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Master Class for Neuroscience Professional Development

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Brain-Informed Use of Hormones: From Oral Contraceptives to Gender Affirming Hormone Therapy

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Learning Objective

Examine the impact of hormone manipulation on brain function among cis-gender and trans-gender individuals.

Objectives

- Cis-Gender Manipulations
  - Contraceptives
  - Menopause hormone therapy
  - Cancer prevention procedures
- Trans-Gender Manipulations
  - Adult
  - Child-Adolescent

https://dpcpsi.nih.gov/sgmro
https://grants.nih.gov/grants/guide/pa-files/PA-17-478.html

WHAT ABOUT THE BRAIN? The Case of OCPs and Other Steroid Contraceptives

OCPs = Oral contraceptive pills

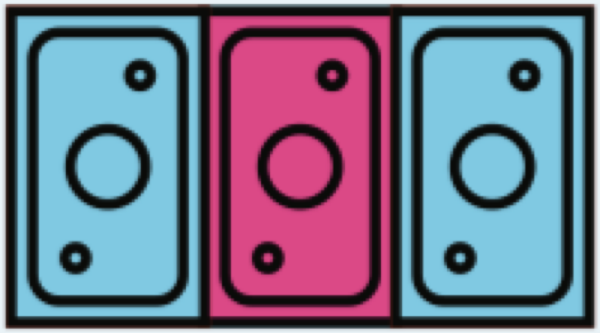
https://dpcpsi.nih.gov/sgmro.; https://grants.nih.gov/grants/guide/pa-files/PA-17-478.html

What Have We Gained?

- **Birth Control Reduces Unintended Pregnancy**
- Access to family planning and effective contraception is responsible for **2.2 million fewer unintended pregnancies each year**
- Contraception accounts for **86% of the recent decline in teenage pregnancy**

Santelli JS, et al. *Am J Public Health.* 2007;97(1):150–156.

What Have We Gained?



Fully one-third of the wage gains women have made since the 1960s are the result of access to oral contraceptives.

Bloomberg Businessweek recently listed contraception as one of the ***most transformational developments in the business sector in the last 85 years.***

Soller K. http://www.businessweek.com/articles/2014-12-04/birth-con- trol-pill-advanced-womens-economic-freedom. Published December 4, 2014. Accessed January 27, 2019.

What About the Brain?

- Type of steroid preparation
  - Progestins are NOT natural progesterone
    - They are NOT converted to neurosteroids
    - Allopregnanolone
      - Reward processes
      - Stress response
      - Neuroprotective, neurotrophic and antiapoptotic effects in animal models of brain injury and neurodegenerative disorders.
  - Do not account for importance of cyclicity
    - Cyclicity may be necessary for synaptic plasticity

Porcu P,et al. *J Neuroendocrinol* 2016;28(2):12351.; Bailey ME, et al. *Neuroscience* 2011;191:148-158.; Hao J, et al. *Proc Natl Acad Sci U S A.* 2007;104(27):11465-11470.; Giatti S, et al. *J Mol Endocrinol*. 2012;49(3):R125–134.

What About the Brain?

- In a prospective nationwide Danish study of more than 1M women 15 to 34 years of age who started a steroid contraceptive, the relative risk (RR) of first use of antidepressant or diagnosis of depression was increased

Total Sample

From 1.2 (95% CI, 1.22 -1.25) for combined oral contraceptive pill to 2.7 (95% CI, 2.45-2.87) for progestin only depot injection.

15-19 year-olds

From 1.8 (95% CI, 1.75-1.84) for combined oral contraceptive pill to 3.1 (95% CI, 2.56-3.71) for progestin patch.

Skovlund CW, et al. *JAMA Psychiatry*. 2016;73(11):1154-1162.

What About the Brain?

- In 2 nationwide Swedish studies observed from 2005-2008, women prescribed oral contraceptive pills were at increased risk for a subsequent prescription for antidepressants
  - N = 917,993 (women aged 16-31 yo)
    - Progestin-only contraceptive users resorted to antidepressants more than users of combined hormonal contraceptives
    - Oral contraceptives containing ethinyl-estradiol combined with lynestrenol or drospirenone had significantly higher odd ratios (antidepressant use for hormonal contraceptive users vs. non-users) than other pills

Wiréhn AB, et al. *Eur J Contracept Reprod Health Care.* 2010;15(1):41-47.; Lindberg M, et al. *Eur J Contracept Reprod Health Care* 2012;17(2):106-118.

What About the Brain?

- Peri/Post Menopause Hormone Therapy Story
  - Preparations were meant to be easy and to avoid any bleeding
  - Focus on vasomotor symptoms
  - Focus on vaginal health and sexual function
- We have little understanding of what dose and regimen is needed to “appropriately” “estrogenize” the human brain

Estradiol Impact On the Brain

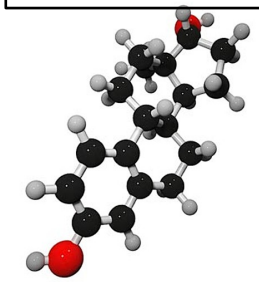
- Important considerations
  - Age
    - Timing of initiation
    - Current age
  - Life history (childhood adversity)
  - Overall health
  - Type of hormone regimen
    - Formulation
    - Route

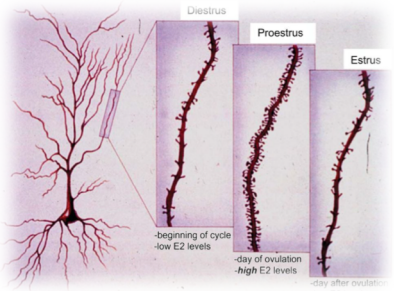
Sheila Shanmugan, MD, PhD

1. Shanmugan S, Epperson CN. *Hum Brain Mapp.* 2014;35(3):847-865.; 2. Shanmugan S, et al. *Neuropsychopharmacology.* 2017;42(12):2398-2406.; 3. Shanmugan S, et al. *Psychoneuroendocrinology*. 2017;84:197-205.

Hormone Effects are Extensive!

ESTRADIOL





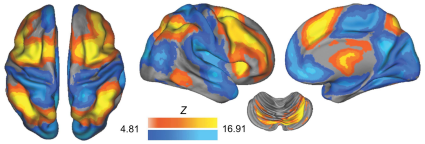
NEUROCHEMISTRY

Serotonin
Dopamine
Norepinephrine
Glutamate
Acetylcholine

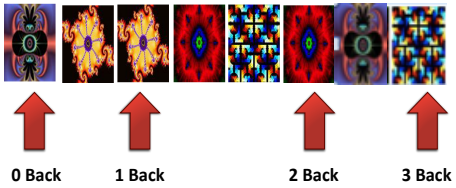
Figure S2

STRUCTURE

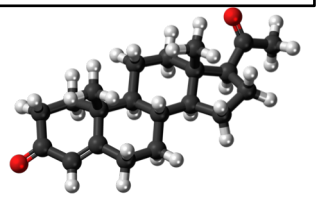
FUNCTION



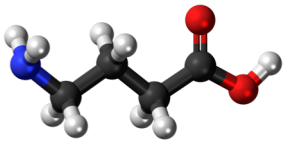
BEHAVIOR

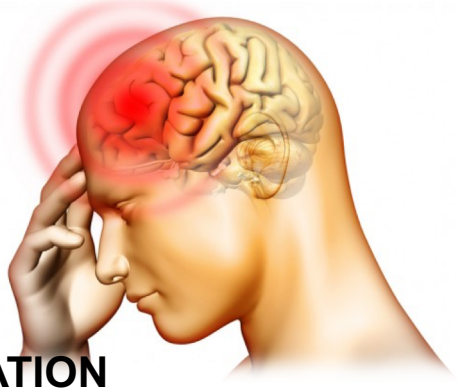


PROGESTERONE



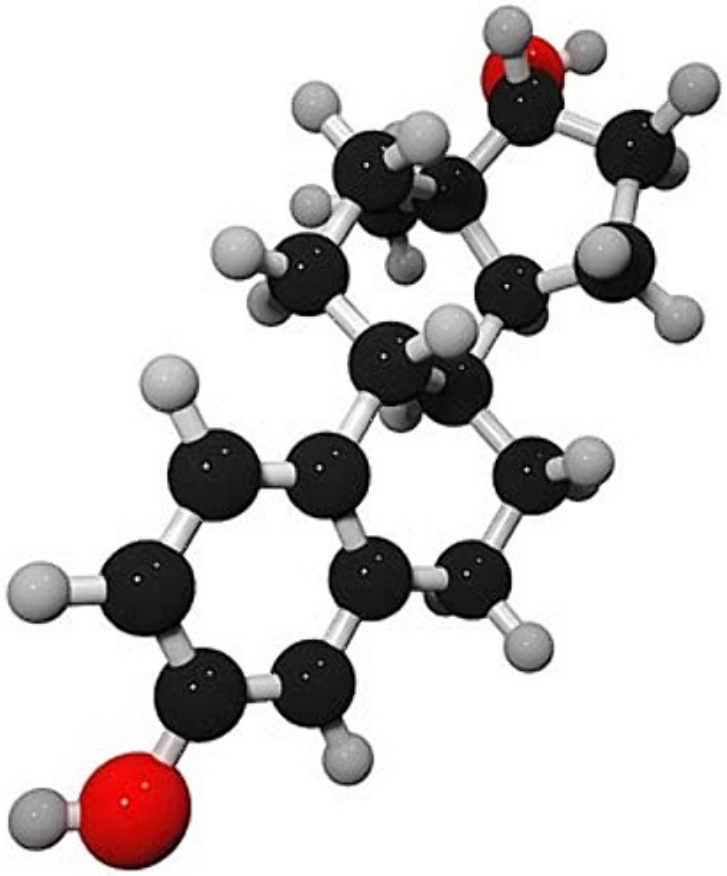
NEUROCHEMISTRY



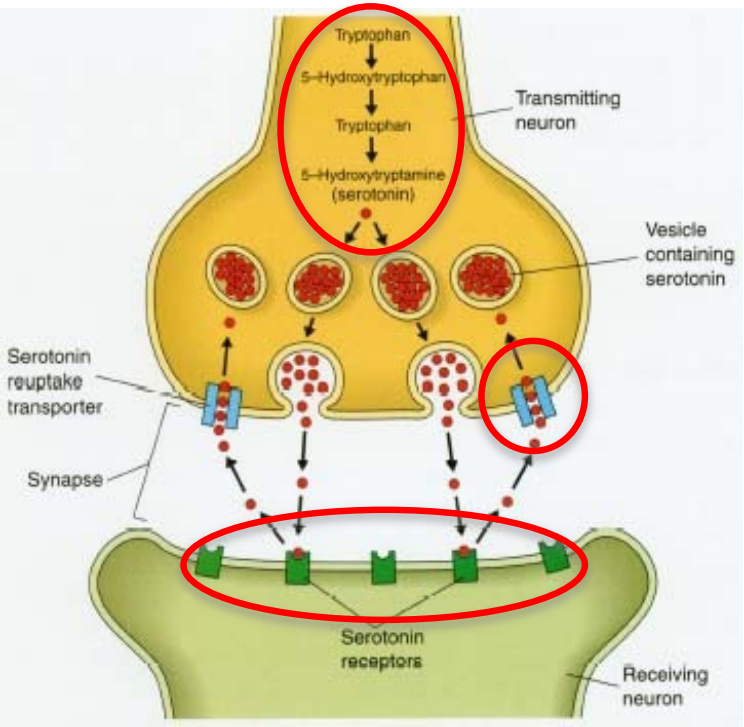


INFLAMMATION

Estradiol 101



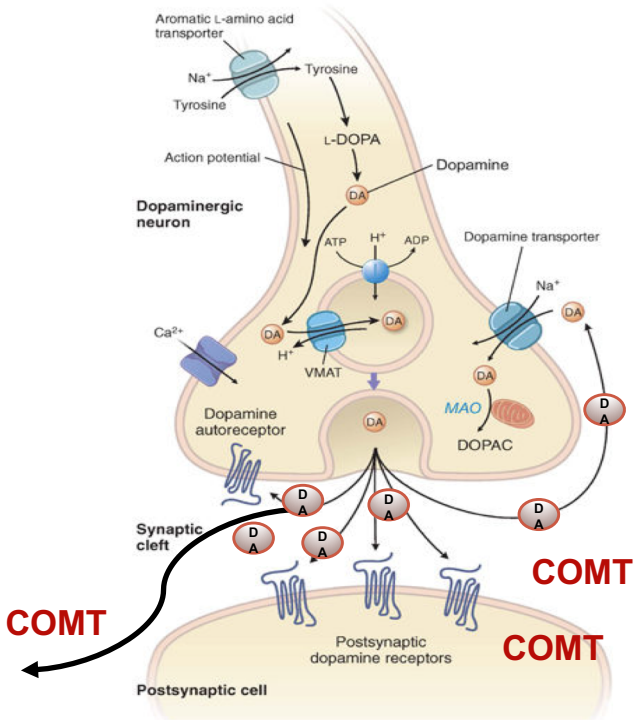
Estradiol and Serotonin



- ↑ Tryptophan hydroxylase mRNA[1]
- ↓ Clearance of 5-HT
  MAO Activity [2]
- ↑ Post-synaptic 5HT-2A
  receptor density[3]
- ↓ Potency of estradiol on
  TPH2 gene expression[4]
- ↓ 5HT1A receptor binding[5]

1. Sanchez RL, et al. *Brain Res Mol Brain Res* 2005;135(1-2):194-203.; 2. Benmansour S, et al. *Neuropsychopharmacology.* 2009;34(3):555-564.*;* 3. Kugaya A, et al. *Am J Psychiatry.* 2003;160(8):1522-11524.; 4. Shively CA, et al. *Pharmacogenomics.* 2003;3(2):114-121.; 5. Murrough JW, et al. *Arch Gen Psychiatry*. 2011;68(9):892-900.

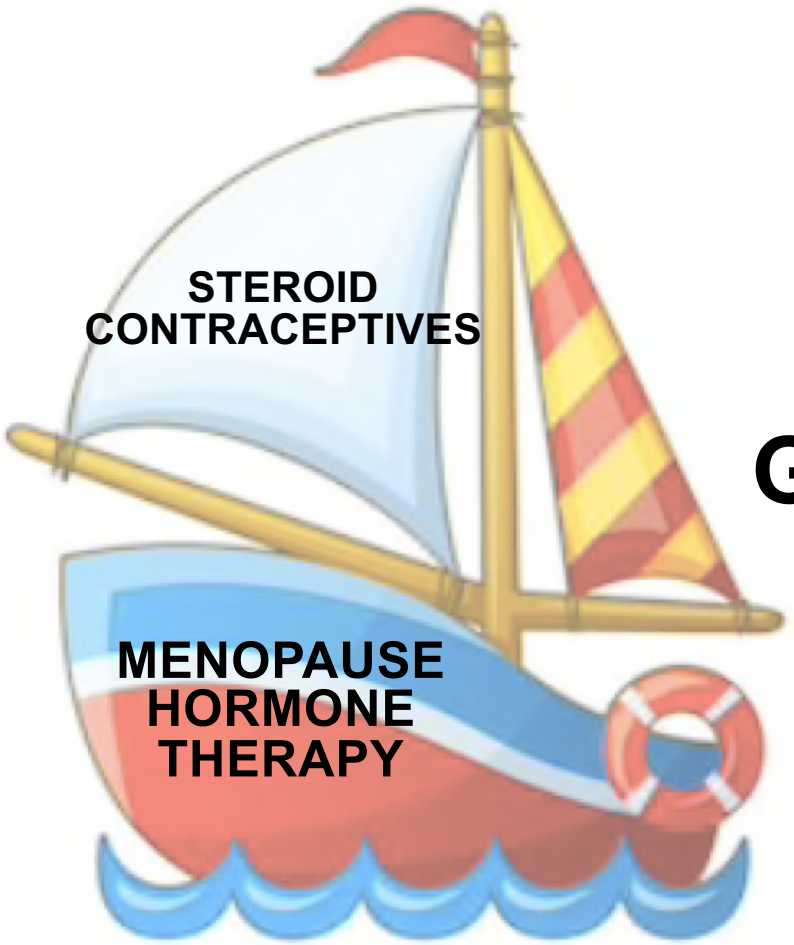
Dopamine Neurons and COMT



- *Met* substitute for *Val* at codon 158 is associated with 2- to 4-fold decrease in catecho-O-methyl transferase (COMT) activity.
  - *Met* allele- higher PFC dopamine
  - *Val* allele- lower PFC dopamine
- Estradiol reduces activity of COMT activity

PFC = Prefrontal cortex, DA = Dopamine

Jacobs E, D'Esposito M. *J Neurosci*. 2011;31(14):5286-5293.

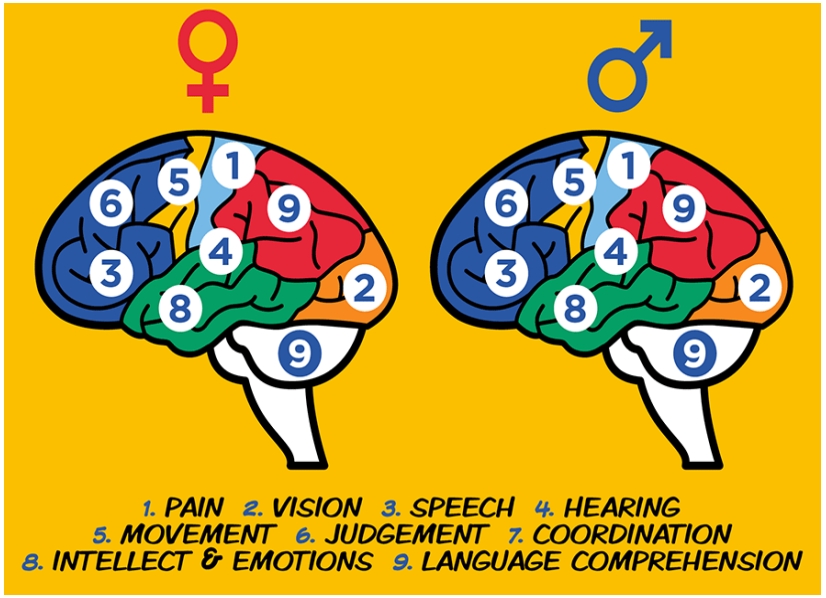


We still have time to inform GAHT methods!

GAHT = Gender-affirming hormone therapy
https://dpcpsi.nih.gov/sgmro
https://grants.nih.gov/grants/guide/pa-files/PA-17-478.html

Sex, Gender, and Hormones

"OH! That explains the difference in our wages"



First Trimester

Male ⟷ Female

Second and Third Trimesters

McCarthy MM, et al. *J Neurosci.* 2012;32(7):2241-2247.
Joel D, et al. *Proc Natl Acad Sci U S A*. 2015;112(50):15468-15473.

Sex Differences: Cis-Gender?

Male

In Utero

Testosterone and its aromatization to estrogen cause masculinization of the fetal brain

Adolescence

Greater grey matter volume and **between-network connectivity**, but less grey matter density. **More accurate on spatial tasks and faster on motor tasks.**

Female

In Utero

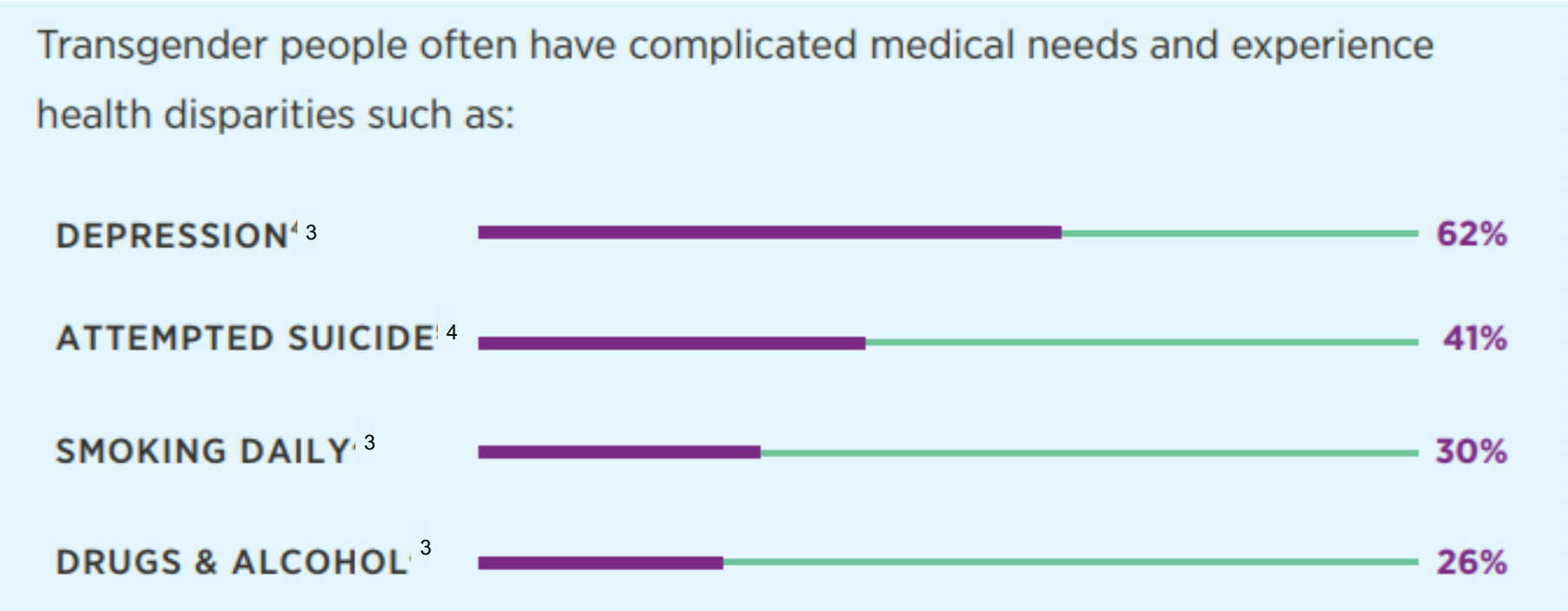
Absence of androgen production and estrogen-binding activity of alpha-fetoprotein cause feminization of the fetal brain

Adolescence

Greater grey matter density and **within-network connectivity,** but less grey matter volume. **Faster on nonverbal reasoning and emotional identification.**

1. Satterthwaite TD, et al. *Cereb Cortex.* 2015;25(9):2393-2394.; 1. Gennatas ED, et al. *J Neurosci*. 2017;37(20):5065-5073.; 3. McCarthy MM, et al. *J Neurosci.* 2012;32(7):2241-2247.; 4. Bakker J, Baum MJ. *Front Neuroendocrinol.* 2008;29(1):1-15.

In 2017, sexual and gender minorities were designated a health disparities population for NIH research, alongside racial/ethnic minorities, socioeconomically disadvantaged populations, and underserved rural populations



1. Reisner SI, et al. *JAMA Pediatr.* 2016;170(5):481-486.; 2. The Fenway Institute. 2015 Transgender Awareness Month. Available at https://cdn2.hubspot.net/hubfs/308746/COM-2316_-_Transgender_Awareness_Month_Infographic_v5.pdf?t=1467397498151.; 3. The Fenway Institute. 2014. Understanding the T in LGBT. October 21, 2015, from lgbthealtheducation.org/training/learning-modules. Accessed January 29, 2019; 4. National Center for Transgender Equality, National Gay and Lesbian Task Force. 2014. National Transgender Discrimination Survey Report on Health and Health Care. October 21, 2015, from thetaskforce.org/static_html/downloads/reports/reports/ntds_report_on_health.pdf. Accessed January 28, 2019.

Previous Neuroimaging Research

- Focus on relative similarities between presumably cis and trans populations
  - Sex biased tasks
  - What is different about the trans brain?
    - Potentially stigmatizing
  - Tendency to treat the trans brain as ”pathologized” as it does not “conform” to the “cis norm”
  - The “Can we fix it?” mentality

Hilary Nguyen, BS

Nguyen HB, et al. *Neuropsychopharmacology*. 2019;44(1):22-37.

Gender-Affirming Hormone Therapy

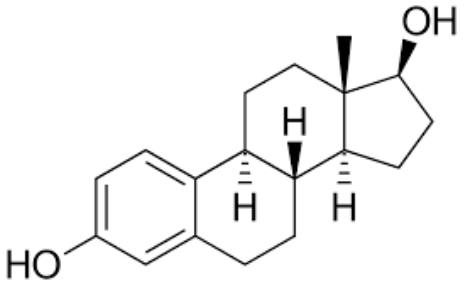
- Gender-affirming hormone therapy (GAHT) is the primary medical intervention sought by transgender people, allowing for the development of secondary sex characteristics more aligned with an individual's gender identity
- At least 80% of trans people have either taken GAHT or want to take GAHT at some point

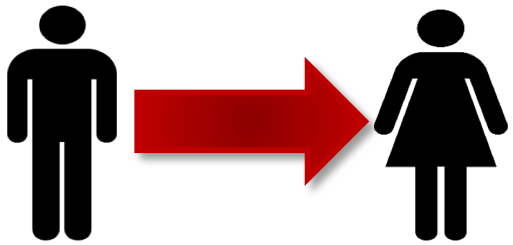
National Transgender Discrimination Survey Report on Health and Health Care, 2010
http://transhealth.ucsf.edu/trans?page=guidelines-feminizing-therapy
http://transhealth.ucsf.edu/trans?page=guidelines-masculinizing-therapy

Gender Affirming Hormone Therapy: 101

Male to Female

- Feminizing therapy
- Estrogens + androgen blockers
  - 17-beta estradiol: transdermal patch, oral tablet, injection, topical cream
  - Anti-androgens: spironolactone, 5-alpha reductase inhibitors

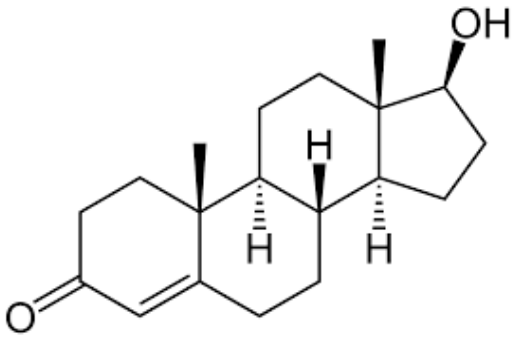


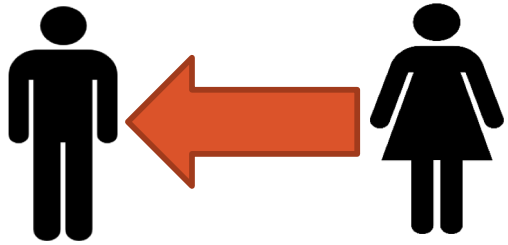


Gender Affirming Hormone Therapy: 101

Female to Male

- Masculinizing therapy
- High dose androgens
  - Testosterone: topical gel or cream, patch, injection
  - Prospective study of 31 FTM
    - Testosterone and estradiol levels were highly variable





Trans Sex Differences Before GAHT

- Most (~75%) cross-sectional neuroimaging research indicates that brain morphology and activation patterns at rest and during cognitive performance are **more congruent with gender identity** than natal sex in untreated MTFs and FTMs

MTF = Male trans female; FTM = Female trans male

Zubiaurre-Elorza L, et al. *Cereb Cortex.* 2013;23(12):2855-2862.; Luders E et al. *J Behav Brain Sci* 2012;2(3):357-362.; Simon L, et al. *PLoS One.* 2013;8(12):e83947.; Rametti G, et al. *J Psychiatr Res*. 2011;45(6):949-954.; Kranz GS, et al. *J Neurosci*. 2014;34(46):15466-15475.; Hahn A, et al. *Cereb Cortex.* 2015;25(10):3527-3534.; Soleman RS, et al. *J Sex Med* 2013;10(8):1969-1977.; Zucker & Bradley, Guildford Press 1995; Cohen-Kettenis PT, et al. *Eur Child Adolesc Psychiatry* 1998;7(4):246-248.; Gizewski ER, et al. *J Sex Med* 2009;6(2):440-448. Junger J, et al. *PLoS One* 2014;9(11):e111672.

Baseline Cross-Sectional Studies

In the majority of studies..
GAHT leads to brain changes that are more consistent with the identified gender.

Prospective Longitudinal Studies of GAHT Effects

Type of Study	MTFs	FTMs
Resting state	3	6
fMRI	3	3
Cognitive	6	7

N = from 6 to 25
GAHT range 4-25 months

N= from 6 to 33
GAHT range 3-4 months

N = from 12 to 35
GAHT range 3-18 months

GAHT Effects on Behavioral Health

Longitudinal & Cross-Sectional Studies in both MTF and FTM trans individuals receiving GAHT:

- LOWER symptoms of anxiety and depression, perceived stress, social distress, global psychopathology
- IMPROVEMENT in quality of life, self-esteem, mood

28 MTFs and 26 FTMs undergoing 24 months of GAHT reported significantly lower subjective levels of gender dysphoria, body uneasiness, and depressive symptoms[1] (Fisher et al., 2016)

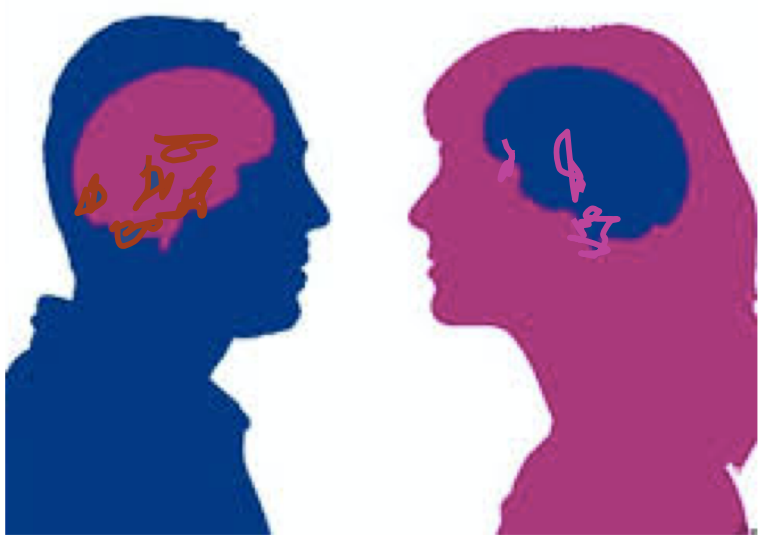
  - Appears to be the longest longitudinal study

1. Fisher AF, et al. *J Clin Endocrinol Metab* 2016;101(11):4260-4269.; 2. Colizzi M. *J Sex Med* 2014;11(4):1093-1095.; 3. Heylens G, et al. *Br J Psychiatry* 2014;204(2):151-156.; 4. Colizzi M,et al. *J Sex Med* 2013;10(12):3049-3058.; 5. Keo-Meier CL, et al. *J Consult Clin Psychol.* 2015;83(1):143-156.; 6. Oda H, Kinoshita T. *BMC Psychiatry* 2017;17(1):256.; 7. Gorin-Lazard A, et al. *J Nerv Ment Dis* 2013;201(11):996-1000.; 8. Bouman MB, et al. *Plast Recomstr Surg* 2016;138(4):614e-623e.; 9. Glynn TR, et al. *Psychol Sex Orientat Gend Divers* 2016;3(3):336-344.; 10. Owen-Smith AA, et al. *J Sex Med.* 2018;15(4);591-600.; 11. Witcomb GL, et al. *J Affect Disord.* 2018;235:308-315. 12. Bonierbale M, et al. *Sci Rep.* 2016;6:24281.

Begs the Question

If one is transgender……

Would their brain be ”healthier” being exposed to the gonadal steroid that compliments their gender identity?



Summary

- Transgender is common
  - 2-3.5 million in the United States alone
- Neuroimaging and cognitive studies
  - Brain is more consistent with gender identity
  - GAHT tends to change brain in the direction of gender identity
  - Psychological well-being tends to improve

Future Directions

- Long term studies are needed
  - Both adults and youth
  - Focus on cognitive domains that are associated with critical day to day functions
  - Consider the gender non-binary
  - Examine impact of various regimens

Call to Action

- Recognize the impact of hormones on mood and cognition in both cisgender and transgender individuals
- GAHT in transgender individuals can positively impact anxiety, mood and quality of life

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.

Supplemental References

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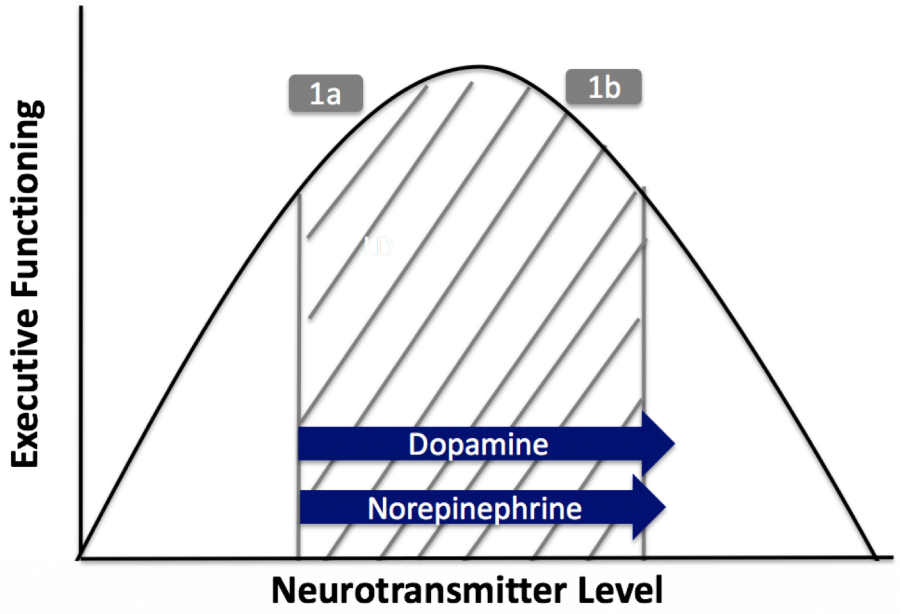
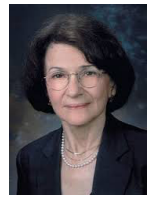
Executive Function



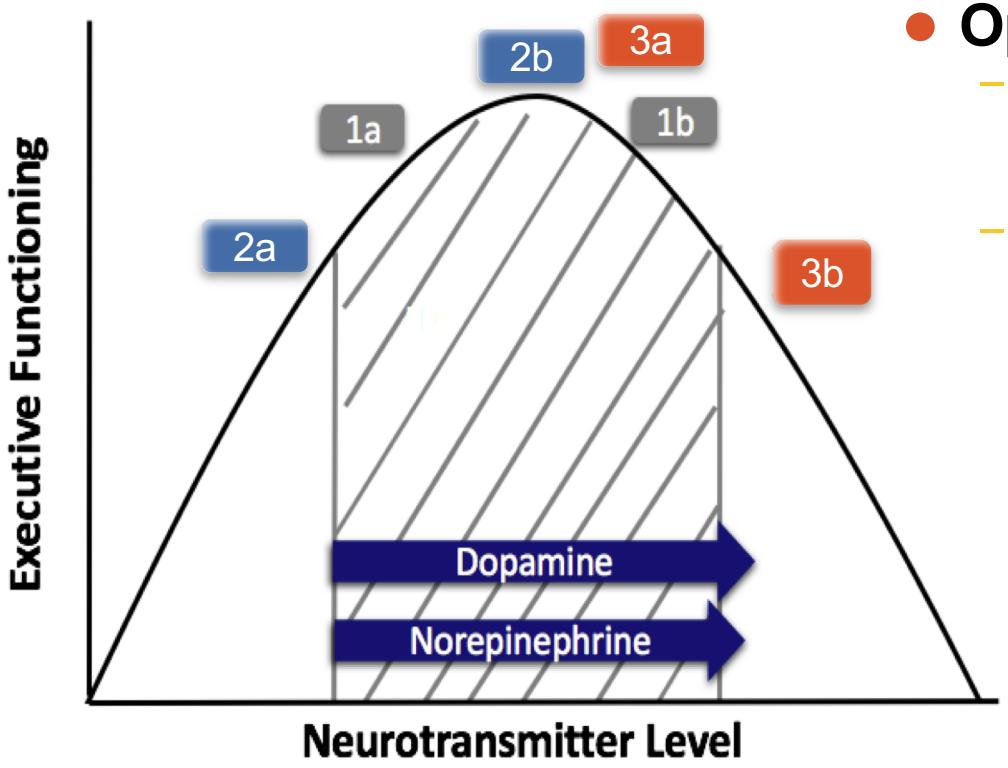
- High estradiol
  - COMT met/met performs worse
- Menstrual cycle pattern
  - Late premenopause
  - Early transition
  - Late transition
  - Postmenopause
- Symptoms

Shanmugan S, Epperson CN. *Hum Brain Mapp.* 2014;35(3):847-865.
Jacobs E, D'Esposito M. *J Neurosci*. 2011;31(14):5286-5293.


Pat Goldman- Rakic


Amy Arnsten

Estrogen Effects on COMT and Prefrontal Dopamine



- **Optimal Executive Function**
  - 1a– *Val* allele
    - Higher COMT activity, lower DA levels
  - 1b- *Met* allele
    - Lower COMT activity, higher DA levels

↗ **Under Conditions of Low Estradiol**

↗ 2a– *Val* allele

↗ 2b- *Met* allele

↗ **Under Conditions of High Estradiol**

↗ 3a– *Val* allele

↗ 3b- *Met* allele

Jacobs E, D'Esposito M. *J Neurosci*. 2011;31(14):5286-5293.

Concerning Hormone Effects in Cisgender Models

LOW ESTROGEN/TESTOSTERONE

Menopause in Cis Females

- Decline in cognitive function, particularly memory and attention
- Increase in risk for major depressive disorder

Premature Menopause and Estrogen Deficiency in Cis Females

- Heightened risk for first onset depression and cardiovascular, neurological, psychiatric diseases

Low Testosterone in Cis Males

- Increased risk for cardiovascular disease, cancer, metabolic syndrome, type 2 diabetes, frailty, depressive symptoms, mortality

HIGH TESTOSTERONE

Polycystic Ovary Syndrome in Cis Females

- Decline in cognitive function, particularly memory and attention
- Risk for psychological, metabolic, reproductive, cardiovascular abnormalities (acne, obesity, type 2 diabetes, heart disease, mood disorders), lower quality of life

Increased androgen levels in Cis Females

- Increases in irritability, anger, hostility, clinical mood disorders (premenstrual syndrome, depression)

See supplemental references at the end of the slide presentation.