The Female Brain
vs
The Male Brain
(page 325 in syllabus)

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and
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Learning Objectives

• Explain the causes and consequences of brain sexual dimorphism

• Understand the influence of sex on prevalence, symptom presentation, and disease course for various psychiatric illnesses

• Utilize knowledge of sexual dimorphism in psychiatric disorders in order to develop optimal treatment plans for individual patients
Pretest Question 1

Jacqueline is a 12-year-old female patient. She has a polymorphism in the gene for $\alpha$-fetoprotein that causes reduced binding of $\alpha$-fetoprotein to estradiol. Jacqueline’s brain was therefore likely exposed to relatively *increased* levels of estradiol during fetal development. Given the organizational effects of estradiol on brain sexual dimorphism, how would you hypothesize that Jacqueline’s behavior would be compared to the average female?

1. Feminized
2. Masculinized
3. The same
Christopher is a 25-year-old male patient having his first depressive episode. Genetic testing reveals that Christopher is homozygous for the “short” allele of the serotonin transporter gene (5-HTTR). Which antidepressant is likely to be most effective for this patient?

1. The SSRI escitalopram
2. The TCA nortriptyline
3. The SSRI fluoxetine
Pretest Question 3

Olivia is a 54-year-old perimenopausal woman with depression who has just begun estrogen replacement therapy to treat hot flashes. Her last episode of depression was in her mid-20s, shortly after the birth of her only child. During this previous depressive episode, she was treated with the SSRI fluvoxamine and was dismayed by the 4-week delay before noticing any antidepressant effects. Another trial of fluvoxamine may yield faster results due to which action of estradiol?

1. Downregulation of 5-HT$_{1A}$ autoreceptor mRNA
2. Induction of tryptophan hydroxylase
3. Downregulation of serotonin transport (SERT) mRNA
4. All of the above
Pretest Question 4

Patricia is a 32-year-old woman with schizophrenia who is currently taking clozapine (metabolized by CYP450 1A2). She very recently discovered that she is pregnant. Given the increased levels of estradiol that occur during pregnancy, how may Patricia’s clozapine need to be adjusted during her pregnancy?

1. Dose increase
2. Dose decrease
3. No dose adjustment necessary
Battle of the Sexes
Let’s Talk About Sex!
How Sex Affects Behavior

Steroidal hormones

Environment

Sexual sex and Y chromosomal genes
Genetic Determinants of Sex

Egg

Sperm

= It’s a Girl!
Genetic Determinants of Sex

Egg $\times$ Sperm = It’s a Boy!
The Sex-Determining Region (SRY Gene)

- On the Y chromosome
- Acts as a molecular switch
  - Acts only briefly
  - Triggers a cascade of molecular and cellular events
  - Initiates formation of male gonads
  - Prohibits events leading to the formation of female gonads
    - Müllerian Inhibiting Substance (MIS)
Sexual Differentiation: Male

- SRY gene present
- Wolffian duct
- Müllerian duct
- Egg
- Sperm
- ON switch
Sexual Differentiation: Female

- Egg
- Sperm
- SRY gene absent
- Wolffian duct
- Müllerian duct
- Ovaries Gonads
Müllerian Inhibiting Substance (MIS) Reaches Beyond the Gonads

- There are MIS receptors found on most developing neurons.
- The actions of MIS on neurons likely influences sexual dimorphism of the brain.
- MIS knockout mice have “feminized” behavior even though they are sexually male.

X-Inactivation
(because we wouldn’t want females to have too much of an advantage!)

- Equalizes the expression of X-chromosome genes between males and females

In some cells of the female body

- Certain traits may show more variability in females

- Not all genes are perfectly silenced
Hormones Over the Lifespan

“That one good novel I thought I had in me turned out to be a hormonal imbalance.”

Organizational Effects

- Both testosterone and estradiol induce cell proliferation in some brain areas and pruning in other areas
- Many masculinizing and defeminizing effects of testosterone may actually be due to estradiol
Organizational Effects of Estradiol in the Brain

- Estradiol exposure may program sexually dimorphic expression of estrogen receptors
- Testosterone freely enters the brain, where it can be converted to estradiol by aromatase
- Estradiol produced in the gonads is sequestered by α-fetoprotein, so very little estradiol enters the brain
- Therefore, males are actually exposed to more estradiol during development
Testosterone

- The greater the testosterone exposure, the more male-typical the behavior
- The 2\textsuperscript{nd} digit:4\textsuperscript{th} digit (2D:4D) ratio is a measure of prenatal androgen:estradiol ratio

Estradiol increases length of 2\textsuperscript{nd} digit

Testosterone increases length of 4\textsuperscript{th} digit

More prenatal testosterone = longer 4\textsuperscript{th} digit = smaller 2D:4D ratio

Activational Effects

- During puberty, preformed neurocircuitry is activated by gonadal hormones.
- The activational effects of the puberty hormone surge depend on prenatal pre-conditioning of neurocircuits.
- Steroids may bind to nuclear receptors (if present) and form a complex:
  - The complex enters the nucleus and binds to hormone response elements (HREs) on DNA.
  - Genes are turned on or off.

Men and Women Are Different

Because Their Brains Are Different
MEN ARE BETTER AT MATH AND SCIENCE

“So my best guess, to provoke you, of what’s behind all of this is that the largest phenomenon, by far, is the general clash between people's legitimate family desires and employers' current desire for high power and high intensity, that in the special case of science and engineering, there are issues of intrinsic aptitude, and particularly of the variability of aptitude, and that those considerations are reinforced by what are in fact lesser factors involving socialization and continuing discrimination. I would like nothing better than to be proved wrong, because I would like nothing better than for these problems to be addressable simply by everybody understanding what they are, and working very hard to address them.”

—Lawrence H. Summers
Former President, Harvard University

“Astronomy did so start out as a guy thing.”
Nature or Nurture?

- Males usually do outperform females on visuospatial tasks, such as mental rotation.
- Some of this sex difference may be attributable to a more “global” strategy used by males vs a more “detail-oriented” strategy used by females.
- Baron-Cohen has hypothesized that the male has a “systematic” brain.
- Social and cultural influences may also play a role.
  - The gender gap in SAT mathematics scores (at the upper extreme) has declined from 13 boys:1 girl to 2.8 boys:1 girl.
  - Nations where women have representation in positions of power show more equivalent mathematics performance.

Look Out, Boys!

- First-grade boys performed better on mental rotation.
- If no special training was given to the kids, boys continued to outperform girls.
- However, with training, girls performed equally well on the task.

MEN ARE SMARTER BECAUSE WOMEN HAVE SMALLER BRAINS

Male brains are ~10% larger

Average male brain volume = 1260 mL
Average female brain volume = 1130 mL
Female Brains Are Smaller, But…

- Females also have smaller bodies
- Females actually have more grey matter (relative to cerebrum size) than males
  - Males have more white matter
- Females have more gyrification in frontal and parietal cortex

Females Have More Densely Packed Neurons

ALL MEN THINK ABOUT IS SEX!

THE MALE BRAIN

THE FEMALE BRAIN

FOOTNOTE: the "Listening to children cry in the middle of the night" gland is not shown due to its small and underdeveloped nature. Best viewed under a microscope.

FOOTNOTE: The "Put Oil Into the Car" and "Be Quiet During the Game" glands are active only when the "SHINY THINGS AND DIAMONDS" Olfactory has been satisfied or when there is a shoe sale.
Blame It on the Hypothalamus

- Organizational effects of hormones lead to a larger hypothalamus in males
  - The sexually dimorphic nucleus in the preoptic area (SDN-POA) of the hypothalamus regulates reproductive hormones and mating behavior
  - Men have more neurons in the SDN-POA, but this sex difference does not become apparent until ~ age 10

Greater Density of Androgen Receptors in Male Hypothalamus


“It's been over for a while now. I caught him trying to fertilize some catfish eggs in June.”
WOMEN REMEMBER EVERY LITTLE DETAIL

Don’t you remember the argument we had 17 years ago on a Tuesday about broccoli?
Women Have a Larger Hippocampus

- Women also have more estrogen receptor mRNA in the hippocampus than men

WOMEN ARE NICER

“I love you too, daddy. But it just kills me that you’re a man.”
Actually, Women Are More Empathizing

- Testosterone increases aggression in both males and females
- Males have a larger amygdala
  - Men also have more androgen receptor mRNA in the amygdala
- Women are better at reading facial cues and tone of voice
- Baron-Cohen proposed the theory that male brains are more “systemizing,” whereas female brains are more “empathizing”
- Men express unhappiness with externalizing physical behaviors (e.g., aggression)
- Women express unhappiness by internalizing (e.g., depression)
- Evolutionary and social variables likely contribute

Sexual Dimorphism in Psychiatric Disorders
Many Psychiatric Disorders Are Sexist

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In This Corner…

- Depression
- PTSD
- Eating disorders
- Anxiety disorders
- Panic disorders
- Later onset of schizophrenia
- ADHD
- Autism
- Alcohol dependence
- Drug abuse
- Antisocial personality disorder
- Earlier onset of schizophrenia
Disease Onset and Course Often Correlate With Hormonal Changes

- Many changes in the brain take place at puberty
- There are also many changes in social environment at this time
- Sex is one factor in the risk for many mental illnesses
  - Both organizational and activational effects of hormones, which differ in the male and female brain, may attenuate or amplify the consequences of underlying brain pathology or genetic predisposition to disease
Monoamine Oxidase (MAO)

- MAO metabolizes 5-HT
- Both testosterone and estradiol decrease MAO
  - Leading to greater 5-HT
- The MAO A gene is on the X chromosome
- The MAO A gene has an androgen response element
- Also, SRY regulates MAO A gene expression
- Incomplete X-inactivation may lead to increased expression of MAO in females
  - Resulting in decreased 5-HT

Serotonin

- 5-HT synthesis is 52% higher in males

Serotonin Synthesis

BH4 = tetrahydrobiopterin; DA = dopamine; NE = norepinephrine; 5-HT = serotonin.
Dietary Factors Can Influence Serotonin Synthesis

• Dietary intake often fluctuates across the menstrual cycle
  – Variable availability of essential amino acids

• Individuals with anorexia or bulimia
  – More common in females

• Tryptophan deficiency

• Folate deficiency

5-HTTR Gene

- In the promoter region of the serotonin transporter gene
- Short variant was associated with poorer antidepressant response – sex-dependent

Mighty Estradiol

- Estradiol increases 5-HT availability
  - Estradiol causes induction of tryptophan hydroxylase
    - Tryptophan hydroxylase is rate-limiting enzyme in 5-HT synthesis
  - Estradiol decreases serotonin transporter (SERT) mRNA

- Estradiol is neuroprotective
  - Induces neurogeneration
  - Suppresses oxidative stress
  - Suppresses glutamatergic excitotoxicity

Estradiol Increases Neuritic Proliferation

Nucleus arcuatus/ventromedialis (19 days in vitro)

Serum

Estradiol/50 ng/ml
Delayed Response to SSRIs (>2 weeks)

Österlund MK. Biochim Biophys Acta 2010;1800(10):1136-44.
Delayed Response to SSRIs (>2 weeks)

Chronic SSRI treatment

5HT1A autoreceptor

Österlund MK. Biochim Biophys Acta 2010;1800(10):1136-44.
Estradiol Antidepressant Actions (<1 week)

Österlund MK. Biochim Biophys Acta 2010;1800(10):1136-44.
Testosterone and Depression

• Results are mixed
  – Some studies show no antidepressant effects of testosterone administration compared to placebo
  – Other studies show positive effects of testosterone on measures of depression

• Use of aromatizable androgens may be more useful as treatments
  – Due to conversion to estradiol

Meyers B et al. Neuroscience 2010;165:850-62;
Schizophrenia

- Females have a later age of onset as well as a 2nd peak in later life

Relative testosterone levels

Relative estrogen levels

First Hospital Admissions Due to Schizophrenia

Symptom Presentation and Illness Course

• Females
  – Less severe illness
  – More preserved verbal memory
    • Possibly due to redundancy and less lateralization
  – Fewer negative symptoms
  – More positive symptoms
  – Degree of cognitive impairment is the same
  – Better prognosis
    • Due to fewer negative symptoms? Less substance abuse?
  – Require lower doses of antipsychotics

Abbs B et al. NeuroImage 2011;56:1865-74;
Altered Sexual Dimorphism in the Schizophrenic Brain

- Men with schizophrenia rely more on detailed processing
- In women with schizophrenia, processing relies on schemas
- Kraepelin observed physical signs of masculinization in females with schizophrenia

Maternal Stress

- Maternal stress during the first trimester of pregnancy has been associated with an increased risk of schizophrenia in males.
- Maternal stress decreases testosterone levels.
- Glucocorticoids interfere with the actions of estradiol, which is critical to prenatal brain development.
- May be due to epigenetic changes related to hormonal modulation of stress circuits and gene expression during critical development periods.

Figueira ML, Ouakinin S. Curr Opin Psychiatry 2010;23:369-72;
Prenatal Androgen:Estradiol Ratio: A Risk Factor for Schizophrenia?

- Elevated prenatal estradiol in females
  - Longer 2\textsuperscript{nd} digit

- Elevated estradiol and/or decreased testosterone in males
  - Longer 2\textsuperscript{nd} digit and shorter 4\textsuperscript{th} digit

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Testosterone and Schizophrenia

• Testosterone levels may be more critical to disease course in males, whereas estradiol may be more critical in females

• Lower levels of testosterone have been found in patients with prominent negative symptoms

• Treatment with 1% testosterone gel in men with schizophrenia led to improvements in negative symptoms

Kulkarni J et al. Arch Gen Psychiatry 2008;65(8):955-60;
Estradiol May Improve Positive Symptoms

- Also, chronic psychosis and relapse rates improve during pregnancy and during high-estrogen phases of the menstrual cycle

Catechol-O-Methyltransferase (COMT)

- COMT breaks down DA
- Males have 17% greater COMT activity in prefrontal cortex
  - The expression level is the same, but activity is higher
  - May be due to presence of a cofactor in males
- The COMT promoter contains estrogen response elements
- In a feedback mechanism, COMT also metabolizes estradiol

Sanchez MG et al. CNS Neurosci Ther 2010;16:e43-71;
YES, MEN AND WOMEN ARE DIFFERENT!

What does this mean for the treatment of mental illness?
## Males and Females Respond Differently to Treatments

<table>
<thead>
<tr>
<th>Women Compared to Men</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
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<tr>
<td>Increased risk for drug-induced arrhythmias</td>
<td>Longer QT interval in women (time it takes to recharge between beats)</td>
</tr>
<tr>
<td>Increased risk of tardive dyskinesia</td>
<td>Fat-soluble drugs remain in women’s bodies longer; estradiol may act on same receptors; dosing may be high for women</td>
</tr>
<tr>
<td>May respond better, but with more side effects</td>
<td></td>
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<tr>
<td><strong>Opioids</strong></td>
<td></td>
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<tr>
<td>May respond better to kappa-receptor opiates with fewer side effects</td>
<td>Estrogen’s effects on receptor density, binding, and signaling</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>May respond better to SSRIs</td>
<td>Estrogen enhancement of serotonergic effects</td>
</tr>
</tbody>
</table>
Why Do Men and Women Respond to Treatments Differently?

- Increased cerebral blood flow in females may lead to better distribution of drugs

- Cytochrome P450 expression is modulated by sex hormones
  - CYP3A4 and CYP2D6 activity is higher in females
  - CYP1A2 and CYP2C19 activity is higher in males
    - Estradiol has inhibitory effects on these enzymes

- Women express ½ the amount of P-glycoprotein (P-gp)
  - P-gp slows uptake into the gut wall, giving CYP450 enzymes time to work
  - Reduced P-gp in women may lead to higher concentrations of drugs in the female brain

Some Specific Drug Differences

- Men clear olanzapine 40% faster than women
- Women have superior cognitive improvement with olanzapine, risperidone, or clozapine treatment
- Estradiol augmentation may be useful, especially in peri- and postmenopausal women
- Selective estrogen receptor modulators, (specifically those that target ERβ) may be especially useful for the treatment of psychiatric disorders
  - Most negative peripheral side effects of estradiol are mediated by ERα

*ER = estrogen receptor


Fun Fact!
Redheaded women (but not men) are more responsive to opiates

Mogil JS et al. PNAS 2003;100:4867-72.
Some Specific Drug Differences: Antidepressants

- SSRIs are more efficacious in treating depression in women < 44 years old
- Women > 50 years old may respond better to SNRIs
- Women respond better to SSRIs than men
  - Plasma levels of sertraline are higher in older women
    - Due to inhibitory effects of estradiol on some CYP450 enzymes
- Men respond better to tricyclics
  - The narrow therapeutic window may be difficult to achieve in women due to fluctuating estradiol levels
  - Estradiol may inhibit synaptic reuptake norepinephrine (one of the mechanisms of TCAs)
  - The anticholinergic side effects associated with TCAs may be more acceptable to men than the sexual dysfunction often associated with SSRIs

Summary

• Sexual dimorphism of the brain is becoming increasingly evident as new imaging techniques are employed

• Differences in the male and female brains are likely due to a combination of prenatal organizational and postnatal activational effects of hormones, differential gene expression, and environmental or social influences

• Sexual dimorphism of the brain may underlie differences in male and female behavior; brain sexual dimorphism may also serve to equalize males and females despite functioning in very different hormone environments

• Brain sexual dimorphism likely contributes to the propensity for different psychiatric disorders and various symptom presentations observed in men and women

• In the age of personalized medicine, gender MUST be taken into account in order to provide optimal psychiatric care for the individual patient