Sexual dimorphism in brain and behavior: Hormonal and genetic regulation
Sexual dimorphism is the difference in form between male and female members of the same species.
Sexual dimorphism in body characteristics
Sexual Dimorphism in Social Behavior
Most striking categories of sexually dimorphic behaviors

• Innate (genetically-predetermined) behaviors
• Controlled by simple sensory signals (e.g. pheromones)
Courtship behavior
Sexual behavior
Aggressive behavior (territoriality)
Parental behavior
The role of hormones in regulation of sexual dimorphism in behavior
In 1849, Berthold conducted one of the first experiments in behavioral endocrinology.

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

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

**Animal model:**
Castration

Castration + Transplantation in the same body

Castration + Transplantation in another body
Findings:

- Males that were castrated as juveniles later showed deficits as adults, in male-typical body characteristics and in behaviors such as aggression, mating and crowing.

- 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).
Ernest Henry Starling (1866-1922), English physiologist

The first to use the term hormone. “Hormones” from Greek “to excite”

“These chemical messengers, however, or <hormones> (from ὀρμέω=I excite or arouse), as we might call them, have to be carried from the organ where they are produced to the organ which they affect by means of the blood stream and the continually recurring physiological needs of the organism must determine their repeated production and circulation through the body”

Starling (1905); Lancet

Hormone: “A substance, usually a peptide or steroid, produced by one tissue and conveyed by the bloodstream to another to effect physiological activity”
Findings: female guinea pigs prenatally exposed to testosterone did not show any female-typical behavior when given estradiol and progesterone during adulthood.
The organization/activation hypothesize

• 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.
Male pup

Castration on day 1

Female pup

Testosterone on day 1

Organizational effect of testosterone

+ Testosterone

Exhibits male behaviours

+ Estrogen

Activational effect of testosterone and estrogen

Exhibits female behaviours
The classic model of brain sexual differentiation

Embryonic

- XY (Male)
  - Bipotential gonad
  - SRY gene
  - Testis
  - Ovary

Perinatal

- Testosterone/Estradiol (Organization, permanent changes)

Adult

- Testosterone (Activation)
- Estradiol & Progesterone (Exhibits female behaviour)
Genetic manipulation of SRY in mice

Parents: XX (female) and XY (male) with Sry on Chr3

Progeny:

- XX (female)
- XY (male)
- XX X Y^- (females) with Sry on Chr3
- XY^- (females) with Sry on Chr3

Sex chromosomes:

- XX: female
- XY: male
- XY^- (females) with Sry on Chr3

Sry on Chr3:

- +: present
- -: absent

Gonads:

- ovaries
- testes

Shorthand:

- XX: Female
- XY: Male
- XX^- (females with Sry on Chr3): Female
- XY^- (females with Sry on Chr3): Female

“Four Core Genotypes (FCG)” in Mice:

- XX (Karotypically & Gonadally Female)
- XX Sry^- (Karotypically Female but Gonadally Male)
- XY Sry^- (Karotypically Male but Gonadally Female)
- XY Sry^- (Karotypically & Gonadally Male)

Effect of gonadal hormones:

- XX: Ovaries, XXF
- XY: Testes, XYF

Effect of sex chromosomes:

- XX: Ovaries, XXF
- XY: Testes, XYM

- XX: Ovaries, XXF
- XY: Testes, XYM
Genetic females expressing SRY gene are gonadally males

XX Sry (XXM)
TH neurons in the AVPV in adult mice/rats

Dimorphic vasopressin fibers in the LS

Arnold et al 2004, Endocrinology
Evidence for the affect of Y-linked genes on brain sexual dimorphism

Arnold 2004 Nat Rev
The Sry gene and other genes on the sex chromosomes regulate sexual dimorphism in social behaviors

**Aggressive behavior**

- % Attacking on first trial
- XX: 15
- XY*: 13
- XX:Sry: 14
- XY-Sry: 10

**Maternal behavior**

- Latency (sec.) to retrieve pup
- XX: *
- XY*: 800
- XX:Sry: 600
- XY-Sry: 400

Gatewood et al 2006, J Neuros
Effect of sex chromosomes on nociception

Hot plate assay

Latency (s)

- **XY Males**
- **XY Females**
- **XX Males**
- **XX Females**

Time after injection (min)

Morphine injection

Gioiosa et al 2008, Horm Behav
Downregulation of SRY in the SN leads to decreased TH expression and deficient sensorimotor behavior.
The Klinefelter syndrome, also known as the XXY genetic disorder

symptoms include:
1. Reduced fertility or full infertility
2. Female-typical body characteristics
Sex difference in brain and behavior in Zebra finches
Gynadromorphic Finch

Male

Female
A gene expressed on the W chromosome

A gene expressed on the Z chromosome
AR expression in the song nucleus HVC (larger in males)

Male  Female

Typical song of a male

Agate et al 2003 PNAS
The classic model of brain sexual differentiation

Embryonic

- SRY gene
- Bipotential gonad
- Testis
- Ovary
- Germ cells
- Testis cord
- Coelomic vessel

Perinatal

- Testosterone/Estradiol
- Estradiol & Progesterone
- Organization (permanent changes)

Adult

- Testosterone
- Estradiol & Progesterone
- Activation
- Exhibits female behaviour
The Sex Hormones

* Both are steroid hormones and secreted in both sexes

**Male** (androgenic) sex hormone
- Also secreted by the adrenal gland

**Female** (estrogenic) sex hormone
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

- 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
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 Tyrosine Hydroxylase (TH) gene in the hypothalamus (AVPV)

ATD= Aromatase inhibitor

Female-typical behavior

Male-typical behavior

Baker et al 2005; Nature neuroscience
Hormonal regulation of social behavior during adulthood

Aggressive behavior

Sexual behavior

Maternal behavior
Maternal behavior in postpartum female rats

- Pup retrieval
- Pup licking
- Nest building
- Pup nursing
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.
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, J Comp Physiol Psychol
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; Endocrinology
Prolactin is released from the pituitary gland

- It was shown that hypophysectomy (removing the pituitary gland) delayed the onset of maternal behavior in estrogen-treated females.

- Prolactin injection with a pituitary gland implanted in the kidney capsule induced maternal care.

Bridges et al. 1990, PNAS
The Hypothalamus-Pituitary-Gonadal Axis

1. Secretion of regulatory hormones to control activity of anterior lobe of pituitary gland

2. Production of ADH and oxytocin

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

Vasopressin
Oxytocin
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.
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
Estrous cycle begins with secretion of gonadotropins from the hypothalamus, which stimulate the growth of ovarian follicles, and ovulation; the ruptured ovarian follicle becomes a corpus luteum and produces estradiol and progesterone.
Hormonal activation of female-typical sexual behavior

- In all rodents, gonadectomy decreases (abolishes) female sexual receptivity
- Estrogen and progesterone replacement reinstates sexual behavior of females

<table>
<thead>
<tr>
<th></th>
<th>0 hours</th>
<th>42 hours</th>
<th>Lordosis?¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil</td>
<td>Oil</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>Oil</td>
<td>Usually low</td>
<td></td>
</tr>
<tr>
<td>(low dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oil</td>
<td>Progesterone</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>Progesterone</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>
The classic model of brain sexual differentiation

Embryonic

- Bipotential gonad
- SRY gene

Testis
- Germ cells
- Testis cord
- Coelomic vessel

Ovary
- Medulla
- Cortex

Perinatal

Testosterone/Estradiol → Organization (permanent changes)

Testosterone/Estradiol

Adult

Testosterone → Activation

Estradiol & Progesterone → Exhibits female behavior
How can the female and male brains explain why females and males are so different?

Are the male and female brains wired differently?

Dimorphic brain functions/structures  ➔  Dimorphic social behaviors?
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)

Anteroventral Periventricular Nucleus (AVPV)

Larger in male
Larger in Female
### Sexual dimorphism: Morphology

<table>
<thead>
<tr>
<th>Region</th>
<th>Volume larger in</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOB</td>
<td>Male</td>
</tr>
<tr>
<td>MeA</td>
<td>Male</td>
</tr>
<tr>
<td>PMv</td>
<td>Male</td>
</tr>
<tr>
<td>Posterior BNST</td>
<td>Male</td>
</tr>
<tr>
<td>Anterior BNST</td>
<td>Female</td>
</tr>
<tr>
<td>Central nucleus</td>
<td>Male</td>
</tr>
<tr>
<td>SDN-POA</td>
<td>Male</td>
</tr>
<tr>
<td>AVPV</td>
<td>Female</td>
</tr>
<tr>
<td>SON</td>
<td>Male</td>
</tr>
<tr>
<td>SCN</td>
<td>Male</td>
</tr>
<tr>
<td>VMN</td>
<td>Male</td>
</tr>
<tr>
<td>Locus Ceruleus</td>
<td>Female</td>
</tr>
<tr>
<td>SNB</td>
<td>Male</td>
</tr>
<tr>
<td>POA</td>
<td>Male</td>
</tr>
<tr>
<td>MePD</td>
<td>Male</td>
</tr>
</tbody>
</table>

**AVPV (F>M)**

- Forger et al. 2004, *PNAS*

**SDN-POA (M>F)**


Adapted from, Wilson & Davis, *Reproduction* 2007; Forger et al. 2015
Sexual dimorphism: Gene expression

Androgen receptor

Progestosterone receptor

Estrogen receptor α

Sexual dimorphism: Gene expression

Androgen receptor

Progestosterone receptor

Estrogen receptor α

Vasopressin fibers

Kisspeptin

Tyrosine Hydroxylase

Juntti et al 2010, Neuron

Yang et al 2013, Cell

Simerly et al 1997, PNAS

(Curtesy Geert de Vries)

Clarkson & Herbison 2006, Endocrinology

Scott et al 2015, Nature
Sex differences in estrogen-receptor-beta in the AVPV of rats can be altered by hormonal manipulation

Orikasa et al 2001, PNAS
<table>
<thead>
<tr>
<th>Xu et al 2012, Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Cckar mRNA</strong></td>
</tr>
<tr>
<td>BNSTtmpm</td>
</tr>
<tr>
<td>E</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>H</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

| MeApd            |
| E                 |
| F                 |
| G                 |
| H                 |
| I                 |
| J                 |
| K                 |
| L                 |

| VMHv1             |
| M                 |
| N                 |
| O                 |
| P                 |
| Q                 |
| R                 |
| S                 |
| T                 |

| Irs4 mRNA         |
| VMHv1             |
| Q                 |
| R                 |
| S                 |
| T                 |
| U                 |
| V                 |
| W                 |
| X                 |

Xu et al 2012, Cell
Xu et al 2012, Cell
Control of female sexual behavior by Cckar

Control of maternal behaviors by Irs4

Maternal care

A. Pup retrieval

- % mothers retrieving pups

B. Time to retrieve first pup

C. Time to retrieve all pups

Maternal aggression

D. Attack behavior

E. Attack latency

F. Attack number

G. Attack duration

H. Time spent attacking

I. Inter-attack interval

Receptivity index across all assays

% Animals

Mounting, Intromission, Ejaculation

Latency (s)

Latency (s)

Latency (s)

% mothers attacking intruder

# of events/assay

Duration (s) per bout

Duration/assay (s)

Inter-attack interval (s)
Sexual dimorphism can NOT be explained just by organization affects of sex hormones.
**Imprinting genes**

**Definition:**
A gene or chromosome region that is expressed when inherited from one (maternal or paternal) parent. But not when inherited from the other parent (i.e. parent-specific inactivation of a gene).

![Diagram of imprinting genes](image-url)
Mechanism:

Imprinting is determined by allele-specific DNA methylation at critical sites (e.g. promoter region) which represses the expression of the gene.
Biological function: “The battle of the sexes theory” or “parental conflict theory”

• The father is more “interested” in the growth of the offspring, at the expense of the mother.
• The mother’s interests are to conserve resources for her survival and provide sufficient nutrition to her offspring.

• Paternal imprinting genes are selected to extract resources from the mother for the fetus, while maternal imprinting genes are selected to inhibit this transfer of resources.

Maternal imprinting genes will repress growth of pups and paternal imprinting genes will enhance growth.
Paternally-imprinted genes

Intact Peg1 enhance maternal care

Peg1 mutant females exhibit deficiency in maternal behaviors

Curley et al 2004 Proc R Soc B
Paternally-imprinted genes (Peg3)

Time to retrieve pups

Latency of nest building

Lefebvre et al 1998; Nature Genetics
Keverne et al 1999; Science
Imprinting genes and human disease

Prader-Willi Syndrome
- Paternal Deletion 70%
- Maternal UPD 28%
- Imprinting Defect 2%
- Normal
- Paternal Gamete
- Maternal Gamete

Angelman Syndrome
- Maternal Deletion 70%
- Paternal UPD 2%
- Imprinting Defect 2-5%
- UBE3A Mutation 5-8%
- UBE3A Mutation 12-15%

Legend:
- Active PWS-related genes
- Inactive PWS-related genes
- Active AS-related genes
- Inactive AS-related genes
- UBE3A Mutation
Effects of exposure to different levels of testosterone in uterus on female/male behavior

High level of testosterone in the surrounding

Low level of testosterone in the surrounding

Rayan and Vandernbergh 2002; Neuroscience and Biobehavioral Reviews
# Effects of exposure to testosterone in uterus on female behavior

<table>
<thead>
<tr>
<th>Sex</th>
<th>0M</th>
<th>2M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiology</strong></td>
<td><strong>Physiology</strong></td>
<td></td>
</tr>
<tr>
<td>♀</td>
<td>Lower fetal testosterone levels</td>
<td>Higher fetal testosterone levels</td>
</tr>
<tr>
<td>♀</td>
<td>Earlier vaginal opening</td>
<td>Later vaginal opening</td>
</tr>
<tr>
<td>♀</td>
<td>Less male offspring</td>
<td>More male offspring</td>
</tr>
<tr>
<td>♀</td>
<td>Mate and impregnated earlier</td>
<td>Mate and impregnated later</td>
</tr>
<tr>
<td>♀</td>
<td>More sensitive to bisphenol-A</td>
<td>Less sensitive to bisphenol-A</td>
</tr>
<tr>
<td>♂ &amp; ♀</td>
<td>Less sensitive to testosterone</td>
<td>More sensitive to testosterone</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td><strong>Morphology</strong></td>
<td></td>
</tr>
<tr>
<td>♀</td>
<td>Shorter AGD</td>
<td>Longer AGD</td>
</tr>
<tr>
<td>♂</td>
<td>Lower 5α-reductase levels</td>
<td>Higher 5α-reductase levels</td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td><strong>Behavior</strong></td>
<td></td>
</tr>
<tr>
<td>♀</td>
<td>Less likely to mount other females</td>
<td>More likely to mount other females</td>
</tr>
<tr>
<td>♂</td>
<td>Less parental behavior</td>
<td>More parental behavior</td>
</tr>
<tr>
<td>♂ &amp; ♀</td>
<td>Smaller home range</td>
<td>Larger home range</td>
</tr>
<tr>
<td>♂ &amp; ♀</td>
<td>Less aggressive</td>
<td>More aggressive</td>
</tr>
</tbody>
</table>

Rayan and Vandemergbergh 2002; Neuroscience and Biobehavioral Reviews
Effect of prenatal stress on sexual dimorphism in brain and behavior
Effect of prenatal stress on sexual dimorphism in the rat brain

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

ES: Environment stress (change in lighting/ temperature)
NS: Nutritional stress (50% of total food of control males)
Sex-Specific Programming of Offspring Emotionality after Stress Early in Pregnancy

Bridget R. Mueller and Tracy L. Bale

Tail suspension assay

Forced swim test

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

Mueller and Bale 2008, JNS
The control of pheromone signals on sexually dimorphic reproductive behaviors
What are pheromones?

Chemical (odor) signals that are emitted by animals to communicate information to their own species

Pheromone signals are largely involved in the regulation of social and reproductive behaviors in most animals (including in human)
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)

Kimchi et al. 2007; Nature
Male-typical sexual behavior in TRPC2-KO females

Animal mounting (%)

Mounting time (sec)

Pelvic thrusting (sec)

Kimchi et al. 2007; Nature
♀ TRPC2⁻/⁻ mutant (light) + ♂ Sexually experienced intruder (dark)
Maternal behavior

Control and mutant maternal behavior study.

- Maternal behavior is assessed over 14 days.
- Day 14: removal of divider.
- Relative time in nest (%) plotted over time (days).
<table>
<thead>
<tr>
<th></th>
<th>TRPC2(^{+/-})</th>
<th>TRPC2(^{-/-})</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight of animals (grams)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (n=15)</td>
<td>25.67 ± 0.66</td>
<td>25.96 ± 0.68</td>
<td>NS</td>
</tr>
<tr>
<td>Females (n=26)</td>
<td>21.41 ± 0.69</td>
<td>22.43 ± 0.56</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Duration of estrous cycle (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females (n=10)</td>
<td>5.20 ± 0.25</td>
<td>5.40 ± 0.26</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Steroid hormone level in blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total testosterone (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (n=5)</td>
<td>3.10 ± 0.30</td>
<td>4.50 ± 0.60</td>
<td>NS</td>
</tr>
<tr>
<td>Females (n=6)</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (n=5)</td>
<td>14.10 ± 1.30</td>
<td>15.30 ± 1.50</td>
<td>NS</td>
</tr>
<tr>
<td>Females (n=6)</td>
<td>0.19 ± 0.07</td>
<td>0.41 ± 0.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>17-(\beta) estradiol (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (n=5)</td>
<td>21.31 ± 3.20</td>
<td>20.58 ± 2.80</td>
<td>NS</td>
</tr>
<tr>
<td>Females (n=6)</td>
<td>14.29 ± 2.10</td>
<td>14.91 ± 1.50</td>
<td>NS</td>
</tr>
</tbody>
</table>
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; Science
2 control (WT) males

4 mutant males
Old model

♀

Old model

♂

New model

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New model

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

Dulac and Kimchi, 2007, CONB
Behavioral phenotype of TrpC2-/- males

Wu et al 2015, Nature
Social and sexual behaviors of male mutant mice

- Aggressive behavior

Failure to discriminate between male and female

Female-typical behavior (pup caring / nursing behavior)

Normal testosterone basal level
Sex-typical networks exist in both sexes

Kimchi et al. 2007, *Nature*
Zilkha et al. 2021, *Curr Opin Neuro*
MeA sensory responses to VNO stimuli

Electrical stimulus to artificially activate the VNO pump

Bergan et al 2014, eLife
Sexual dimorphism in neural responses of the adult medial amygdala (MeA) to chemosignals

Bergan et al 2014, eLife
Sexual dimorphism in neural responses of the adult medial amygdala (MeA) to chemosignals

ArKO=aromatase knockout mice

Bergan et al 2014, eLife
Parental care- evolutionary conserved behavior
Dimorphism of the brain: differentiation and activation

- Bipotential gonad
  - SRY gene
  - Estradiol & Progesterone
  - Testosterone & Estradiol

**Testosterone & Estradiol**

- Organization (permanent changes)

**Estradiol & Progesterone**

**Sex-specific behaviors**
How are sexually dimorphic reproductive behaviors encoded by the male and female brain?

Dimorphic brain functions/structures $\Rightarrow$ Dimorphic social behaviors?
Sexual dimorphism in pup-directed behaviors

Virgins
- Parental
- Aggression

Parents
- Parental

Venn diagram showing the comparison between virgins and parents in terms of parental and aggressive behaviors.
Sexual dimorphism in tyrosine hydroxylase-positive neurons in the Anteroventral Periventricular Nucleus (AVPV)

TH= Tyrosine hydroxylase
TH-expressing neurons in the AVPV can produce dopamine.
Selective manipulations of TH\textsuperscript{+} AVPV neurons in adult males and females

Neuronal ablation

6-OHDA

Neuronal over-expression

TH-overexpression

Neuronal activation using light stimulation (optogenetics)

TH-ChR2

Scott et al. 2015, Nature
In females, hypothalamic dopaminergic (TH⁺ AVPV) neurons promote maternal care.

Crouching over the pups

Pup retrieval back to the nest

Optogenetic activation

Parental duration (% of control)

Over-expression

Ablation

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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

Zilkha et al. 2021, Curr Opin Neuro
Functional identification of an aggression locus in the mouse hypothalamus (VMH)

Immediate early gene (FOS) induction during fighting and mating in the VMH

Lin et al 2011, Nature
Falkner and Lin 2014, Front Sys Neuros
Functional identification of an aggression locus in the mouse hypothalamus (VMH)

Lin et al. 2011, Nature
Falkner and Lin 2014, Front Sys Neuros
Activation of aggressive behavior using optogenetics in the VMH

Lin et al 2011, Nature
Sexual dimorphism in human behavior: Nature versus Nurture
Time contact (%)

- **Females**
- **Males**

- **Orange ball**
- **Police car**
- **Doll**
- **Red Pan**

**“Male Toys”**

**“Female” Toys**

Alexander and Hines, 2002, Evol Hum Behav
Congenital Adrenal Hyperplasia (CAH) - Genetic disease

Elevated exposure to testosterone during development

Female-typical games
Male-typical games

Play time (%)

Pasterski et al 2005, Child Develop
The boy who was raised as a girl

Twins Bruce and Brian Reimer were born in Canada as two perfectly normal boys.

Bruce’s penis was damaged during an unsuccessful surgery for urinary problems.

Suggested the “ideal” sex change experiment.

Dr. John Money was a psychologist specializing in sex changes.
At the age of ~2 years old Bruce is castrated and treated with female sex hormones.

Dr. Money genuinely believed that Bruce had a better chance of living a happy life as a woman than as a man without a penis.

Bruce raised as Brenda

Suggested the “ideal” sex change treatment
The boy who was raised as a girl

At the age of 15 Brenda switched again to a male named David.

David got married but later became depressed.

At the age of 38 David committed suicide (2 years after his brother died from a drug overdose).

http://youtube/MUTcwqR4Q4Y
http://www.bbc.co.uk/news/health-11814300