COGS17 Neurobiology of Cognition

Lecture 9: Sexual Development and Behavior

REMINDERS: **Hypothalamus** controls Endrocrine (hormone) systems via effect on adjacent **Pituitary Gland** (the "Master Gland")
- Produces Releasing Hormones that flow via **blood vessels** to **Anterior** Pituitary stimulating gland to release its own hormones
- Produces other Hormones (e.g. Oxytocin) sent (like NTs) via **axons** to **Posterior** Pituitary, then circulate in bloodstream

Reproductive Hormones have Organizing Effects (on anatomy in fetal devel & puberty) & Activating Effects (influence behavior)
- Both sexes have female (**Estrogens**) and male (**Androgens**) hormones, just in different proportions
  - These Steroid Hormones are produced mainly in Ovaries/Testes, but also in Hypothalamus and Adrenal Glands
- NOTE: Typically, males have **XY** sex chromosomes, females have **XX,** but hormone activity is required to determine gender!

ORGANIZING EFFECTS

Fetal Development of Sexual Anatomy
- Every mammalian fetus has the anatomical precursors for BOTH sexes
  - e.g. Gonads, earliest sex structure to develop, same initial structure will become Testes or Ovaries
  - e.g. Gentalia, same initial structures in all fetuses, develop into male or female anatomy, depending on Androgens/Not
  - e.g. Each fetus has both **Wolffian** and **Muellerian** ducts; Their development depends on Androgens/Not
    - These become ether Vas Defrens & Prostate or Fallopian Tubes & Uterus respectively; Other system degenerates
- The genes controlling male/female body & brain development are also present in BOTH sexes, EXCEPT…
  - The "switch" is on the male's **Y Chromosome**; it signals production of the **Testis-Determining Factor** (**TDF**) Enzyme
    - Occurs during Critical Period of fetal development (TDF appears : 6^{th}–8^{th} week; Genitals developed by 4^{th} month)

- **If TDF is NOT present => Female**
  - Ovaries differentiate, Mullerian system develops, Wolffian regresses, female genitalia develop – regardless of geneotype!
    - If fetus is XY, but lacks specific gene for TDF (or other TDF deficit), will develop internally & externally as female
    - If fetus is XO (**Turner's Syndrome**, no Y Chromosome) will develop internally & externally as female
      - Both non-XX above will be infertile, however, since two Xs required to produce ova (eggs)

- **If TDF is present => Male**
  - Testes differentiate, producing Androgens, including **Testosterone** => Wolffian ducts and male genitalia develop
    - Testes also produce **Anti-Muellerian Hormone**, inhibits development of Muellerian system
  - If XY fetus is **Androgen-Insensitive**, it's testes still produce Androgens and Anti-Muellerian Hormone, but since its Wolffian system's androgen receptors are absent, it not develop, and its Muellerian System is inhibited
    - So individual has no internal sex organs (& so is infertile) except rudimentary, internal testes
    - But external body develops as a female, although without androgen-stimulated pubic, or other secondary, hair
  - If XX fetus is exposed to **Testosterone** during critical period, develops male, or semi-male form, sometimes infertile
    - Some tendency for these individuals to be homosexual, tho per body, brain, and/or societal influences??

-**PLUS**: Testosterone enters fetal cells, where it is converted ("aromatized") into **Estradiol** (an Estrogen!) => **Male** development
  - So, why doesn't Mom's estradiol masculinize every fetus? Answer: **Apha-Fetoprotein!**
    - Apha-Fetoprotein in fetal/infant blood, binds with Estrogen, preventing it from entering fetal cells (later inactivated)
    - Excessive Estrogens (e.g. DES, synthetic estrogen to prevent miscarriage) can overwhelm safeguard, masculinize fetus

Secondary Sexual Characteristics at Adolescence
- In both sexes, Hypothalamus releases **Gonadotropin-Releasing Hormones** (**GnRH**), causing Anterior Pituitary to release the Gonadotropic Hormones: **Lutenizing Hormone (LH)** and **Follicle Stimulating Hormone (FSH)**
- In Males, these hormones >> Testes produce sperm and Testosterone (and other Androgens, and low levels of Estrogens) >> facial & other secondary hair growth (& later baldness), muscular development, enlargement of larynx, stop bone growth
- In Females, these hormones >> Ovaries produce ova and Estradiol (and other Estrogens, and low levels of Androgens) >>breast development, alteration of fat deposits, menstrual cycle of egg release & uterine build-up/decline, stop bone growth
  - Female secondary hair growth via **Androstenedione** (an Androgen) released by **Adrenal Glands**

Sexual Differences in Brain Development
- Presence/Absence of **Testosterone** during prenatal period and early infancy => differences in brain
  - **Medial Preoptic Area (MPOA)** of Hypothalamus, has Androgen receptor sites, is esp active during Male sexual behavior
    - This area includes the **Sexually Dimorphic Nucleus** (**SDN**) which is 2.5X larger in Males than Females
    - Early Testosterone is required for this devel, and w/o it adult Male will not respond normally to androgen activity
  - **Ventro-Medial Hypothalamus** (**VMH**), has Estrogen receptor sites, is especially active during Female sexual behavior
    - Develops (esp sensitivity to estrogens) in absence of early Testosterone (Area also implicated in control of eating)

- Other sexual dimorphisms in brain anatomy (may be related to early Testosterone levels, but insufficient data) include:
  - **Connectivity** patterns in cortex, per diffusion-based imaging
    - Males show more intra(within)-hemispheric connections while females show more inter(between)-hemispheric
    - Suggests males may better integrate perception & action, females better integrate analytic & intuitive processing
      - May help account (with Culture) for better spatial abilities in males, better communication abilities in females
  - **INAH3,** part of Sexually-Dimorphic Nucleus, larger in Heterosexual Males, smaller in Females and Homosexual Males
    - In homosexual males, not clear if such differences are cause or effect of behavior?

ACTIVATING EFFECTS

Neural and Hormonal Activation of Sexual Behavior - All depend on pre-established "Organizing Effects"

- *In Males*:
  - **Medial Preoptic Area (MPOA)** of Hypothalamus, including Sexually Dimorphic Nucleus, is critical for sexual behavior
    - Releases **GnRH** (Gonadotrophin Releasing Hormone) > Anterior Pituitary releases the Gonadotrophins LH & FSH
      - These Gonadotrophins travel through bloodstream > Testes release Testosterone
    - Testosterone feeds back to MPOA, escalating arousal
    - Circuit includes **VTA** (Ventral Tegmental Area) > **Nucleus Accumbens** (*Pleasure!*) near Basal Forebrain
      - Releases **Dopamine** to Nuceus Accumbens in response to sexual stimulation
      - Area also implicated in addiction to amphetamines, cocaine, and chocolate; Rats will stimulate area to death
    - MPOA also stimulates Basal Ganglia which communicates with Spinal Nucleus of the Bulbocavernosus (SBN)
      - Motor neurons of SBN => rhythmic contractions for ejaculation
      - At orgasm, MPOA signals Posterior Pituitary to release **Oxytocin**
      - After ejaculation, Anterior Pituitary releases **Prolactin**, producing Refractory Period before male can respond again
  - **MPOA** also *responds* to input from **Medial Amygdala**, implicated in **Aggression** (see Emotion lecture)
    - Some correlation between high Testosterone and Aggression (as in violent crime, tho not nec sexual crime)
    - NOTE: Medial Amygdala also likely receives Pheromone input, as well as Somatosensory info from genitals
      – In rodents, smell can inhibit aggression toward females, increase aggression toward rival males
    - Also responds to input from Cerebral Cortex (**Learning** plays a greater role in human sexual activity than in nonhumans)
      - Includes Sensory (including visual identification), Memory, Prefrontal evaluation, and Motor organization
      - Can lead to idiosyncratic partner-, place- or object-specific sexual responses
- *In Females*:
  - **Androstenedione** (chemically like Testosterone), an **Androgen** produced by **adrenals**, for sexual **motivation**
    - Gets converted into Testosterone in bloodsteam, activates **MPOA**
    - Then, just as in Males, **MPOA** > **GnRH** >**LH & FSH** > stimulates Ovaries and Adrenals (short-term positive feedback)
      - Estrogens from Ovaries stimulate **Ventro-Medial Hypothalamus (VMH)**,
        - This is region most activated during female sexual **behavior**
      - VMH *and* MPOA stimulate pleasure circuit: **VTA** releases Dopamine to **Nucleus Accumbens** for reinforcement
        > Basal Ganglia > SBN for rhythmic contractions, as in males
      - VMH also stimulates **Periaqueductal Gray Area** which produces Endorphins, in part to suppress Pain
      - Also signals Posterior Pituitary to release **Oxytocin** (at time of orgasm)
        - Oxytocin also linked to release of milk in lactating females, aids in bonding with offspring
      - After sex, females do not show same Prolactin release or Refractory Period
        - Note: Instead, **Prolactin** in pregnant females, stimulates milk production
  - -- **VMH** also *responds* to input from **Medial Amygdala** (Pheromones) and from Cerebral Cortex (**Learning** etc)

Role of Pheromones in Mediating Sexual Behavior

- **Pheromones** = Hormones released by one individual that affect behavior/physiology of conspecific; Found in sweat of humans
  - In most mammals, detected by **Vomeronasal Organ (VNO)** – specialized olfactory receptors, respond only to pheromones
    - Direct connections to Medial Amygdala and Medial Preoptic Area of Hypothalamus
    - VNO controversial in humans: Exist / Not? Vestigial / Functional?
  - However, humans DO appear to respond to pheromones (Pheromones *control* rat behavior, *influence* human behavior)
    - In Women: Sweat in alcohol swabbed on upper lip of other women (!) vs. placebo => synchronized menstrual cycles
    - In Men: Aftershave spiked with male pheromone vs. placebo => increased # of sexual interactions (inc'd attractiveness)