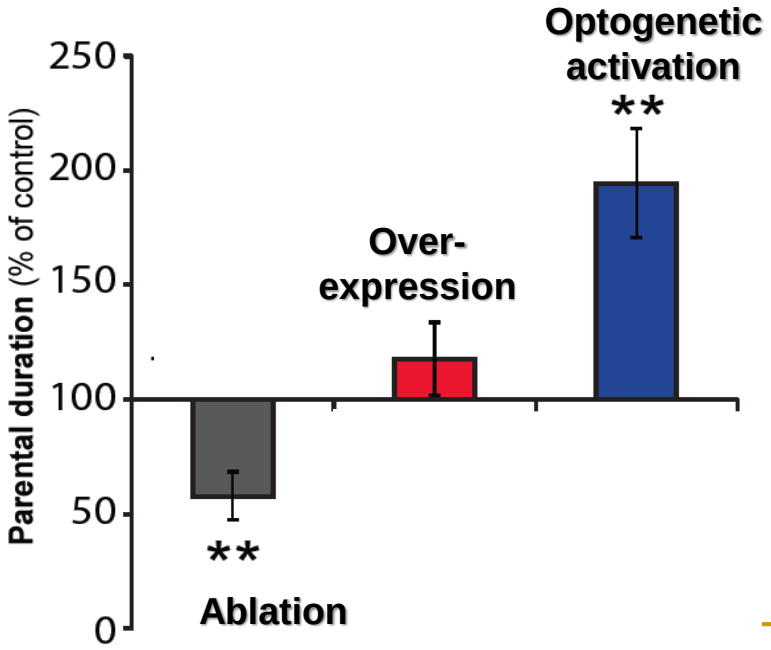
6-OHDA

Scott et al. 2015

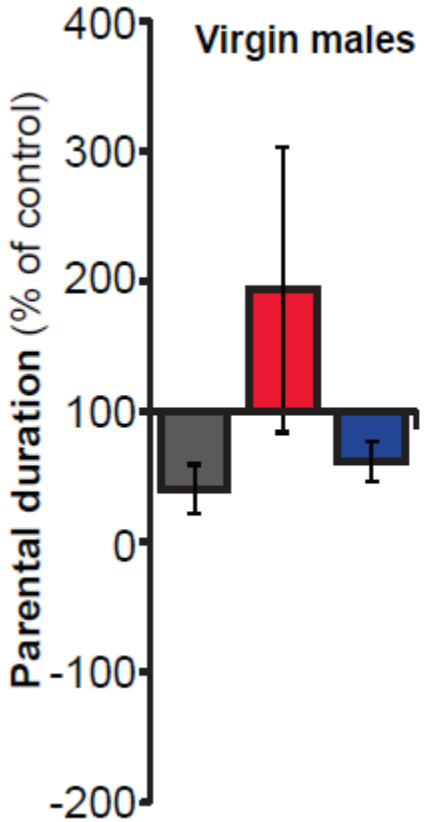
In females, hypothalamic dopaminergic (TH^+ AVPV) neurons promote maternal care

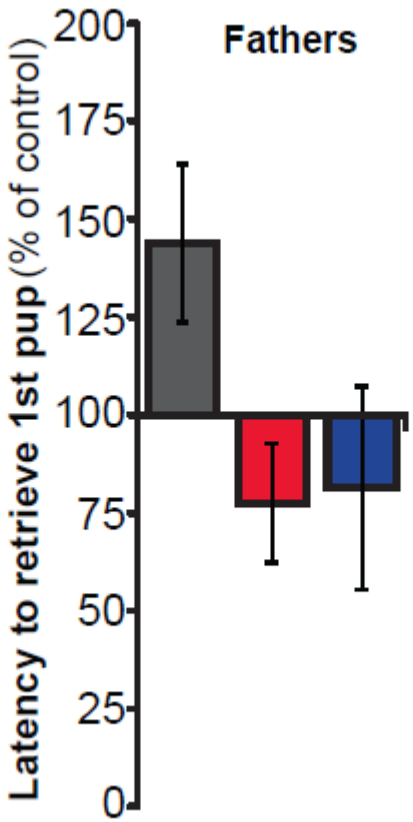
Crouching over the pups

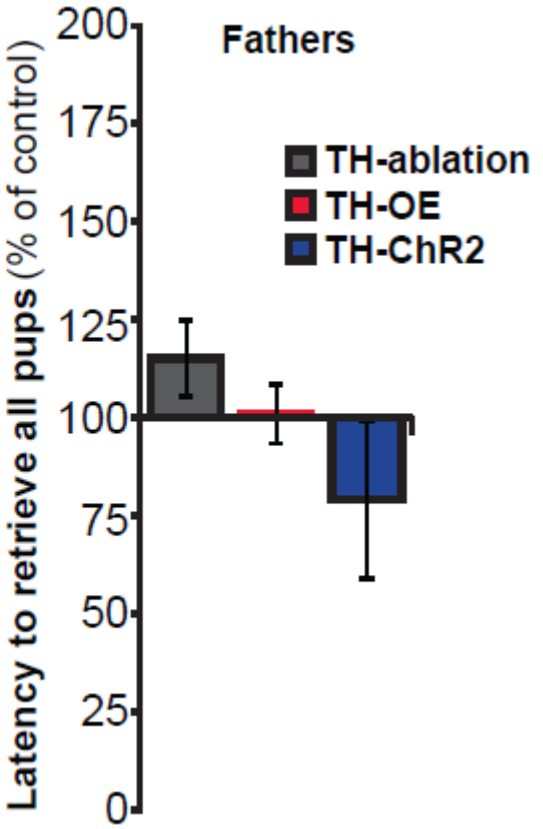
Pup retrieval back to the nest



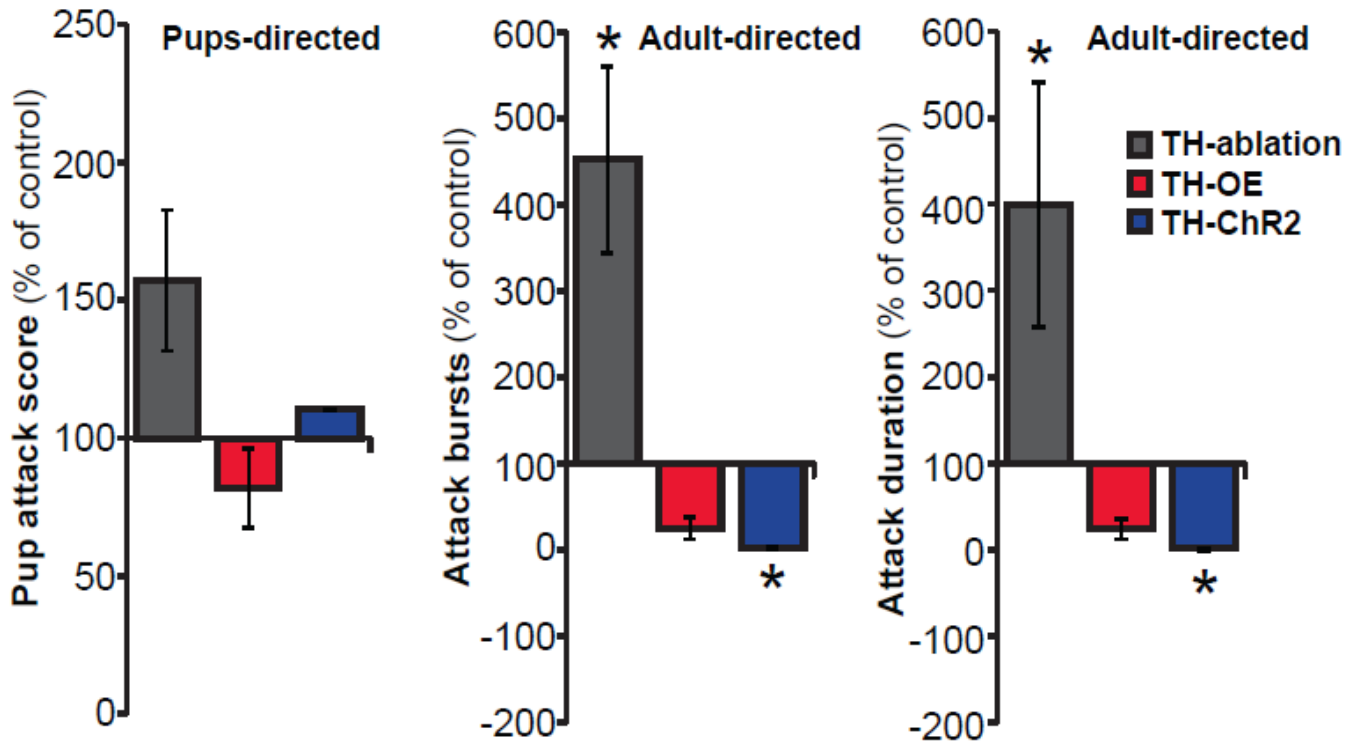
TH^{+} AVPV neurons are not involved in the regulation of parental behavior in males



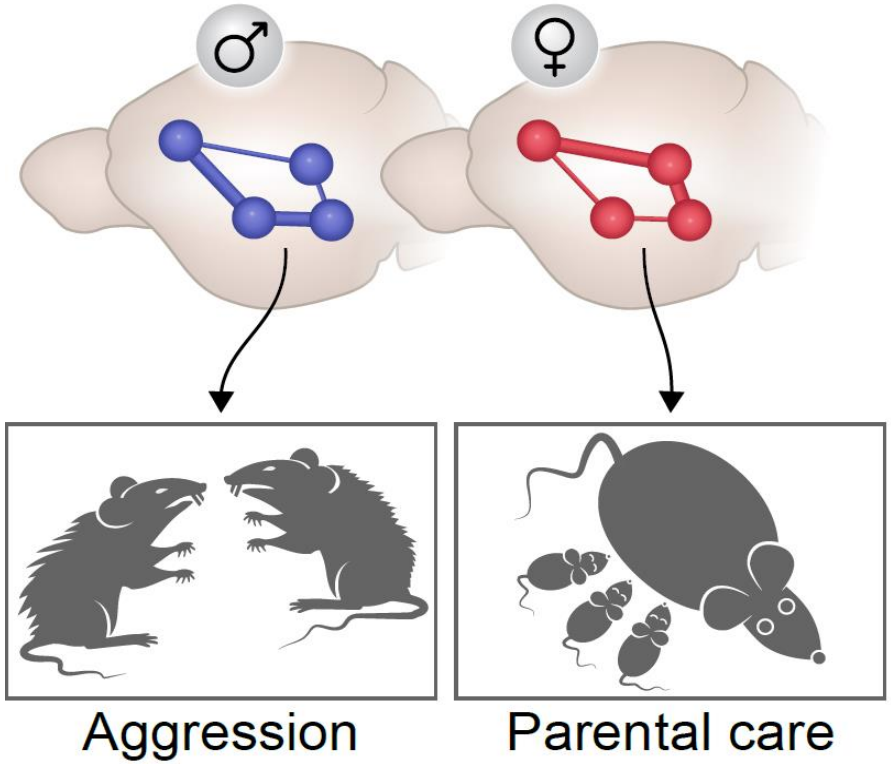




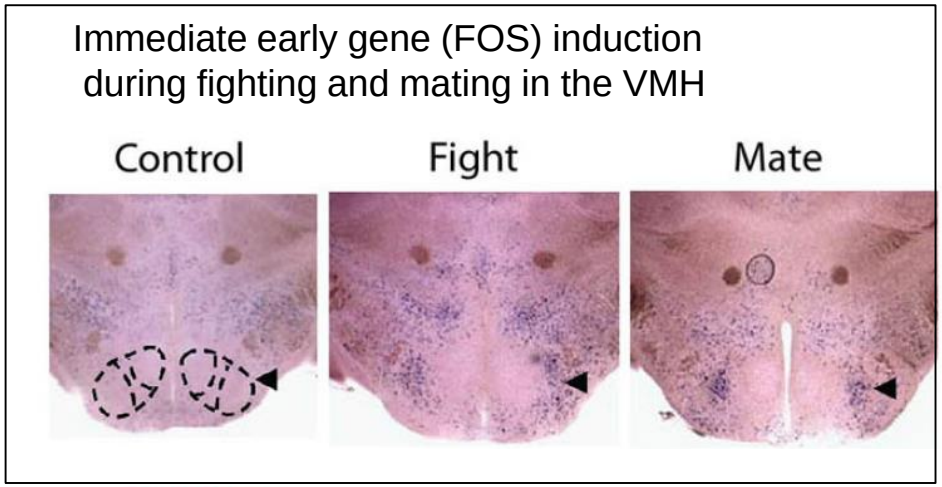
TH^+ AVPV neurons are involved in suppression of conspecific aggressive behaviors

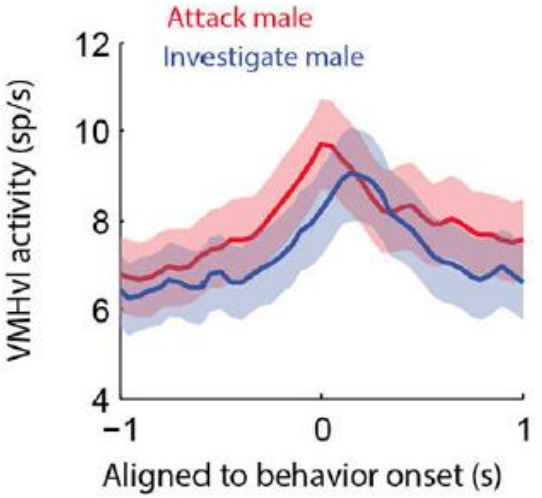


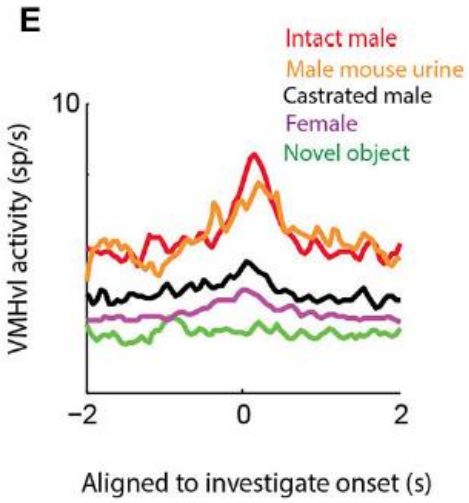
Dimorphic TH$^+$ AVPV neurons control sex-typical behavior in both sexes



Functional identification of an aggression locus in the mouse hypothalamus (VMH)

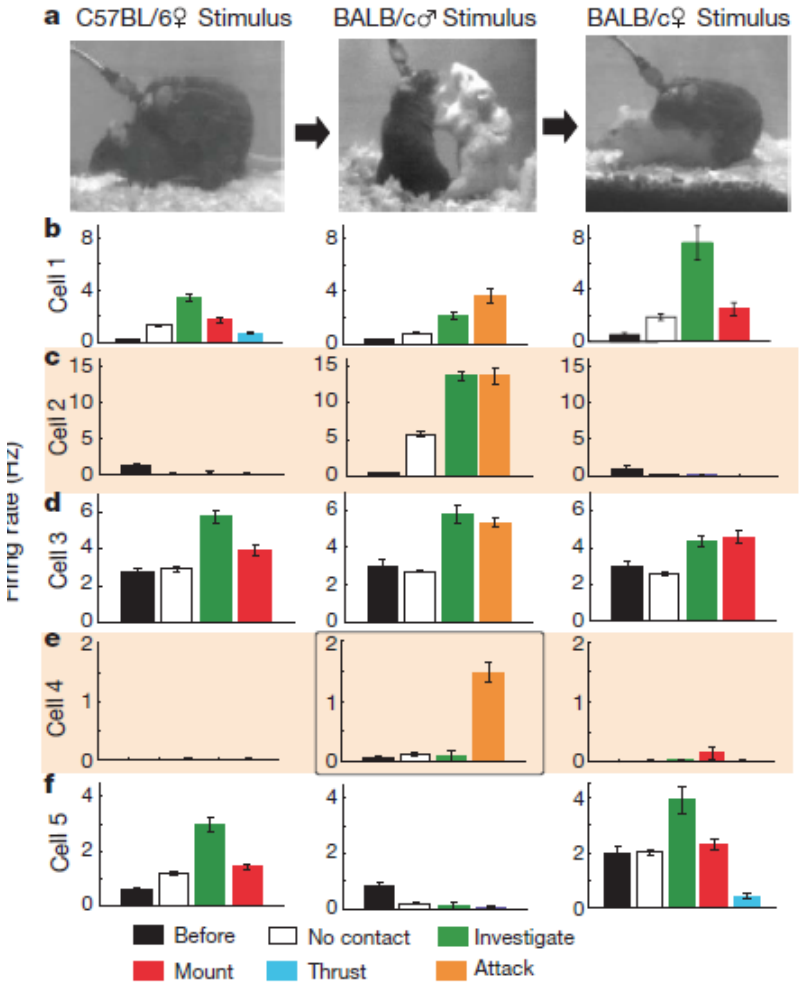






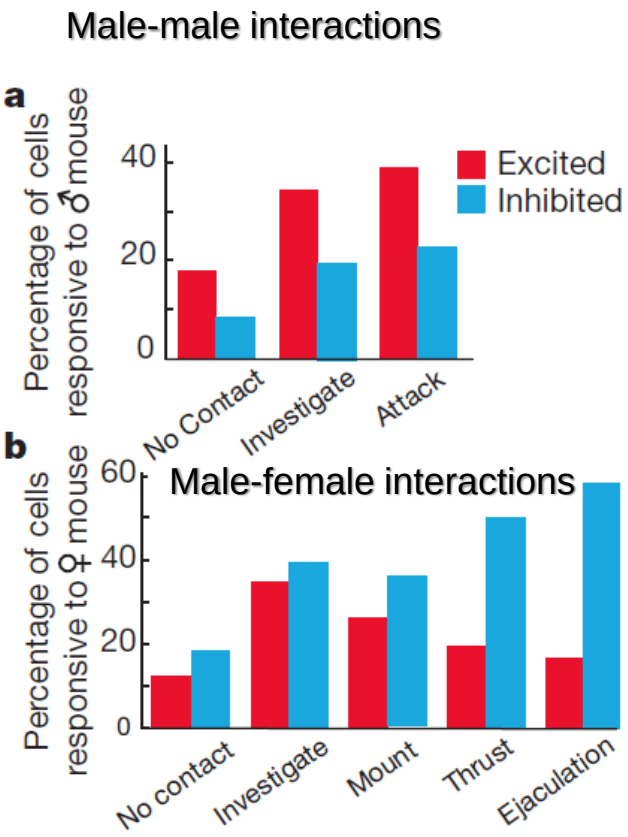
Lin et al 2011
Falkner and Lin 2014

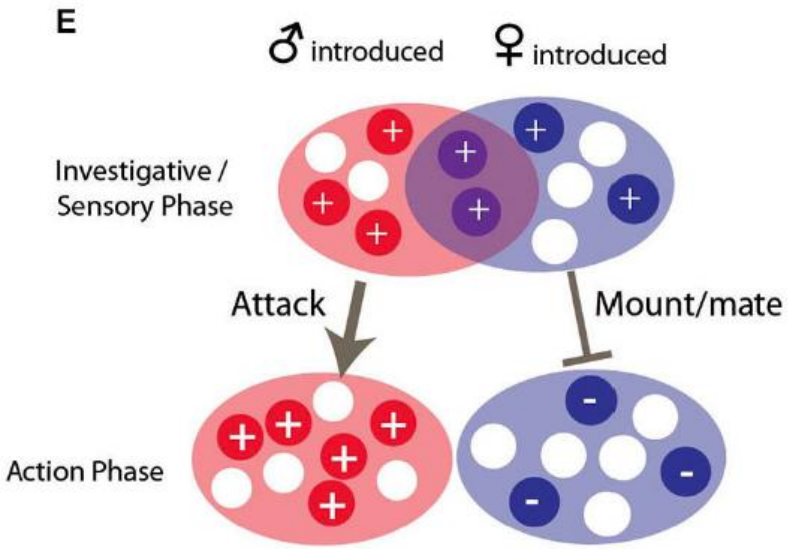
Functional identification of an aggression locus in the mouse hypothalamus (VMH)



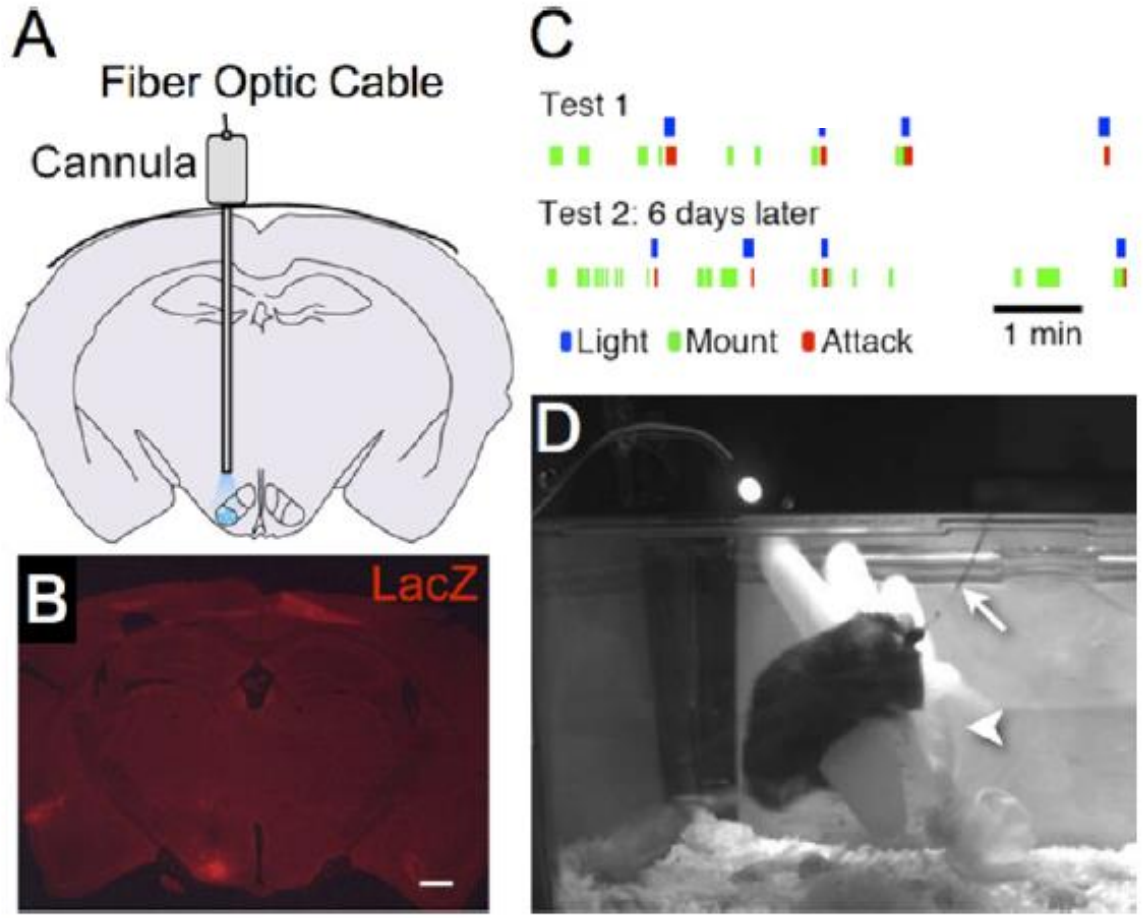
Lin et al 2011
Falkner and Lin 2014

Cell responses in VMH during mating and fighting





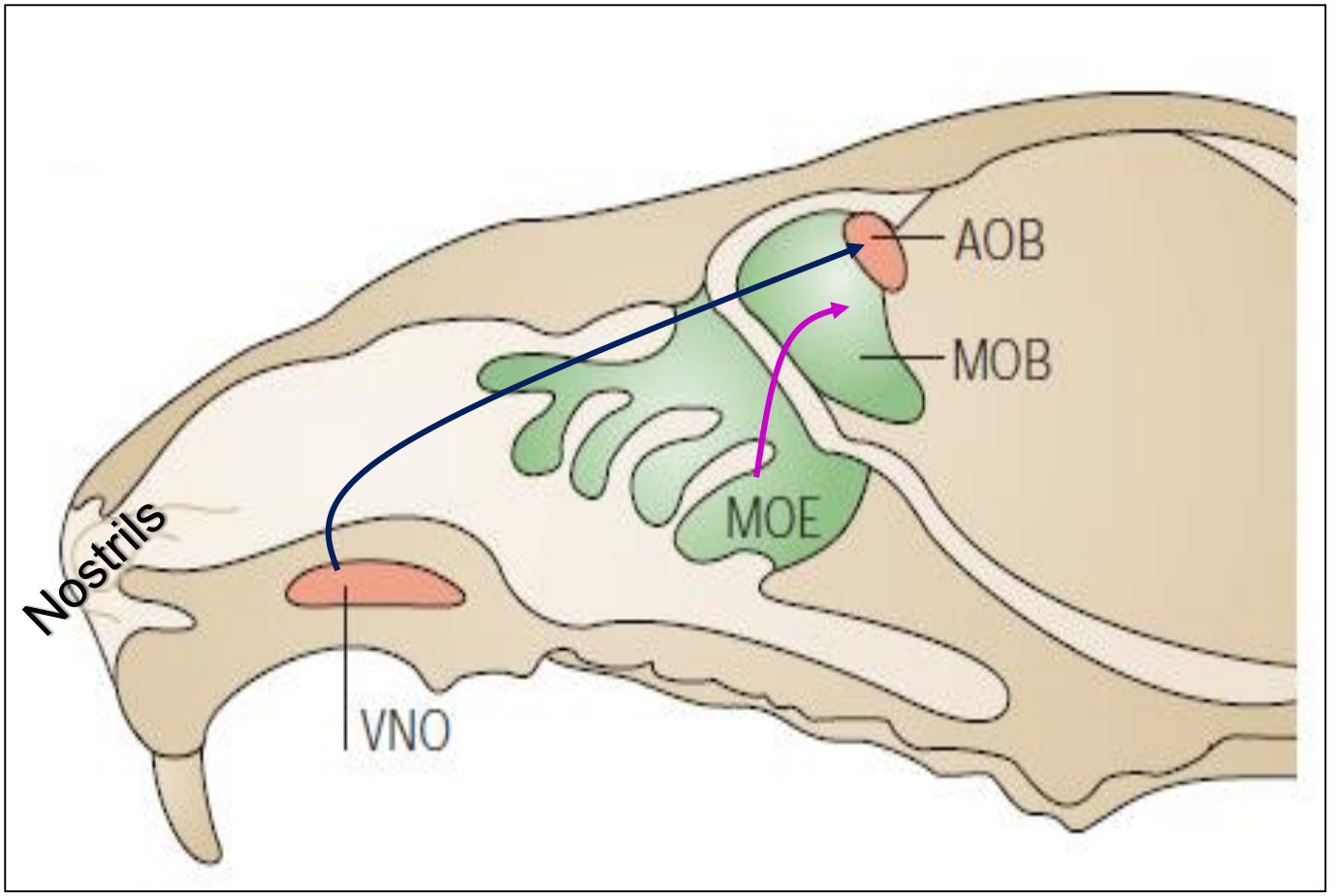
Activation of aggressive behavior using optogenetics in the VMH



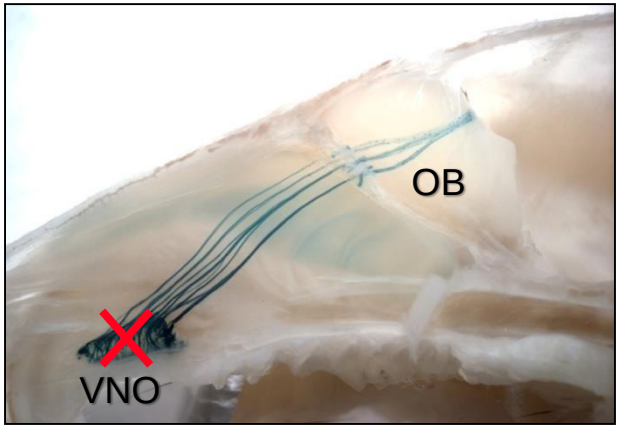
Lin et al 2011

The control of pheromone signals on sexually dimorphic reproductive behaviors

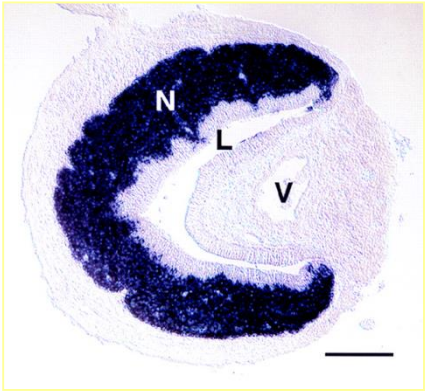
The olfactory systems

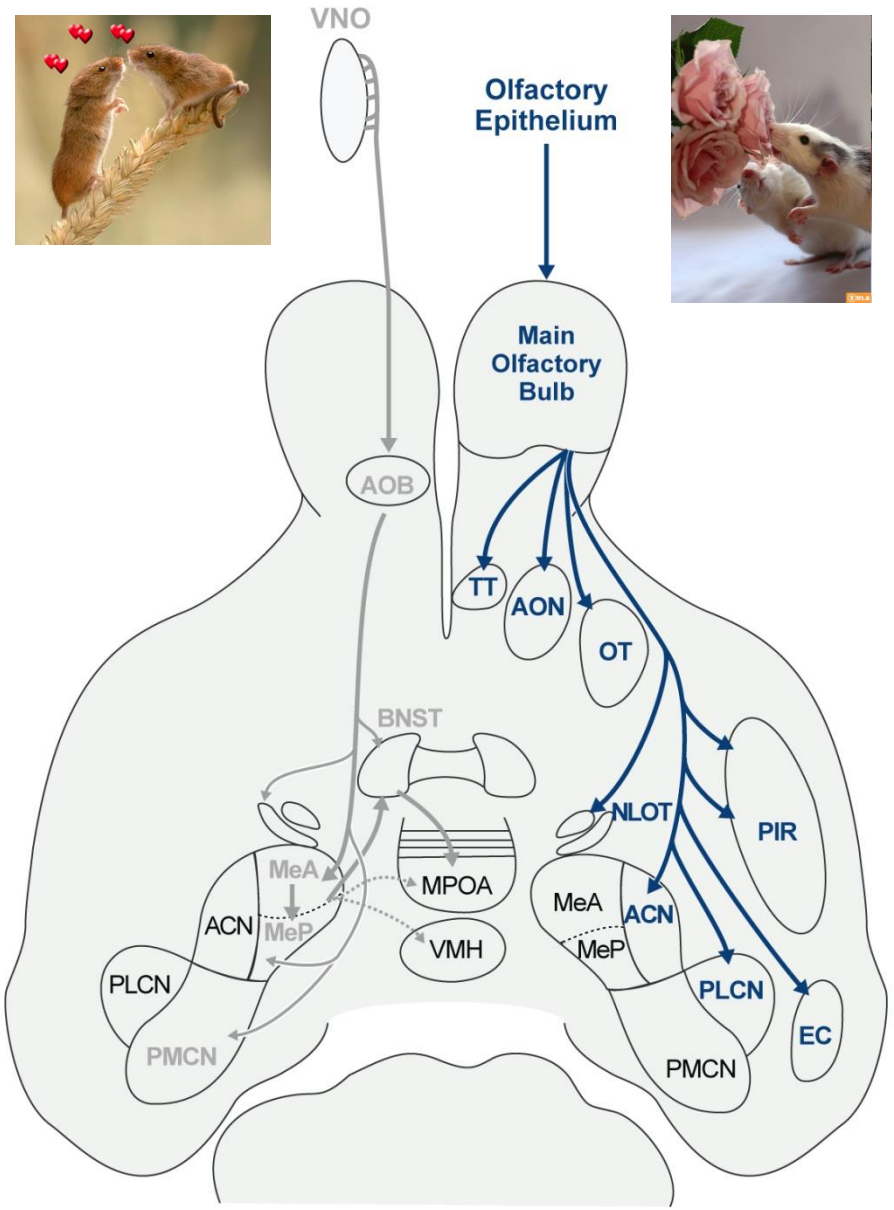


Detection of chemosensory signals in mice

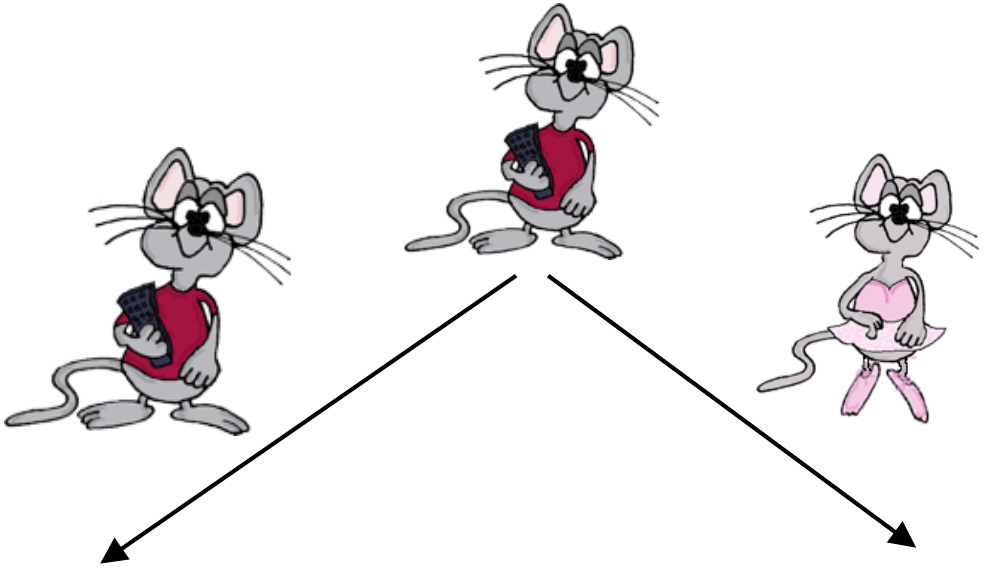


TRPC2 expression in the VNO





Typical male-female reproductive behaviors



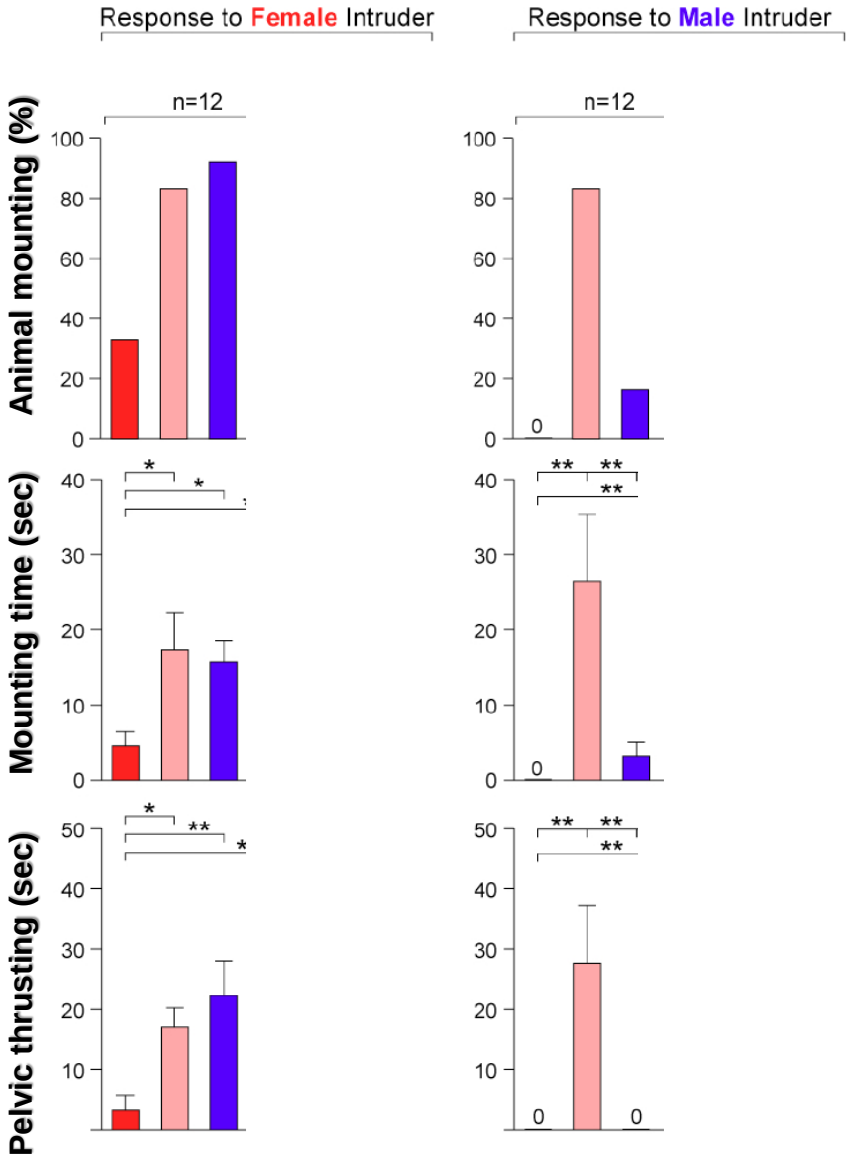
Aggressive behavior

Sexual behavior

Sexual behavior of TRPC2-KO lab females

TRPC2 mutant female (brown) with normal male (black)

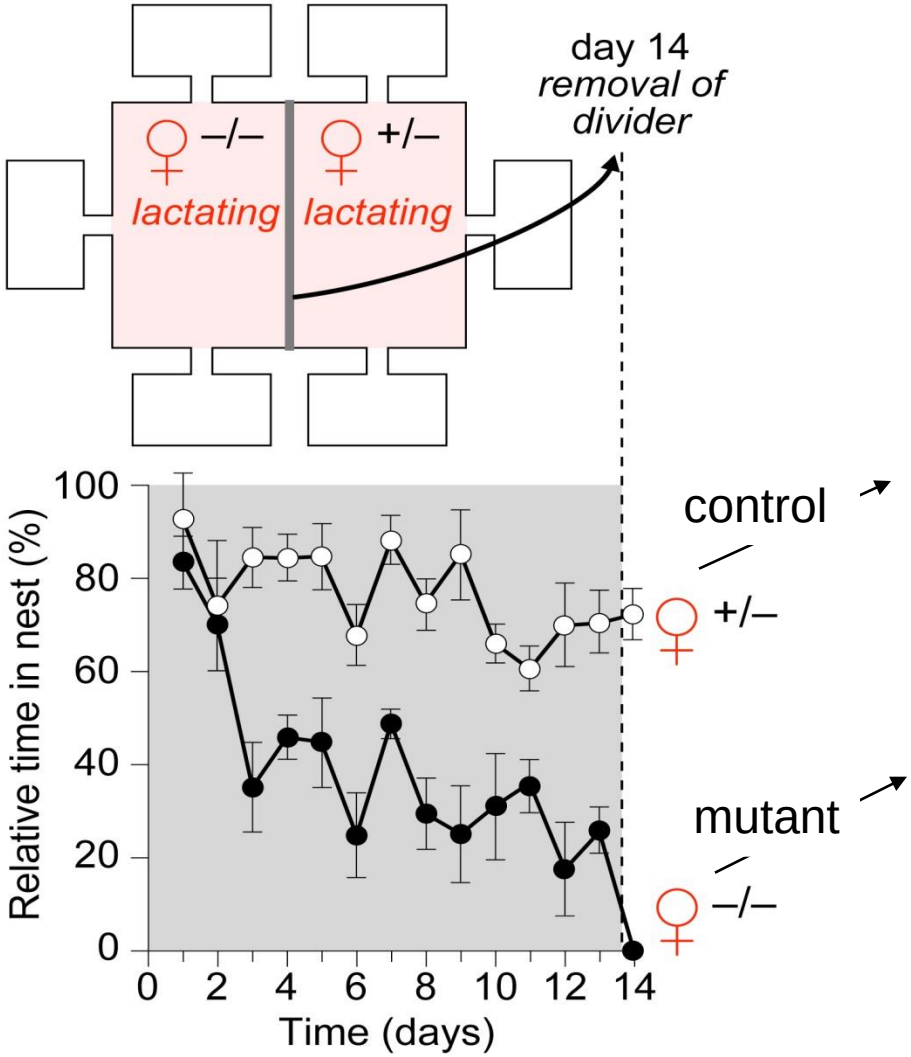
Male-typical sexual behavior in TRPC2-KO females



Kimchi et al. 2007

♀ **TRPC2$^{-/-}$ mutant (light) +**
♂ **Sexually experienced intruder (dark)**

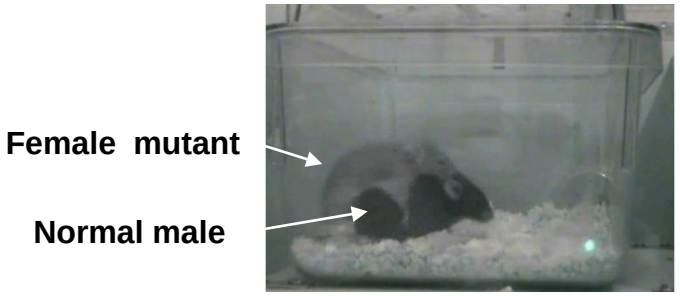
Maternal behavior



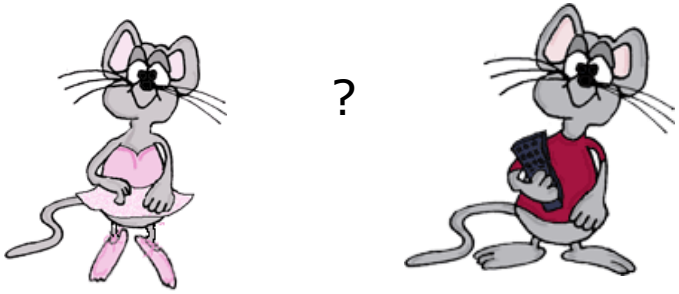
	$TRPC2^{+/-}$	$TRPC2^{-/-}$	P value
Weight of animals (grams)			
Males (n=15)	25.67 ± 0.66	25.96 ± 0.68	NS
Females (n=26)	21.41 ± 0.69	22.43 ± 0.56	NS
Duration of estrous cycle (days)			
Females (n=10)	5.20 ± 0.25	5.40 ± 0.26	NS
Steroid hormone level in blood			
Total testosterone (ng/ml)			
Males (n=5)	3.10 ± 0.30	4.50 ± 0.60	NS
Females (n=6)	<0.1	<0.1	
Free testosterone (pg/ml)			
Males (n=5)	14.10 ± 1.30	15.30 ± 1.50	NS
Females (n=6)	0.19 ± 0.07	0.41 ± 0.03	<0.05
17-β estradiol (pg/ml)			
Males (n=5)	21.31 ± 3.20	20.58 ±2.80	NS
Females (n=6)	14.29 ± 2.10	14.91 ± 1.50	NS

Behavioral phenotype of TRPC2-KO females

↑ Male-typical sexual behavior
(courtship and mounting behaviors)

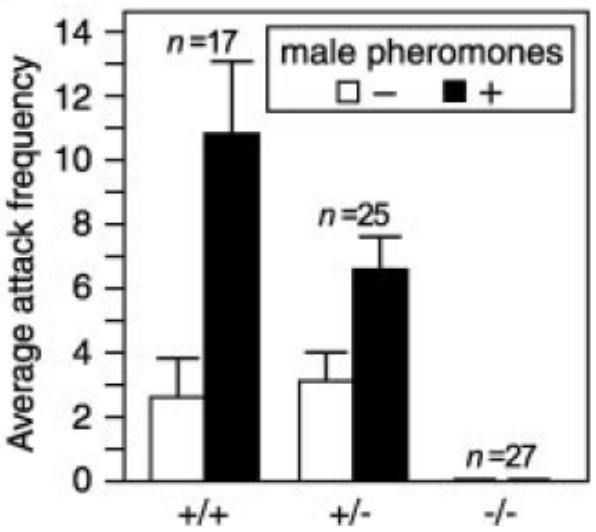


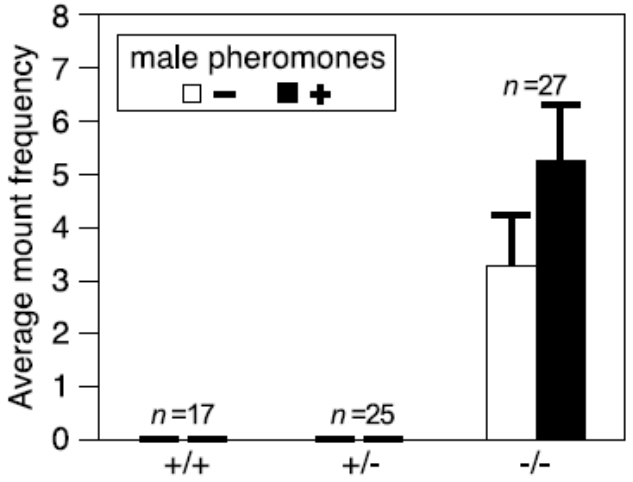
Failure to discriminate between
male and female

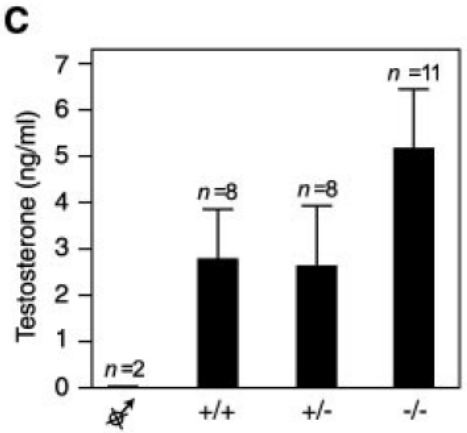


↓ Female-typical behavior
(maternal behavior)

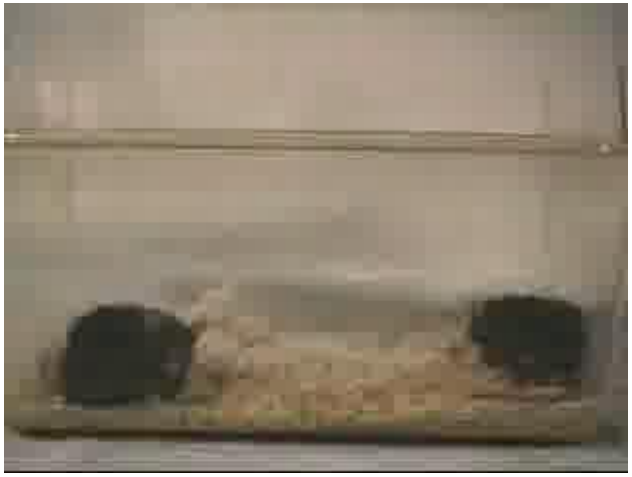
Behavioral phenotype of TrpC2$^{-/-}$ males







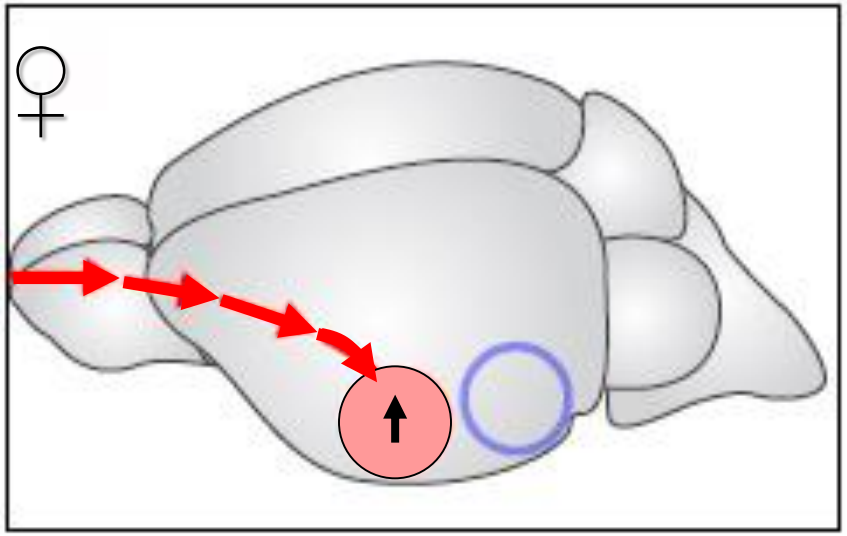
Stowers et al 2002

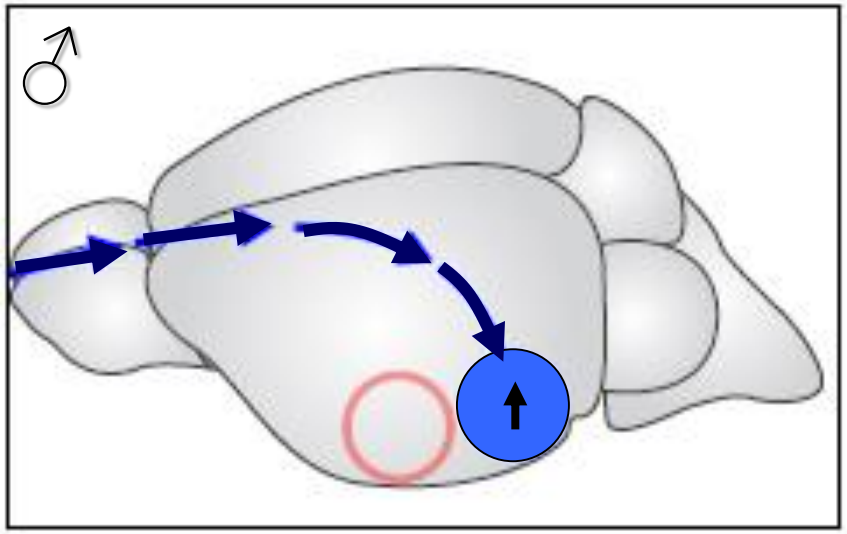


2 control (WT) males

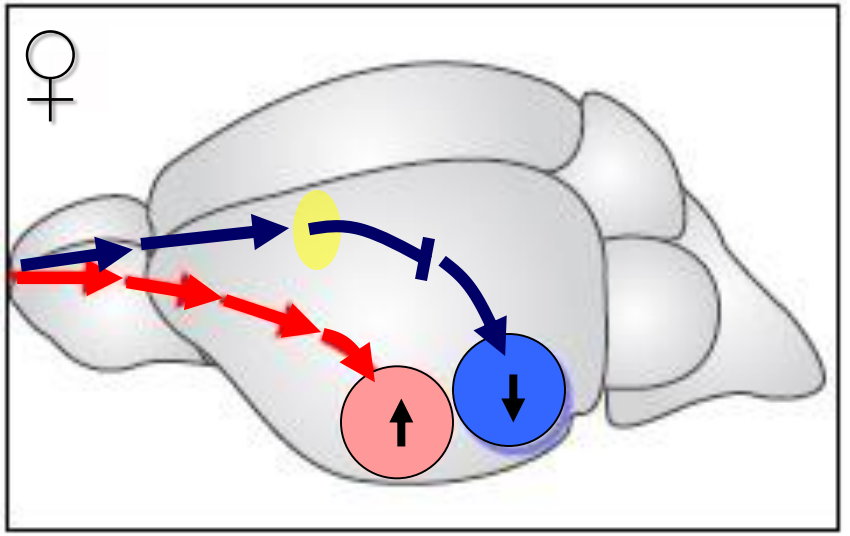
4 mutant males

Old model



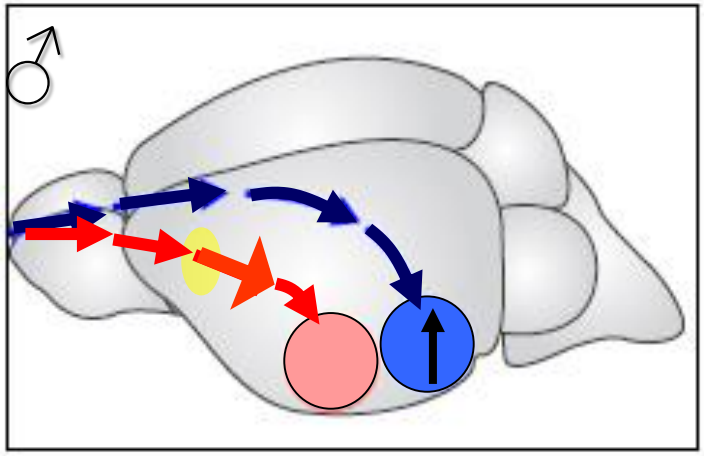


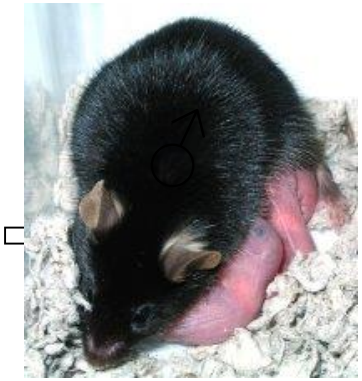
New model



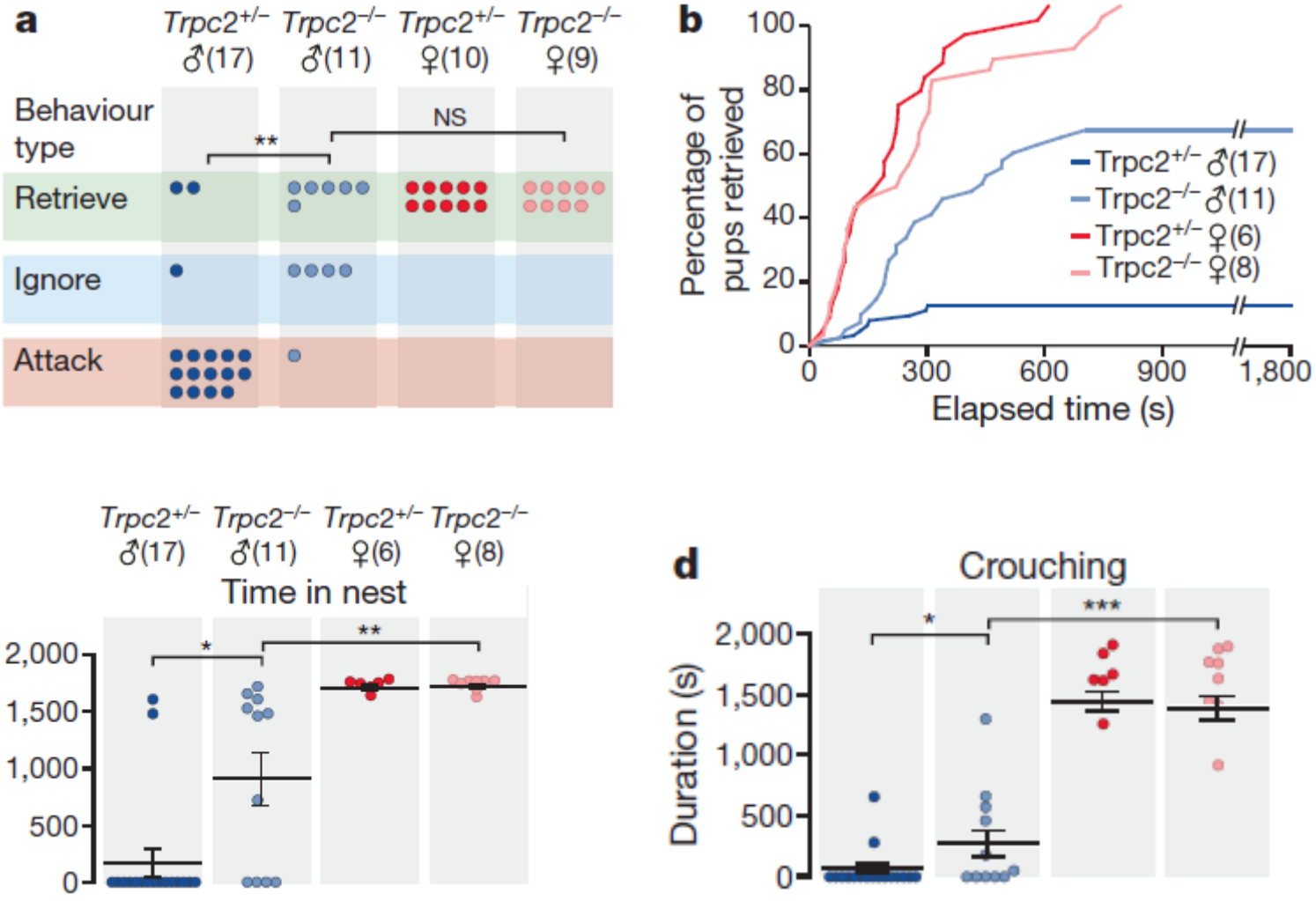
Model: Pheromonal inputs repress neuronal circuits for female-typical behavior in males

Sex-specific pheromone signals



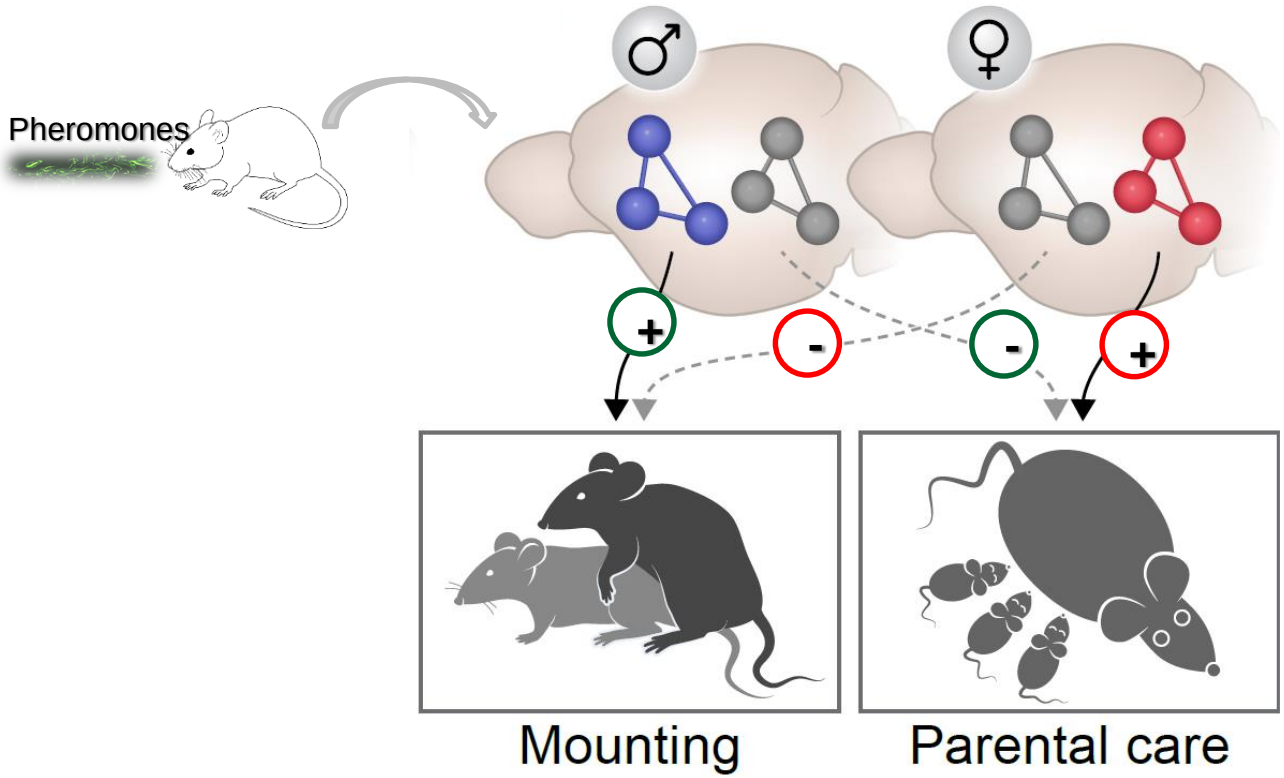


Behavioral phenotype of TrpC2$^{-/-}$ males

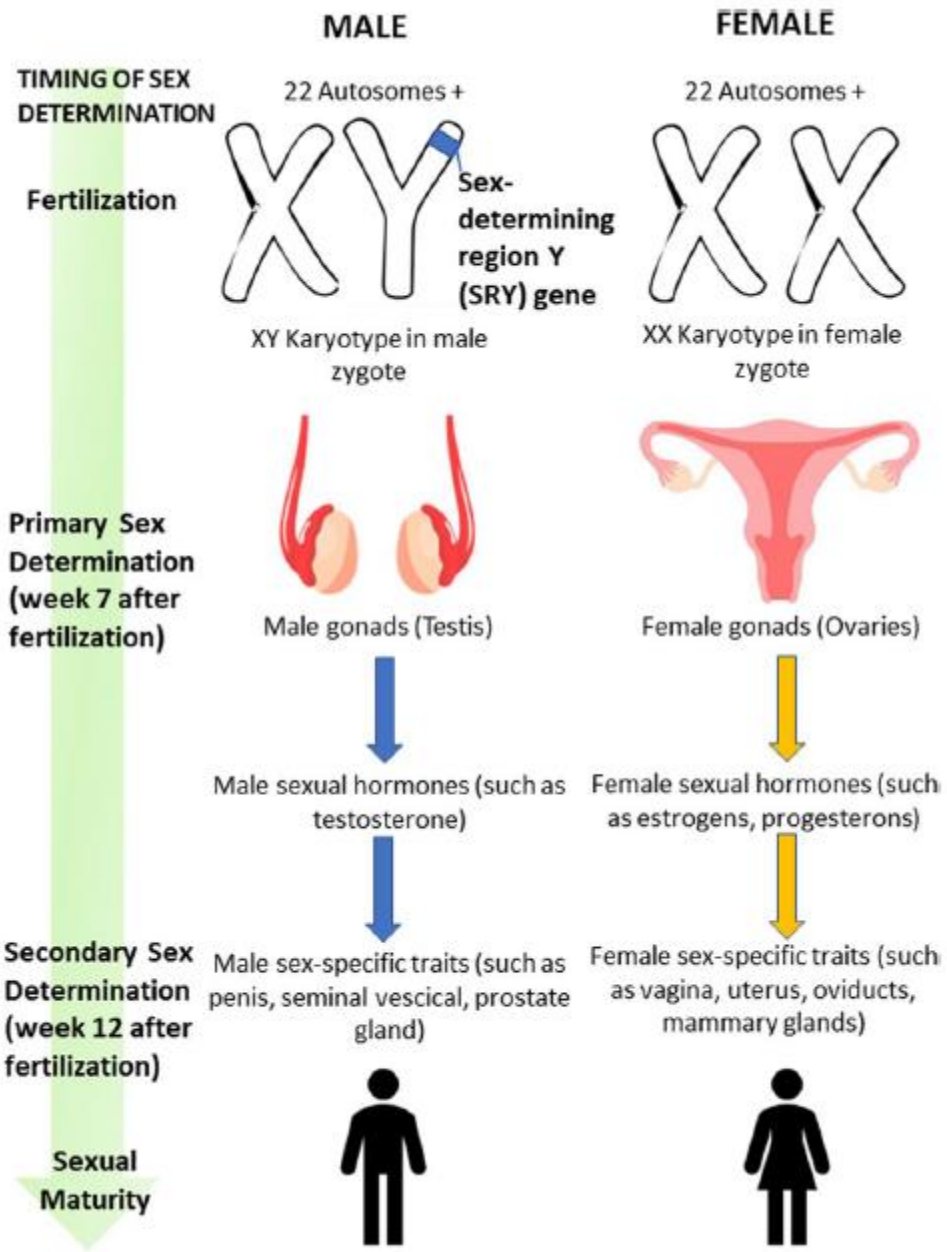


Wu et al 2015

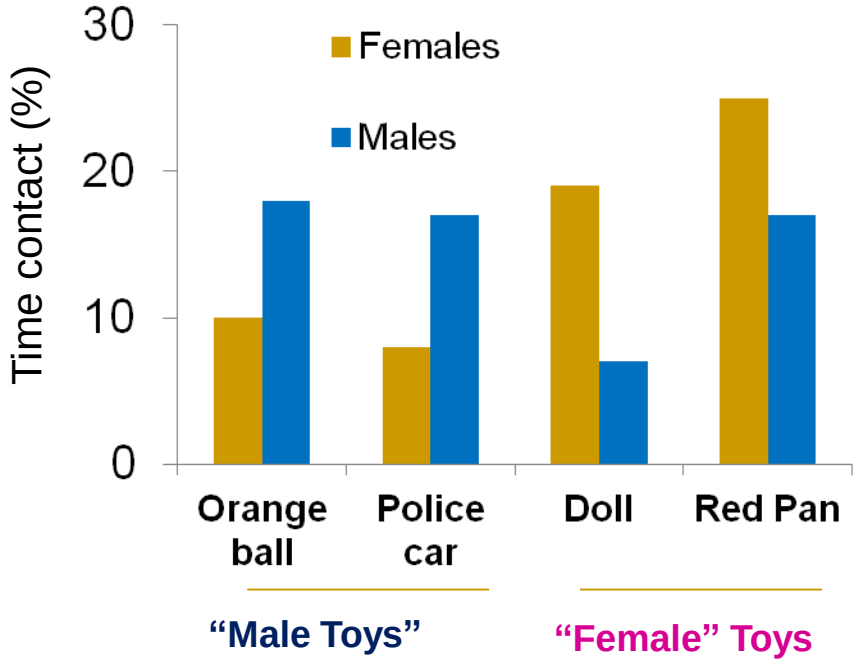
Sex-typical networks exist in both sexes



Human


MALE
FEMALE
TIMING OF SEX DETERMINATION
Fertilization
22 Autosomes +
22 Autosomes +
Sex-determining region Y (SRY) gene
XY Karyotype in male zygote
XX Karyotype in female zygote
Primary Sex Determination (week 7 after fertilization)
Male gonads (Testis)
Female gonads (Ovaries)
Male sexual hormones (such as testosterone)
Female sexual hormones (such as estrogens, progesterons)
Secondary Sex Determination (week 12 after fertilization)
Male sex-specific traits (such as penis, seminal vescical, prostate gland)
Female sex-specific traits (such as vagina, uterus, oviducts, mammary glands)
Sexual Maturity

Sexual dimorphism in human behavior: Nature versus Nurture

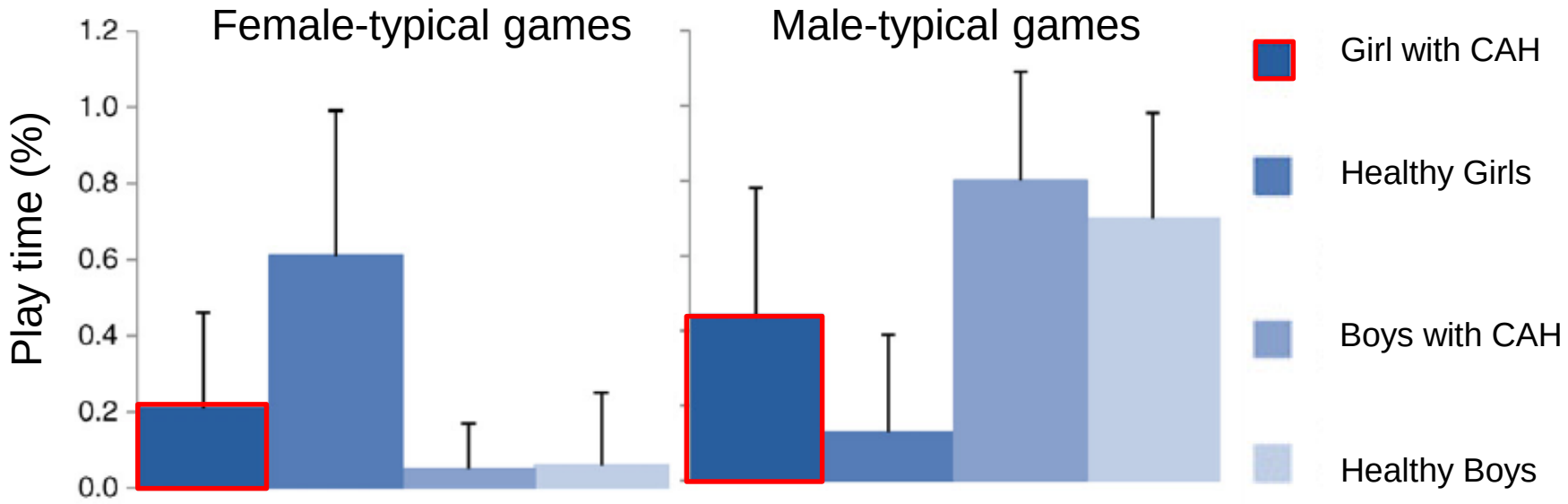


Alexander and Hines, 2002

The role of hormones in sexual dimorphism in behavior

Congenital Adrenal Hyperplasia (CAH)- Genetic disease

Elevated exposure to testosterone during development



Pasterski et al 2005

The Boy That Was Raised as a Girl | The Tragic Tale of David Reimer

https://www.youtube.com/watch?v=G41-tXRMK20