Hormones are chemical messengers, just like a neurotransmitter, that are secreted directly into the blood. These chemical messengers travel through the blood to activate receptors located on organs and tissues of the body to exert their functions. Hormone receptors are binding sites on the target cell (either on the surface or in the cytoplasm or nucleus of the target cell) that are activated only when specific hormones bind to them. If a hormone does not/cannot bind to its receptor, then will be no physiologic effect.

**ACTIVATING EFFECTS**

This usually occurs once a physiological system has developed and there is a response when the hormone activates the receptors. However, once the hormone is no longer present, then the responses stop. Therefore, activating effects are temporary.

For example, when thyroid stimulating hormone (TSH) is released from the pituitary gland, it stimulates the receptors in the thyroid gland to release the hormone thyroxine. If there is no TSH present, then there will be no release of thyroxine.

Some typical **ACTIVATING EFFECTS** of hormones include:
1. Cell metabolism
2. Sexual motivation and reproduction
3. Cognitive function and mood
4. Maintenance of body temperature and thirst
5. Transport substances into and out of the cell

ORGANIZING EFFECTS

The organizing effects of hormones occur at a specific time early in development, called CRITICAL PERIOD. These organizing effects can alter the course of development and have long lasting or permanent effects. For example, growth hormone was released from the pituitary early in development, activated the receptors on the cells of your body, and those cells grew in size and number. As a result, you grew bigger and you have stayed big even when growth hormone is no longer present in the high concentrations it was early in your life. So was this a long lasting effect? In addition, you are now past the critical period when those cellular changes can happen, so I can inject high levels of growth hormone into you and you will not grow taller.

Some typical ORGANIZING EFFECTS of hormones include:

1. Development and growth
2. Fetal development and sexual differentiation

TYPES OF HORMONES

Hormones fall into 2 general classes based on their molecular structure and synthesis.

1. PROTEINS and AMINO ACID DERIVATIVES - the body uses amino acids which it can either manufacture directly from glucose or obtain by the digestion of proteins. The PROTEINS are amino acids strung together by peptide bonds, according to the genetic code supplied by the genes. There are only 20 amino acids that when combined in the right order make the thousands of proteins for all the cells of your body. Ten of these amino acids are made internally (nonessential amino acids) and the other ten must be obtained from your diet (essential amino acids). The chart below shows the 20 amino acids (not on the test) and next to it is a picture of a longer protein.

Most of the hormones of your body are proteins. The actual making of the protein/hormone is eventually done by the ribosomes and is called protein synthesis. For example, Thyrotrophic Releasing Hormone (TRH) consists of the amino acids glutamate, histidine, and proline. Other proteins/hormones can be very large consisting of many amino acids strung together in the correct order.

Alternatively, amino acids can be metabolized to form hormones. For example, the amino acid TYROSINE is metabolized in to form the hormones DOPAMINE (brain), NOREPINEPHRINE & EPINEPHRINE (adrenal glands) and THYROXINE (thyroid gland).
Once the protein or amino acid derivative hormones are synthesized they are stored in vesicles. When the cells in those glands are stimulated Ca\(^{++}\) channels open, Ca\(^{++}\) enters, the vesicles containing the hormone fuse to the membrane and they release the hormone into the blood vessels. The hormone circulates in the blood until they encounter metabotrophic receptors on the target cells. SEE FIGURE BELOW. The hormone interacts with the receptor to activate a G protein, which activates adenyl cyclase, ATP is converted to cyclic AMP, and cyclic AMP activates protein kinase. Please review the section on metabotrophic receptors in the PART 1. This is turn alters the metabolic functions of the cell, such as:

A. Activate enzymes  
B. Alter cell permeability and increase transport of substances into the cell  
C. Cause contraction or relaxation of muscle  
D. Cause protein synthesis  
E. Cause secretion

2. STEROID HORMONES are synthesized from cholesterol in the adrenal cortex, ovaries, and testes.  
   (A) They are SMALL which helps the steroid to pass through the cell membrane.  
   (B) They are FAT SOLUBLE which means they can dissolve through fat. Since the cell membrane is a lipid (fat) bilayer, this also allows the steroid to pass through the cell membrane. See #1 in the figure below.  
   (C) Once the steroid is released into the blood stream it passes through the membranes and into the cell, and then bind to a receptor protein in the cytoplasm. See #2 in the figure below.  
   (D) The steroid hormone/receptor complex enters the nucleus to activate specific genes to form messenger RNA. See #3 & 4 in the figure below.
This causes the formation of new proteins (protein synthesis) at the ribosomes. See #5 & 6 in the figure below.

For example, aldosterone is secreted by the adrenal cortex into the blood. It enters cells in the renal tubules and a receptor within the cytoplasm. This activates the DNA to form new proteins that promote Na uptake. To form these new proteins takes 45 minutes.

**THE PITUITARY**

The pituitary gland is about 1.0 cm in diameter and lies within the sella turcica at the base of the brain. It connects with the hypothalamus via the hypophyseal stalk. It is an important link between the nervous and endocrine systems and releases many hormones which affect growth, sexual development, metabolism and human reproduction.

All of the hormones from the pituitary are proteins. So these hormones activate metabotrophic receptors on the target cells.

The pituitary is functionally divided into two distinct regions.

1. Anterior Pituitary
2. Posterior Pituitary

While the pituitary gland has previously been considered to be a single structure in the body, further study...
of its structure has revealed that in fact it is made of two structurally and functionally distinct regions. The anterior pituitary gland or adenohypophysis is a true hormone-producing gland made of glandular epithelium. The posterior pituitary gland or neurohypophysis is an extension of nervous tissue from the hypothalamus that stores and releases two hormones produced in the hypothalamus.

In the picture below you can see that the neurons from the hypothalamus extend axons and terminals directly into the posterior pituitary. These neurons release hormones directly into the blood vessels in the posterior pituitary. Neurons from the hypothalamus do not extend axons into the anterior hypothalamus.

1. **Anterior Pituitary** or adenohypophysis is formed from epithelial tissue during development. The hormones of the anterior pituitary play important roles in the metabolism of cells throughout the body. There are 6 important hormones:

   **(1) Growth Hormone (GH)** - also called somatotrophin is a protein containing 188 amino acids. Its secretion during development increases the size and number of cells in most every tissue in the body. It does this by activating the metabotropic receptors of the cells, causing the cells to increase protein synthesis, increase the uptake of amino acids (make more available for protein synthesis) and inhibit the breakdown of active proteins.

   GH is also important in adulthood. During periods of malnourishment and protein levels are low, GH is secreted to increase protein synthesis and prevent protein breakdown.

   **Dwarfism** - when there are deficient levels of GH secreted during development, dwarfism will result. The person will be extremely short (usually under 4’10””) with proportional body parts. The technical term today is growth-hormone deficiency.

   **Gigantism** - if during development large quantities of GH may be produced. All the body tissues grow rapidly; the person may grow to 8 or 9 feet.
Acromegaly- occurs when excessive GH is produced after puberty. Some of these individuals may have had gigantism during development as well.

Features that result from high level of GH or expanding tumor include:

- Soft tissue swelling visibly resulting in enlargement of the hands, feet, nose, lips and ears, and a general thickening of the skin.
- Soft tissue swelling of internal organs, notably the heart with attendant weakening of its muscularity, and the kidneys, also the vocal cords resulting in a characteristic thick, deep voice and slowing of speech
- Generalized expansion of the frontal skull
- Pronounced brow protrusion, often with ocular distension (frontal bossing)
- Pronounced lower jaw protrusion (prognathism) with attendant macroGLOSSIA (enlargement of the tongue) and teeth spacing

ANDRE THE GIANT WAS A FAMOUS WRESTLER THAT HAD ACROMEGALY

(2) Thyroid Stimulating Hormone (TSH) is a protein that regulates the secretion of thyroxine
from the thyroid gland. Thyroxine activates metabotrophic receptors that increase the metabolic activity of cells in most of the body. The metabolic rate may increase 60 - 200%. Once thyroxine is released into the blood, it takes 2 - 3 days before metabolic rates begin to rise (very long onset) and will continue to peak 10 - 12 days later but still last 1 ½ - 2 months. (very long duration). The release of TSH occurs in response to the cold. The release of TSH and then the release of thyroxine from the thyroid gland increases cell metabolism which warms the body and is how many animals can survive the cold during winter. During development the cells require higher concentrations of thyroxine, a period when high metabolism is necessary for the cell. If TSH and thyroxine are lower than normal during development, the person develops Cretinism. The baby will become very sluggish and can result in both physical and mental retardation. Many of the effects can be countered by appropriate hormone replacement therapy. Therefore, the brain needs thyroxine for normal development.

(3) Adrenocorticotrophin Hormone (ACTH) is a protein that controls the release of cortisol and corticosterone from the adrenal cortex. The adrenal gland is composed of two parts, the inner medulla and outer cortex. The cortex releases steroid hormones which include aldosterone, cortisol, and corticosterone. Of interest to many in Psychology is that the pituitary releases ACTH during stress. When ACTH is released it activates metabotrophic receptors in the cortex of the adrenal gland. The adrenal cortex will release two steroid hormones cortisol and corticosterone. Cortisol and corticosterone are steroid hormones so they are synthesized from cholesterol and are small and fat soluble. They will activate receptors located inside of the cells.

Cortisol and corticosterone has three primary functions:

1. Cause cells in the liver to release stored glucose into the blood called gluconeogenesis.
2. They will also cause the cells of the fat to release fatty acids which can be used for energy by the cells of the body (except for neurons).
3. Cause the breakdown of muscle in order to release amino acids. Although amino acids can be used by cells for energy, breaking down the muscle is a last resort for the body during periods of starvation.

So during stress the body may need to use a lot of energy (during that football game) and the ACTH gets all the energy stores of glucose, fatty acids, and in extreme conditions amino acids mobilized and ready.

Two well-known diseases that involve ACTH are Addison’s Disease and Cushing’s Disease.

Addison’s Disease became well known because President John F. Kennedy had the condition. In Addison's disease, the adrenal glands don't make enough cortisol and in many cases not enough aldosterone. Addison’s disease symptoms usually develop slowly, often over several months, and may include:

1. Muscle weakness and fatigue
2. Weight loss and decreased appetite
3. Darkening of your skin (hyperpigmentation)
4. Low blood pressure, even fainting
5. Salt craving
Cushing's Disease is a hormonal disorder caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol. Sometimes called "hypercortisolism," it is relatively rare and most commonly affects adults aged 20 to 50.

Some of the symptoms of Cushing's Disease include:
1. Upper body obesity, rounded face, increased fat around the neck, and thinning arms and legs.
2. Children tend to be obese with slowed growth rates.
3. The skin, which becomes fragile and thin. It bruises easily and heals poorly. Purplish pink stretch marks may appear on the abdomen, thighs, buttocks, arms and breasts.
4. Weak bones so that routine activities such as bending, lifting or rising from a chair may lead to backaches, rib and spinal column fractures.
5. Most people have severe fatigue, weak muscles, high blood pressure and high blood sugar.
6. Irritability, anxiety and depression are common.
7. Women usually have excess hair growth on their faces, necks, chests, abdomens, and thighs. Their menstrual periods may become irregular or stop.
8. Men have decreased fertility with diminished or absent desire for sex.

(4) Prolactin a protein that promotes mammary gland development and milk production. Prolactin also plays an essential role in metabolism, regulation of the immune system, and pancreatic development.

(5) Follicle Stimulating Hormone (FSH) stimulates the ovarian cells in the follicles to grow in females. The ovaries start releasing estrogen and it is critical to maintain the reproductive cycle, increase sexual drive, and many other functions. FSH in males is important for spermatogenesis.

(6) Luteinizing Hormone (LH) is very important for final follicle growth and triggers ovulation. Also, the corpora lutea of the ovary increases in progesterone and estrogen secretion. Progesterone develops the endometrium in the uterus. In males LH is important for the secretion of testosterone and testosterone is also critical for spermatogenesis.

THE HYPOTHALAMUS OF THE BRAIN CONTROLS THE RELEASE OF ANTERIOR PITUITARY HORMONES

In 1955, Guilleman and Schally independently demonstrated that when the pituitary is tissue cultured in a test tube there is no secretion of hormones from the anterior pituitary. However, if you take that same pituitary and add some of the hypothalamus, then the anterior pituitary starts releasing large amounts of hormones. So there was something about the hypothalamus that controls the release of hormones.

The research by Guilleman & Schally hypothesized that the hypothalamus secretes a RELEASING HORMONE to regulate the release of anterior pituitary hormones. In addition, these RELEASING
HORMONES are most likely proteins, so you just had to find the right sequence of amino acids. Easier said than done.

It wasn’t until 16 years later in 1971 that both Guilleman and Schally independently found THYROID STIMULATING HORMONE-RELEASING HORMONE (TSH-RH). The search for the chemicals from the hypothalamus that control pituitary hormone secretion began intensely. These results demonstrated how the hypothalamus controls the release of anterior pituitary hormones and opened a new field of research called neuroendocrinology. For their work Guilleman and Schally won the Nobel Prize in Physiology or Medicine in 1977.

The other releasing hormones were discovered afterward. These are the releasing hormones for the six anterior pituitary hormones.

1. **THYROID STIMULATING HORMONE - RELEASING HORMONE (TSH-RH)**
2. **GROWTH HORMONE RELEASING HORMONE (GH-RH)**
3. **CORTICOTROPHIN RELEASING HORMONE (CRH) controls the release of ACTH from the pituitary.**
4. **PROLACTIN RELEASING HORMONE (PRH) is probably dopamine.**
5 & 6. **GONADOTROPHIN - RELEASING HORMONE (Gn-RH) controls the release of both Follicle Stimulating Hormone and Luteinizing Hormone**

Some of these releasing hormones control the pituitary by stimulating the release of the hormones (TSH-RH & CRH) while others have found both stimulating (RELEASING HORMONE, RH) and inhibiting (INHIBITING HORMONE, IH) releasing hormones (GH-RH/GH-IH for growth hormone &, PRH/PIH for prolactin, Gn-RH/Gn-IH for both follicle stimulating hormone and luteinizing hormone). For this class we will always refer to them as releasing hormones (RH).

Neurons in the hypothalamus synthesize (make) the hormone and store them in synaptic vesicles. The axon terminals synapse onto and release the hormone into blood vessels located in the hypothalamus. These blood vessels carry the releasing hormone directly to the anterior pituitary gland where they can activate the receptors of the specific cells for that hormone. The dense set of blood vessels between the hypothalamus and anterior pituitary gland are called the HYPOTHALAMIC-HYPOPHYSEAL PORTAL VESSIONS.

The figure below shows the neurons in the hypothalamus excreting RELEASING HORMONES into the blood vessels that connect with the anterior pituitary gland. These releasing hormones control the release of hormones from the anterior pituitary. Some releasing hormones stimulate the release of hormones from the anterior pituitary, while other releasing hormones actually inhibit the release of hormones from the anterior pituitary.
The figure below shows the list of releasing and inhibiting hormones that have been discovered in the hypothalamus. These hormones from the hypothalamus are released by neurons directly into the blood vessels and regulate the release of specific hormones in the anterior pituitary gland.
2. **Posterior Pituitary** develops embryo logically from neural tissue, it is actually an extension or outgrowth of the hypothalamus and has been called the neurohypophysis. The posterior pituitary secretes two important hormones.

(1) **Antidiuretic Hormone (ADH) or VASOPRESSIN** - hormones controls the rate of H2O excretion at the renal tubules of the kidney. Composed of the amino acids Tyro-Pro-Glut-Aspar-Gly-Cystine-Phenyl-Arginine.

(2) **Oxytocin** helps in the delivery of milk during suckling, also aids in the contraction of the uterus during delivery. Also seems to be necessary for orgasm. Composed of the amino acids Tyro-Pro-Glut-Aspar-Gly-Cyst-Leu-isoleu.

The neurons that contain OXYTOCIN and VASOPRESSIN are located within two nuclei of the hypothalamus, SUPRAOPTIC AND PARAVENTRICULAR NUCLEI. The axons of these neurons project directly into the pituitary (posterior portion). When the neurons become active, the neurotransmitter is released into the blood to act on the target organs. Important to note that these two hormones are transmitters manufactured at the soma of neurons in the hypothalamus released from the terminals located in the pituitary.
This slide shows the location of the supraoptic (SON) and paraventricular (PVN) nuclei whose neurons produce vasopressin and oxytocin. The axons of these neurons extend down to the pituitary gland where they release the hormone/neurotransmitter.

If a rat becomes severely dehydrated the cell bodies in the nucleus increase in size and increase in metabolic activity in order to manufacture and release **VASOPRESSIN** into the blood for water conservation in the kidneys.

At times a tumor of the hypothalamus can kill neurons in the SO and PVN. Therefore, plasma levels of VASOPRESSIN fall below normal and the person can no longer retain water and becomes constantly thirsty, this condition is called **Diabetes Insipidus**. A person with this problem may lose 4-12 liters of fluid per day. It is treated by inhaling powered vasopressin through the nose several times a day.

VASOPRESSIN has also been shown to develop pair bonding in males.

**THE HYPOTHALAMUS CONTROLS THE RELEASE OF POSTERIOR PITUITARY HORMONES**

This drawing shows the neurons of the hypothalamus that either contain the hormone ADH (vasopressin) or oxytocin. The axons extend down into the posterior pituitary where their terminals contact the blood vessels. At the appropriate time action potentials initiate the release of these hormones directly into the blood.
VASOPRESSIN

Arginine vasopressin (AVP), also known as vasopressin, antidiuretic hormone (ADH) or argipressin, is a mammalian hormone that is mainly released when the body is low on water; it causes the kidneys to conserve water by concentrating the urine and reducing urine volume. It also causes vasoconstriction. A very similar substance, lysine vasopressin (LVP) or lypressin, has the same function in pigs and is often used in human therapy.

Vasopressin is a peptide hormone liberated from a preprohormone precursor, the bulk of which is synthesized by the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus, and transported to the posterior part of the pituitary gland from where it is secreted into the blood stream. Some of it is also released directly into the brain from the dendrites of the magnocellular neurons as well as from other brain neurons (see below).

Control

Vasopressin is secreted from the posterior pituitary gland in response to reductions in plasma volume and in response to increases in the plasma osmolality:

1. Secretion *in response to reduced plasma volume* is activated by pressure receptors in the veins, atria, and carotids.

2. Secretion *in response to increases in plasma osmotic pressure* is mediated by osmoreceptors in the hypothalamus.

The neurons that make vasopressin, in the supraoptic nucleus and paraventricular nucleus, are themselves osmoreceptors, but they also receive synaptic input from other osmoreceptors located in regions adjacent to the anterior wall of the third ventricle. These regions include the organum vasculosum of the lamina terminalis and the subfornical organ.

Many factors influence the secretion of vasopressin:

Ethanol and caffeine reduce vasopressin secretion. The resulting decrease in water reabsorption by the kidneys leads to a higher urine output. Coffee is an example of a food product that suppresses the body's release of antidiuretic hormones, due to its level of caffeine. This intake of caffeine causes the body to lose more water and may lead to dehydration if consumed excessively.

Sources

The vasopressin that is measured in peripheral blood is almost all derived from secretion from the posterior pituitary gland (except in cases of vasopressin-secreting tumors). However there are two other sources of vasopressin with important local effects:

Vasopressin is secreted from parvocellular neurons of the paraventricular nucleus at the median eminence into the short portal vessels of the pituitary stalk. These vessels carry the peptide to the anterior pituitary gland, where it is an important releasing factor for ACTH, acting in conjunction with CRH.

Vasopressin is also released into the brain by several different populations of neurons (see below).

Central actions

Vasopressin released within the brain has many actions:
It has been implicated in memory formation, including delayed reflexes, image, short- and long-term memory, though the mechanism remains unknown, and these findings are controversial. However, the synthetic vasopressin analogue desmopressin has come to interest as a likely nootropic.

Vasopressin is released into the brain in a circadian rhythm by neurons of the suprachiasmatic nucleus of the hypothalamus.

Vasopressin released from centrally-projecting hypothalamic neurons is involved in aggression, blood pressure regulation and temperature regulation.

In recent years there has been particular interest in the role of vasopressin in social behavior. It is thought that vasopressin, released into the brain during sexual activity, initiates and sustains patterns of activity that support the pair-bond between the sexual partners; in particular, vasopressin seems to induce the male to become aggressive towards other males.

In several species, that the distribution of vasopressin and vasopressin receptors in the brain is associated with species-typical patterns of social behavior. In particular, there are differences between monogamous species and promiscuous species in the distribution of vasopressin receptors, and sometimes in the distribution of vasopressin-containing axons, even when closely-related species are compared. Moreover, studies involving either injecting vasopressin agonists into the brain, or blocking the actions of vasopressin, support the hypothesis that vasopressin is involved in aggression towards other males. There is also evidence that differences in the vasopressin receptor gene between individual members of a species might be predictive of differences in social behavior.

**OXYTOCIN** levels rise during the last stages of pregnancy. Stimulation of the cervix relays signals back to the hypothalamus that will increase production and release of oxytocin. Oxytocin will coordinate the contraction of the muscles around the uterus for delivery. If a person has low levels of oxytocin available during pregnancy, labor will be considerably prolonged. This is why the drug PITOCIN (a synthetic oxytocin) is administered to help delivery.

Stimulation of the breasts will send neural signals back to the hypothalamus to increase the release of oxytocin which then delivers milk to the breast for the infant. This is called MILK LETDOWN.

OXYTOCIN is critical for the bonding behavior in females with an infant or with a mate (discussed later). Blocking oxytocin in female rats immediately following delivery prevents the female rat from bonding to the infant.

Other research has shown that OXYTOCIN is important for orgasm in males and females.

**EDITED FROM WIKIPEDIA**

**Actions of oxytocin within the brain**

Oxytocin secreted from the pituitary gland cannot re-enter the brain because of the blood-brain barrier. Instead, the behavioral effects of oxytocin are thought to reflect release from centrally projecting oxytocin neurons, different from those that project to the pituitary gland. Oxytocin receptors are expressed by neurons in many parts of the brain and spinal cord, including the amygdala, ventromedial hypothalamus, septum and brainstem.

- **Sexual arousal.** Oxytocin injected into the cerebrospinal fluid causes spontaneous erections in rats, [12] reflecting actions in the hypothalamus and spinal cord.
• **Bonding.** In the Prairie Vole, oxytocin released into the brain of the female during sexual activity is important for forming a monogamous pair bond with her sexual partner. Vasopressin appears to have a similar effect in males. [13] In people, plasma concentrations of oxytocin have been reported to be higher amongst people who claim to be falling in love. [citation needed] Oxytocin has a role in social behaviors in many species, and so it seems likely that it has similar roles in humans.

• **Maternal behavior.** Sheep and rat females given oxytocin antagonists after giving birth do not exhibit typical maternal behavior. By contrast, virgin female sheep show maternal behavior towards foreign lambs upon cerebrospinal fluid infusion of oxytocin, which they would not do otherwise. [17]

• **Increasing trust and reducing fear.** In a risky investment game, experimental subjects given nasally administered oxytocin displayed “the highest level of trust” twice as often as the control group. Subjects who were told that they were interacting with a computer showed no such reaction, leading to the conclusion that oxytocin was not merely affecting risk-aversion. [18] Nasally administered oxytocin has also been reported to reduce fear, possibly by inhibiting the amygdala (which is thought to be responsible for fear responses). [19] There is no conclusive evidence for access of oxytocin to the brain through intranasal administration, however.

• **Preparing fetal neurons for delivery.** Crossing the placenta, maternal oxytocin reaches the fetal brain and induces a switch in the action of neurotransmitter GABA from excitatory to inhibitory on fetal cortical neurons. This silences the fetal brain for the period of delivery and reduces its vulnerability to hypoxic damage. [22]

• **Certain learning and memory functions** are impaired by centrally administered oxytocin.[12]. Also, systemic oxytocin administration can impair memory retrieval in certain aversive memory tasks. [23]

**Peripheral (hormonal) actions of oxytocin**

The actions of oxytocin are mediated by specific, high affinity oxytocin receptors. The peripheral actions of oxytocin mainly reflect secretion from the pituitary gland.

• **Letdown reflex** – in lactating (breastfeeding) mothers, oxytocin acts at the mammary glands, causing milk to be ‘let down’ into a collecting chamber, from where it can be extracted by compressing the areola and sucking at the nipple. Sucking by the infant at the nipple is relayed by spinal nerves to the hypothalamus. The stimulation causes neurons that make oxytocin to fire action potentials in intermittent bursts; these bursts result in the secretion of pulses of oxytocin from the neurosecretory nerve terminals of the pituitary gland.

• **Uterine contraction** – important for cervical dilation before birth and causes contractions during the second and third stages of labor. Oxytocin release during breastfeeding causes mild but often painful uterine contractions during the first few weeks of lactation. This also serves to assist the uterus in cloting the placental attachment point postpartum. However, in knockout mice lacking the oxytocin receptor, reproductive behavior and parturition is normal. [4]

• **Both sexes secrete oxytocin - what about its role in males?** Males synthesize oxytocin in the same regions of the hypothalamus as in females, and also within the testes and perhaps other reproductive tissues. Pulses of oxytocin can be detected during ejaculation. Current evidence suggests that oxytocin is involved in facilitating sperm transport within the male reproductive system and perhaps also in the female, due to its presence in seminal fluid. It may also have effects on some aspects of male sexual behavior.
SEX HORMONES

The sex hormones play a critical role in our physiology and behavior. The critical sex hormones include Gn-RH (from the hypothalamus), FSH & LH (from the pituitary), and Testosterone (testes) & Estrogen (ovaries). These sex hormones have two major effects:

(1) Activating Effects

The presence of the hormone activates physiology and behavior. The effects are not permanent, the sex hormones must be present at the time and if the sex hormones subside so will the effect. The activating effects of these hormones usually occur at or after puberty, and it does not have a critical period.

Activating Effects on Behavior, Anatomy and Physiology

Why is it that birds sing, nest, mate, and have offspring in the spring? Each spring testosterone increases in the male song bird that activates neurons in the brain for singing (which attracts females), defend territory, and mate. These are activating effects so that if the testosterone disappears that behavior will also go away. So, if you castrate a male song bird there will be no singing, defending territory, or mating. If you ovariectomize a female song bird, they will not display any sexual behavior.

Rats show similar activating effects with the sex hormones testosterone and estrogren.

In this figure male guinea pigs that were castrated dramatically decreased their sexual behavior. However, if you supplement the castrated guinea pigs with testosterone the sexual behavior returns.

Testosterone has less of an effect in activating female sexual behavior. This is because females have fewer testosterone receptors in a critical area for the brain called the medial preoptic nucleus (MPO). The MPO for both males and females is critical for activating sexual behavior and it controls the release of reproductive hormones by using Gn-RH.
In this figure ovariectomized female rats showed almost no sexual behavior measured by the Lordosis Score. However, when those female rats were supplemented with estrogen the sexual behavior returned.

The photograph shows the difference in the distribution of estrogen receptors in the MPO region in a female and male rat hypothalamus. There is a high concentration of estrogen receptors in the female MPO region.

Estrogen activates the receptors in the hypothalamus (MPO) to initiate female sexual behavior. Estrogen is not effective in initiating male sexual behavior because there are fewer receptors for estrogen in the MPO region.

Humans

People had observed that the sexual drive in humans usually occurs at the onset of puberty when testosterone and estrogen levels increase. This suggests that there are activating effects of testosterone and estrogen in humans similar to what has been seen in animal experiments.
An early study by Davidson et al (1979) examined males with a history of low sex drive and when measured also had an abnormally low level of blood testosterone. Davidson divided the subjects into three groups: Control Group was given a placebo and had no change in their sex drive. Experimental Group 1 was given a daily dose of 100 mg testosterone and those subjects reported a slight increase in their sex drive. Experimental Group 2 was given a daily dose of 400 mg testosterone and they reported very significant increases in their sex drive (they didn’t want the experiment to end!).

ONE PERSON’S REPORT ON CASTRATION

http://sherrylanina.tripod.com/castrationeffects.htm

The elimination of testosterone causes a variety of physical and emotional effects in each person. Many of the effects are common, although they do vary from person to person. The effects can be a blessing to those who wanted castration yet devastating to those who don't really want to become a eunuch.

I went without any hormones for more than two years since my castration and can testify to the effects. However, each person is unique and your own effects, particularly regarding changes in weight and hot flashes, may turn out to be very different from mine. I do focus on what I myself have experienced between the time of my castration and the day I started taking estrogen, yet I have included the experiences which I have heard from many others, because not everyone will have the same effects that I had, and some will experience things which I did not.

DECREASED LIBIDO - One of the first things I noticed in the days following my castration was the drastic decrease in my sex drive. I was hoping for this to happen, and it happened quickly.

My sex drive did not go away entirely, but it did decrease to a weak level. I have experienced what most eunuchs have also experienced: my libido is under control. I went from masturbating once daily (sometimes more) pre castration to not at all post castration.

I still have occasional nocturnal erections at night, and less often I even have orgasms in my sleep. About half of these are dry orgasms while the others are accompanied by only a small amount of clear fluid. Otherwise I don't feel aroused unless I want to. Many eunuchs also report being in complete control of their sexuality. If I did want to get an erection I could, but it would take more effort. I don't have erections only because I don't want them.

Eunuchs who do remain sexually active usually have sex much less often, but report that when they do it is more special, and some of their spouses feel the same way. Because the eunuch does not arouse so quickly, he can take more time on the foreplay and afterglow.

INFERTILITY - One thing is certain: castration will make you infertile, and this effect is absolutely irreversible. It is still possible to orgasm and even ejaculate, but your body will no longer produce any sperm. Any ejaculation that does occur will be clear and probably in smaller amounts.

The only way to reproduce after castration is to bank some sperm prior to castration. I opted not to do this, because I do have gender issues to deal with and I am relieved that I don't have to put a wife or any kids through this. Both of my parents were outcasts in school, and I too suffered from outcastism. I don't want to bring any children into this cruel world. Since I can't reproduce the female way, I won't reproduce at all.

FEELING CALM - Four days after my castration I was walking across downtown Philadelphia to meet someone new, and as I walked it seemed that waiting for traffic lights and other little annoyances did not bother me so much. Was this an effect of castration? Six days’ post castration I returned to work. This workday was unusually hectic because it was a Monday and the plant had just installed some new lines but
didn't yet know how to run them smoothly. All of this happened while I still felt some pain where the surgery was done, and yet I still felt so calm when the day was all over. I was definitely feeling the effects of castration and most certainly felt better all the time without testosterone. Ten days’ post castration I felt as a feather floating around everywhere. I just kept feeling better and better. For me the serenity was the strongest of the castration effects, followed by the decrease in libido.

POST SURGERY DEPRESSION? - Many eunuchs who do in fact benefit from castration do experience a temporary depression shortly after their surgery. Many people go through this depression after any surgery. Interestingly I did not experience this at all. I did feel depressed on the fifth day after, but that was because I left Philadelphia that day and was leaving behind several newly met friends, and I usually experience that feeling upon returning home from any overnight vacation. I experienced the same thing five months later when I returned home from a trip to my relatives in Phoenix after meeting some transgendered sisters there, and I also feel this whenever I start driving back home from an electrolysis session in Dallas. These post-vacation depressions do feel stronger since my castration, so I think the lack of testosterone does allow more emotion to surface. I never suffered any depression directly related to castration.

HOT FLASHES? - This definitely varies from person to person. Some eunuchs have written about sweat dripping off of their head at random times, while others seem to have no problem with this. I was one of the lucky ones in spite of not taking any hormones, as I experienced nothing more than feeling a little warm occasionally. I did lower my thermostat a few digress that first summer. Later on I did feel cold a little more easily as my metabolism slowed, and became more sensitive to variations in temperature.

LOSS OF PHYSICAL STRENGTH - I was not expecting this at all because I had little upper body strength to begin with, yet I was noticeably weaker after a few months. Even before castration it often amazed me that all of my male peers seemed to have much more strength than I, and I felt as if they could just push me around as they wished. Now I am definitely weaker them before.

I got into some trouble at work seven months’ post castration when I was expected to do some heavy lifting and found it to be more difficult than before, though I never should have been put in that position anyway because of my obviously small size. Eventually I transferred out of that department and I now work where nobody expects me to lift anything. Any heavy lifting wears me out much more quickly than it used to, and I also have difficulty with opening jars.

The more muscular you were before castration, the more you will lose after castration. As testosterone levels drop, muscle mass does decrease.

DECREASED ENERGY - In addition to losing physical strength, a eunuch will often experience a decrease in metabolism and energy. Doing heavy lifting and other efforts do wear me out more quickly than before. I also feel chilly more easily than before and have become more sensitive to small changes in temperature.

WEIGHT GAIN? - The few sources of information about castration that I could find indicated that eunuchs tended to put on some pounds after castration as energy decreased and metabolism slowed. I did experience the decrease in metabolism and energy, but my appetite seems to have decreased with it. Consequently, I have actually lost a few pounds since castration. Before castration I used to average around 130, and I weighed 134 at the end of 1998. But I did lose a few pounds after castration, and now I average around 125. The amount of weight gain will vary from person to person.

BODY HAIR - Many eunuchs have reported that their body hair became softer and finer after castration. This is something else that varies from person to person. I hoped for mine to decrease, but this is one effect that I have not been fortunate with. I have noticed some decrease in body hair density, though not as much as I had hoped for, and it has been more than two years now. Still, I am passable as
long as I shave the hairs on my hands and wrists, as my body hair is still above the female average, but I have seen women with more arm hair than what I have. Even those who do experience significant thinning of body hair usually experience little or no change in facial hair density. My own facial hairs remained as dense and numerous as before, but they did seem to grow more slowly after castration. Underarm and pubic hairs did not change with castration either. I am currently getting electrolysis to lose the facial hairs, and I hope that eventual estrogen replacement will thin out my body hairs some more.

PHYSICAL APPERANCE - As testosterone levels drop, muscle mass either fades away or turns into fat, and some fat redistribution occurs. The more muscular you were before castration, the more you will lose. I didn't have much to lose, and I lost some anyway. My limbs do appear smoother, and my friends in my PFLAG group tell me that my arms do appear feminine. My hips appeared more flabby a few months after castration, and I think that was the first purely physical effect that I noticed. However, the body will not feminize to the same extent as if you were taking estrogen. Bone size does not shrink, but bone density can decrease.

HEAD HAIR - I started to lose my hair when I was only 19, and this continued unabated until my castration at age 31. Since my castration I don't see so many hairs on the shower floor anymore, and the elimination of testosterone has prevented further hair loss, but I have had practically no regrowth of all that I lost before castration and will certainly need a hair replacement system for transition. Hairs not affected by baldness have grown thicker and longer. If you did not suffer hair loss before castration, it is very unlikely you will ever go bald after castration unless you take testosterone replacements.

Castration is a bad idea for anyone merely seeking to treat or prevent hair loss because it causes so many other effects that the vast majority of men dislike. Using Finasteride or Minoxidil can arrest most cases of MPD without causing the effects of castration.

VOICE - Contrary to popular belief, the voice does not rise after castration. Not even female hormones will raise the voice (although male hormones will lower the voice), and even voice surgeries have been mostly unsatisfactory for the male to female transsexual. Non transgendered men seeking castration don't need to worry about their voice because it will not change, but transsexuals and transgenderists will need to retrain their voice to sound more feminine.

SHRINKING GENITALS? - I personally have not noticed any shrinkage of my own genitals, but many eunuchs have reported that their penis did shrink after castration. It seems that those who have no erections at all after castration were most likely to notice genital shrinkage.

MENTAL EFFECTS - Toward the end of 1999 I noticed some decline in my memory and concentration, and I also became disoriented more easily. Many eunuchs and post-menopausal women have also reported similar effects. Upon starting a low dose of estrogen in November 2001, my memory has improved to what it was before castration.

HEALTH RISKS - Many eunuchs not on hormones experience decalcification or loss of bone density. Males tend to start out with stronger bones (than females) before castration, but once hypogonadal they can lose bone density as any post-menopausal woman. The younger a person is castrated, the greater the risk.

Some sources cite increased risk of heart disease, stroke, and digestive problems, but I have seen disagreement among different sources. While there may be an increased incidence of such problems in eunuchs and post-menopausal women, the only thing I've seen proven without a doubt is the increased risk of osteoporosis. Eunuchs may wish to study the issues of post-menopausal women as they face many of the same issues.

Anyone considering castration and not planning on taking any hormones afterwards needs to consider the possible risks of hypogonadism and determine if the benefits of castration for them will outweigh the
disadvantages. I was aware of the risks beforehand and I determined that I wanted the impotence, serenity, and other effects of castration badly enough to take these chances. To date I have not had any bone density scan done because even if I did find a problem I still would not take testosterone replacement since I am too happy without male hormones.

UPDATE: On November 6th, 2001, with the help of a certain therapist, a doctor in my area has now started me on a low dose of Estradiol. I still retain the benefits of castration such as reduced stress, impotence, and feeling calm. I felt a lot better after castration, and now I feel even better on estrogen.

My cholesterol levels have remained at healthy levels. My blood pressure was normal and healthy before castration, averaging 120/80, and this decreased after castration. Now two years post castration my blood pressure averages around 100/70. I strongly suspect that castration did reduce my blood pressure, though I am not sure if it was a direct reaction or if because I was emotionally antagonistic to testosterone (please do not get castrated just to reduce high blood pressure, there are less drastic ways to treat that). I do not smoke or drink, so I feel that I don't need to worry too much about the other possible risks besides bone density loss.

I did start taking 1200mg Caltrate daily starting the week after my castration. Some eunuchs perform weight bearing (not weightlifting, but walking and running) exercises to help maintain bone density.

If there are health risks, there are also a few trade-offs. Once the testicles are removed, it is impossible to develop testicular cancer. Castration also decreases the risk of prostate cancer, and some men have an orchiectomy performed to treat this cancer. The younger a person is castrated, the lower their risk of prostate cancer. I had my orchiectomy done at age 31, so my odds of ever getting prostate cancer are now astronomical. Best of all, my stress levels have been reduced after I eliminated the testosterone from my body and I think that decreases the chances of a variety of ailments.

Curiously I did experience an increase in dental cavities the year after my castration. I am not sure that castration had anything to do with that, though it's possible. For now, I believe that was a random fluctuation in dental cavities which may have happened to me anyway were I not castrated.

In summary castration causes a variety of effects. For those who wish castration many of the effects such as impotence and feeling calm can be beneficial. If you are thinking about castration, I would urge you to consider all of the effects and whether or not you really want this for the rest of your life. Castration is a minor procedure, but it is a permanent one and is something you can never change your mind on. You need to proceed with caution.

(2) Organizing Effects

Organizing effects occur when hormones have long lasting or permanent changes in anatomy, physiology, and behavior that occur early in life (i.e. the changes caused by sex hormones occur early in development). In addition, the organizing effects of these hormones have a CRITICAL PERIOD, a defined period when the hormone can make the physiological changes and once the early period of development is passed, sex hormones can no longer have a permanent effect.

ORGANIZING EFFECTS OF REPRODUCTIVE HORMONES

One of the most basic observations we make about humans is that males and females are physically and behaviorally different. How do these physical differences occur? What about behavior? Many researchers believe that male and female behavior is determined by cultural factors - sex roles. However, the influence
of biological/genetic factor may also play an important role. **This section will examine the distinct differences between males and females specifically in the release of their reproductive hormones, sexual development, and differences in the brain & behavior.**

**CYCLIC VERSUS NONCYCLIC**

One of the distinct differences between males and females are in the pattern in which they release their reproductive hormones from the hypothalamus and pituitary. The reproductive hormone from the hypothalamus is **GONADOTROPIN RELEASING HORMONE (Gn-RH)**. The reproductive hormones released from the pituitary are **FOLLICLE STIMULATING HORMONE (FSH)** and **LUTENIZING HORMONE (LH)**.

Puberty begins when the neurons in the hypothalamus that contain Gn-RH mature and start releasing the hormone into the blood vessels. Gn-RH flows through the blood vessels to the pituitary and stimulates the cells to release **FSH & LH**. This starts the reproductive cycle.

Diagram of a male shows the blood concentrations of testosterone (T) and Anti-Mullerian Hormone (AMH). Testosterone levels are high before birth and do not increase again until puberty when the Gn-RH neurons in the hypothalamus mature and become active. Anti-Mullerian Hormone remains high before birth through childhood and then decreases at puberty.

Males and females differ in the way these hormones are release by the neurons in the hypothalamus. For females, the neurons in the hypothalamus that contain Gn-RH become very active approximately once a month that starts the reproductive cycle, causing an increase of circulating estrogen and progesterone and eventually the ovaries producing an egg that can be fertilized. **So females have a CYCLIC PATTERN of reproductive hormones.** The Gn-RH neurons in the male hypothalamus appear to release Gn-RH all of the time since there is a constant production of testosterone and sperm, so that there is no cyclic pattern. In reality, researchers have found that males produce a very fast cycle of release of about 90 minutes. **However, we will still refer to males as having a NONCYCLIC PATTERN of reproductive hormones.**

Diagram illustrates the cyclic release of Gn-RH and LH in a female rat.

When the Gn-RH neurons in the hypothalamus get too old they will eventually stop releasing the hormone. **This is onset of MENOPAUSE.** Unfortunately, these neurons don’t shut down easily or all of them together at the same time. This is why there are so many side effects associated with menopause (e.g. hot flashes).
Diagram shows the decreasing levels of testosterone in men and estrogen in women with age. The decrease in these hormones leading to menopause is due to the reduced activity of Gn-RH neurons in the hypothalamus.

The full description of the reproductive hormones and their function are described in the diagrams below.

**MALES**

1. Release Gn-RH from the MPO of the hypothalamus in a **noncyclic** pattern.
2. Gn-RH activates cells in the anterior pituitary to release the hormone FSH and LH.
3. FSH activates Sertoli Cells in the testes to begin spermatogenesis.
4. LH activates Leydig Cells in the testes to release testosterone.

**FEMALES**

1. Release Gn-RH from the MPO of the hypothalamus in a **cyclic** pattern.
2. Gn-RH activates cells in the anterior pituitary to release the hormone FSH and LH.
3. FSH activates follicle cells to grow and release estrogen.
4. LH triggers ovulation in the follicle and stimulates the corpora lutea to release progesterone.
ORGANIZING EFFECTS ON SEX ORGAN DEVELOPMENT

The 23rd pair of chromosomes are called the sex chromosomes which are responsible for the genetic differences between males and females. Females have two XX chromosomes, males have one X and a much shorter Y chromosome. The presence or absence of this Y chromosome is a critical factor in sexual development.

Early during development the fetus has the potential to develop three sets of sex organs.

1. Gonads have a medulla and a cortex that can develop into either a testes or ovaries.
2. Wolffian System - male reproductive system, includes the epididymis, vas deferens, seminal vesicles, and prostrate.
3. Mullerian system - female reproductive system includes the fallopian tubes, uterus, and inner vagina.

MALE XY CHROMOSOME - The Y chromosome contains the SRY GENE that codes for a protein called TESTES DETERMINING FACTOR. The gene causes cells to produce and secrete TDF which stimulates the medulla of the gonads to grow. Therefore, there is a large medulla and small cortex and the gonads have now developed into the testes. The medulla secretes the hormones testosterone and Mullerian-inhibiting hormone (often called Anti-Mullerian Hormone). Both testosterone and estrogen are steroid hormones that are synthesized from cholesterol and are small and fat soluble which allows them to enter into cells. When testosterone levels increase during the “critical period” in males, testosterone enters into the cells. The enzyme AROMATASE breaks down testosterone into both dihydrotestosterone (DHT) and estradiol (same as estrogen, yes the female hormone!!). Depending on the cell and species, receptor proteins for one or both of these metabolites are located in the cytoplasm, which allows them to enter the nucleus. This affects the DNA and causes the cell to increase protein synthesis for growth and development. If these changes do not occur the Wolffian system will automatically degenerate. The Mullerian inhibiting hormone activates receptors on the cell membrane (metabotropic receptors) that eventually stops protein synthesis and causes degeneration of the Mullerian system. Due to the small cortex, only a little estrogen is released. Following this short period of development, the testes will stop producing the testosterone and Anti-Mullerian Hormones. In the end the male has all of his reproductive organs with the testes and Wolffian system.

FEMALE XX CHROMOSOME - The XX chromosomes do not contain the SRY gene for TESTES DETERMINING FACTOR. Without TDF the cortex of the gonads is preprogramed to grow. Therefore, for females (XX) there is a large cortex and small medulla and the gonads have now developed into the ovaries. The cortex secretes the hormone estrogen. Due to the small medulla, no testosterone or Anti-Mullerian Hormone is released. One of the interesting features is that the estrogen could promote development of the Wolffian system, because it is actually estrogen that combines with the receptor in males. However, in females the blood contains high levels of alpha-fetoprotein that combines with the estrogen, so now estrogen cannot enter into the neurons. Therefore, without activating the receptors the Wolffian system is now preprogrammed to degenerate. Since there is no Mullerian inhibiting hormone the Mullerian system will develop. Following this short period of development, the ovaries will stop producing the estrogen. In the end the female will have all of her sexual organs with the ovaries and Mullerian system.
**MALES**: TESTOSTERONE IS SMALL & FAT SOLUBLE SO IT ENTERS THE WOLFFIAN CELLS. TESTOSTERONE IS BROKEN DOWN INTO ESTROGEN AND IT IS THE ESTROGEN THAT COMBINES WITH THE RECEPTOR TO ENTER THE NUCLEUS AND AFFECT THE DNA.

**FEMALES**: IF ESTROGEN ENTERS THE WOLFFIAN CELLS, IT COULD DIRECTLY ACTIVATE THE SAME RECEPTORS AND CAUSE DEVELOPMENT OF THE WOLFFIAN SYSTEM (RED BROKEN ARROW). NOT GOOD FOR FEMALES. ESTROGEN IS BLOCKED FROM ENTERING THE CELLS BECAUSE IT BINDS TO ALPHA-FETOPROTEIN IN THE BLOOD WHICH IS ONLY FOUND IN DEVELOPING FEMALES.
WHAT HAPPENS IF THERE ARE CHROMOSOMAL ABNORMALITIES THAT INTERFERE WITH THE NORMAL PATTERN OF SEXUAL DEVELOPMENT?

**TURNER’S SYNDROME - XO chromosome pattern.**

Turner syndrome (TS) is a chromosomal condition that describes girls and women with common features that are caused by complete or partial absence of the second sex chromosome. TS occurs in approximately 1 of every 2,000 live female births and approximately 10% of all miscarriages.

At the basic level, the missing genetic material keeps the female body from maturing naturally. Turner syndrome is variable and no female is exactly the same. There are a few available treatments for TS and our Society is currently working with researchers to develop additional treatment options and to find out more insights.

**Causes**

Turner syndrome occurs when all or part of one of the X chromosomes is lost before or soon after the time of conception. It is not connected to or passed on from either parent and there is nothing a person can do to increase or decrease the chance of this happening.

**Diagnosis**

A female can be diagnosed with TS before birth with an amniocentesis or anytime during their life with a specific blood test called a karyotype. A karyotype shows the number and visual appearance of the chromosomes as found in the cells of a person.

Turner syndrome is usually diagnosed before or during teen years when one would expect to see the signs of puberty that TS may prevent. Diagnosis can occur in any stage of life.
Signs and Symptoms (may include any number of the following):

- In some TS individual there is a partial amount of the complimentary X chromosome and their symptoms will be much less.
- Without a complimentary X on the chromosome (XO), the ovaries fail to develop - other sexual organs develop normally. As a result, the person is usually sterile.
- Without ovaries there is no estrogen produced and there is no puberty. So they are usually short and immature looking.
- Normal intelligence
- Noncompetitive & Nurturing
- Difficulty with spatial-temporal processing (imagining objects in relation to each other)
- Difficulty with nonverbal memory and attention
- A variety of physical & physiological characteristics

See Figure below.

Video of women talking about living with Turner’s Syndrome.
https://www.youtube.com/watch?v=8ObFJ3DnV04
KLINEFELTER SYNDROME - XXY CHROMOSOME PATTERN

The syndrome was named after Harry Klinefelter, who first described the condition in nine men in 1942, at Massachusetts General Hospital.

Klinefelter syndrome is a genetic disorder that affects males. Klinefelter syndrome occurs when a boy is born with one or more extra X chromosomes. Most males have one Y and one X chromosome. Having extra X chromosomes can cause a male to have some physical traits unusual for males.

Many men with an extra X chromosome are not aware that they have it, and they lead normal lives. Klinefelter syndrome occurs in about 1 out of 450 males.

What causes Klinefelter syndrome?

About 60% of embryos with Klinefelter syndrome do not survive the fetal period. Most commonly, a male with Klinefelter syndrome will be born with 47 chromosomes in each cell, rather than the normal number of 46. The extra chromosome is an X chromosome. This means that rather than having the normal XY combination, the male has an XXY combination. Because people with Klinefelter syndrome have a Y chromosome, they are all male. The presence of an extra X chromosome in males most often occurs when the genetic material in the egg splits unevenly. But it can also occur when the genetic material in the sperm splits unevenly. Even though Klinefelter syndrome is a genetic disorder, it is not passed down through families. So, parents who have a child with Klinefelter syndrome are not any more likely than other couples to have another child with the condition. Males with more than one additional extra X chromosome, such as 48, XXXY, are usually more severely affected than males with 47, XXY.

What are the symptoms?

Many men who have Klinefelter syndrome do not have obvious symptoms. Others have sparse body hair, enlarged breasts, and wide hips. In almost all men the testicles remain small. In some men the penis does not reach adult size. Their voices may not be as deep. They usually cannot father children. But they can have a normal sex life.

Some boys with Klinefelter syndrome have language and learning problems.
How is Klinefelter syndrome diagnosed?

Klinefelter syndrome usually is not diagnosed until the time of puberty. At this point, the boy's testicles fail to grow normally and you may start to notice other symptoms.

Klinefelter syndrome can be detected before birth (prenatally) through genetic tests on cells collected from amniocentesis or chorionic villus sampling (CVS). But this is not routinely done.

In adult men, lab tests in addition to a karyotype may be done, such as hormone tests or a semen analysis, if Klinefelter syndrome is suspected.

How is it treated?

Males with Klinefelter syndrome can be given testosterone, a hormone needed for sexual development. If treatment is started around the age of puberty, it can help boys have more normal body development.

Testosterone is given by injection or through a skin patch or gel. The treatment usually continues throughout a man's life but does not help infertility.

Speech therapy and educational support can help boys who have language or learning problems.

If a man with Klinefelter wants to have children, he may be able to have his sperm collected through testicular sperm extraction (TEST). During TEST, sperm are obtained using a thin needle inserted into the testicle or through a small cut made in the testicle. Normal sperm are identified and then used for in vitro fertilization.
47, XYY Male

What is 47, XYY Syndrome

XYY syndrome is a chromosomal disorder of the sex chromosome, wherein an additional copy of the Y chromosome is present. This is a condition that occurs only in the male population and is characterized by developmental delays and disabilities in learning, motor movements, emotional and behavioral difficulties.

47, XYY Syndrome Symptoms

There are not very many symptoms that are visible and clearly point to the presence of the XYY syndrome. However, based on the symptoms given below, a physician may be able to determine, whether an individual is afflicted with the XYY syndrome.

- Most of the males with XYY syndrome have no physical abnormalities. They may be of normal weight and size at birth, but grow rapidly in childhood. The size differences become apparent after the age of five or six, and results in an average height of about 6 feet, 3 inches by adulthood. Hence the men with XYY syndrome tend to be taller than the average male population.
- Muscle movement and their coordination are lacking. Hence the individuals may have an awkward gait or posture and may walk clumsily.
- Most of the individuals with XYY syndrome are fertile and have normal sex lives. However, in some cases, the hormone responsible for sperm production may have some defects resulting in decreased sperm count and production as well as infertility.
- Males with XYY syndrome have normal intelligence but may be the intelligence may be lower than their siblings.
- They have learning disabilities and delays in speech development. Also, they may not be able to process information or understand what is being said to them as fast as others of the same age.
- Males with XYY syndrome are at an increased vulnerability for behavioral problems. Childhood may bring increased incidences of temper tantrums and hyperactivity. Adulthood may be characterized by behavior that is high in impulsivity or poor impulse control and emotional immaturity. In some cases, they may be psychotic or overly aggressive.

47, XYY Syndrome Causes

People normally have 46 chromosomes in each cell. Two of the 46 chromosomes, known as X and Y, are called sex chromosomes because they help determine whether a person will develop male or female sex characteristics. Females typically have two X chromosomes (46, XX), and males have one X chromosome and one Y chromosome (46, XY).

47, XYY syndrome is caused by the presence of an extra copy of the Y chromosome in each of a male's cells. As a result of the extra Y chromosome, each cell has a total of 47 chromosomes instead of the usual 46. It is unclear why an extra copy of the Y chromosome is associated with tall stature, learning problems, and other features in some boys and men.
It occurs in 1 out of 1,000 male births.

**Treatment for XYY syndrome**

There is no cure for XYY syndrome. However, the symptoms of XYY syndrome can be treated.

- Physical and speech therapy may improve the muscle tone and speech.
- Behavioral therapy will help in behavior modification.
- Prenatal testing can be done to determine whether the fetus is affected by the disorder, in case there is a high likelihood of that happening, like the father being an XYY syndrome candidate.

**ANDROGEN INSENSITIVITY SYNDROME (AIS)** - see photograph.

These are genetic males (XY), however, their gene for testosterone/androgen receptors is completely nonfunctional, so they don’t have any receptors for androgens/testosterone (androgens and testosterone are the same). Therefore, testosterone cannot perform its normal function during development. This condition is called **COMPLETE ANDROGEN INSENSITIVITY SYNDROME (CAIS)** - the human is completely insensitive to androgen. External genitals develop along purely female lines.

Other individuals with **ANDROGEN INSENSITIVITY SYNDROME** have a gene that is partially defective so that they produce fewer than normal testosterone receptors. This condition is called **PARTIAL ANDROGEN INSENSITIVITY SYNDROME (PAIS)** - there is some sensitivity to testosterone because there are some receptors, but less than normal. How the genitals develop depends on how many testosterone receptors that person produces. The individual may look completely male or female, or neither (in between). Some may have a slightly enlarged clitoris while others have a penis which is almost fully formed.

Approximately 1 in every 20,400 male births has AIS. Complete AIS (CAIS) is believed to be more common than Partial AIS (PAIS).

**Let’s look at what happened during development.**

- Since this is a genetic male the SRY gene does its job to produce Testes Determining Factor that will cause the gonads to develop into testes.
- The testes will secrete its two hormones testosterone and Anti-Mullerian Hormone.
- The testosterone enters into the Wolffian cells, but since there are no receptors it can’t turn on the DNA. As a result, the Wolffian System degenerates.
- Anti-Mullerian Hormone activates the receptors of the Mullerian cells to turn off the DNA as in any male. As a result, the Mullerian System degenerates.
- The testes remain, but are underdeveloped and since there is no scrotum for them to descend into,
they remain up in the body. Since the testes are underdeveloped there is no sperm production.
• The external genitalia look similar to that of females, but there are no true labia or clitoris and the uterus is underdeveloped.
• They will not have a menstrual cycle or have puberty.
• They are usually raised as a female.

Eden Atwood (January 1969 —) is an American jazz singer.

She is outspoken about Androgen Insensitivity Syndrome and intersex issues, working with national organizations and discussing her condition openly in liner notes on the Waves album. Eden lives in Missoula, Montana and has an adopted son with former husband Bruce Anderson. She now also works as a music teacher and all of the kids love her.

Videos of a women talking about their experiences with AIS.
https://www.youtube.com/watch?v=yuXL-3eoB-o
https://www.youtube.com/watch?v=ETIxoQGVjos

PROGESTIN AND ADRENAL INDUCED HERMAPHRODITISM

In the 1940s a synthetic steroid drug (progestin) was used to prevent miscarriages. The drug was not effective. However, because it had the properties of testosterone the progestin had the side effect of masculinizing the external genitalia of the developing fetus in females. Newborn females had a very large clitoris and there was a fusing of labia to form a scrotum. All the children had normal internal female sex organs.

Some of these progestins included: ethisterone, northynodrel (Enovid), norethisterone (Norlutin), medroxyprogesterone acetate (Provera), norethisterone acetate (Norlutate), and dydrogesterone (Duphaston) in 1962.

CONGENITAL ADRENAL HYPERPLASIA (CAH) is the most common cause of induced hermaphroditism. This occurs when the adrenal gland of the mother causes high levels of steroid hormones to be produced during pregnancy. Poor cortisol production is a hallmark of most forms of CAH. Inefficient cortisol production results in rising levels of ACTH, which in turn induces overgrowth (hyperplasia) and over activity of the
steroid-producing cells of the adrenal cortex. The adrenal cortex releases abnormally high levels of testosterone and aldosterone. Yes, the adrenal gland does produce testosterone! Usually, it is not enough to have much effect on the developing fetus. The defects causing adrenal hyperplasia are congenital (i.e. present at birth).

The most obvious sign of classic congenital adrenal hyperplasia in girls is often abnormal-appearing genitals that look more male than female, which may include an enlarged clitoris — a condition called ambiguous external genitalia. Other signs and symptoms in girls also reflect exposure to higher levels of male sex hormones (androgens) while in the womb.

The condition is not typically as easily seen in baby boys, although some affected male infants have an enlarged penis.

Signs and symptoms of classic congenital adrenal hyperplasia in infants include:

- Ambiguous genitalia in girls
- Enlarged penis in boys
- Poor weight gain
- Weight loss
- Dehydration
- Vomiting

Signs and symptoms of classic congenital adrenal hyperplasia in children and adults include:

- Very early puberty
- Rapid growth during childhood, but shorter than average final height
- Irregular menstrual cycles in women
- Infertility in women and men

Organizing Effects on the Brain

In the rat distinct hypothalamic nuclei exhibit distinct male-female differences in terms of neural organization. Roger Gorski (1977, 1978) demonstrated that a portion of the medial preoptic nucleus (MPO) called the sexually dimorphic nucleus is different in size between male and female rats & hamsters.

The MPO in males is 7-8 times larger in volume than in females. The photograph below shows the difference in size of the MPO in a normal male (left) versus a normal female (middle) rat. It is identified as SDN-POA in the figure which stands for sexually dimorphic nucleus of the preoptic area, we will just call it the MPO.
It was hypothesized that the presence of testosterone early in development for males is the reason for the size difference. Testosterone activated the receptors to change the DNA to enhance protein synthesis, and as a result the size and number of neurons in the MPO increased. When male rats were castrated at birth to reduce the exposure to testosterone there was a 50% reduction in volume of the MPO.

In addition, when newborn female rats are injected with testosterone at birth the MPO grows much larger than that of normal females (see photograph on the right). These experiments clearly demonstrated that the presence of testosterone early in development affects the size of the MPO in the brain (organizing effects).

Organizing Effects on Physiology

The onset of puberty occurs when the neurons mature in the hypothalamus and start secreting Gonadotrophin Releasing Hormone (GN-RH) from the hypothalamus into the hypothalamic-hypophyseal portal vessels. Gn-RH causes cells in the pituitary to release FSH and LH. As we discussed before the release of Gn-RH, FSG, & LH is cyclic in females and noncyclic in males, one of the major physiological differences between the sexes.

One of the important discoveries was that the Gn-RH neurons are located in the MPO! Males have a large MPO and noncyclic release of Gn-RH. The larger MPO is necessary because males release Gn-RH all of the time, release FSH & LH all of the time from the pituitary, and releases testosterone and produces sperm form the testes all of the time. Females have a small MPO and a cyclic release of Gn-RH. Females don’t need a large MPO because they release Gn-RH, FSH & LH, estrogen, progesterone, and ovulate cyclically.

Therefore, it was hypothesized that the cyclic versus noncyclic release of Gn-RH from neurons in the MPO is determined by the presence or absence of testosterone early in development.

MALES CASTRATED AT BIRTH resulted in a small MPO and cyclic release of Gn-RH (just like a female).

FEMALES INJECTED WITH TERSOSTERONE AT BIRTH resulted in a large MPO and noncyclic release of Gn-RH (just like a male).

These results demonstrate that testosterone has organizing effects on the MPO and the release of Gn-RH.

Organizing Effects on Behavior

Rats and hamsters have stereotypical male and female sexual behaviors.

MALE SEXUAL BEHAVIOR: approach female, sniff and lick genitals, mount, intromission, pelvic thrusting, and ejaculation.

FEMALE SEXUAL BEHAVIOR: sniff genitals of male, dart about, wiggle ears, and lordosis (this posture exposes vagina and supports weight of male rat while he is mounting).

If you lesion the MPO in either a male or female rat, they will no longer display any sexual behavior. Therefore, the MPO is critical for sexual behavior.

These differences in male-female sexual behavior are because the sexual behavior programs that are
located in the MPO of the hypothalamus are structurally different. This can be seen by the differences in the number and concentration of receptors for estrogen and testosterone in the MPO region described previously. Those pictures are reproduced below.

**MALE MICE HAVE A MUCH HIGHER CONCENTRATION OF TESTOSTERONE RECEPTORS IN THE MPO AREA THAN THAT OF FEMALE MICE. THIS EXPLAINS WHY TESTOSTERONE HAS A GREATER EFFECT ON INITIATING MALE SEXUAL BEHAVIOR.**

Therefore, it was hypothesized that the presence or absence of testosterone early in development could have an organizing effect in determining the type of sexual behavior a rat will display.

**MALE RATS CASTRATED AT BIRTH RESULTS IN:**

- **FEMININIZATION**-acquired female characteristics.
  - Small MPO
  - Cyclic release of Gn-RH
  - Displays female sexual behavior

- **DEMASULINIZATION**-lost the normal male characteristics
  - Lost the large MPO
  - Lost the noncyclic release of Gn-RH
  - Lost male sexual behavior

**FEMALE RATS INJECTED WITH TESTOSTERONE AT BIRTH**

- **MASCULINIZATION**-acquired male characteristics.
  - Large MPO
  - Noncyclic release of Gn-RH
  - Displays male sexual behavior

- **DEFEMININIZATION**-lost the normal female characteristics
• Lost the small MPO
• Lost the cyclic release of Gn-RH
• Lost female sexual behavior

HOMOSEXUAL BEHAVIOR

The previous rodent studies demonstrated that the presence or absence of testosterone early in development can determine the type of sexual behavior a rat will perform as an adult. Is this relevant to Human Behavior? All studies to date have not shown a difference in the levels of testosterone or estrogen in adult heterosexuals versus homosexuals. Therefore, the alternative hypothesis is that different concentrations of steroid hormones early in development causes differences in the development of the hypothalamus, especially the MPO region. Could a male exposed to low levels of testosterone cause the MPO to develop smaller than normal predisposing the person to become a male homosexual? Could a female exposed to higher concentrations of testosterone cause the MPO to develop larger than normal predisposing that person to become a female homosexual?

One of the first to examine this was done by Gladue et al. (1984). When ESTROGEN is administered to an adult female, the estrogen feedback to the MPO to increase release of Gn-RH, causing the release of LH from pituitary. This increase in LH in response to an injection of estrogen in females is called the LH surge and the process is called the Estrogen Test.

**Females Injected with Estrogen > MPO releases Gn-RH > Pituitary releases LH (LH surge)**

The ESTROGEN TEST does not work in males because they release Gn-RH and LH at high levels all of the time.

**Males Injected with Estrogen > MPO no change in GN-RH > No LH surge**

Gladhue was interested in comparing the ESTROGEN TEST results between male heterosexuals (no LH surge) with male homosexuals (possible LH surge?). If male homosexuals have an LH surge in response to estrogen, this would suggest that their MPO is structurally different than male homosexuals.

The ESTROGEN TEST showed that male homosexuals responded with a surge half way between males and females. In addition, when this was more closely examined the male homosexuals could be separated into two groups; one group responded with no LH surge like any heterosexual male and the other group had an LH surge that was similar to that of females. This study suggests that for male homosexuals that had no LH surge that the psychological and social factors are the main reasons for their homosexuality. For those male homosexuals that had an LH surge then psychological, social, and biological factors might contribute to their becoming homosexual. That biological factor might be that testosterone was low early in development and MPO remained small.

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A neuroendocrine component, the positive estrogen feedback effect, thought to be related to sexual orientation and, indirectly, to sexual differentiation, was evaluated in healthy, noninstitutionalized research volunteers. Men and women with a lifelong heterosexual orientation and men with a lifelong homosexual orientation were administered an estrogen preparation known to enhance the concentration of luteinizing hormone in women but not in men. The secretory pattern of luteinizing hormone in the homosexuals in response to estrogen was intermediate between that of the heterosexual men and that of the women. Furthermore, testosterone was depressed for a significantly longer period in the homosexual men than in the heterosexual men. These findings suggest that biological markers for sexual orientation may exist.
Now the question is whether male homosexuals have a different MPO from that of heterosexual males? The first to examine this was Swaab and Hoffman (1988) who found that the MPO of homosexual men was significantly smaller than that of heterosexual men.


LeVay (1991) examined MPO in 6 females; 16 heterosexual males (6 died of AIDS); 19 male homosexuals (all died of AIDS). LeVay examined the volume of several nuclei in the MPO area and found one significant difference in area INAH-3.


Although there are average differences in the size of INAH-3 between females, males, and male homosexuals, there is significant overlap in the overall distributions. If you look at the distribution of male homosexuals you can see that some homosexual males have an INAH-3 as large as any heterosexual male. We might conclude that those male homosexuals were influenced by psychological and social factors. Other male homosexuals have an INAH-3 that is significantly smaller like that of most females so that we might suggest that their homosexuality was influenced by psychological, social, and biological factors.

As you can see that having a small INAH-3 does not mean that you will automatically become a male homosexual. When you look at the distribution of male heterosexuals some of them have an INAH-3 just as small as any female, yet they are not homosexual. So INAH-3 size does not automatically determine your sexual orientation. It is only one small factor, so that other nuclei, neurotransmitters, and receptors might be involved that cannot be measured by the size of a nucleus. There is much that we need to research on this issue and do not underestimate the influence of psychological can social factors.
NEUROBIOLOGY OF STRESS

Stress has been an integral part of Psychology since its origins. Just go to the PSYCHOLOGY isle in a bookstore and you will see that most of those books address stressful situations in your life. Anxiety, depression, relationships, dealing with your kids, job, self-image the list goes on and on. When you add to that the number of medications on the market dealing with stress and you can say that stress keeps psychologists employed. That is why the topic of STRESS is such a central issue. So, what is stress and in this course we will focus on the biology.

**Stress is the psychological & physiological response to perceived challenges & threats.** There are two basic forms of stress.

- **Eustress** is the good form of stress (usually mild)
  - This type of stress is challenging, motivating, enhances learning and creativity, we learn to better cope with stress, it is exciting and fun. For example, going on a roller coaster is fun for many and it initiates a stress reaction. Also, without a little stress you would not be motivated to study for the exam. We also find that mild stress gets your brain to learn and perform better.
  - Researchers found that mildly stressed newborn rats became healthier, smarter, & lived longer. Who wouldn’t want that!

- **Negative Stress** is usually severe or prolonged and results in negative consequences.
  - When the stress is too great there is a failure to cope leading to physiological & psychological problems.
  - This is how psychologists make money! This lecture will focus on the negative aspects of stress.

There are a number of negative consequences associated with too much stress and the inability to cope.

- **DEPRESSED IMMUNE SYSTEM**-the stress hormone cortisol acts to depress immune function which makes us more susceptible to colds & infection.
- **HYPERTENSION**-an overactive sympathetic division increases blood pressure. When the sympathetic division becomes too active due to stress a new set point of baseline for you blood pressure is established creating chronic high blood pressure. 63 million in US have hypertension resulting in 32,000 deaths each year.
- **STROKE**-high blood pressure is a key risk factor for stroke. High blood pressure can cause intracerebral hemorrhage or blood leakage into the brain. In addition, high blood pressure can damage to blood vessels which can start the process that can lead to a stroke.
- **HEART DISEASE**-stress hormones like cortisol release the fatty acids from the liver into the blood to use for energy. However, if you do not use those fatty acids during that stressful time, you might eat potato chips to cope with stress, the fatty acids can collect around the heart. Combine that with high cholesterol and you could get heart disease.
- **FATIGUE & EXHAUSTION**-I am sure we have all experienced this.

**HANS SELYE-GENERAL ADAPTATION SYNDROME**

Scientist Hans Selye (1907-1982) introduced the General Adaptation Syndrome model in 1936 showing in three phases what the alleged effects of stress has on the body. Before Has Selye’s General Adaptation
Syndrome people couldn’t conceive that stress, especially psychological stress, can have a physical effect on the body. Stress causes the body to react in a series of stages that if not adequately addressed can lead to physical consequences.

**ALARM REACTION STAGE**

Your body first reacts to the stress. The hypothalamus activates the sympathetic division of the autonomic nervous system so there is an increase in heart rate, body temperature, blood pressure, and stops digestion when blood moved from the gut to the muscles. In addition, the hypothalamus initiates the stress hormone response where Corticotrophin Releasing Hormone is released from the hypothalamus into the pituitary, cells in the pituitary release ACTH, and then the adrenal cortex releases cortisol and corticosterone. These are all of your classic stress hormones.

At this stage everything is working as it should – you have a stressful event, your body alarms you with a sudden jolt of hormonal changes, and you are now immediately equipped with enough energy to handle it.

**RESISTANCE STAGE**

The body shifts into this second phase with the source of stress being possibly resolved. Homeostasis begins restoring balance and a period of recovery for repair and renewal takes place.

Stress hormone levels may return to normal but you may have reduced defenses and adaptive energy left.

If a stressful condition persists, your body adapts by a continued effort in resistance and remains in a state of arousal.

Problems begin to manifest when you find yourself repeating this process too often with little or no recovery. Ultimately this moves you into the final stage.

**EXHAUSTION STAGE**
At this phase, the stress has continued for some time. Your body’s ability to resist is lost because its adaptation energy supply is gone. Often referred to as overload, burnout, adrenal fatigue, maladaptation or dysfunction — Here is where stress levels go up and stay up!

The adaptation process is over and not surprisingly; this stage of the general adaptation syndrome is the most hazardous to your health.

Chronic stress can damage nerve cells in tissues and organs. Particularly vulnerable is the hippocampus section of the brain. Thinking and memory are likely to become impaired, with tendency toward anxiety and depression.

There can also be adverse function of the autonomic nervous system that contributes to high blood pressure, heart disease, rheumatoid arthritis, and other stress related illness.

The progressive stages of the general adaptation syndrome clearly show where having excessive stress can lead.

Below is the general picture of how we cope with stress and the potential consequences. Hopefully we have coping strategies that results in successful adjustment. Unfortunately, these discussions are for another class, we will focus on the biology of stress.

![RESPONSES TO STRESS](image)

Stephen Ransom (early 1930’s) was one of the early researchers to show the critical role of the hypothalamus in stress reactions. He stimulated the hypothalamus in anesthetized cats and he was able to
measure the release of ACTH from the pituitary and activation of the sympathetic division, key stress responses. So the hypothalamus was critical for initiating stress responses.

The hypothalamus is critical for the initiation of the stress response which activates the sympathetic division of the autonomic nervous system and the release of the stress hormones. What is important to know is that these responses have a coordinated effect on the adrenal gland. The adrenal gland is composed of two parts. The inner adrenal medulla releases its two hormones norepinephrine and epinephrine. The outer portion of the adrenal gland is the cortex which releases steroid hormones. The two stress hormones that are released from the adrenal cortex are cortisol and corticosterone. This coordinated activation of the adrenal gland is important for the body’s response to stress.

You can follow the stress response in the figure. Stress activates the hypothalamus to get the body to respond. The fight-flight response from the Autonomic Nervous System is activated; the SYMPATHETIC DIVISION activates the adrenal medulla, which then activates the adrenal medulla to release its hormones norepinephrine and epinephrine. These sympathetic hormones maintain the body’s response to stress for a long period of time such as increased heart rate, body temperature, blood pressure, and stopping digestion. In addition, stress activates the hypothalamus to release CRH which flows down to activate cells in the anterior pituitary. The anterior pituitary releases ACTH which will flow through the blood to eventually activate the adrenal cortex to release its two hormones. This stress hormone response is called the HYPOTHALAMIC-PITUITARY-ADRENAL AXIS or the HPA Axis.

The hormones cortisol and corticosterone have four main effects; they activate:

1. Liver to release stored glucose, called gluconeogenesis.
2. Fats to release fatty acids which the cells of the body can use for energy, except neurons.
3. Muscles to release amino acids which when all else is exhausted can be used for energy. This is used as a last resort because in this situation you are sacrificing muscle to stay alive.
4. Suppress the immune system.

There is a specific pattern of cortisol release that occurs during stress. However, inappropriate patterns of HPA Axis activation can occur during prolonged and repeated periods of high stress and anxiety that can damage the brain and lead to future disorders. SEE ILLUSTRATION.
NORMAL: Under normal conditions we respond to stress with the release of cortisol from the adrenal cortex. **CORTISOL** will feed back onto cortisol receptors in the **PARAVENTRICULAR NUCLEUS (PVN)** to reduce the release of CRH and moderate the HPA Axis. Once the stress is over then cortisol goes back to baseline.

ALARM REACTION PHASE: Under some conditions of intense stress we might have a heightened increase in the release of cortisol that can cause reactive emotional and aggressive reactions.

RESISTANCE PHASE: If the stress occurs over a long period, even when the stressor is no longer present. For example, you have an argument and even when it is over you can’t stop thinking about it all of the time. Cortisol feeds back to the PVN to reduce activity in the HPA Axis. During this time the cortisol can actually help the limbic system to control the emotional impulses and outburst. After a period of time the cortisol goes back to baseline.

EXHAUSTION PHASE: When stress and high levels of cortisol goes on too long there can be severe negative consequences leading to anxiety disorder and even depression. You can see situations where Cortisol remains above baseline or in some cases goes below baseline.
CORTISOL AND CORTICOSTERONE ALSO AFFECT THE BRAIN

Receptors for cortisol and corticosterone have been found in several critical areas of the brain.

![CORTISOL RECEPTORS IN THE RAT BRAIN](image)

Photo shows the distribution of cortisol receptors in the rat brain. The HIPPOCAMPUS shows the most intense labelling (b & c at high magnification). Other areas of the brain that contain higher levels of cortisol receptors include the AMYGDALA, ENTORHINAL CORTEX, FRONTAL LOBES, PARAVENTRICULAR NUCLEUS OF THE HYPOTHALAMUS and THALAMUS.


Mild stress can be stimulating to the brain, increase protein synthesis, increase growth of dendrites and synapses. Remember that mildly stress rats were smarter, had larger brains, & lived longer. In addition, cortisol and corticosterone activate receptors in the entorhinal cortex, hippocampus, amygdala, and frontal lobes that are important for memory. This is why mild stress is stimulating for the brain and improves performance.

PROLONGED OR SEVERE STRESS MAY HAVE NEGATIVE CONSEQUENCES.

The insert below shows that prolonged stress can decrease memory performance, especially as you get older.


Stress and memory

While mild stress can increase memory performance other studies have shown that high levels of cortisol can actually impair memory performance.

"While we know that stress hormones affect memory, this research explains how the receptors they engage with can switch good memory to poorly-functioning memory in old age," according to Dr. Joyce Yau of the University's Centre of Cardiovascular Science.

Stress hormone receptors

The study, by the University of Edinburgh, found that one receptor was activated by low levels of cortisol, which helped memory. However, once levels of this stress hormone were too high they spilled over onto a second receptor. This activates brain processes that contribute to memory impairment.

The study found that high levels of the stress hormone in aged mice made them less able to remember how to navigate a maze. The memory recall problem was reversed when the receptor linked to poor memory was blocked.
The research helps explain why too much stress over a prolonged period interferes with the normal processes in storing everyday memories.

This is despite the fact that a little bit of stress can help us better remember emotional memories.

Another study gave injections of cortisol to individuals and tested them on memory performance. The placebo group shows the normal level of performance. When subjects were injected with low levels of cortisol the performance did not change. However, when subjects were given high doses of cortisol memory performance significantly declined.

In addition, Kerr et al. 1991 found that older rats subjected to prolonged stress caused more neurons to die in the hippocampus. Therefore, over stimulation of cortisol & corticosterone receptors in the hippocampus negatively affects the DNA and protein synthesis that leads to cell death. In addition, Anderson (2014) demonstrated that high cortisol levels resulted in 20% fewer synapses in the prefrontal cortex (needed for short-term memory) and those rats had a decline in memory performance.

Sapolsky has done a number of studies showing the damaging effects of stress in the hippocampus in both rats and primates. He examined baboons in the wild and measured their blood cortisol concentrations in the males. Those males with the highest cortisol levels had difficulty maintaining their level of dominance and when their brains were examined there was a significantly smaller hippocampus and amygdala.

Other studies have demonstrated that high levels of cortisol can cause a retraction in the dendrites and a loss of dendritic spines in the hippocampus. Therefore, the hippocampus can be impaired and affect memory performance before neurons die or there is a measurable shrinkage in the volume in the hippocampus.
These studies seem to indicate that high levels of stress causes the release of high levels of cortisol and corticosterone that activate receptors in the brain. However, if the cortisol and corticosterone levels are too high or last too long it can activate receptors that result in the loss of dendritic spines, retraction of dendrites, and the death of neurons seen in the hippocampus and amygdala. This causes a decline in memory performance.

Human studies with Post Traumatic Stress Disorder

Traumatic stress: effects on the brain J. Douglas Bremner, Dialogues Clin Neurosci v.8(4); 2006 Dec


Studies have shown that those suffering from PTSD such as child abuse victims and Vietnam Vets have persistent elevated levels of cortisol when measured from the CSF. Studies showed that they had poor verbal memory function, poor episodic memory, signs of anterograde amnesia, and MRI scans show significantly smaller hippocampus and frontal lobes.

PET and fMRI studies show abnormally low activity in the hippocampus, frontal lobes, and cingulate gyrus which reflect the poor performances in memory. In addition, very high activity levels were found in the amygdala which is consistent with its function in fear and emotions.

The hippocampus is especially vulnerable to high levels of stress and cortisol because there are so many cortisol receptors.
Walter Hes was one of the major pioneers in biological psychology. In one of his studies he stimulated the hypothalamus in cats that were fully awake. He found the same responses that Stephen Ransom showed, ACTH release & sympathetic activation. However, since these cats were awake he could also see how stimulation of the hypothalamus could affect behavior. When he stimulated the hypothalamus the cats displayed AGGRESSIVE ATTACKING BEHAVIOR. That was one pissed off cat! It was the first time that it was shown that the hypothalamus is critical for emotional behavior. For tis and so many other studies, Walter Hes is often considered the Father of Physiological Psychology, and he won the Nobel Prize 1949.

Wasman & Flynn (1962) also stimulated the hypothalamus in awake cats, but due to advancement of technology they were able to stimulate specific parts of the hypothalamus. These are the results when stimulating specific parts of the hypothalamus:

**Medial Hypothalamus** >> Affective Attack - this is when the cat shows all the features of a highly emotional attacking behavior.

**Lateral Hypothalamus** >> Quiet Biting Attack - this is when the cat attacks and bite prey without any emotion. This may have actually stimulated a feeding response.

**Dorsal Hypothalamus** >> Fear

These past studies demonstrate the role of the hypothalamus in emotions, but many other researchers were discovering the extensive interconnections the hypothalamus has with other parts of the brain. Collectively these interconnected parts of the brain became known as the limbic system and it was discovered that these other structures also mediate emotions.

**AMYGDALA IN FEAR & AGGRESSION**
The amygdala has extensive interconnections with the frontal cortex, orbitofrontal cortex, temporal lobe, olfactory system, hippocampus, septum, and other parts of the limbic system.

It has been shown that the amygdala plays a critical role in fear and panic.

Edited from http://serendip.brynmawr.edu/exchange/node/1749

Through the usage of fear conditioned rats in laboratory settings, researchers have been able to effectively map out the “fear circuit”. Through these experiments, it has been determined that the amygdala is required for both the fear circuit and the memory of fear (conditioned fear) associated with stimuli. Only when selective lesions were made on the amygdala, did the laboratory animals not respond to the frightening stimuli. Occasionally, there can be debilitating problems associated with hyperactivity of the amygdala. Being the storehouse for the memory of fear, it can misinterpret signals from the body and cause inappropriate actions. This can lead to panic. Panic is a heightened stage of anxiety and fear feeding itself in a positive feedback loop and jumping to faulty conclusions, which focus on impending danger, madness, harm, or death.

The amygdala also plays a role in aggression.

Stimulation of the amygdala in rats & monkeys can induce aggressive behavior, while lesions of the amygdala can reduce aggression. In addition, it has been shown that high levels of stress can kill neurons in the amygdala and that amygdala becomes highly active. Matthies et.al. (2012) showed that highly aggressive boys have a smaller amygdala.


ONE OF THE CLASSIC EXPERIMENTS looking at the function of the amygdala was done by Kluever and Bucy (1939). They lesioned the temporal lobes in rhesus monkeys, which included the amygdala. The results were a reduction of fear and the monkeys became very docile. Other changes in behavior were visual agnosia, an increased tendency to explore items by mouth, altered sexual behavior and differences in diet. This collective change in behavior became known as the KLUEVER-BUCY SYNDROME.

It is rare to see the Kluever-Bucy Syndrome in humans. It is occasionally found in brain trauma patients and was first noted in 1955. You often find similar behaviors originally described in the monkeys. It causes individuals to put objects in their mouths and engage in inappropriate sexual behavior. Other symptoms may include visual agnosia (inability to visually recognize objects), loss of normal fear and anger responses, memory loss, distractibility, seizures, and dementia. However, these studies reinforce the role of the amygdala in fear and aggression.

SWEET, MARK, & ERVIN (1969) had the opportunity to stimulate the amygdala in human patient. The following comes from their notes:
“following termination of the stimulus she directed an attack against the wall, which she suddenly pounded furiously with her fists....a similar kind of attack was provoked the next day. This time she suddenly swung her guitar past the nose of her astonished psychiatrist, smashing the expensive instrument against the wall...”

Narabayashi (1961) was a physician from Japan that was treating a group of children that were hyperactive, mentally retarded, and extremely aggression. They were so aggressive that they had to be institutionalized because the parents found them to be too dangerous. These children also had epilepsy with an abnormal EEG pattern in temporal lobe and in the region of the amygdala. This region was the focal region for the epilepsy. Narabayashi performed a bilateral lesion of the amygdala (lesioned the amygdala on both sides of the brain). Afterwards the EEG became normal and the children no longer had epileptic seizures. Another surprising outcome was that the children were no longer aggressive or hyperactive and were able to return to family. A very dramatic finding, but he couldn’t determine if there were any negative consequences on learning and memory function since the children were mentally retarded.

Balasubmaranian (1970) in the United States also had a group of children he was treating who were hyperactive and very aggressive. However, unlike the children treated by Narabayashi, these children did not have epilepsy and had a normal EEG. However, seeing the results of Narabayashi he decided to perform the same procedure. Following bilateral lesions of the amygdala the children showed less aggression & hyperactivity. This treatment sparked a debate as to whether this type of surgery should be performed in children.


HORMONES AND AGGRESSION

CORTISOL AND AGGRESSION

Cortisol and corticosterone are two of primary adrenal cortex hormones involved in the hypothalamic—pituitary—adrenal (HPA) axis, often in response to stress. There are many cortisol/corticosterone receptors located in neurons throughout the brain. Many of the structures include parts of the limbic system such as the amygdala, hippocampus, hypothalamus, and entorhinal cortex which involve emotions. It would not be surprising that stress and the stress hormones might be related to aggressive behavior. Cortisol appears to affect the brain in three phases and we can use Hans Selye’s stages to the General Adaptation Syndrome for reference.

ALARM REACTION PHASE: When a stressful situation occurs the HPA Axis is activated and cortisol is immediately released and will feedback to the limbic structures. At first it activates the limbic system which can lead to aggressive behavior. This type of aggression is in reaction to an immediate stress or threat is called REACTIVE AGGRESSION. Reactive aggressive behaviors are unplanned and impulsive, and are usually a response to feelings of fear, anxiety, anger, or a need to retaliate against someone. You may have heard examples that they reacted in the heat of the moment or it was a crime of passion. People with high levels of impulsivity and underlying anger tend to engage in this type of anger expression. Some research suggests that females display more reactive aggression than males.

RESISTANCE PHASE: After the initial arousal to stress, the sustained activity of the HPA Axis and the longer exposure to cortisol will activate a separate set of receptors in the brain in order to inhibit the limbic system and prevent inappropriate behaviors such as aggression and impulsivity. This has been demonstrated to occur when chronic exposure to cortisol induces submissive behavior, feelings of submissiveness, inhibition, and low levels of aggression (van Goozen et al., 1998; Goldsmith and Lemery, 2000; McBurnett et al., 2000; Pajer et al., 2001; van de Wiel et al., 2004; Oosterlaan et al., 2005; Denson et al., 2009).

EXHAUSTION PHASE: When stress situations and the stress hormones are sustained for very long periods of time the HPA axis becomes less active resulting in chronic low levels of cortisol and corticosterone. The lower levels of cortisol and corticosterone means that the limbic system is no longer controlled resulting in more emotional and aggressive behavior. Chronic reduction of corticosterone levels can produce abnormally aggressive behavior in rats and hamsters. Adult mice with low baseline levels of corticosterone are more likely to become dominant than are mice with high baseline corticosterone levels.

The same relationship between aggression and low levels of cortisol has been found in humans. McBurnett et al (2000) evaluated 38 boys aged 7-12 who had been referred to a clinic for behavioral problems. They were evaluated annually for 4 years and salivary cortisol level measurements were taken on the 2nd and 4th year. They found that boys with lower cortisol concentrations exhibited three times more aggressive symptoms than those with higher levels. Virkkunen (1985) reported low levels of cortisol in violent offenders. Similarly, Tennes and Kreye (1985) reported low levels of cortisol in aggressive school children.

TESTOSTERONE AND AGGRESSION

The type of aggressive most associated with chronic low levels of cortisol in humans has been called PROACTIVE AGGRESSION. Proactive aggressive behaviors are planned, calculated, and have some motive other than harming someone. For example, a person robs a store for money and to get drugs. Proactive aggression is a more manipulative type of aggression and is associated with individuals who exhibit interpersonal impairments, egocentric personalities, and narcissistic traits. Since cortisol is low and no longer regulates the limbic system, especially the amygdala and prefrontal cortex, the person has no fear or concern with the consequences of their actions. This is why males with the lowest levels of anxiety toward punishment and threat engaged in the highest levels of proactive aggression which tends to be more physical.

Exactly how and why these highly aggressive individuals had low cortisol levels could not be determined. Could it be due to exposure to a chronic stress environment or be caused by a genetic predisposition? In addition, people suffering from PTSD and major depression have prolonged stress, but maintain very high levels of cortisol. Further research will be necessary.
Other neurotransmitters involved? What part of the brain is activated to cause aggressive behavior? Could there be organizing effects of hormones such as testosterone that causes differences in the brain?

The figure on the left demonstrates the role testosterone plays in aggression if male mice. Mice are cute, but they fight all of the time. In this example they measured the number of biting attacks a male mouse makes each day. You can see that the mouse reaches a peak of 800 biting attacks. After the mouse is castrated you can see that number of biting attacks declines immediately to almost zero. However, when the mouse is supplemented with testosterone the biting attacks return. This suggests that testosterone causes aggression.

This figure shows that testosterone can also cause aggressive behavior in female mice. Injections of Estradiol (estrogen) did not increase aggression. However, injections of testosterone significantly increase female aggressive behavior.

Could the difference between males and females in aggression be as simple as how much testosterone in produced?

Several studies in humans have suggested that testosterone can have an activating effect on human aggression, especially for males. Males who exhibited more aggressive behaviors were correlated with higher concentrations of testosterone in the blood.
What areas of the brain does testosterone activate to cause the aggressive behavior and are there structural differences caused by organizing effects during development?

High concentrations of testosterone receptors are located in the amygdala (AMY), medial preoptic area (MPOA), ventromedial hypothalamus (VMN), nucleus accumbens, bed nucleus of stria terminalis (BNST), and septum (septum). These are all portions of the limbic system which is involved in emotions. Studies of the rabies virus have shown that the virus attacks the limbic system causing the rage-like behavior. In addition, people with tumors in the amygdala have difficulty controlling their emotions resulting in very violent behavior.

Photographs show the location of testosterone receptors in male and female hamsters. Higher concentrations of testosterone receptors can be seen for male hamsters in the SEPTUM (A & B), the BED NUCLEUS OF THE STRIA TERMINALIS (C & D) and the MPO area (E & F).

Both the septum and the bed nucleus of the stria terminalis are important parts of the limbic system and potentially contribute to the greater aggressive behavior observed in males.

The difference in the number of testosterone receptors in the MPO reflects the differences between males and females in sexual behavior and reproductive hormone release such as Gn-RH.

the male has a high concentration of testosterone receptors. Therefore, it has been suggested that the amygdala plays an important role in emotions and may be one of the underlying reasons why males are more aggressive than females.

This photograph of the human amygdala shows that the males have a significantly larger amygdala than that of a female. The amygdala of
A structural difference in the amygdala between males and females was first seen by Bradley et.al. (1998). When newborn male rats were castrated the amygdala was much smaller like that of a female. When newborn females were injected with testosterone they had a large amygdala like that of a male. Therefore, the presence of testosterone early in development has an organizing effect on the amygdala.


It appears that the SEPTUM, BED NUCLEUS OF THE STRIA TERMINALIS, and the AMYGDALA are significantly different between males and females. The differences in size and concentration of testosterone receptors may be the reason why there are significant differences in aggression between males and females. These differences are caused by the organizing effects of testosterone early in development. Testosterone activates the receptors in these areas of the hypothalamus to initiate aggressive behavior. Although testosterone can activate aggression in both males and females, females have very low concentrations of testosterone while the males produce high levels of testosterone and have a brain that is much more responsive (with more receptors in the limbic system) to the hormone.

NEUROTANSMITTERS AND AGGRESSION

The neurotransmitter SEROTONIN has many functions, but research has shown that low levels of serotonin in the brain have been associated with an increased susceptibility to impulsive behavior, aggression, depression, alcohol abuse, and violent suicide.

Serotonin is broken down (metabolized) by Monoamine Oxidase (MAO) into 5-hydroxyindoleacetic acid (5-HIAA) which can be measured in the cerebrospinal fluid (CSF). Low levels of 5-HIAA in the CSF would indicate that serotonin was not active in the brain. High levels of 5-HIAA in the CSF would indicate that serotonin was very active in the brain. In the mid-1970s researchers doing postmortem examinations on suicide victims noticed that these people had reduced levels of a major metabolite of serotonin called 5-hydroxyindoleacetic acid (5-HIAA) in their cerebrospinal fluid. Subsequent studies found lower levels of 5-HIAA in people who had attempted suicide, had severe depression, or had shown tendencies to harm themselves or others. This issue of serotonin in depression and suicide will be examined in the next section of the course.

Researchers from the National Institute of Alcohol Abuse and Alcoholism (NIAAA) took blood and CSF samples from 49 2-year-old male rhesus monkeys and then set them free on their home island. Over the next 4 years, they closely and systematically observed the animals' behavior, paying particular attention to aggressive interactions.


Monkeys with low concentrations of 5-HIAA (low serotonin activity) had very high mortality rates (46%!!) at the end of 4 years. By contrast, no monkeys from the highest 5-HIAA concentration group died. The researchers observed that the monkeys that turned up dead or missing were the ones most likely to initiate
or escalate aggressive encounters. Not surprisingly, these aggressive animals stood the greatest risk of suffering trauma or injury.

Another classic study involving serotonin was with vervet monkeys.


See the results below.

![Serotonin and Aggression in Male Vervet Monkeys](image)

When a serotonin antagonist drug is given to vervet monkeys, there is less serotonin activity in the brain, and the result is that there is a significant increase in aggression (red bar). When these same animals are then treated with a serotonin agonist drug which increases the availability of serotonin in brain, there is no increase in aggressiveness (blue bar).

Humans also show significant differences in concentration of serotonin receptors between males and females. The PET scans show that women had significantly higher serotonin receptors compared to men especially in the temporal lobes. Fewer serotonin receptors in males would indicate lower serotonin activity in the brain and a greater likelihood for aggressive behavior.


**AGGRESSION AND THE FRONTAL LOBE**

Early in the course we discussed Phineas Gage who damaged his frontal lobe. One of the changes in his behavior was that he could no longer control his emotions, displayed a violent temper, and became aggressive. There is an interesting history in how other researchers have found a similar function between the frontal lobe and aggression.
Canon (1925) removed the cerebral cortex in cats. The result is that the cats exhibited SHAM RAGE. Sham rage occurs when the cat is just slightly touched and they go off into a rage like behavior...keep back! So removing the cortex seemed to keep the cat from controlling their aggressive behavior.

Philip Bard (1928) removed cerebral cortex to produce SHAM RAGE. However, when he later lesioned the hypothalamus in cats, the cats no longer produced SHAM RAGE. It was concluded that the cerebral cortex inhibits the hypothalamus from producing sham rage.

Future studies will demonstrate that the Orbitofrontal Cortex is critical for mediating emotional behavior.

In the 1930’s Carlyle Jacobsen and John Fulton were using chimpanzees to do research on learning and memory. Unfortunately, there were two chimpanzees that so violent and aggressive that they could not be used for the study. In a last effort to make use of the chimpanzees Jacobsen cut the frontal lobes. Although the chimpanzees had residual learning and memory deficits, the aggression was gone and they became very docile. He never saw such a dramatic change in animal behavior.

The researcher Egas Moniz (1935) from Portugal learned about the work of Jacobsen and Fulton at a meeting where they presented their results. Moniz decided that it might be a good way to treat serious psychological disorder. You have to realize that there were no good treatments for major depression or schizophrenia then. People with major psychological illnesses were basically warehoused in institutions (insane asylums). Moniz developed the frontal lobotomy to treat psychological disorder in which the connections with the prefrontal lobe are cut away. It has also been called the prefrontal lobotomy. Moniz hypothesized that mental illness was caused by inappropriate connections in the brain that prevented the patients from getting better. His treatment cut those connections so that the patients could establish new and healthy connections which would cure their mental illness. The frontal lobotomy became a popular treatment in the United States. Although there are very few documented cases were patients improved with the procedure, frontal lobotomies continued for years. Egas Moniz eventually won the Nobel Prize for Physiology or Medicine in 1964.

Frontal lobotomy procedure using a leucotome; this was a cannula that was 11 centimeters (4.3 in) in length and 2 centimeters (0.79 in) in diameter. Basically it was a fancy icepick!

What Egas Moniz and Balasubmaranian developed became known as PSYCHOSURGERY. PSYCHOSURGERY
is intentional brain damage to treat a psychological disorder, without the presence of pathology. This means that I might act very strange or violently because I have a tumor in my amygdala. The doctors take out my tumor and I act normally again. THIS IS NOT PSYCHOSURGERY.

PYSCHOSURGERY is when you act strangely, maybe I am a little violent and hyperactive, but no problem can be seen in the brain. The doctors do surgery such as a frontal lobotomy or lesion the amygdala to change my behavior. Hey, but you found nothing wrong with my brain and you cut into it!!! THAT IS PSYCHOLSURGERY.

There has been some debate as to whether PSYCHOSURGERY should ever be performed. It is not always a clear answer because surgery has been done on the brain to correct obsessive-compulsive disorder and Parkinson’s Disease on parts of the brain that we do not have a clear answer as to whether it is functioning properly or not. Yet these surgeries have been done with many doing better than before.

Later studies more clearly demonstrated how the cerebral cortex mediates aggressive behavior.

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In the study cited above violent behavior in adolescent boys was directly related to the activity level and thickness of the frontal lobe, specifically the ventromedial prefrontal cortex (VmPC). Very aggressive boys had a thin cortex and low overall activity in the ventromedial prefrontal cortex (VmPC). It is possible that the thinner cortex indicated a delay in development and that as they matured the thickness of the cortex would become normal and the aggression reduced (no proof of this, just speculation).

The location of the Ventromedial Prefrontal Cortex is pictured in red and overlaps the Orbitofrontal cortex.

Another study of Vietnam Veterans who sustained significant head injury was examined to determine if there was an increase in aggressive behavior. “The results indicated that patients with frontal ventromedial lesions consistently demonstrated Aggression/Violence Scale scores significantly higher than controls and patients with lesions in other brain areas.”


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Additional studies involving PET & MRI scans compared the frontal lobes of murderers and psychopaths to see if reduced activity could be an underlying cause of their violent behavior. The prediction was that those individuals might have lower activity levels in the frontal lobes.
This PET scan shows that the murderer has significantly lower activity in the frontal lobes. This is most evident in the orbitofrontal and Ventromedial Prefrontal Cortex which play an important role in the control of emotions.

Compare the lower activity in the frontal lobes to the location of the ventromedial prefrontal cortex in the previous illustration.

It is possible that low frontal lobe activity can predispose someone to violent behavior and in some cases resulting in murder.

PET scans of a normal person versus that of a Psychopath shows the lower activity in the frontal lobe. Another study compared the brains of 20 prisoners with a diagnosis of psychopathy with the brains of 20 other prisoners who committed similar crimes but were not diagnosed with psychopathy. The study showed that psychopaths have reduced connections between the ventromedial prefrontal cortex (VmPFC), the part of the brain responsible for sentiments such as empathy and guilt, and the amygdala, which mediates fear and anxiety.

In the new study, researchers conducted functional MRI brain imaging on 80 prisoners ages 18 to 50, all of whom had tests done to measure their levels of psychopathy.

Researchers found that those who scored higher on the psychopathy test experienced less activation in the amygdala, ventromedial prefrontal cortex, lateral orbitofrontal cortex, and periaqueductal gray brain regions, compared with those who scored lower on the test.

In summary:

**AREAS OF THE BRAIN INVOLVED WITH AGGRESSION**

- Amygdala, Septum, Bed Nucleus of the Stria Terminalis, and the Frontal Lobe, especially the ventromedial prefrontal cortex

**HORMONES INVOLVED IN AGGRESSION**

- Low Cortisol/corticosterone
- High Testosterone

The best predictor of aggression is when a person has low cortisol and high testosterone. In support of the dual-hormone hypothesis is research demonstrating that low levels of cortisol and high levels of testosterone characterize aggressive clinical populations such as violent offenders, psychopathic individuals, and adolescents with conduct disorder (Dabbs et al., 1991; Popma et al., 2007; Glenn et al., 2011). Two previous studies on testosterone—cortisol interactions and aggression were conducted in males using reports of aggression (Dabbs et al., 1991; Popma et al., 2007). Dabbs et al. (1991) reported that endogenous testosterone positively correlated with severity of violence among male adolescent offenders only when cortisol was low. Popma et al. (2007) reported the same dual-hormone interaction on self-reported impulsive aggression in delinquent adolescent males.

>[Endogenous testosterone and cortisol jointly influence reactive aggression in women Thomas F. Denson, Pranjal H. Mehta, Daniela Ho Tan. Psychoneuroendocrinology (2012).]

**NEUROTRANSMITTERS INVOLVED IN AGGRESSION**

- Low levels of Serotonin

  If you have a person with low serotonin, low cortisol, and high testosterone then they will be predisposed to aggressive behavior.
ANXIETY DISORDERS

Anxiety disorders are a group of mental disorders characterized by heightened feelings of anxiety and fear, and an over-reaction to stress. These feelings may cause physical symptoms, such as a racing heart and shakiness. Anxiety disorders are the most common mental illness in the U.S., affecting 40 million adults in the United States age 18 and older (18% of U.S. population). Anxiety disorders are highly treatable, yet only about one-third of those suffering receive treatment. Anxiety disorders cost the U.S. more than $42 billion a year, almost one-third of the country's $148 billion total mental health bill, according to "The Economic Burden of Anxiety Disorders," a study commissioned by ADAA (The Journal of Clinical Psychiatry, 60(7), July 1999). More than $22.84 billion of those costs are associated with the repeated use of health care services; people with anxiety disorders seek relief for symptoms that mimic physical illnesses. People with an anxiety disorder are three to five times more likely to go to the doctor and six times more likely to be hospitalized for psychiatric disorders than those who do not suffer from anxiety disorders. Anxiety disorders develop from a complex set of risk factors, including genetics, brain chemistry, personality, and life events.

TYPES OF ANXIETY DISORDERS

Panic Disorder
Panic disorder is characterized by recurring and unexpected panic attacks, which are instances of extreme fear or discomfort that start abruptly and build to a rapid peak, usually within the span of ten minutes. Panic disorder affects 6 million people in the US, is more often found in women, and usually appears between late adolescence and the mid-thirties.

Phobias
Phobias are exaggerated, involuntary, and irrational fears of particular situations/things that affect 19 million people in the US.

Types:

- **Specific (simple) phobia**: a phobia that is triggered by a specific object or situation; these usually appear in childhood and are more common in women.
- **Social phobia (social anxiety disorder)**: a phobia characterized by extreme fear of social situations for fear of meeting new people and/or being embarrassed, humiliated, or judged by others; this usually appears in the mid-teens
- **Agoraphobia**: an intense fear of being trapped in particular places or situations, and of not being able to find help in the event of an anxiety or a panic attack; usually those with agoraphobia will avoid such situations

**Obsessive-Compulsive Disorder**
Obsessive compulsive is a disorder in which one is constantly plagued with repetitive, intrusive, irrational and unwelcome thoughts or images (obsessions), and feels the need to then perform rituals (compulsions) to prevent or get rid of these obsessions; performing these rituals is not pleasurable, but does result in a feeling of temporary relief from the anxiety that is caused by not performing them. It affects 2.2 million people in the US
equally between men and women. The median age of onset is 19, with 25 percent of cases occurring by age 14. One-third of affected adults first experienced symptoms in childhood.

- **Common obsessions:** fear of contamination, losing control, harming yourself or someone else, unwanted sexual images, excessive doubt, concern about evenness or exactness, or religious obsessions
- **Common compulsions:** ritualistic hand washing, counting, hoarding, repeating, arranging, or checking

**Post-Traumatic Stress Disorder**
Post-Traumatic Stress Disorder (PTSD) consists of persistent frightening thoughts/memories, or re-living of a terrifying event that resulted in feelings of intense fear, helplessness, or horror. Experiences in war, rape, and child abuse may cause PTSD. It affects 7.7 million people in the US.

**Generalized Anxiety Disorder**
Generalized anxiety disorder causes excessive anxiety and worry about several everyday events or activities, to the point where this worry interferes with daily work and social settings; the worry cannot be overcome despite the fact that the person realizes that their worry is exaggerated. GAD affects 6.8 million people in the US with twice as many more likely to be female.

**STRESS & CORTISOL**
Stress activates the HPA axis.

1. It starts when the limbic system and the **LOCUS COERULEUS** activate the **PARAVENTRICULAR NUCLUES (PVN)** in the hypothalamus. The PVN contains **CRH** which is released into the blood vessels.
2. **CRH** flows to the anterior pituitary which releases **ACTH**.
3. **ACTH** activates the adrenal cortex to release **cortisol** and **corticosterone**. These are the classic stress hormones.
4. When the limbic system activates the **LOCUS COERULEUS** sympathetic division of the autonomic nervous system is activated. The **LOCUS COERULEUS** uses the neurotransmitter norepinephrine.
5. **CORTISOL** can feedback to receptors located in the brain. In the figure below the cells with **CORTISOL RECEPTORS** are labelled in the **cornu ammonis (CA) and dentate gyrus (DG)** of the **HIPPOCAMPUS, AMYGADALA (AMG)**, and **PARAVENTRICUARL NUCLEUS (PVN)**. Other areas that have many **CORTISOL RECEPTORS** include the **LOCUS COERULEUS, RAPHE NUCLEI, and VENTROMEDIAL PREFRONTAL CORTEX**.
AREAS OF THE BRAIN WITH CORTISOL RECEPTORS

- HIPPOCAMPUS (CA & DG)
- AMYGADALA (AMG)
- PARAVENTRICUALR NUCLEUS (PVN)
- LOCUS COERULEUS
- RAPHE NUCLEI
- VENTROMEDIAL PREFRONTAL CORTEX

*PICTURE TO THE RIGHT SHOWS LABELING OF CORTISOL RECEPTORS IN THE RAT BRAIN. DENSE RECEPTORS IN THE PARAVENTRICUALR NUCLEUS (PVN), AMYGADALA (AMG) AND AREAS OF THE HIPPOCAMPUS (CA & DG).*

A RECENT REPORT: People with mild cognitive impairment (MCI) are at increased risk of converting to Alzheimer’s disease within a few years, but a new study warns the risk increases significantly if they suffer from anxiety.

The findings were reported on Oct. 29 online by *The American Journal of Geriatric Psychiatry*, ahead of print publication, scheduled for May 2015.

Led by researchers at Baycrest Health Sciences’ Rotman Research Institute, the study has shown clearly for the first time that anxiety symptoms in individuals diagnosed with MCI increase the risk of a speedier decline in cognitive functions - independent of depression (another risk marker). For MCI patients with mild, moderate or severe anxiety, Alzheimer’s risk increased by 33%, 78% and 135% respectively.

The research team also found that MCI patients who had reported anxiety symptoms at any time over the follow-up period had greater rates of atrophy in the medial temporal lobe regions of the brain, which are essential for creating memories and which are implicated in Alzheimer’s.

ANXIETY DISORDER AND THE AMYGDALA

Many experiments have been done to demonstrate that that the amygdala is central for developing **fear responses, anxiety, and aggression**. The emotion, fear, has been hard-wired into almost every individual, due to its vital role in the survival of the individual. If you lesion the amygdala in a rat, it will lose its ability to learn fear responses and reduce aggressive behavior. There have been human cases that had amygdala lesions and they subsequently failed to exhibit fear-related behaviors.

How might CORTISOL and the AMYGDALA cause anxiety disorder?

**In the figure below the AMYGDALA is central for mediating ANXIETY, FEAR, and AGGRESSION.**

During Stress the limbic system is activated to stimulate the neurons in the PVN to release CRH, starting the HPA Axis. In the end there is the release of CORTISOL from the adrenal cortex.
In addition, the limbic system activates the sympathetic division of the autonomic nervous system which also activates the LOCUS COERULEUS. The LOCUS COERULEUS uses the neurotransmitter NOREPINEPHRINE to arouse the brain, activate the sympathetic portions of the spinal cord, and also activate the PVN to release even more CRH.

Under normal conditions, mild stressors activate the HPA Axis and sympathetic division, but the release of CORTISOL from the adrenal cortex feeds back to inhibit the PVN so that the HPA Axis does not become hyperactive.

Both CORTISOL and NOREPINEPHRINE from the LOCUS COERULEUS can activate the AMYGDALA to increase arousal. However, if the stress is too great this can stimulate the AMYGDALA into reactive responses of anxiety, fear, and aggression. This is the ALARM REACTION phase.

When the stress is prolonged the CORTISOL feeds back to the PVN to reduce the activity of the HPA Axis. Cortisol also stimulates the VENTROMEDIAL PREFRONTAL CORTEX and RAPHE NUCLEI to decrease activity in the AMYGDALA and reduce the likelihood of impulsive anxiety, fear, and aggression. So there is a brief time when CORTISOL can actually prevent the AMYGDALA from getting too active and cause impulsive emotions and aggression. This is the RESISTANCE phase.
When the stress is too great or lasts too long then the high levels of CORTISOL can have negative consequences. This is the **EXHAUSTION phase**.

**High levels of CORTISOL over a long period of time can cause:**

- **LOSS OF SYNAPSES**
- **LOSS OF DENDRITIC SPINES**
- **LOSS OF DENDRITES**
- **KILL NEURONS**

The effects of CORTISOL will occur in those areas of the brain that have high numbers of CORTISOL RECEPTORS. Those areas of the brain include the HIPPOCAMPUS, AMYGADALA (AMG), PARAVENTRICUALR NUCLEUS (PVN), LOCUS COERULEUS, RAPHE NUCLEI, and VENTROMEDIAL PREFRONTAL CORTEX.

High levels of cortisol can atrophy and kill neurons in the AMYGDALA. Children with anxiety disorders tend to have a smaller amygdala. Although the amygdala gets smaller it actually becomes hyperactive! **A hyperactive and smaller amygdala has been linked to social anxiety, obsessive and compulsive disorders, post-traumatic stress, and depression.**

The amygdala becomes hyperactive to cause anxiety, fear, and aggression disorders for two primary reasons. Both the RAPHE NUCLEI which uses the neurotransmitter serotonin and the VENTROMEDIAL PREFRONTAL CORTEX help to control the AMYGDALA from getting over excited. However, under conditions of prolonged stress the CORTISOL will degenerate and kill neurons in the RAPHE NUCLEI and VENTROMEDIAL PREFRONTAL CORTEX and become less active. Remember that cortisol reduces their synapses, dendritic spines, dendrites, and kills the neurons. **With the inhibition by the RAPHE NUCLEI and VENTROMEDIAL PREFRONTAL CORTEX removed the AMYGDALA becomes hyperactive causing fear, anxiety, aggression, anxiety disorder, and depression.**

There can be situations when under the conditions of prolonged stress that the CORTISOL levels will actually decline below baseline levels.

This can happen for two reasons:

1. Cortisol can cause the atrophy and loss of PVN neurons resulting in a reduced release of CRH.
2. The adrenal cortex experiences a burnout condition where it can no longer produce or release enough CORTISOL.

This **reduced level of CORTISOL** is typical of people suffering from PTSD.

**What is interesting is that following successful treatment of anxiety disorder there is a recovery in the size of the amygdala whether it is by drug therapy or psychotherapy.**
DRUG TREATMENT

There are many standard treatments for anxiety disorders. Education programs, counseling, and cognitive therapy have been effective. However, if these types of therapy are not effective then a person may be helped with drug therapy.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SSRIs relieve symptoms by blocking the reabsorption, or reuptake, of serotonin by certain nerve cells in the brain. This leaves more serotonin available, which improves mood. SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) generally produced fewer side effects when compared with tricyclic antidepressants. However, common side effects include insomnia or sleepiness, sexual dysfunction, and weight gain. They are considered an effective treatment for all anxiety disorders, although the treatment of obsessive-compulsive disorder, or OCD, typically requires higher doses.

SSRI’s such as Paxil have become a standard drug treatment for ANXIETY DISORDERS such as Generalized Anxiety Disorder, Panic Disorder, Social Anxiety Disorder, Post-Traumatic Stress Disorder, and Obsessive-Compulsive Disorder. During Anxiety Disorder the high levels of stress and cortisol can cause the RAPHE NUCLEI to atrophy and lose neurons. Therefore, the RAPHE NUCLEI are less effective in using SEROTONIN to control the AMYGDALA resulting in anxiety, fear, and aggression. The SSRI’s may be effective because they block the reuptake of SEROTONIN resulting in an increased activity of the RAPHE NUCLEI so that it can regain control over the AMYGDALA.

SSRI’s are preferred because they are effective and do not produce the level of drowsiness and sleepiness compared to other treatments. If an SSRI does not work then the patient may be switched to another type of antidepressant such as SNRI, Tricyclic Antidepressant, or MAO Inhibitor.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

The serotonin-norepinephrine reuptake inhibitor, or SNRI, class (venlafaxine and duloxetine) is notable for a dual mechanism of action: increasing the levels of the neurotransmitters serotonin and norepinephrine by inhibiting their reuptake back into the terminals. As with other medications, side effects may occur, including stomach upset, insomnia, headache, sexual dysfunction, and minor increase in blood pressure. These medications are considered as effective as SSRIs, so they are also considered a first-line treatment, particularly for the treatment of generalized anxiety disorder.
ANXIOLYTICS or BENZODIAZEPINES

This class of drugs is frequently used for short-term management of anxiety. Benzodiazepines (alprazolam, clonazepam, diazepam, and lorazepam) are highly effective in promoting relaxation and reducing muscular tension and other physical symptoms of anxiety. Long-term use may require increased doses to achieve the same effect, which may lead to problems related to tolerance and dependence. They are very effective in reducing the anxiety levels associated with Anxiety Disorder. They reduce overall activity of the brain by making GABA receptors more sensitive. However, there is some concern when using them over the long term (4-6 weeks) such as:

- **Addiction:** Although the addiction potential of benzodiazepines is regarded as being low if utilized for their intended purpose, many people have become addicted to these drugs. It is relatively easy to take a benzodiazepine every time you feel anxiety to cope with it. The problem is that tolerance is easily built and people continuously require more of the drug to feel the same anxiolytic effect. Antidepressants aren't considered addictive and aren't associated with developing a rapid tolerance which is why they are preferred.

- **Controlled substance:** Benzodiazepines are considered “Schedule IV” controlled substances. They are classified as such due to the fact that they are associated with physical and psychological dependence. Therefore, it is important that people who are taking benzos only take them if absolutely necessary. Antidepressants are not considered a federally regulated substance and are safer to distribute.

- **Dementia risk:** Recently, it was discovered that consistent usage of benzodiazepines can significantly increase risk of developing dementia. Although people with severe anxiety may be willing to take the risk of developing dementia, if an antidepressant works well to control anxiety, there's no need to even risk it. It is always important to consider the long-term effects of benzodiazepines before taking them.

- **Dependence:** The consistent usage of benzodiazepines for anxiety can create dependence, both physically and mentally. People who use benzos on a daily basis will eventually become reliant on them for functioning. If the supply is cut or dosage is dropped, the individual may experience heightened anxiety and various physical symptoms. The risk of dependence is low with antidepressants, hence them being a preferred option.

- **Interactions:** Benzodiazepines tend to interact with many other drugs and thus can intensify their effects. For this reason, a psychiatrist should keep close tabs on your medication profile if a benzo is prescribed. As a potent depressant, these drugs can have a lethal reaction when ingested with alcohol and/or other depressants. It is already known that combining an antidepressant and alcohol can be dangerous, but if a benzo is thrown into the mix, it could be a fatal combination.

- **Safety:** Operating a motor vehicle and/or heavy machinery is strongly advised against while taking a benzodiazepine. While on these drugs, it is easy to become heavily sedated, while losing coordination and motor skills. Additionally, if you play sports or
require hand-eye coordination for your job, most antidepressants will not impair you nearly as much as a benzo.

- **Tolerance**: It is extremely easy to become tolerant to the effects of benzodiazepines. If you are taking them every day, tolerance can build rapidly. Before you know it, you're taking a very high dose just to get the same initial anxiolytic effect. Ultimately consistent benzodiazepine usage is unsustainable – tolerance develops quickly.

- **Withdrawal**: Another difficult aspect that those who’ve been on benzodiazepines have to deal with is that of withdrawal. The withdrawal process is thought to be among the toughest of any drugs and if not conducted properly, can be fatal. A very gradual taper needs to be conducted and during withdrawal, a person will typically experience a significant increase in overall anxiety. In fact, anxiety during withdrawal may be higher than the person has ever experienced.

There are many types of benzodiazepines and only a few are listed below.
- Diazepam Types include: Apzepam, Hexalid, Pax, Stesolid, Stedon, and Valium.
- Alprazolam Types include: Helex, Xanax, Xanor, Onax, Alprox, Restyl, and Tafil.
- Triazolam Types include: Halcion and Rilamir.

**Tricyclic Antidepressants**

Concerns about long-term use of the benzodiazepines led many doctors to favor tricyclic antidepressants (amitriptyline, imipramine, and nortriptyline). Although effective in the treatment of anxiety, they can cause significant side effects, including orthostatic hypotension (drop in blood pressure on standing), constipation, urinary retention, dry mouth, and blurry vision.

**EPINEPHRINE-DOPAMINE REUPTAKE INHBITOR (EDRI)**

**Wellbutrin (Bupropion)** has gained popularity as a treatment for anxiety disorders. It works by blocking the reuptake of norepinephrine and to lesser amount dopamine without affecting serotonin.

**DRUGS USED TO TREAT EPILEPSY**

Several drugs used to treat epilepsy are being studied to determine their effectiveness in the treatment of Anxiety Disorder. Recent studies have shown that pregabalin to be useful in social phobia and generalized anxiety disorders, lamotrigine in post-traumatic stress disorder, and gabapentin in social anxiety.

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**Additional information from a very good article not needed for the test.**

**ARTICLE FROM THE NEW YORK TIMES**

**Generalized Anxiety Disorder In-Depth Report**

**Background**

Fear and stress reactions are essential for human survival. They enable people to pursue important goals and to respond appropriately to danger. In a healthy individual, the stress response (fight, fright, or flight) is provoked by a genuine threat or challenge and is used as a spur for appropriate action.
An anxiety disorder, however, involves an excessive or inappropriate state of arousal characterized by feelings of apprehension, uncertainty, or fear. The word is derived from the Latin, *angere*, which means to choke or strangle. The anxiety response is often not triggered by a real threat. Nevertheless, it can still paralyze the individual into inaction or withdrawal. An anxiety disorder persists, while an appropriate response to a threat resolves, once the threat is removed.

Anxiety disorders are classified according to the severity and duration of their symptoms and specific behavioral characteristics. Categories include:

- Generalized anxiety disorder (GAD)
- Panic disorder
- Phobias
- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Separation anxiety disorder (which is almost always seen in children)

GAD and panic disorder are the most common. Anxiety disorders are usually caused by a combination of psychological, physical, and genetic factors, and treatment is, in general, very effective.

**GENERALIZED ANXIETY DISORDER**

Generalized anxiety disorder (GAD) is the most common anxiety disorder. It affects about 5% of Americans over the course of their lifetimes. It is characterized by:

- A more-or-less constant state of worry and anxiety, which is out of proportion to the level of actual stress or threat in one's life.
- This state occurs on most days for more than 6 months despite the lack of an obvious or specific stressor. (It worsens with stress, however.)
- It is very difficult to control worry. For a clear diagnosis of GAD, the specific worries should be differentiated from those that would define other anxiety disorders, such as fear of panic attacks or appearing in public. Moreover, they are not obsessive such as those that occur with obsessive-compulsive disorder.
- Patients with GAD may experience physical symptoms (such as gastrointestinal complaints) in addition to, or even in place of, mental worries. (This latter case may be more common among people from non-Western cultures.)
- People with GAD tend to be unsure of themselves, overly perfectionist, and conforming.

Given these conditions, a diagnosis of GAD is confirmed if three or more of the following symptoms are present (only one for children) on most days for 6 months:

- Being on edge or very restless
- Feeling tired
- Having difficulty with concentration
- Being irritable
- Having muscle tension
- Experiencing disturbed sleep

Symptoms can cause significant distress and impair normal functioning. To be classified as GAD, they should not be due to a medical condition, another mood disorder, or psychosis. GAD rarely occurs by itself. It typically occurs along with another type of anxiety disorder, depression, or substance abuse.
PANIC DISORDER

Panic disorder is characterized by periodic attacks of anxiety or terror (panic attacks). Panic attacks usually last 15 - 30 minutes, although residual effects can persist much longer. The frequency and severity of acute states of anxiety determine the diagnosis. (Panic attacks can occur in nearly every anxiety disorder, not just panic disorder. In other anxiety disorders, however, there is always a cue or specific trigger for the attack.) A diagnosis of panic disorder is made under the following conditions:

- A person experiences at least two recurrent, unexpected panic attacks.
- For at least a month following the attacks, the person fears that another will occur.

Symptoms of a Panic Attack. During a panic attack a person feels intense fear or discomfort with at least four or more of the following symptoms:

- Rapid heart beat
- Sweating
- Shakiness
- Shortness of breath
- A choking feeling or a feeling of being smothered
- Dizziness
- Nausea
- Feelings of unreality
- Numbness
- Either hot flashes or chills
- Chest pain
- A fear of dying
- A fear of going insane

Women may be more likely than men to experience shortness of breath, nausea, and feelings of being smothered. More men than women have sweating and abdominal pain. Panic attacks that include only one or two symptoms, such as dizziness and heart pounding, are known as limited-symptom attacks. These may be either residual symptoms after a major panic attack or precursors to full-blown attacks.

Frequency of Panic Attacks. Frequency of attacks can vary widely. Some people have frequent attacks (for example, every week) that occur for months; others may have clusters of daily attacks followed by weeks or months of remission.

Triggers of Panic Attacks. Panic attacks may occur spontaneously or in response to a particular situation. Recalling or re-experiencing even harmless circumstances surrounding an original attack may trigger subsequent panic attacks.

PHOBIC DISORDERS

Phobias, manifested by overwhelming and irrational fears, are common. In most cases, people can avoid or at least endure phobic situations, but in some cases, as with agoraphobia, the anxiety associated with the feared object or situation can be incapacitating.

Agoraphobia. Agoraphobia is described as fear of being in public places or open areas. (The term is derived from the Greek word agora, meaning outdoor marketplace.) In its severest form, agoraphobia is characterized by a paralyzing terror of being in places or situations from which the patient feels there is neither escape nor accessible help in case of an attack. Consequently, people with agoraphobia confine themselves to places in which they feel safe, usually at home. The patient with agoraphobia often makes complicated plans in order to avoid confronting feared situations and places.

Social Phobia. Social phobia, also known as social anxiety disorder, is the fear of being publicly scrutinized and humiliated and is manifested by extreme shyness and discomfort in social settings. This
Social phobia often leads people to avoid social situations and is not due to a physical or mental problem (such as stuttering, acne, or personality disorders). Social phobia has been termed "the neglected anxiety disorder" because it is often not properly diagnosed.

The associated symptoms vary in intensity, ranging from mild and tolerable anxiety to a full-blown panic attack. (Unlike a panic attack, however, social phobia is always directly related to a social situation.) Symptoms include sweating, shortness of breath, pounding heart, dry mouth, and tremor.

The disorder may be further categorized as generalized or specific social phobia:

- **Generalized social phobia** is the fear of being humiliated in front of other people during nearly all social situations. People with this subtype are the most socially impaired and also the most likely to seek treatment.
- **Specific social phobia** usually involves a phobic response to a specific event. Performance anxiety ("stage fright") is the most common specific social phobia and occurs when a person must perform in public. These patients usually feel comfortable in informal social situations. Children with social anxiety develop symptoms in settings that include their peers, not just adults, and these symptoms may include tantrums, blushing, or not being able to speak to unfamiliar people. These children are often able to have normal social relationships with familiar people, however.

**Specific Phobias.** Specific phobias (formerly simple phobias) are an irrational fear of specific objects or situations. Specific phobias are among the most common medical disorders. Most cases are mild and not significant enough to require treatment.

The most common phobias are fear of animals (usually spiders, snakes, or mice), flying (pterygophobia), heights (acrophobia), water, injections, public transportation, confined spaces (claustrophobia), dentists (odontiatophobia), storms, tunnels, and bridges.

When confronting the object or situation, the phobic person experiences panicky feelings, sweating, avoidance behavior, difficulty breathing, and a rapid heartbeat. Most phobic adults are aware of the irrationality of their fear, and many endure intense anxiety rather than disclose their disorder.

**OBSESSIVE-COMPULSIVE DISORDER**

Obsessive-compulsive disorder (OCD) is time-consuming, distressing, and can disrupt normal functioning. Much research suggests that a critical feature in this disorder is an overinflated sense of responsibility, in which the patient's thoughts center around possible dangers and an urgent need to do something about them.

- **Obsessions** are recurrent or persistent mental images, thoughts, or ideas. The obsessive thoughts or images can range from mundane worries about whether one has locked a door to bizarre and frightening fantasies of behaving violently toward a loved one.
- **Compulsive behaviors** are repetitive, rigid, and self-directed routines that are intended to prevent the manifestation of an associated obsession. Such compulsive acts might include repetitive checking for locked doors or unlit stove burners or calls to loved ones at frequent intervals to be sure they are safe. Some people are compelled to wash their hands every few minutes or to spend inordinate amounts of time cleaning their surroundings in order to subdue the fear of contagion.

Over half of patients with OCD have obsessive thoughts without the ritualistic compulsive behavior. Although individuals recognize that the obsessive thoughts and ritualized behavior patterns are senseless and excessive, they cannot stop them in spite of strenuous efforts to ignore or suppress the thoughts or actions. OCD often accompanies depression or other anxiety disorders. Some patients find that their symptoms subside over time, while others experience a worsening of symptoms.
Symptoms in children may be mistaken for behavioral problems (taking too long to do homework because of perfectionism, refusing to perform a chore because of fear of germs). Children do not usually recognize that their obsessions or compulsions are excessive.

Associated Obsessive Disorders. Certain other disorders that may be part of, or strongly associated with, the OCD spectrum include:

- Body dysmorphic disorder (BDD). In BDD, people are obsessed with the belief that they are ugly, or part of their body is abnormally shaped.
- Hypochondriasis. People who have hypochondriasis have an excessive fear of having a serious disease.
- Anorexia nervosa. OCD frequently accompanies this eating disorder, where the compulsive behavior focuses on food restriction and thinness.
- Trichotillomania. People with trichotillomania continually pull their hair, leaving bald patches.
- Tourette syndrome. Symptoms of Tourette syndrome include jerky movements, tics, and uncontrollably uttering obscene words.

Obsessive-Compulsive Personality. OCD should not be confused with obsessive-compulsive personality, which defines certain character traits (being a perfectionist, excessively conscientious, morally rigid, or preoccupied with rules and order). These traits do not necessarily occur in people with obsessive-compulsive disorder.

POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) is a severe, persistent emotional reaction to a traumatic event that severely impairs one’s life. It is classified as an anxiety disorder because of its symptoms. Not every traumatic event leads to PTSD, however. There are two criteria that must be present to qualify for a diagnosis of PTSD:

- The patient must have directly experienced, witnessed, or learned of a life-threatening or seriously injurious event.
- The patients' response is intense fear, helplessness, or horror. Children may behave with agitation or with disorganized behavior.

Triggering Events. PTSD is triggered by violent or traumatic events that are usually outside the normal range of human experience. War is a prime example. There is some evidence that events most likely to trigger PTSD are those that involve deliberate and destructive behavior (murder, rape) and those that are prolonged or physically challenging. Such events include, but are not limited to, experiencing or witnessing sexual assaults, accidents, military combat, natural disasters (such as earthquakes), or unexpected deaths of loved ones. PTSD may also occur in people who have serious illness and receive aggressive treatments or who have close family members or friends with such conditions.

Symptoms of PTSD. There are three basic sets of symptoms associated with PTSD. They may begin immediately after the event or can develop up to a year afterward:

- Re-experiencing. In such cases, patients persistently re-experience the trauma in at least one of the following ways: in recurrent images, thoughts, flashbacks, dreams, or feelings of distress at situations that remind them of the traumatic event. Children may engage in play, in which traumatic events are enacted repeatedly.
- Avoidance. Patients may avoid reminders of the event, such as thoughts, people, or any other factors that trigger recollection. They tend to have an emotional numbness, a sense of being in a daze or of
losing contact with their own identity or even external reality. They may be unable to remember important aspects of the event.

- **Increased Arousal.** This includes symptoms of anxiety or heightened awareness of danger (sleeplessness, irritability, being easily startled, or becoming overly vigilant to unknown dangers).

To further qualify for a diagnosis of PTSD, patients must have at least one symptom in the re-experiencing category, three avoidance symptoms, and two arousal symptoms. Symptoms are chronic (3 months or more). Symptoms should also not be associated with alcohol, medications, or drugs and should not be intensifications of a pre-existing psychological disorder.

**Acute Stress Disorder.** In a syndrome called acute stress disorder, symptoms of PTSD occur within 2 days to 4 weeks after the traumatic event. Most people with acute stress disorder go on to develop PTSD.

**Long-Term Outlook.** The long-term impact of a traumatic event is uncertain. PTSD may cause physical changes in the brain, and in some cases the disorder can last a lifetime.

**SEPARATION ANXIETY DISORDER**

Separation anxiety disorder almost always occurs in children. It is suspected in children who are excessively anxious about separation from important family members or from home. For a diagnosis of separation anxiety disorder, the child should also exhibit at least three of the following symptoms for at least 4 weeks:

- Extreme distress from either anticipating or actually being away from home or being separated from a parent or other loved one
- Extreme worry about losing or about possible harm befalling a loved one
- Intense worry about getting lost, being kidnapped, or otherwise separated from loved ones
- Frequent refusal to go to school or to sleep away from home
- Physical symptoms such as headache, stomach ache, or even vomiting, when faced with separation from loved ones

Separation anxiety often disappears as the child grows older, but if not addressed, it may lead to panic disorder, agoraphobia, or combinations of anxiety disorders.

**Causes**

A person's genetics, biochemistry, environment, history, and psychological profile can all contribute to the development of anxiety disorders. Most people with these disorders seem to have a biological vulnerability to stress, making them more susceptible to environmental stimuli than the rest of the population.

**BIOCHEMICAL FACTORS**

Studies suggest that an imbalance of certain substances called neurotransmitters (chemical messengers in the brain) may contribute to anxiety disorders. The neurotransmitters targeted in anxiety disorders are gamma-aminobutyric acid (GABA), serotonin, dopamine, and epinephrine. Serotonin appears to be specifically important in feelings of well-being, and deficiencies are highly related to anxiety and depression. Stress hormones such as cortisol also play a role.

**BRAIN STRUCTURE FACTORS**

Studies using imaging techniques, particularly magnetic resonance imaging (MRI), have helped to identify different areas of the brain associated with anxiety responses.
An MRI (magnetic resonance imaging) of the brain creates a detailed image of the complex structures in the brain. An MRI can give a three-dimensional depiction of the brain, making location of problems such as tumors or aneurysms more precise.

In particular, research has focused on changes in the amygdala, which is sometimes referred to as the "fear center." This part of the brain regulates fear, memory, and emotion and coordinates these resources with heart rate, blood pressure, and other physical responses to stressful events. Some evidence suggests that the amygdala in people with anxiety disorders is highly sensitive to novel or unfamiliar situations and reacts with a high stress response.

Obsessive-compulsive disorder (OCD) is the anxiety disorder most strongly associated with specific brain dysfunction. For example, abnormalities in a specific pathway of nerves have been linked to OCD, attention deficit disorder, and Tourette syndrome. The symptoms of the three disorders are similar and they often coexist.

A number of imaging studies have reported less volume in the hippocampus in people with post-traumatic stress disorder. This important region is related to emotion and memory storage.

GENETIC FACTORS

Up to 50% of people with panic disorder and 40% of patients with generalized anxiety (GAD) have close relatives with the disorder. (About half of GAD patients also have family members with panic disorder, and about 30% have relatives with simple phobias.)

Obsessive-compulsive disorder (OCD) is also strongly related to a family history of the disorder. Close relatives of people with OCD are up to 9 times more likely to develop OCD themselves. Researchers are making progress in identifying specific genetic factors that might contribute to an inherited risk. Of particular interest are genes that regulate specific neurotransmitters (brain chemical messengers), including serotonin and glutamate.

Risk Factors

Up to 25% of American adults experience intense anxiety sometime in their lives. The prevalence of true anxiety disorders is much lower, although they are still the most common psychiatric conditions in the United States and affect more than 20 million Americans.

GENERAL RISK FACTORS FOR ANXIETY DISORDERS

Gender. With the exception of obsessive-compulsive disorder (OCD), women have twice the risk for most anxiety disorders as men. A number of factors may increase the reported risk in women, including cultural pressures to meet everyone else's needs except their own, and fewer self-restrictions on reporting anxiety to doctors.

Age. In general, phobias, OCD and separation anxiety show up early in childhood, while social phobia and panic disorder are often diagnosed during the teen years. Studies suggest that 3 - 5% of children and adolescents have some anxiety disorder. Children and adolescents who have an anxiety disorder are at risk of later developing other anxiety disorders, depression, and substance abuse.

Personality Factors. Children's personalities may indicate higher or lower risk for future anxiety disorders. For example, research suggests that extremely shy children and those likely to be the target of bullies are at higher risk for developing anxiety disorders later in life. Children who cannot tolerate...
uncertainty tend to be worriers, a major predictor of generalized anxiety. In fact, such traits may be biologically based and due to a hypersensitive amygdala -- the "fear center" in the brain.

Family History and Dynamics. Anxiety disorders tend to run in families. Genetic factors may play a role in some cases, but family dynamics and psychological influences are also often at work. Several studies show a strong correlation between a parent's fears and those of the offspring. Although an inherited trait may be present, some researchers believe that many children can "learn" fears and phobias, just by observing a parent or loved one's phobic or fearful reaction to an event.

Social Factors. Several studies have reported a significant increase in anxiety levels in children and college students in the past two decades compared to children in the 1950s. In several studies, anxiety was associated with a lack of social connections and a sense of a more threatening environment. It also appears that more socially alienated populations have higher levels of anxiety. For example, a study of Mexican adults living in California reported that native-born Mexican Americans were three times more likely to have anxiety disorders (and even more likely to be depressed) as those who had recently immigrated to the U.S. The longer the immigrants lived in the U.S., the greater their risk for psychiatric problems. Traditional Mexican cultural and social ties seemed to protect recently arrived immigrants from mental illness.

Traumatic Events. Traumatic events may trigger anxiety disorders, especially in individuals who are susceptible to them because of psychological, genetic, or biochemical factors. The clearest example is post-traumatic stress disorder. Specific traumatic events in childhood, particularly those that threaten family integrity, such as spousal or child abuse, can also lead to other anxiety and emotional disorders. Some types of specific phobias, for instance of spiders or snakes, may be triggered and perpetuated after a single traumatic exposure.

Medical Conditions. Although no causal relationships have been established, certain medical conditions have been associated with increased risk of panic disorder. They include migraines, obstructive sleep apnea, mitral valve prolapses, irritable bowel syndrome, chronic fatigue syndrome, and premenstrual syndrome.

SPECIFIC RISK FACTORS FOR GENERALIZED ANXIETY (GAD)

GAD affects about 1 - 5% of Americans in the course of their lives and is more common in women than in men. It is the most common anxiety disorder among the elderly. GAD usually begins in childhood and often becomes a chronic ailment, particularly when left untreated. Depression commonly accompanies this anxiety disorder and depression in adolescence may be a strong predictor of GAD in adulthood.

SPECIFIC RISK FACTORS FOR PANIC DISORDER

Age and Panic Disorder. Studies indicate that the prevalence of panic disorder among adults is between 1.6 - 2% and is much higher in adolescence, 3.5 - 9%. Panic disorder usually first occurs either in late adolescence or in the mid-30s.

Gender and Panic Disorder. Women have about twice the risk for panic disorder as men. Panic attacks are very common after menopause. In one study, nearly 18% of older women reported panic attacks within a 6-month period, with over half of these attacks being full-blown. They tended to be associated with stressful life events and poor health. The effects of pregnancy on panic disorder appear to be mixed. It seems to improve the condition in some women and worsen it in others.

SPECIFIC RISK FACTORS FOR OBSESSIVE-COMPULSIVE DISORDER (OCD)

Obsessive-compulsive disorder occurs equally in men and women, and it affects about 2 - 3% of people over a lifespan. Most cases of OCD first develop in childhood or adolescence, although the disorder can occur throughout the life span.

SPECIFIC RISK FACTORS FOR SOCIAL PHOBIAS
Social anxiety disorder is currently estimated to be the third most common psychiatric disorder in the U.S. Studies have reported a prevalence of 7 - 12% in Western nations.

*Age and Phobias.* The onset of social anxiety disorder is usually during the early teenage years.

*Gender and Phobias.* Women are more likely to develop social anxiety disorder than men, although equal numbers of men and women seek treatment for it. Most people seeking treatment have had symptoms for at least 10 years.

**SPECIFIC RISK FACTORS FOR POST-TRAUMATIC STRESS DISORDER**

Traumatic events are the main risk factor for PTSD, but some people can go through such events and not experience PTSD. Studies estimate that 6 - 30% or more of trauma survivors develop PTSD, with children and young people being among those at the high end of the range. Women have the twice the risk of PTSD as men.

After the September 11 attack on the World Trade Towers, about 7.5% of New York City’s population reported PTSD within the month of the event, which declined to 0.6% at 6 months.

Researchers are trying to determine factors that might increase vulnerability to catastrophic events and put people at risk for develop PTSD. Some studies report the following may be risk factors:

- Pre-existing emotional disorder. People are at higher risk for PTSD if they have a history of an emotional disorder, particularly depression, before a traumatic event.
- Drug or alcohol abuse
- A family history of anxiety
- A history of physical or sexual abuse, neglect, or abuse within the family
- An early separation from parents
- Lack of social support and poverty
- Sleep disorders. Insomnia and excessive daytime sleepiness even within a month after a traumatic event are important predictors for the development of PTSD. One specific sleep disorder -- sleep apnea -- may even intensify symptoms of PTSD, including sleeplessness and nightmares. Sleep apnea occurs when tissues in the upper throat (or airway) collapse at intervals during sleep, thereby blocking the passage of air. Sleep apnea has also been associated with a risk for panic disorder.

**Possible Complications**

All types of anxiety disorders can be very debilitating and seriously affect a person’s quality of life.

**ASSOCIATION WITH DEPRESSION AND BIPOLAR DISORDERS**

*Depression.* Depression is very common in people with an anxiety disorder, and it is sometimes difficult to distinguish one from the other because either or both can be accompanied by anxious feelings, agitation, insomnia, and problems with concentration.

The combination of depression and anxiety is a major risk factor for both substance abuse and suicide.

*Bipolar Disorder.* Symptoms of panic disorder are very common in people with bipolar disorder. Furthermore, anxiety worsens bipolar disorder.

**INCREASED RISK FOR SUICIDE**

Panic disorder is associated with a risk for suicidal thoughts. Studies report that up to 18% of people with panic disorder attempt suicide and up to 38.5% regularly harbor suicidal thoughts, with the risks being higher in people with both panic disorder and depression. Social phobias and OCD also increase the risk of suicide. If a person has an anxiety disorder and a mood disorders (such as depression), the risk for suicide is even higher. <!--[For more information on suicide risks and prevention, see In-Depth Report #8: Depression .]-->
Severely depressed or anxious people are at high risk for alcoholism, smoking, and other forms of addiction. Anxiety disorders are highly prevalent among people with alcoholism. Moreover, long-term alcohol use can itself cause biologic changes that may actually produce anxiety and depression.

**Risk for Substance Abuse in Specific Anxiety Disorders.** The following are some observations on specific anxiety disorders and substance abuse:

- Some people with GAD and panic disorders may use alcohol or drugs to self-medicate.
- Social phobia appears to pose a particular risk for alcohol abuse. People with this disorder are likely to drink in order to boost confidence. Alcohol itself has no direct beneficial effect on anxiety, but studies suggest that the belief in its effect appears to relieve anxious feelings.
- Heavy smoking and substance abuse are common in people with PTSD. In adolescents, PTSD not only increases the risk for drug and alcohol use but also for eating disorders.

**EFFECTS ON WORK, SCHOOL, AND RELATIONSHIPS**

Anxiety disorders can have negative effects on work and relationships.

**PHYSICAL EFFECTS OF ANXIETY DISORDERS IN ADULTS**

Anxiety disorders are associated with many different physical illnesses. Research suggests that people who have both an anxiety disorder and a physical illness have a worse quality of life and greater risk for disability than those who have only a physical illness. Anxiety disorders often tend to occur before the development of physical disorders.

*Heart Disease.* Anxiety has been associated with several heart risk factors, including unhealthy cholesterol levels, thicker blood vessels, and high blood pressure. Both anxiety and depression have been associated with a poorer response to treatment in heart patients, including a worse outcome after heart surgery. The role of anxiety disorders in triggering serious cardiac events remains unclear.

Cholesterol is a soft, waxy substance that is present in all parts of the body including the nervous system, skin, muscle, liver, intestines, and heart. It is made by the body and obtained from animal products in the diet. Cholesterol is manufactured in the liver and is needed for normal body functions including the production of hormones, bile acid, and vitamin D. Excessive cholesterol in the blood contributes to atherosclerosis and subsequent heart disease. The risk of developing heart disease or atherosclerosis increases as the level of blood cholesterol increases.

*Gastrointestinal Disorders.* Anxiety frequently accompanies gastrointestinal conditions. Of note, half the cases of irritable bowel syndrome are associated with anxiety.

*Headache.* Both tension and migraine headaches are associated with anxiety disorders.

*Respiratory Problems.* Studies report an association between anxiety in patients with obstructive lung conditions (such as asthma, emphysema, and chronic bronchitis) and more frequent relapses.

*Obesity.* Anxiety disorders may lead to obesity, and the reverse may also be true.

*Allergic Conditions.* Anxiety disorders are associated with numerous allergic conditions including hay fever, eczema, hives, food allergies, and conjunctivitis.
Other Conditions. People with obsessive-compulsive disorders can experience skin problems from excessive washing, injuries from repetitive physical acts, and hair loss from repeated hair pulling (behavior known as trichotillomania).

PHYSICAL EFFECTS OF ANXIETY DISORDERS IN CHILDREN

Children with anxiety disorders often suffer from recurrent stomach aches. Anxiety has been associated with a higher risk for sleep disorders in children, such as frequent nightmares, restless legs syndrome, and bruxism (the grinding and gnashing of the teeth during sleep).

Diagnosis

A physical examination and medical and personal history is essential. Because anxiety accompanies so many medical conditions, some serious, it is extremely important for the doctor to uncover any medical problems or medications that might underlie or be masked by an anxiety attack.

The patient should describe any occurrence of anxiety disorders or depression in the family and mention any other contributing factors, such as excessive caffeine use, recent life changes, or stressful events.

It is very important to be honest with your doctor about all conditions, including excessive drinking, substance abuse, or other psychological or mood states that might contribute to, or result from, the anxiety disorder.

Diagnosing children with an anxiety disorder can be very difficult, since anxiety often results in disruptive behaviors that overlap with attention-deficit hyperactivity or oppositional disorder. Other conditions with symptoms similar to anxiety disorders include pervasive developmental disorders such as Asperger syndrome, learning disabilities, bipolar disorder, and depression. Many children have anxiety disorder and a co-occurring condition, which should be treated along with anxiety.

OTHER CONDITIONS WITH SIMILAR SYMPTOMS

People with anxiety disorders are more likely to see a family doctor before a mental health specialist, since their symptoms are often physical. Symptoms can include muscle tension, trembling, twitching, aching, soreness, cold and clammy hands, dry mouth, sweating, nausea or diarrhea, or urinary frequency. Anxiety attacks can mimic or accompany nearly every acute disorder of the heart or lungs, including heart attacks and angina (chest pain). In fact, nearly all individuals with panic disorders are convinced that their symptoms are physical and possibly life-threatening.

Heart Problems. Some patients who enter the emergency room with chest pain, and who have a low-to-moderate risk for a heart attack, are actually suffering from panic attacks. It is often difficult even for specialists to distinguish between heart conditions and a panic attack:

- Women who are having an actual heart attack or acute heart problem are much more likely to be misdiagnosed as having an anxiety attack than are men with similar symptoms.
- Mitral valve prolapse, a common and usually mild heart problem, may have symptoms that are nearly identical to those of panic disorder. The two conditions, in fact, frequently occur together.

Mitral valve prolapse is a disorder in which the mitral valve does not close properly when the heart contracts. When the valve does not close properly it allows blood to backflow into the left atrium. Some symptoms can include palpitations, chest pain, difficulty breathing after exertion, fatigue, cough, and shortness of breath while lying down.
• People with a heart-rhythm disturbance called paroxysmal supraventricular tachycardia have many of the same symptoms as those with panic attacks.

Asthma. Asthma attacks and panic attacks have similar symptoms and can also coexist.

Hyperthyroidism. Hyperthyroidism can cause many of the same symptoms of generalized anxiety disorder and must be ruled out.

Other Medical Conditions. In addition, anxiety-like symptoms are seen in many other medical problems, including hypoglycemia, recurrent pulmonary emboli, and adrenal-gland tumors. Women can also experience intense anxiety attacks with hot flashes during menopause.

Medication Side Effects. Many drugs, including some for high blood pressure, diabetes, and thyroid disorders, can produce symptoms of anxiety. Withdrawal from certain drugs, often those used to treat sleep disorders or anxiety, can also precipitate anxiety reactions.

Substance Abuse. People with anxiety disorders often drink alcohol or abuse drugs in order to conceal or eliminate symptoms, but substance abuse and dependency can also cause anxiety. In addition, withdrawal from alcohol can produce physiologic symptoms similar to panic attacks. Clinicians often have difficulty determining whether alcoholism or anxiety is the primary disorder. Overuse of caffeine or abuse of amphetamines can cause symptoms resembling a panic attack.

SCREENING TESTS

Clinicians use various screening tests to determine the causes, type, severity, and frequency of anxiety. Such tests include the Hamilton Anxiety Rating Scale, the Beck Anxiety Inventory, the Social Phobia Inventory, the Penn State Worry Questionnaire, the Generalized Anxiety Disorder Scale, and the Yale-Brown Obsessive Compulsive Scale.

Treatment

The standard approach to treating most anxiety disorders is a combination of talk therapy, such as cognitive-behavioral therapy (CBT), and an antidepressant medication. A selective serotonin reuptake inhibitor (SSRI) is typically the first choice, with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor) being an alternative. If patients do not respond to these drugs, tricyclic antidepressants may be helpful. Benzodiazepines may be recommended for patients who are not helped by antidepressants or who need help rapidly (antidepressants take several weeks to be effective). A healthy lifestyle that includes exercise, adequate rest, and good nutrition can also help to reduce the impact of anxiety.

TREATMENT OPTIONS FOR SPECIFIC ANXIETY DISORDERS

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>Medications</th>
<th>Cognitive-Behavioral Therapy (CBT) and other Non-Drug Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>Antidepressants, benzodiazepines, and buspirone are helpful but have varying side effects. Investigational drugs include pregabalin and other anticonvulsants.</td>
<td>Cognitive-behavioral therapy or anxiety management therapy. Anxiety management therapy involves education, relaxation training, and exposure to anxiety-provoking stimuli but does not include cognitive restructuring.</td>
</tr>
<tr>
<td>Panic Attacks</td>
<td>SSRIs are treatment of choice. If patients do not respond to SSRIs, short-term treatment with a benzodiazepine may be used, or patients may switch to another type of antidepressant such as venlafaxine or tricyclics.</td>
<td>Cognitive-behavioral therapy, provided in 12 - 16 sessions over 3 - 4 months, focuses on recreating fear symptoms and helping patients change their response to them.</td>
</tr>
<tr>
<td>Social Anxiety Disorder</td>
<td>SSRIs or venlafaxine are first-line drug treatments. Benzodiazepines may help patients who do not respond to these</td>
<td>Cognitive-behavioral therapy can help improve symptoms after 6 - 12 weeks.</td>
</tr>
</tbody>
</table>
Obsessive-Compulsive Disorder

SSRIs are the first choice for adults. Clomipramine (a tricyclic antidepressant) is an alternative for adult patients who do not respond to SSRIs. For children, SSRIs do not seem to work as well for OCD as for other types of anxiety disorders.

Cognitive-behavioral therapy is the first treatment choice for children. For adults, either CBT or drug therapy may be offered as initial treatment. CBT techniques focus on exposure and response prevention (ERP).

Post-Traumatic Stress Disorder

Antidepressants, particularly SSRIs (sertraline and paroxetine approved for PTSD). The atypical antipsychotic olanzapine may be added to an antidepressant for patients who do not respond to a SSRI alone.

Trauma-focused psychological treatments include exposure therapy, trauma-focused cognitive therapy, and eye movement desensitization and reprocessing.

Note: For anxiety disorders in adults, the most effective treatments are usually combinations of drugs and CBT techniques. For children, CBT is usually the first treatment.

Medications

Selective serotonin-reuptake inhibitors (SSRIs), or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor), are the primary first-line treatment for anxiety disorders. For patients who are not helped by these drugs or who need help rapidly, benzodiazepines may be prescribed, either alone or in combination with an antidepressant. Other types of antidepressants, including tricyclic antidepressants, may also be used to treat patients with severe or chronic forms of anxiety disorders.

Drug therapies for anxiety disorders work best in combination with cognitive behavioral therapy or some other forms of psychotherapy.

ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors (SSRIs). SSRIs include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro).

SSRIs can cause agitation, nausea, and diarrhea. Sexual function side effects include low sex drive, inability to have an orgasm, and impotence. Over time, many SSRI-treated patients gain weight, although the degree of weight gain varies depending on the drug. Elderly people taking these drugs should take the lowest effective dose possible, and those with heart problems should be monitored closely.

There have been many concerns about SSRIs and increased risk for suicidal behavior. Concern is greatest for children, but both adults and children who are treated with SSRIs should be carefully monitored for any worsening of depressive symptoms or changes in behavior. This is especially important during the first few months of antidepressant treatment.

Paroxetine has been linked to heart-related birth defects when women took this drug during the first trimester of pregnancy. It should not be taken by women who are pregnant or planning on becoming pregnant. Other SSRIs are generally considered safe for use during pregnancy and breastfeeding. Still, women who are pregnant or who are considering becoming pregnant should discuss the potential risks of these drugs with their doctors.

Serotonin-norepinephrine reuptake inhibitors (SNRIs). SNRIs are known as dual inhibitors because they work on two neurotransmitters -- norepinephrine and serotonin. Venlafaxine (Effexor) is an SNRI that is approved for treatment of generalized anxiety disorder, social anxiety disorder, and panic disorder in adults. (It is not approved for children.) As with many SSRIs, venlafaxine impairs sexual function. Venlafaxine can increase blood pressure and heart rate and should be used with caution in patients with high blood pressure or heart disease. Some patients report severe withdrawal symptoms, including dizziness and nausea. This drug has a serious risk for overdose. Venlafaxine should not be taken during the last trimester of pregnancy because the drug can cause complications in newborn infants.
Duloxetine (Cymbalta) also acts on both serotonin and norepinephrine. It is approved for treatment of generalized anxiety disorder. Side effects are generally mild and include dry mouth, nausea, and sleepiness. Patients with narrow-angle glaucoma or patients with liver or kidney diseases should not take duloxetine. Because duloxetine can cause liver damage, patients who drink large quantities of alcoholic beverages should not take it.

Mitrazapine (Remeron) is another type of SNRI that is sometimes used for treatment of post-traumatic stress disorder and social anxiety disorder.

Tricyclic Antidepressants. Tricyclics are an older type of antidepressant. Tricyclics used for treatment of anxiety disorder include imipramine (Tofranil, for generalized anxiety disorder, panic disorder), nortriptyline (Pamelor, for panic disorder), desipramine (Norpramin, for panic disorder), and clomipramine (Anafranil, for obsessive compulsive disorder). Clomipramine is approved specifically for OCD, but because of its severe side effects it is usually used only if SSRIs have failed to help.

Side effects of TCAs include sleep disturbance, abrupt reduction in blood pressure upon standing, weight gain, sexual dysfunction, and mental disturbance. Elderly patients and those with a history of seizures, cardiac problems, closed-angle glaucoma, and urinary retention or obstruction should be closely supervised when taking tricyclics.

Benzodiazepines are effective medications for most anxiety disorders and have been the standard of treatment for years. However, their long-term daily use has been associated with a risk for dependency and abuse. Therefore, they have been supplanted in most cases by SSRIs and other newer antidepressants. For anxiety disorders, benzodiazepines are most often used to treat panic disorder, and are sometimes used for social anxiety disorder and generalized anxiety disorder. These drugs include alprazolam (Xanax), clonazepam (Klonopin), and lorazepam (Ativan).

Benzodiazepines can have many side effects, generally associated with chronic use. The most common are daytime drowsiness and a hang-over feeling. In rare cases, they can cause agitation. They may worsen respiratory problems. Benzodiazepines are potentially dangerous when used in combination with alcohol. Overdoses can be serious, although they are very rarely fatal.

The elderly are more susceptible to side effects and should usually start at half the dose prescribed for younger people. These drugs increase the risk of falling, which can increase the risk for hip fracture in older people. Also of concern are studies showing a high risk of automobile accidents in people who take benzodiazepines. Benzodiazepines taken during pregnancy are associated with birth defects (such as cleft palate), and they should not be used by pregnant women or by nursing mothers.

Loss of Effectiveness and Dependence. Eventually these drugs can lose their effectiveness with continued use at the same dosage. As a result, patients may want to increase their dosage to prevent anxiety. This causes dependency, which can occur after taking these drugs for several weeks.

Withdrawal and its Treatments. Withdrawal symptoms can be very severe, even in people who rapidly discontinue benzodiazepines after taking them for only 4 weeks. Symptoms include sleep disturbance and anxiety, which can develop within hours or days after stopping the medication. Some patients experience stomach distress, sweating, and insomnia, which can last 1 - 3 weeks. The longer the drugs are taken and the higher their dose, the more severe these symptoms can become. Tapering off gradually is the best approach to stop taking these drugs. Certain medications (such as anti-seizure drugs, antidepressants, and buspirone) may also help with withdrawal.

AZAPIRONES (BUSPIRONE)

Azapirones, such as buspirone (BuSpar), act on serotonin receptors called 5-HT(1A). Buspirone appears to work as well as a benzodiazepine for treating generalized anxiety disorder. It usually takes several days to weeks for the drug to be fully effective. It is not useful against panic attacks.

Buspirone does not produce any immediate euphoria or change in sensation, so some people believe, erroneously, that the drug doesn't work. Such qualities result in a very low potential for abuse. Unlike the benzodiazepines, buspirone is not addictive, even with long-term use, so it may be particularly useful for the patient whose anxiety disorder coexists with alcoholism or drug abuse.

Buspirone tends to have less pronounced side effects than benzodiazepines and no withdrawal effects, even when the drug is discontinued quickly. Common side effects include dizziness, drowsiness, and nausea. Buspirone should not be used with monoamine oxidase inhibitors (MAOIs).
BETA BLOCKERS
Beta blockers, including propranolol (Inderal) and atenolol (Tenormin), block the nerves that stimulate the heart to beat faster. They affect only the physiologic symptoms of anxiety (particularly rapid heart rate) and are most helpful for phobias, particularly performance anxiety. They may be taken before entering a situation where anxiety symptoms tend to occur. Beta blockers are less effective for other forms of anxiety.

ATYPICAL ANTIPSYCHOTICS
Atypical antipsychotics are mostly used for treating schizophrenia, bipolar disorder, and major depressive disorder. Doctors sometimes use the atypical antipsychotic olanzapine (Zyprexa) for treating severe cases of post-traumatic stress disorder. However, olanzapine has severe side effects, including weight gain and increased high blood sugar levels, which can increase the risk for diabetes. <ref>[For more information, see In-Depth Report #47: Schizophrenia.]</ref>

ANTICONVULSANTS (ANTISEIZURE DRUGS)
Pregabalin (Lyrica) and gabapentin (Neurontin) are drugs used to treat seizures and other conditions. Researchers are investigating whether these drugs may be useful for certain anxiety disorders, such as social anxiety disorder and general anxiety disorder. Their exact role in the treatment of anxiety disorders is not clear, however.

Psychotherapy and Other Treatments
COGNITIVE-BEHAVIORAL THERAPY
The goal of cognitive-behavioral therapy (CBT) is to regain control of reactions to stress and stimuli, thus reducing the feeling of helplessness that often accompanies anxiety disorders. CBT works on the principle that the thoughts that produce and maintain anxiety can be recognized and altered using various techniques that change behavioral responses and eliminate the anxiety reaction.

CBT and medication are each effective alone but many studies have shown that a combination of CBT and medication is the best approach for treating anxiety disorders. Combination CBT and medication is particularly effective for children and adolescents. Evidence clearly supports the combination approach’s benefits for treating pediatric cases of generalized anxiety disorder, separation anxiety, social phobia, and obsessive compulsive disorder.

Studies suggest that CBT is also helpful for patients who have additional conditions, such as depression, a second anxiety disorder, or alcohol dependency. (It may take longer to achieve a successful outcome in such cases, however.) CBT is often given along with drug treatment.

Both individual and group treatments work well. However, people with social phobia may do better in individual sessions. Several recent studies also indicate that telephone-based behavioral therapy works well for people with OCD, generalized anxiety disorder, and panic disorders.

Anxiety disorders are chronic and recurrence is common, even after successful short-term therapy. Some patients with anxiety disorders may require long-term or intensive therapy of at least a year or 50 sessions. Medications, then, are also generally recommended for most patients.

Basic Cognitive Therapy Techniques. Treatment usually takes about 12 - 20 weeks. The essential goal of cognitive therapy is to understand the realities of an anxiety-provoking situation and to respond to reality with new actions based on reasonable expectations.

• First, the patient must learn how to recognize anxious reactions and thoughts as they occur. One way of accomplishing this is by keeping a daily diary that reports the occurrences of anxiety attacks and any thoughts and events associated with them. A patient with OCD, for instance, may record repetitive thoughts.
• These entrenched and automatic reactions and thoughts must be challenged and understood. Again, using the OCD example, one approach is to record and play back the words of the repetitive thoughts, over exposing the patient to the thoughts and reducing their effect. One effective approach for patients with generalized anxiety disorder targets their intolerance of uncertainty and helps them develop methods to cope with it.
• Patients are usually given behavioral homework assignments to help them change their behavior. For example, a person with generalized social phobia may be asked to buy an item and then return it the next day. As the patient performs this action, they observe any unrealistic fears and thoughts triggered by such an event.
As the patient continues with self-observation, they begin to perceive the false assumptions that underlie the anxiety. For example, patients with OCD may learn to recognize that their heightened sense of responsibility for preventing harm in non-threatening situations is not necessary or even useful.

At that point, the patient can begin substituting new ways of coping with the feared objects and situations.

Systematic Desensitization. Systematic desensitization is a specific technique that breaks the link between the anxiety-provoking stimulus and the anxiety response. This treatment requires the patient to gradually confront the object of fear. There are three main elements to the process:

- Relaxation training
- A list composed by the patient that prioritizes anxiety-inducing situations by degree of fear
- The desensitization procedure itself, confronting each item on the list, starting with the least stressful

This treatment is especially effective for simple phobias, social phobias, agoraphobia, and post-traumatic stress syndrome.

Exposure and Response Treatment. Exposure treatment purposefully generates anxiety by exposing the patient repeatedly to the feared object or situation, either literally or using imagination and visualization. It uses the most fearful stimulus first. (This differs from the desensitization process because it does not involve relaxation or a gradual approach to the source of anxiety.)

Exposure treatments are usually known as either flooding or graduated exposure:

- Flooding exposes the person to the anxiety-producing stimulus for as long as 1 - 2 hours.
- Graduated exposure gives the patient a greater degree of control over the length and frequency of exposures.

In both cases, the patient experiences the anxiety over and over until the stimulating event eventually loses its effect. Combining exposure with standard cognitive therapy may be particularly beneficial. This approach has helped certain patients in most anxiety disorder categories, including post-traumatic stress disorder.

Modeling Treatment. Phobias can often be treated successfully with modeling treatment:

- The therapy typically uses an actor who approaches an anxiety-producing object or engages in a fear-provoking activity that is similar to the patient's specific problem. Either a live or videotaped situation may be used, although the live model is considered to be more effective.
- The patient observes this event and tries to learn how to behave in a comparable manner.

Anxiety Management Therapy. Anxiety management therapy is sometimes used as an alternative to CBT for generalized anxiety disorder. It involves patient education, relaxation training, and exposure to anxiety-provoking stimuli but does not include exercises in cognitive retraining.

OTHER FORMS OF PSYCHOTHERAPY
Other forms of psychotherapy, commonly called emotion-based psychotherapy (EBT), psychodynamic therapy, or "talk" therapy, deal more with the roots of anxiety and usually, although not always, require longer treatments. They include interpersonal therapy, supportive psychotherapy, attention intervention, and psychoanalysis. All work is done during the sessions. Some research indicates that such therapies might be more useful for generalized anxiety, which may require more sustained work to process and recover from early traumas and fears. Studies suggest that although emotion-based psychotherapies are not as effective as cognitive-behavioral therapy (CBT) in treating panic disorders, patients tend to stay longer in EBT than in CBT. Some doctors suggest adding elements of EBT to the usual CBT and medication treatments.

RELAXATION TRAINING AND RELATED THERAPIES

Relaxation Training. Relaxation techniques use muscle relaxation and mental visualization to help focus attention towards a calming feeling. Some people find meditation helpful.

Breathing Retraining. Breathing retraining techniques may help reduce the physical effects of anxiety. For example, hyperventilation is one of the primary physical manifestations of panic disorders. This involves rapid, tense breathing, resulting in chest pain, dizziness, tingling of the mouth and fingers, muscle cramps, and even fainting. By practicing measured, controlled breathing at the onset of a panic attack, patients may be able to prevent full attacks.

Biofeedback. Biofeedback uses special sensors that allow patients to recognize anxiety states by changes in specific physical functions, such as changes in pulse rate, skin temperatures, and muscle tone. Eventually they learn to modify
these changes, which in turn helps relieve anxiety. While commonly used, there are not many rigorous studies showing that biofeedback helps patients reduce or eliminate their symptoms over the long term.

PSYCHOLOGICAL THERAPIES FOR POST-TRAUMATIC STRESS DISORDER (PTSD)

Several types of psychological treatments have been designed specifically for treating patients with PTSD. These approaches include a special type of CBT known as trauma-focused cognitive behavioral therapy (TFCBT), and a psychotherapy treatment called eye movement desensitization and reprocessing (EMDR).

With TFCBT, patients are taught stress management skills. The therapist helps the patient develop a narrative (verbal, written, or artistic) about the traumatic event. Patients may be exposed to reminders about the trauma and are taught how to cope with future reminders. Through the process, the patient learns how to reprocess their thoughts, feelings, and behaviors.

With EMDR, the patient focuses on remembering the traumatic experience while visually following the rhythmic movement of the therapist’s fingers. The patient recounts to the therapist what memories have been provoked during the exercise. EMDR may help patients recall details and sensations that they had blocked out. Through this breakthrough, patients learn how to regain emotional control.

HERBS AND SUPPLEMENTS

Generally, manufacturers of herbal remedies and dietary supplements do not need FDA approval to sell their products. Just like a drug, herbs and supplements can affect the body's chemistry, and therefore have the potential to produce side effects that may be harmful. There have been a number of reported cases of serious and even lethal side effects from herbal products. Always check with your doctor before using any herbal remedies or dietary supplements.

Some studies suggest that the dietary supplement inositol may have benefits for panic disorder and, possibly, obsessive compulsive disorder. Inositol is part of the vitamin B complex.

Some patients use aromatherapy as a relaxation aid. Aromatherapy is in general safe, but some plant extracts in these formulas have been linked to skin allergies.

There is no evidence supporting the efficacy of valerian, St. John's wort, or passionflower for treatment of anxiety. The herbal remedy kava has been associated with liver problems and should be avoided. Kava can also interact dangerously with medications that are metabolized by the liver.

DEEP BRAIN STIMULATION (DBS)

Deep brain stimulation (DBS) is a surgical approach that involves implanting in the brain a small device similar to a pacemaker. In 2009, the FDA approved a deep brain stimulation device (Reclaim) for treatment of chronic, severe, and disabling obsessive compulsive disorder (OCD). This is the first medical device approved for treatment of OCD.

The device is similar to other DBS devices used for treating movement disorders like Parkinson’s disease. It uses four electrodes that are surgically implanted into the brain and connected by wires to a small generator that is implanted near the abdomen or collar bone. The generator delivers precisely controlled electrical pulses to target specific areas of the brain.

Another brain stimulation approach, transcranial magnetic stimulation (TMS), does not involve surgery or implantation. It uses an external machine to generate high frequency magnetic pulses to target and stimulate areas of the brain. TMS is also being studied as a possible treatment for OCD.

SURGERY

A surgical technique called cingulotomy involves interrupting the cingulate gyrus, a bundle of nerve fibers in the front of the brain. It is sometimes used as a last resort for patients with severe OCD. A variation of this procedure using magnetic resonance imaging (MRI) to guide the surgeon has resulted in long-term improvement in about 25 - 33% of OCD patients in whom it is performed. The procedure is generally safe with few serious complications and does not affect intellect or memory.

Resources

www.nimh.nih.gov -- National Institute of Mental Health
www.adaa.org -- Anxiety Disorders Association of America
www.nami.org -- National Alliance on Mental Illness
www.psych.org -- The American Psychiatric Association
www.apa.org -- The American Psychological Association
A diagnosis of posttraumatic stress disorder (PTSD) is often challenging for both patients and health care providers. The disorder can be difficult to detect because the symptoms may resemble those of anxiety disorders, major depression, or other medical conditions. To ensure accurate diagnosis, the key clinical features of PTSD should be identified and considered for all patients who present with symptoms of anxiety or depression. The evidence supporting the diagnosis of PTSD includes the following:

- Trauma exposure: The patient has experienced or witnessed a traumatic event.
- Intrusion: Recurrent memories, dreams, or flashbacks of the traumatic event.
- Avoidance: The patient actively avoids any stimuli that might remind them of the trauma, which can lead to a decrease in social functioning.
- Hyperarousal: The patient experiences increased vigilance, restlessness, irritability, or difficulty concentrating for at least one month after the traumatic event.

Early psychological interventions can prevent the development of PTSD in individuals who have experienced a traumatic event. These interventions may be provided in a single session or over multiple sessions. The effectiveness of these interventions has been supported by systematic reviews and meta-analyses. For example, a Cochrane review found that early psychological interventions prevented PTSD in children and adolescents who had experienced a traumatic event (Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Multiple session early psychological interventions for the prevention of posttraumatic stress disorder. Cochrane Database Syst Rev 2009 Jan;166(1):34-71. Epub 2009 Dec 1.).

Pharmacotherapy can be used as a treatment option for individuals with PTSD. However, it is important to note that medications alone are typically not sufficient to treat PTSD and should be combined with psychological interventions. Selective serotonin reuptake inhibitors (SSRIs) are commonly used in the treatment of PTSD, but their efficacy has been inconsistent in randomized controlled trials (Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Scientific review: pharmacological augmentation strategies in the treatment of posttraumatic stress disorder. J Clin Psychiatry 2008 Apr;69(4):461-32). Other medications, such as mood stabilizers and antipsychotics, may also be beneficial in some cases (Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Scientific review: pharmacological augmentation strategies in the treatment of posttraumatic stress disorder. J Clin Psychiatry 2008 Apr;69(4):461-32).

In summary, PTSD is a complex disorder that requires a multidisciplinary approach for effective treatment. Early psychological interventions, combined with medications when necessary, can help prevent the development of PTSD and provide有效治疗 for those who already have the disorder. It is important for health care providers to be aware of the key features of PTSD and to implement appropriate interventions to improve outcomes for patients.


THE NEUROBIOLOGY OF PLEASURE

In the 1954, the psychologists James Olds and Peter Milner from McGill University were using brain stimulation in the arousal centers of the brain to determine if that could improve performance on certain tasks. One day they tested a rat that preferred the region of the test apparatus where it received electrical brain stimulation the most. In fact, they found the rat would do most anything to keep his brain stimulated. Maybe the rat found the experience pleasurable, but since you can’t ask a rat we might say the brain stimulation was rewarding and they may have found the parts of the brain that mediate reward. Olds and Milner immediately wanted to know what part of the brain they were stimulating in the rat, so took out the brain and prepared it for histology. Unfortunately, they lost the brain! They then did a systematic examination of areas of the brain that activated this reward pathway. One of the very interesting demonstrations Olds and Milner did was to modify their stimulating chamber so that a lever press would deliver direct brain stimulation through deep implanted electrodes. This method was called SELF-STIMULATION, the rat could stimulate his own brain! I think the rats liked it because they would press the lever as many as 20,000 to 40,000 times per day. This was a pleasure center, a reward circuit, the activation of which was much more powerful than any natural stimulus.

A series of subsequent experiments revealed that rats preferred self-stimulation to food (they refused to eat) and water (they didn’t want to stop to drink!). Self-stimulating male rats would ignore a female in heat and would repeatedly cross foot-shock-delivering floor grids to reach the lever. Rats would not cross the foot-shock-delivering floor grid for food, they would starve to death. But, the rats would immediately cross to get to the lever and self-stimulate. Female rats would abandon their newborn nursing pups to continually press the lever. They had to be unhooked the rat for period of time otherwise they would starve to death or even burn out their brain. The rat’s behavior had all of the signs of addiction.

One of the important parts of the brain that could be stimulated to get this effect was the MEDIAN FOREBRAIN BUNDLE. The MEDIAN FOREBRAIN BUNDLE was a group of axons in which the cell bodies of those neurons were located in the VENTRAL TEGMENTAL AREA (VTA). In humans it only contains about 450,000 neurons. The VTA neurons project to many other limbic parts of the brain including the hippocampus, amygdala, cingulate gyrus, nucleus accumbens, and prefrontal cortex. However, which one of these projections mediated this rewarding behavior? By selectively lesioning different nuclei they were able to determine that just one circuit was responsible for all of the reward behavior and that was the connection between the VTA and Nucleus Accumbens.
DOPAMINE (DA) is the only neurotransmitter the neurons in the VTA use to communicate with the Nucleus Accumbens (Fibiger & Phillips 1979: Wise 1978). When Wise (1976) would inject the drug Pimozide, a DA antagonist, the rats would stop self-stimulating. However, the injections of Pimozide blocked DA receptors in all parts of the brain. So Stellar, Kelly, & Corbett (1983) injected another DA antagonist, Spiroperidol, directly into the nucleus accumbens. When this was done the rats stopped self-stimulating. They tried blocking other limbic structure, but the only nucleus that could stop self-stimulation with a DA antagonist drug was the NUCLEUS ACCUMBENS.

Are there rewarding pathways in humans? One of the first to examine this was Heath in the early 1960’s.


In one procedure, Dr. Heath wired up the pleasure centers of a gay man. During a three-hour session, the subject, code-named B-19, electrically self-stimulated his reward circuitry some 1,500 times.

"During these sessions, B-19 stimulated himself to a point that he was experiencing an almost overwhelming euphoria and elation, and had to be disconnected, despite his vigorous protests."


IF BLOCKING DA PREVENTS PLEASURE, WHAT ABOUT DRUGS THAT INCREASE DA?

Two classic drugs that increase DA in neurons are AMPHETAMINE and COCAINE. Amphetamine increases the release of DA. Cocaine blocks the reuptake of DA at the terminals. If amphetamine and cocaine increases DA in the nucleus accumbens, could that be the underlying cause for their addiction?
ROBERTS & ZITO (1987) set up a self-injecting rat system like the picture. The rats would self-inject themselves with cocaine for long periods of time. They would press the bar continuously and they would overdose themselves to death if you didn’t give them rest periods.

They set up the self-injecting rats and then injected pimozide, the DA antagonist into the nucleus accumbens. The result is that the rats would stop self-injecting cocaine.

This suggests that this reward pathway may mediate the addictive nature of amphetamine and cocaine.

Researchers also wondered if this same reward pathway mediates the addictive nature of the OPIATE Drugs (opium, morphine, & heroin). They found that rats would continuously self-inject themselves with morphine or heroin. In addition, they found that injections of morphine releases DA into the nucleus accumbens in the rats. The receptors for the opiates are called ENKEPHALIN RECEPTORS and there is a high number of them found in the VTA and the nucleus accumbens so that activation of these receptors excites the neurons to release DA into the nucleus accumbens. MATHEWS & GERMAN (1984) injected pimozide, the DA antagonist, into the nucleus accumbens and the rats stopped self-injecting.

Other researchers have found acetylcholine receptors IN VTA and when stimulated the neurons release DA into the nucleus accumbens. This was of interest because those acetylcholine receptors are activated by nicotine, so this may mediate the addictive nature of smoking. Rats would self-inject themselves with nicotine and the administration of DA antagonist drugs would stop the behavior.

The graph shows that the drugs amphetamine, cocaine, nicotine, and heroin increase the release of DA. This activates the reward pathway between the VTA and nucleus accumbens. It shows why DA antagonist drugs can block the reward pathway and stop the addictive behavior.

The VTA to nucleus accumbens is the primary pathway for drugs of abuse. Opiates and nicotine stimulate neurons in VTA. The VTA neurons become very active and release large amounts of dopamine into the nucleus accumbens. Amphetamine and cocaine act on the terminals of VTA neurons in the nucleus accumbens. Amphetamine increases the release of dopamine into the nucleus accumbens. Cocaine blocks the reuptake of dopamine by neurons in the nucleus accumbens. THC the active ingredient in marijuana
activates both the nucleus accumbens and VTA. Activation of this pathway that results in an increase of DA into the nucleus accumbens results in addictive behavior.

The additive properties of these drugs and the reward pathway have been found in numerous human studies. These drugs have been found to release DA into the nucleus accumbens and the reward pathway discovered by Olds and Milner has been the basis for understanding drug addiction.


This pathway has been used to understand other properties of drug abuse such as tolerance and withdrawal. For example, opioids such as heroin and morphine produce tolerance because the receptors gradually become less responsive so that more drugs are needed to stimulate the VTA. Therefore, more drugs are needed to produce pleasure comparable to that provided in previous drug-taking episodes.


In addition, researchers have discovered a potential mechanism for withdrawal and psychological addiction involving the reward pathway.


In these studies, rats & monkeys are given long term exposure to cocaine or heroin. Then they no longer receive the drug and go through the withdraw process. They found that DA release into the NUCLEUS ACCUMBENS was below normal and may be the basis for the intense craving (psychological addiction) of the drug. In addition, they found that the release of DA never came back to normal.

In summary:

Drugs of abuse activate the reward pathway between the VTA and nucleus accumbens. These drugs cause the release of DA into the nucleus accumbens which mediates the addictive behavior. DA antagonist drugs can block the effect of DA in the nucleus accumbens and the addictive behavior.

Tolerance occurs when the receptors for these drugs decrease in sensitivity.

The continuing drug dependence occurs because the release of DA falls below baseline.

IN THE FIGURE BELOW. Alcohol and nicotine increase the release of dopamine in the rat brain. When nicotine (black circles) enters the brain (smoking), it acts on the nicotinic receptors on the dopamine-containing neurons in the VTA, resulting in increased dopamine release (shaded circles) in the NUCLEUS ACCUMBENS. Alcohol activates the neurons in the VTA and their terminals in the NUCLEUS ACCUMBENS resulting in an increase in the release of dopamine. The combined effects of alcohol and nicotine can cause an even greater amount of dopamine release in the NUCLEUS ACCUMBENS.
A RECENT REPORT FROM National Institute on Drug Abuse

Details of the role of glutamate, the brain's excitatory chemical, in a drug reward pathway have been identified for the first time.

This discovery in rodents -- published in Nature Communications (2014) -- shows that stimulation of glutamate neurons in a specific brain region (the dorsal raphe nucleus) leads to activation of dopamine-containing neurons in the brain's reward circuit (dopamine reward system). Dopamine is a neurotransmitter present in regions of the brain that regulate movement, emotion, motivation, and feelings of pleasure. Glutamate is a neurotransmitter whose receptors are important for neural communication, memory formation, and learning.

The research was conducted at the Intramural Research Program >http://irp.drugabuse.gov/> (IRP) of the National Institute on Drug Abuse (NIDA), which is part of the National Institutes of Health. The research focused on the dorsal raphe nucleus, which has long been a brain region of interest to drug abuse researchers, since nerve cells in this area connect to part of the dopamine reward system. Many of the pathways are rich in serotonin, a neurotransmitter linked to mood regulation. Even though electrical stimulation of the dorsal raphe nucleus promotes reward-related behaviors, drugs that increase serotonin have low abuse potential. As a result, this region of the brain has always presented a seeming contradiction, since it is involved in drug reward but is also abundant in serotonin - a chemical not known for a role in drug reinforcement. This has led researchers to theorize that another neurotransmitter may be responsible for the role that the dorsal raphe nucleus plays in reward.

"We now have strong evidence of a reward pathway that starts with stimulation of glutamate neurons in the dorsal raphe nucleus and ends in activation of the dopamine reward system," said NIDA Director Dr. Nora D. Volkow. "These findings help us better understand the brain's reward circuitry and opens up new avenues of research into the neurobiology of drug addiction."
In these rodent models, researchers used special tracers and labelling compounds to confirm that this circuit in the reward pathway begins with glutamate cells in the dorsal raphe nucleus that connect to dopamine cells in the ventral tegmental area, which in turn travel to the nucleus accumbens, a brain structure linked to motivation, pleasure, and reward. After verifying the pathway, investigators used optogenetic techniques (using light to control activity of modified cells) and chemical blockers to confirm that glutamate, not serotonin, is responsible for activating this reward circuitry.

"This glutamatergic pathway is the first fully characterized link between electrically stimulated reward circuitry and the dopamine system on which it depends," said Dr. Marisela Morales, NIDA IRP scientist and senior author on the paper. "The discovery of this specific brain pathway opens new avenues to examine its participation in a variety of disorders related to motivation."
Neural mechanisms of pair bonding in voles

How could we ever understand the neural, genetic, and molecular mechanisms of a behavior as complex as love or pair bonding? Psychologists have learned a great deal about the importance of bonding — the formation of social attachments — in social development.

But surprisingly it was field biologists, back in the 1980’s, who laid the foundations for the astounding discoveries in the following decades that have started to reveal the neural and molecular mechanisms underlying bonding. The field biologists discovered that several species of voles — small mouse-like burrowing rodents — appear very similar on the outside, but form strikingly different social structures in the wild. Montane voles and meadow voles, like 95% of all mammals, are polygamous. Meadow voles are loners: they are solitary, and mate promiscuously — a different partner each time. The males don’t take part in raising offspring, and even the females abandon their offspring soon after birth. Prairie voles could not be more different. They are a model of family values. They naturally form life-long monogamous pair bonds. Once they have mated, they vary rarely mate with a different partner for the rest of their life. After bonding, the males react aggressively towards other males. Both males and females prefer the company of their mate to others, build a nest together, and provide extensive and prolonged bi-parental care. By discovering this naturally occurring difference in pair bonding in such closely related species in the wild, the field biologists opened the door for neuroscientists, chiefly Tom Insel and his colleagues at NIMH, to try to bring these animals into the lab, where they could quantify these behavioral differences, and start to decipher the neural mechanisms underlying pair bond formation.

Quantifying partner preference

In order to study pair bonding quantitatively, Insel built a wide variety of mazes and chambers of different shapes and sizes. Each apparatus was designed to test a different aspect of bonding behaviors. Here we will focus on partner preference. The basic setup for testing preferences is to use a 3-part apparatus. In this case, after mating has occurred and bonding has been established, we want to test the preference of a vole for their partner, compared to a stranger. We tether the partner in one chamber, and the stranger in another. Then we place the test animal in the neutral chamber in the middle, and record the amount of time they spend in each chamber. Prairie voles spend the most time in the partner chamber. Montane voles, on the other hand, spend the most time alone in the neutral chamber.
Oxytocin and vasopressin: Oxytocin and vasopressin are ancient neuropeptides that are at least 700 million years old. They (or close analogs) are found in such widely disparate species such as hydra, worms, insects, and vertebrates. What is a hydra, you might ask? Hydra is a genus of freshwater multicellular organisms that are typically about 1 mm in length. To give you a sense of how long ago 700 million years is, recall that dinosaurs roamed the earth 60 million years ago. 700 million years ago (that’s pre-Cambrian!), there was only a single supercontinent, the earth was covered by glacial ice sheets even at the equator, and the first multicellular organisms are thought to have emerged. That’s pretty ancient! Oxytocin and vasopressin are both 9 amino acids in length, and differ by only 2 amino acids. Vasopressin influences male socio-sexual behaviors: erection, ejaculation, aggression, territoriality, and pair bonding, from rodents to humans. Oxytocin influences female socio-sexual behaviors: intercourse, childbirth, lactation, maternal bonding, pair bonding. At the end of pregnancy, a surge of oxytocin starts labor contractions. You may have heard of Pitocin, the trade name for oxytocin. I was introduced to Pitocin when the doctors gave my wife an I.V. drip of it to induce labor. It’s very effective at this! Oxytocin is also released during suckling, and acts to stimulate lactation (the “let-down” reflex). Injecting oxytocin into the spinal cord of male rats causes spontaneous erections. Clearly, these versatile hormones have a wide variety of socio-sexual actions. We now know that they are also involved in pair bonding in voles (and perhaps us as well).

Effects of oxytocin and vasopressin in pair-bonding:
In the 1990’s, a series of experiments from the Insel lab showed that oxytocin and vasopressin are involved in the formation of pair bonding in prairie voles. Insel injected vasopressin into the ventral forebrain of male prairie voles, and then housed the male with an unreceptive female. Normally, since the animals do not mate when the female is unreceptive, no bonding would occur. But the vasopressin induced the formation of a pair bond, which could be measured with the partner preference test. After vasopressin, males spent much more time with the partner than with a stranger. Control injections of cerebrospinal fluid (CSF) did not produce any bonding, and neither did oxytocin: after these control injections, males spent the same amount of time with either the partner or the stranger.

![Graph showing % time spent with partner, neutral, and stranger](image)

**Injecting vasopressin into male brains induces partner preference.**

**Neural mechanisms of pair bonding in voles**

What happens if you inject oxytocin into female vole brains? Although oxytocin had no effect on males, it caused pair bonding in females. Before mating, when normally no bonding has occurred, oxytocin caused a huge increase in partner preference. Then they took a different set of females, and let them mate with males in order to form normal pair bonds. In some of these females, they injected an oxytocin antagonist that blocks the effect of oxytocin naturally released during mating. The antagonist prevented the formation of pair bonding, and these females showed no partner preference, spending equal amounts of time with the partner and stranger. Insel’s group also demonstrated that injecting males with a vasopressin antagonist prevents pair bonding in males. So what do these experiments demonstrate about the roles of oxytocin and vasopressin in pair bonding? Are the hormones necessary? Are they sufficient?
IN SUMMARY

FOR MALES
VASOPRESSIN CAUSES PAIR BONDING
VASOPRESSIN ANTAGONISTS PREVENTS PAIR BONDING

FOR FEMALES
OXYTOCIN CAUSES PAIR BONDING
OXYTOCIN ANTAGONISTS PREVENTS PAIR BONDING

Ventral forebrain:
Where are the receptors for these powerful hormones? We'll focus on vasopressin, since that's the one manipulated by Lim et al. Insel’s group has demonstrated that of the several vasopressin receptors, only one (V1aR) appears to be involved in pair bonding.
The others mediate a huge range of other actions, from regulating urine excretion in the kidney to causing the release of stress hormones from the adrenal glands. V1aR vasopressin receptor expression is very strong in the ventral forebrain in prairie voles, but not in meadow voles.

Can we get any more specific than “ventral forebrain,” which is pretty vague? It appears that the relevant area is the ventral pallidum (VP in the figures). The ventral pallidum is one of the nuclei of the basal ganglia, which are part of the limbic system. The dorsal part of this structure is called the globus pallidus, which is Latin for “pale globe,” although nobody knows who named it or understands how it got that name, since it isn’t shaped like a globe at all. More recently, people have proposed simply calling it the pallidum. The ventral part of this structure is therefore referred to as ventral pallidum. As if this terminology weren’t arbitrary enough, the ventral pallidum lies within a structure with my all-time favorite name, the substantia innominata (which is Latin for un-named substance).

Now we have all the pieces in place to understand what Lim et al. did. (By the way, these experiments were done by Larry Young’s group at Emory University in Atlanta. Young used to be a postdoc in Insel’s lab). They used one of the molecular techniques we learned about earlier in the course, and built a virus (adeno-associated virus, or AAV) that infects cells and delivers a genetic payload encoding V1aR. By injecting the virus through a needle carefully placed at the coordinates of the ventral pallidum, they tried to cause expression of V1aR where it is not normally expressed in meadow voles (but where it is expressed in prairie voles). In other words, they tried to turn meadow voles into prairie voles. Of course, some of their injections missed the target. But the beauty of this experiment is that afterwards, they could look to see where the receptors were expressed. They used a clever trick to visualize the receptors: they took advantage of the fact that the receptors are very, very good at selectively binding to vasopressin.

So they applied radioactively-tagged vasopressin to brain slices, and then pressed the slices against unexposed film. Where the radiolabeled ligand is bound to the receptors, the radioactivity exposes the film, and you get a nice image of your expression pattern of receptors. In this way they could identify animals for which the injection missed the target. This is a nice control, because it demonstrates just how precise the V1aR expression pattern needs to be. They also used a control virus that didn’t encode V1aR. Of course, they probably would have preferred to have injections that hit the target every time. But this is a great example of taking an experimental bug and turning it into a feature.
So what did they find? After they overexpressed V1aR in the ventral forebrain of male meadow voles, they paired each male with a receptive female for 24 hours. Afterwards they ran the partner preference test, to compare how much time the males spent with the partner or the stranger. Normal meadow voles, and those with control injections, spent equal time huddling with either the partner and the stranger, and spent more time alone in the neutral chamber. But the meadow voles with the injections acted like prairie voles. They spent much more time with the partner. This is strong evidence that they had formed a pair bond.
In prairie voles, pair bonding can be blocked by pretreating them with a dopamine antagonist before pairing. This indicates that dopaminergic transmission is necessary for pair bond formation (although, since the antagonist was delivered systemically, we don’t know where the critical dopamine transmission is taking place). With the genetically altered meadow voles, pair bonding is also susceptible to dopaminergic blockers. This suggests that pair bonding in both prairie voles and transgenic meadow voles depends on dopaminergic signaling. We read last time about the role of dopamine as an error signal in reinforcement learning, which causes animals to place a high value on the states of the world that lead up to reward. The fact that pair bonding depends on dopamine suggests that reward pathways may act to increase partner preference by means of reinforcement learning. Perhaps love, in addition to being mediated by vasopressin V1aR receptors in the ventral pallidum, can also be expressed as a highly valued state that is the end product of temporal difference reinforcement learning.

HOW MIGHT THIS BE RELATED TO HUMANS?

Humans display individual variation in the gene that regulates vasopressin receptors (AVPR1A) the same as voles. So depending on the alleles that you have inherited from your parents we have different genes that result in different numbers of vasopressin receptors in our brain. The important question is whether males that have genes that have different numbers of vasopressin receptors show differences in their pair bonding behavior such as monogamy, marriage fidelity, and quality of relationships.

Lichtenstein et.al. (2008) studied males with a specific gene variant (allele 334) that causes fewer vasopressin receptors. Since these men have fewer vasopressin receptors in the brain, will they have different partner experiences?
• Men who carried two copies of allele 334 were more than twice as likely (34 percent) to report serious marital or relationship problems, such as facing threat of divorce, as men who had did not carry it (15 percent)

• Men with two copies of allele 334 were almost twice as likely to be unmarried (32 percent) as men with no copies (17 percent), despite having a long term relationship with their mate

• Women married to men with one or two copies of allele 334 reported lower scores on measures of marital quality than women married to men not carrying this allele.

• Allele 334 has also been shown to be associated with increased activity in the amygdala, a brain region involved in regulating emotions.

• 4 out of 10 men had at least one allele 334 (study done in Sweden)

Many more studies need to be done before we can make conclusive statements, but the initial study is quite interesting.