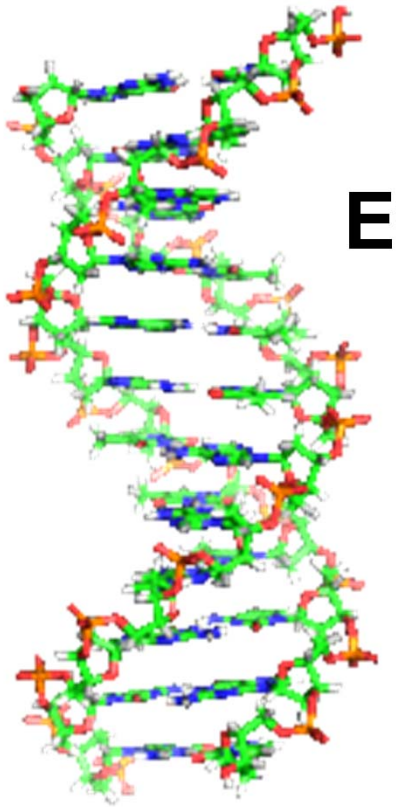
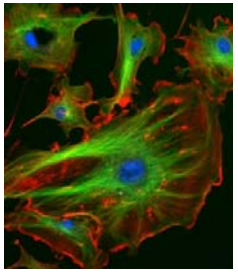


Lecture 8: From Mutation & Evolution to Behavior & Epigenetics



Section A: From Nature to Concepts

Genes & Society
LSM 1302 / GEK 1527

"Natural selection involves no plan, no goal, and no direction — just genes increasing and decreasing in frequency depending on whether individuals with those genes have, relative to other individuals, greater or lesser reproductive success."
— Randolph M. Nesse (Physician, Evolutionary Psychology & Medicine)

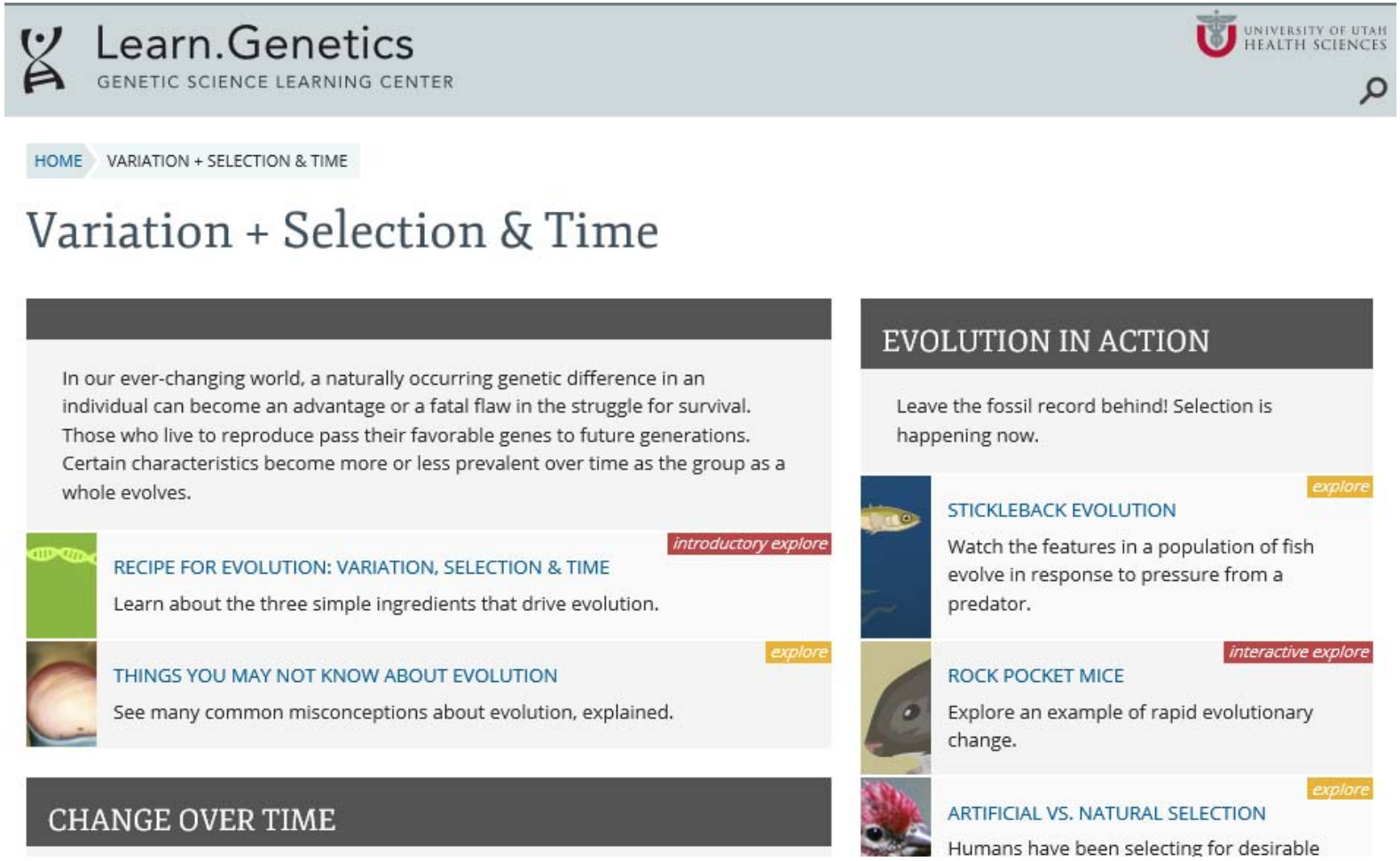
Overview

- **Mutation & Evolution, Selection and Infection**
- **Genes, Brain and Behavior**
- **Epigenetics**

"Walking to the subway, Aomame kept thinking about the strangeness of the world. If, as the dowager had said, we were nothing but gene carriers, why do so many of us have to lead such strangely shaped lives? Wouldn't our genetic purpose – to transmit DNA – be served just as well if we lived simple lives, not bothering our heads with a lot of extraneous thoughts, devoted entirely to preserving life and procreating? Did it benefit the genes in any way for us to lead such intricately warped, even bizarre, lives?

… how could it possibly profit the genes to have such people existing in this world? Did the genes merely enjoy such deformed episodes as colorful entertainment, or were these episodes utilized by them for some greater purpose?"

— in 1Q84 by Haruki Murakami, Novelist.

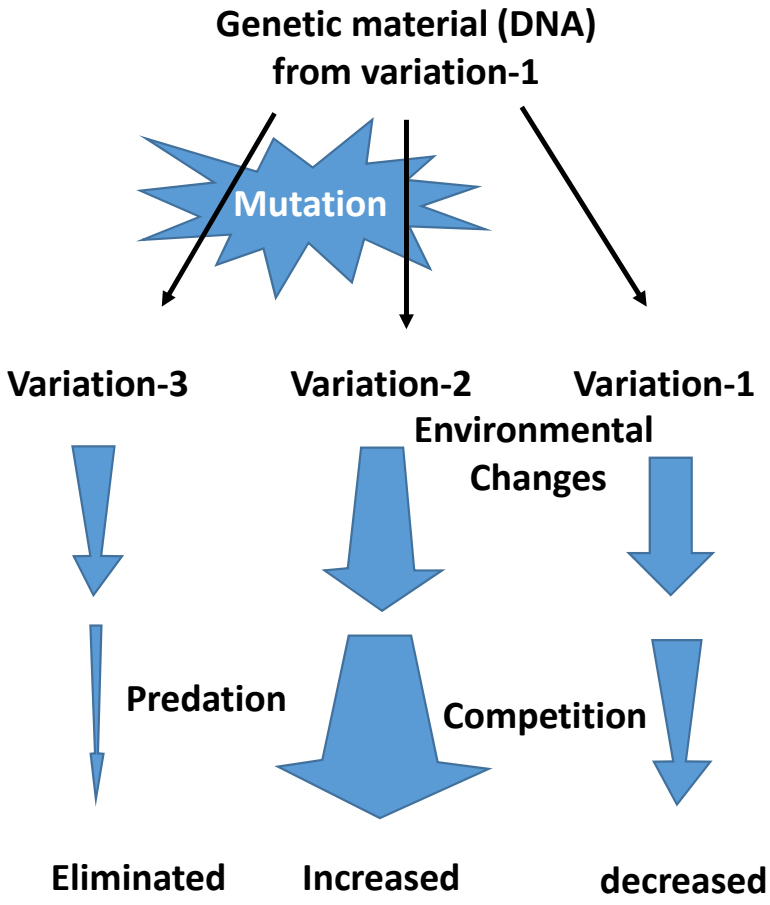


http://learn.genetics.utah.edu/content/selection/

Mutation and Evolution

Three important factors that drive evolution are **variations** (arising from mutation and recombination), **natural selection** (arising from environmental pressure) and **time**. They work together to determine which variations are successful in passing their genetic materials to subsequent generation within a certain environment over time.

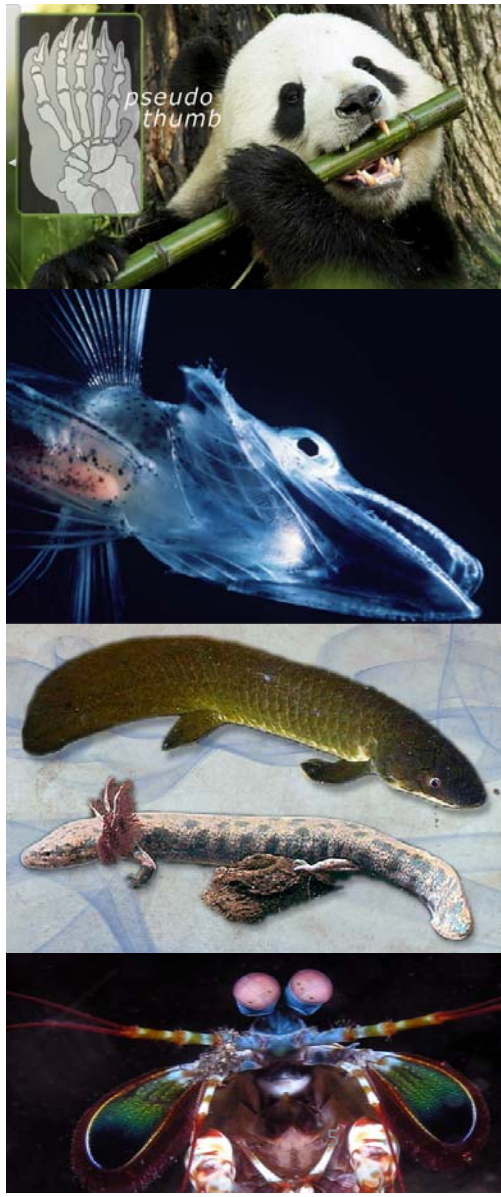
1. **Variation** is a result of recombination and mutation of genetic material (DNA/RNA). Mutations can affect the way a gene works, which may in turn cause changes in an animal's appearance, or behavior, hence producing variations.
2. **Natural selection** (e.g. competition, predation, changing environment) determines which variations will be successful to reproduce and which variations will fail. Sometimes, a new gene variant may mean the animal is better adapted to its surroundings, improving its chances of survival and finding a mate hence more likely to have offspring which therefore successfully passed on the beneficial gene variant to the next generation.
3. **Over time** individuals with the combination of genes that encode the most favorable variations will be successful in passing the genes to the next generation and increased in numbers while those with less favorable variations will be reduced in number or eliminated from the population.



Some Concepts of Evolution

1. In evolution, better is good enough, you need not be the best.
2. Evolution can only evolved from existing or available genetic structure hence do not produce entirely new (unless lost) but different structures.
3. In evolution, if you don't use or need it, you will lose it. Hence evolution can go from complex to less complex.
4. Natural selection maintains genetic elements that are necessary for survival (conservation) and eliminate harmful mutations from the gene pool. Therefore while variation arising from mutation can be random, selection of successful variation is not.
5. Evolution does not explain how life began, but rather how lives has changed and diversified over time (origin of species not origin of life)
6. Evolutionary change is not linear hence evolutionary relationship is branch-like (like tree branches) rather than a straight line.
7. Humans are not the most advanced/complex organism (depending on traits, there are organisms that are more complex/advanced, but the human brain is likely the most complex)

http://learn.genetics.utah.edu/content/selection/misconceptions/



Mutation, Selection and Infection: Social Implications

Mutation and selection of virulent factors (offensive)

- **Virus (H5N1, HINI, SARS, Nipah, Ebola virus) – cross infection from animal to human.**
- **Watch IVLE Multimedia Short Movies: West Nile Virus-Animal to Humans**

Mutation and selection of resistant factors (defensive)

- **Watch IVLE Multimedia Short Movies: Selection of Super Rats**
- **Mutation and Superbug – development of drug resistant pathogenic bacteria**

Some Protein Synthesis Inhibitors		
Inhibitor	**Cells Inhibited**	**Mode of Action**
Initiation		
Aurintricarboxylic acid	Prokaryotic	Prevents IF binding to 30S subunit
Kasugamycin	Prokaryotic	Inhibits fMet-tRNA$_i^{fMet}$ binding
Streptomycin	Prokaryotic	Prevents formation of initiation complexes
Elongation: Aminoacyl-tRNA Binding		
Tetracycline	Prokaryotic	Inhibits aminoacyl-tRNA binding at A site
Streptomycin	Prokaryotic	Codon misreading, insertion of improper amino acid
Kirromycin	Prokaryotic	Binds to EF-Tu, preventing conformational switch from EF-Tu:GTP to EF-Tu:GDP
Elongation: Peptide Bond Formation		
Sparsomycin	Prokaryotic	Peptidyl transferase inhibitor
Chloramphenicol	Prokaryotic	Binds to 50S subunit, blocks the A site and inhibits peptidyl transferase activity
Clindamycin	Prokaryotic	Binds to 50S subunit, overlapping the A and P sites and blocking peptidyl transferase activity
Erythromycin	Prokaryotic	Blocks the 50S subunit tunnel, causing premature peptidyl-tRNA dissociation
Elongation: Translocation		
Fusidic acid	Both	Inhibits EF-G:GDP dissociation from ribosome
Thiostrepton	Prokaryotic	Inhibits ribosome-dependent EF-Tu and EF-G GTPase activity
Diphtheria toxin	Eukaryotic	Inactivates eEF-2 through ADP-ribosylation
Cycloheximide	Eukaryotic	Inhibits translocation of peptidyl-tRNA
Premature Termination		
Puromycin	Both	Aminoacyl-tRNA analog, binds at A site and acts as peptidyl acceptor, aborting peptide elongation
Ribosome Inactivation		
Ricin	Eukaryotic	Catalytic inactivation of 28S rRNA via *N*-glycosidase action on A^{4256}

Table 30-10, p. 1018

New antimicrobial peptides cultivated from the horse dung

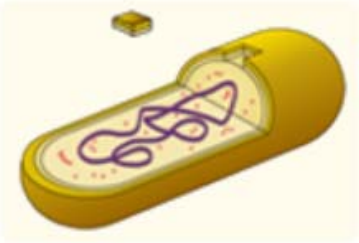
Nov 28, 2014

Copsin, a novel peptide-based fungal antibiotic interfering with the peptidoglycan synthesis. J Biol. Chem. (2014) Essig A. et al. doi/10.1074/jbc.M114.599878.

The design of new antimicrobial drugs may call for inspiration from unusual sources. In a recent study, scientists isolated a new antimicrobial peptide, named copsin, from the mushroom, *Coprinopsis cinerea*, which makes its home in piles of horse dung and other herbivores. Researcher believe the unique structure of copsin may become a scaffold for the design of new types of antimicrobial drugs.

What are the unique characteristics of its structure?

The structure of copsin is stabilized by 6 disulfide bonds, an N-terminal pyroglumate and a C-terminal cysteine. The new antimicrobial peptide was able to retain activity at a temperature of 90°C and exhibited resistance to multiple proteases. Additionally, copsin was able to effectively kill a number of gram positive bacteria such as *Enterococcus* and L. *monocytogenes* by preventing the cell wall construction.



FDA reports antibiotic resistance decreasing for select drugs

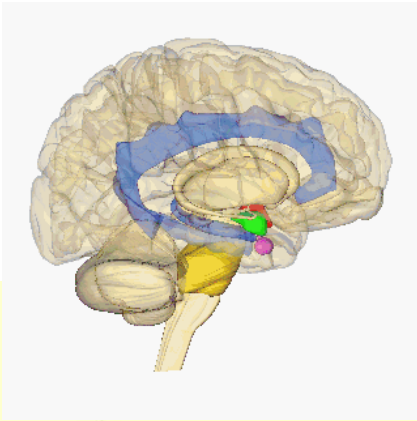
Aug 29, 2014

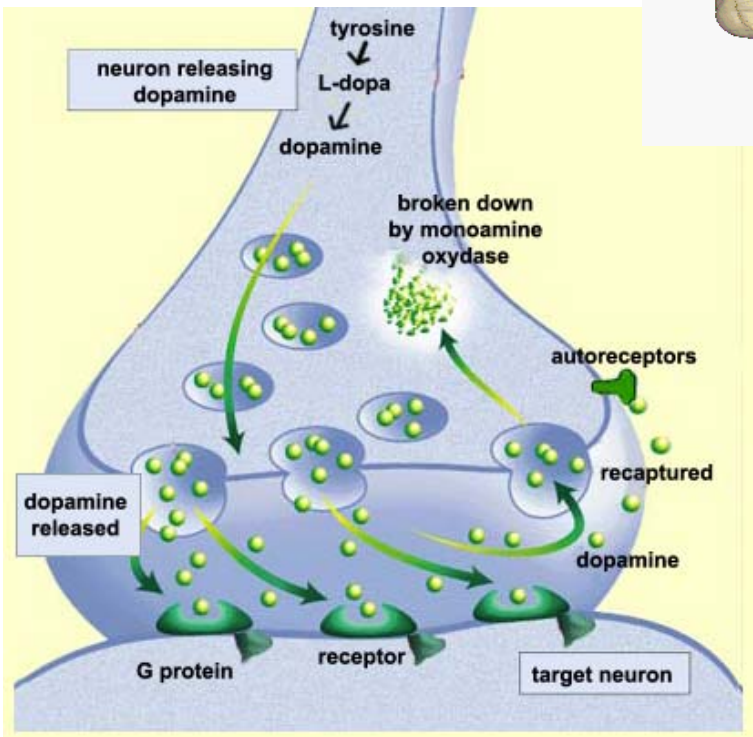
NARMS 2011 Executive Report

A recent publication on the state of antibiotic resistance provides a glimmer of hope for those trying to thwart the epidemic. The National Antimicrobial Resistance Monitoring System (NARMS), which summarizes data reported by the FDA, CDC, and USDA has released its annual report in which antimicrobial susceptibility is tested in isolates from humans, retail meats, and food producing animals. The report cites a number of common antibiotics for which resistance is on the decline including the combined resistance to ampicillin, chloramphenicol, streptomycin, sulfonamide and tetracycline (ACSSuT) for salmonella in human isolates.

Genes and brain : How genes affect behavior

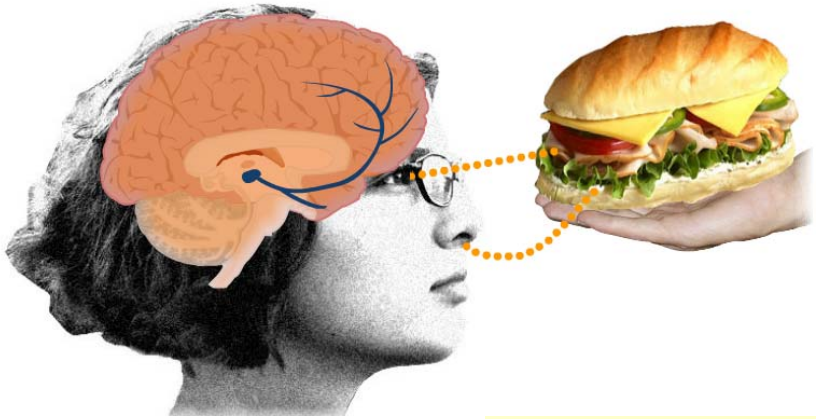
- **Neuro-messages are transmitted via electrochemical signaling involving neurotransmitters binding to neuro-receptors.**
- **Neurotransmitters are synthesized by enzymes and neuro-receptors are proteins encoded by genes.**
- **Mutation in genes (alleles) encoding enzymes involved in neurotransmitter biosynthesis or neuro-receptors can affect the levels of neurotransmitters and the activity/function of neuro-receptors, respectively.**
- **This in turn can affect transmission of neuro-signal and influence response and behavior.**





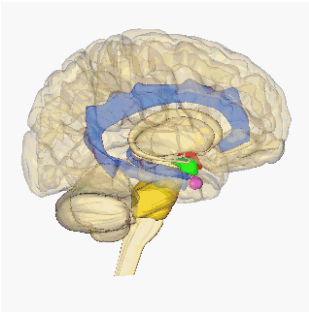
Other, more recent data now suggest that the release of dopamine can even be triggered by the environment associated with the reward, without the reward itself even having to be present! Dopamine would then be responsible for a whole set of behaviours designed to obtain the reward.

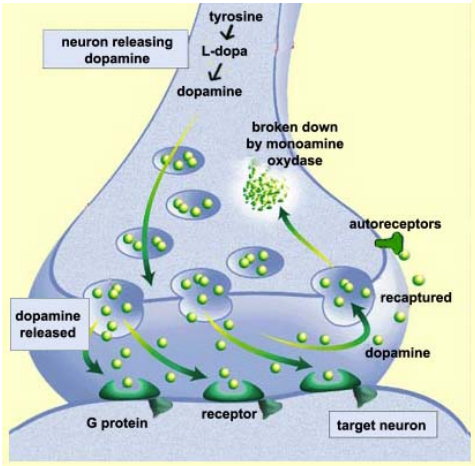
http://thebrain.mcgill.ca/flash/i/i_03/i_03_m/i_03_m_que/i_03_m_que.html

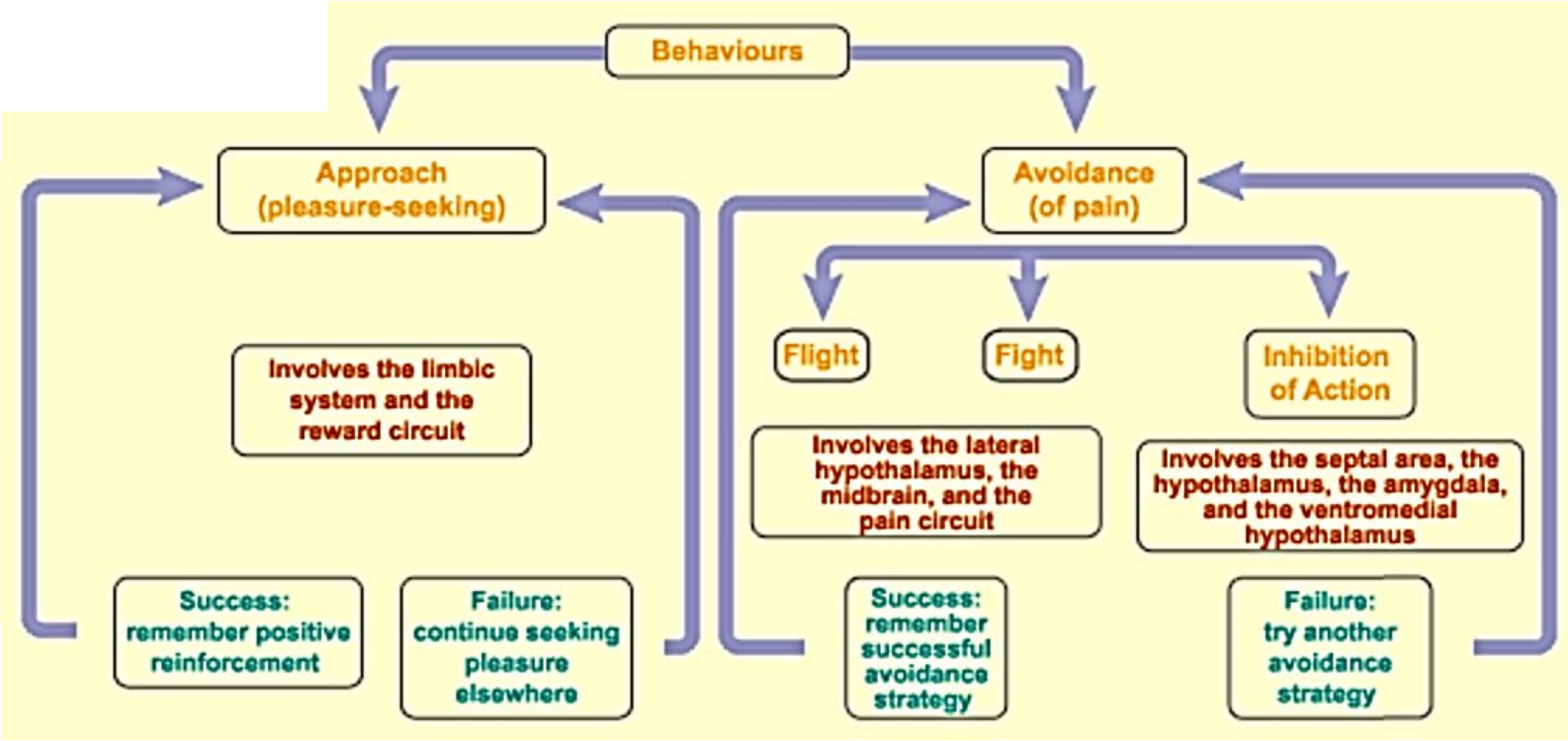


Brain and behavior

Reward Circuit reinforced positive behavior to aid survival.
Pain Circuit reinforced avoidance negative experience.



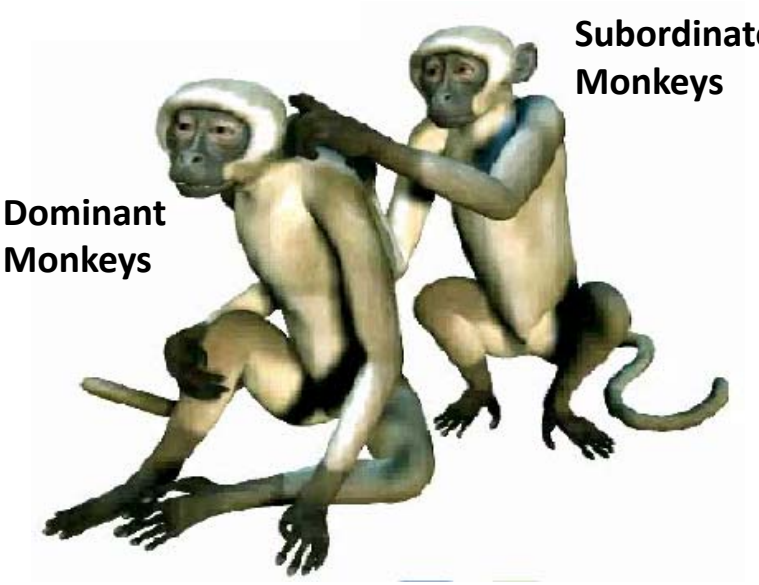


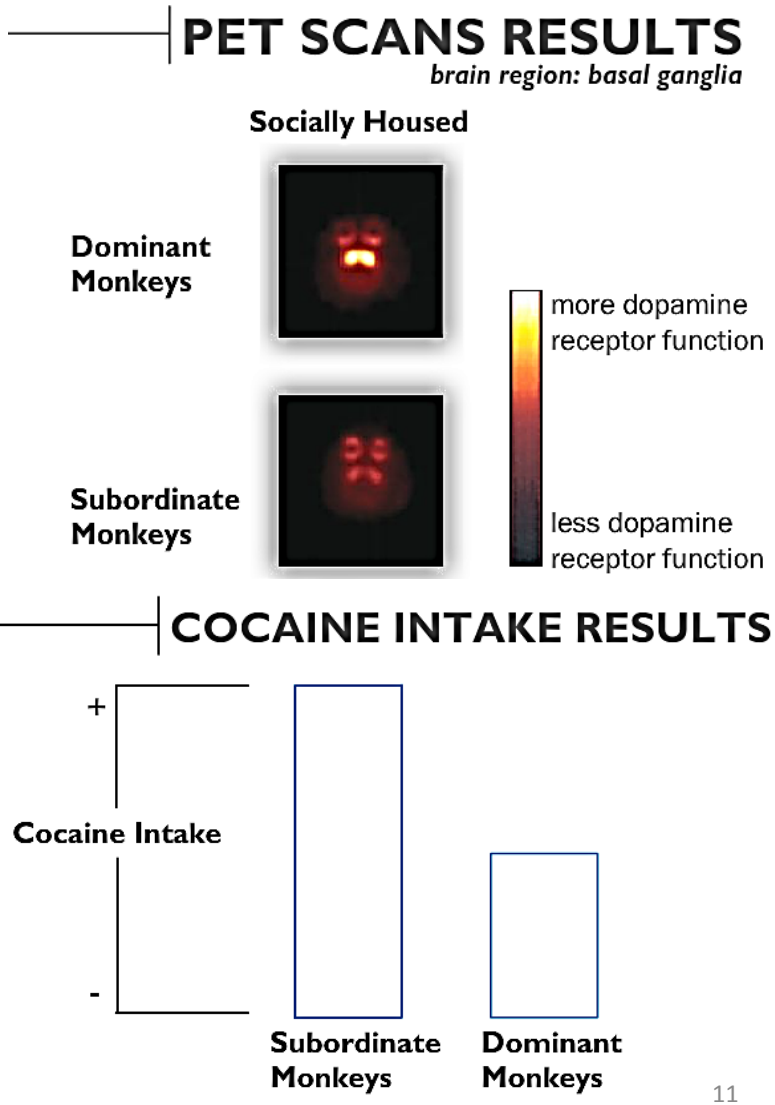


http://thebrain.mcgill.ca/flash/a/a_01/a_01_p/a_01_p_fon/a_01_p_fon.html

Social Environment Impacts the Reward Circuit

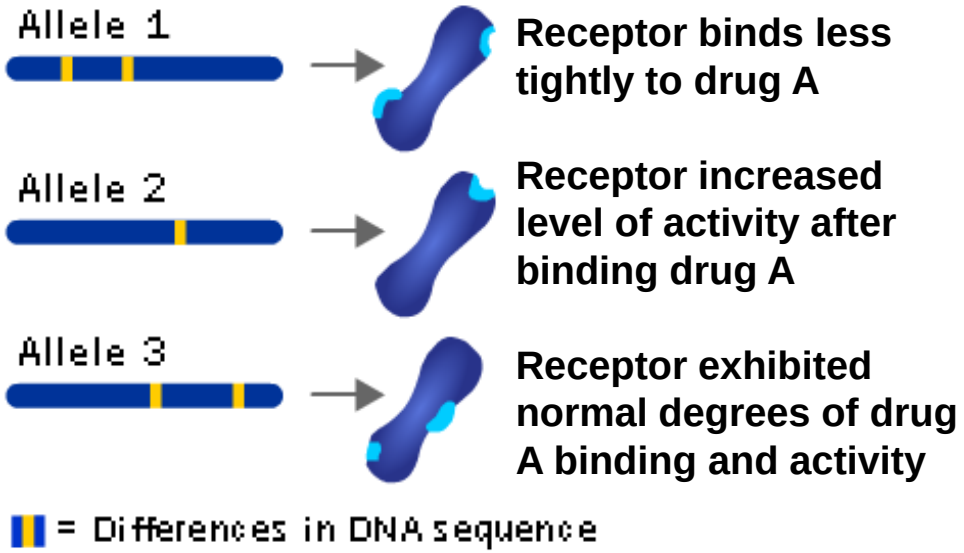
http://learn.genetics.utah.edu/content/addiction/social/

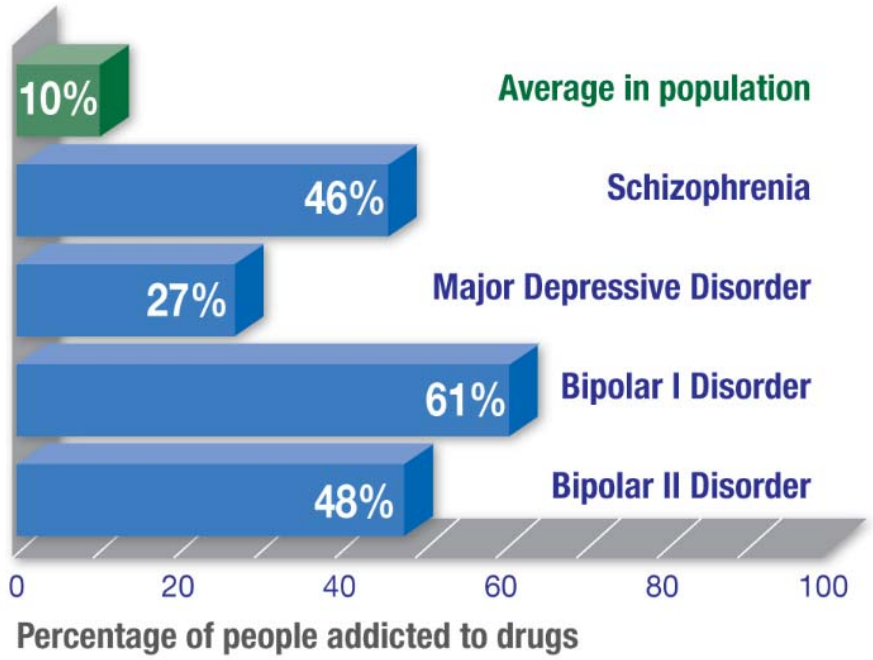




In monkeys and humans, not getting pleasure from natural activities may make drug use a more attractive alternative.

Genes & Addiction





Allele 2 is significantly more common in addicts compared to alleles 3 and 1. However, not everyone who has allele 2 is addicted, and not everyone who is addicted has allele 2, as there are other factors.

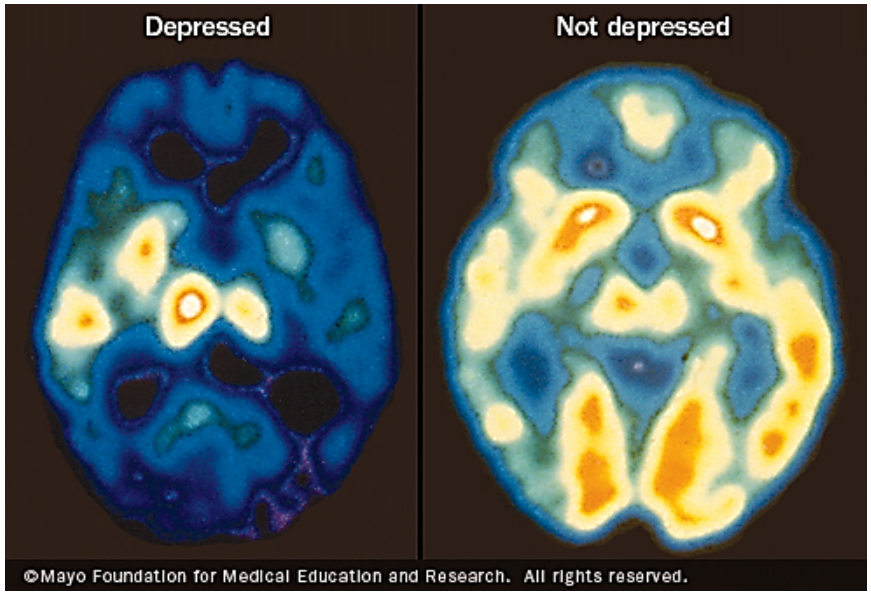
http://learn.genetics.utah.edu/content/addiction/candidate/

Mental illness and drug addiction often occur together. This condition of dual diagnosis presents a challenge to physicians. The patient has two brain diseases that influence one another, and which both need treatment.

http://learn.genetics.utah.edu/content/addiction/mentalillness/

Genes & Mental illness

A recent study reported that individuals with a particular variant of the COMT (catechol-o-methyltransferase) gene may be more likely to develop schizophrenia if they smoke marijuana regularly. As many as 1 in 4 people may have this variant.

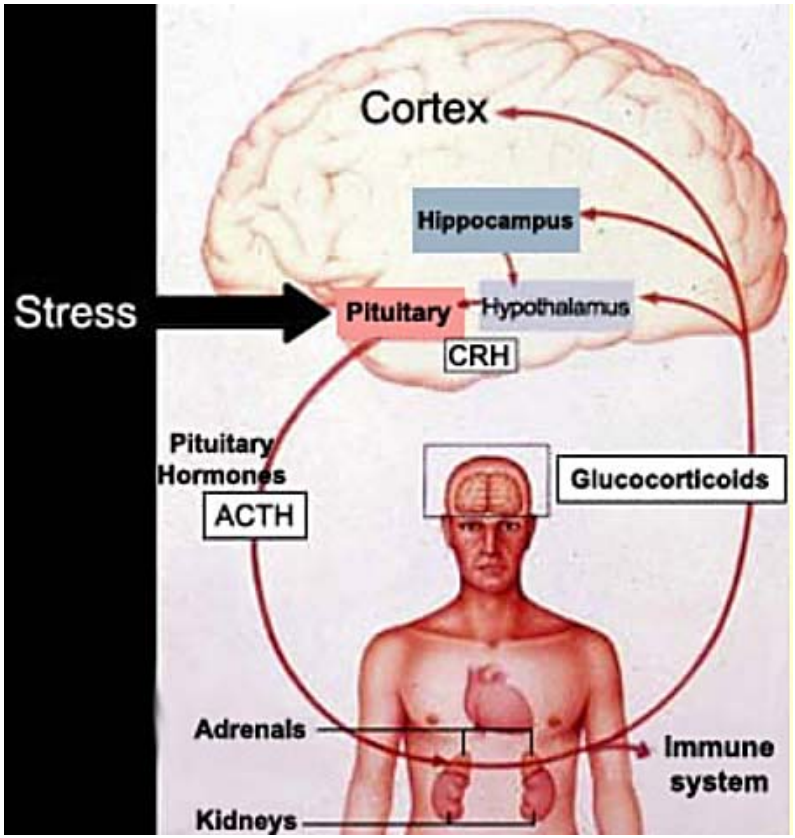


Some people have reduced serotonin function naturally, perhaps a genetic characteristic. Low brain serotonin activity in particular has been associated with a greater risk of depression and attempted or completed suicides. Sustained stress (and, among various animals, a loss of social rank) has been shown to lower brain serotonin levels. A combination of stress (tragic episodes), neuro-psychological and genetic factors may trigger depression.

http://learn.genetics.utah.edu/content/addiction/mentalillness/

http://cenitpsicologos.com/la-psicoterapia-restablece-el-cerebro-afectado-por-la-depresion/

Genes & Mental illness



http://thebrain.mcgill.ca/flash/a/a_08/a_08_m/a_08_m_dep/a_08_m_dep.html

When someone experiences a stressful event, the level of glucocorticoids in their blood rises. Via specific receptors in the hippocampus, this activates the hypothalamus, which then secretes corticotropin-releasing hormone (CRH). The CRH in turn causes the pituitary gland to release adrenocorticotropic hormone (ACTH) into the bloodstream, from which it enters the adrenal glands and causes them to secrete cortisol.

This process creates a negative feedback loop in which the excess cortisol activates the brain's glucocorticoid receptors and suppresses the production of CRH. In depressed patients, however, this loop no longer works, resulting in excess production of CRH and hence of cortisol. Chronic stress and/or a high level of glucocorticoids alters certain serotonergic receptors. Many seriously depressed patients have high blood levels of cortisol, caused by chronic stress.

Why would evolution maintain a circuit that can cause depression?

Complex social concerns with drug addiction, drug treatment of mental disorders and drug enhancement of mental performance

Peptide-based nasal spray developed for treatment of depression

April 18, 2014

Intranasal delivery of a peptide with antidepressant-like effect. Brown V, Liu F, Neuropsychopharmacology (2014) DOI: 10.1038/npp.2014.61.

In a study published in *Neuropsychopharmacology*, researchers describe a novel treatment for Major Depressive Disorder, in the form of a peptide-based nasal spray. The active peptide at the center of the treatment is an interfering peptide which disrupts D1-D2 dopamine receptor interactions.

Novel peptide enhances memory

April 4, 2014

Memory enhancement by targeting Cdk5 regulation of NR2B.Plattner et al. (2014) Neuron 81: 1070–1083.

In a study published in Neuron, researchers not only characterize elements of a neuronal signal transduction pathway that plays a fundamental role in learning and memory, they also test the application of their findings by designing novel peptides whose action on the pathway results in memory and learning enhancement in aged mice.

Ritalin is the most commonly prescribed medication for ADHD (attention deficit hyperactivity disorder). This treatment has helped thousands of people control their symptoms.

But because Ritalin is a stimulant like cocaine, it may cause undesirable changes in the brain over time. It also has the potential for abuse, and because it's a legal prescription drug, many wrongly assume that it is not dangerous. Some have taken to help focus and learning. http://learn.genetics.utah.edu/content/addiction/ritalin/

Can phenotype change and possibly inherited/passed on to the next generation without changing the DNA sequence (without mutation)?

Epigenetic Changes

- **refers to changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence, hence the name *epi-* (Greek: over; above) *-genetics*.**
- **Increased or decreased expression of genes at the wrong time and wrong place can cause abnormality to cell function.**
- **These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations.**
- **However, there is no change in the underlying DNA sequence of the organism; instead, non-genetic factors cause the organism's genes to behave (or "express themselves") differently.**

Check out http://learn.genetics.utah.edu/content/epigenetics/

Epigenetics

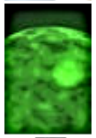
WHAT IS EPIGENETICS?

As an organism grows and develops, carefully orchestrated chemical reactions activate and deactivate parts of the genome at strategic times and in specific locations. Epigenetics is the study of these chemical reactions and the factors that influence them.

introductory video

THE EPIGENOME AT A GLANCE

Meet the epigenome and learn how it influences DNA.



interactive explore

GENE CONTROL

Change the level of gene expression in a cell with the turn of a dial!

learn more

THE EPIGENOME LEARNS FROM ITS EXPERIENCES

Epigenetic tags record the gene-regulating signals the cell receives.

learn more

EPIGENETICS & INHERITANCE

Parents have a role in shaping the epigenomes of their offspring.

EPIGENETICS & THE ENVIRONMENT

The epigenome dynamically responds to the environment. Stress, diet, behavior, toxins, and other factors regulate gene expression.

video explore

INSIGHTS FROM IDENTICAL TWINS

Why do identical twins become more different as they age? See how the environment affects the epigenome in a pair of twins over time.

interactive explore

LICK YOUR RATS

What kind of mother are you? Care for a rat pup and shape its epigenome.

learn more

NUTRITION & THE EPIGENOME

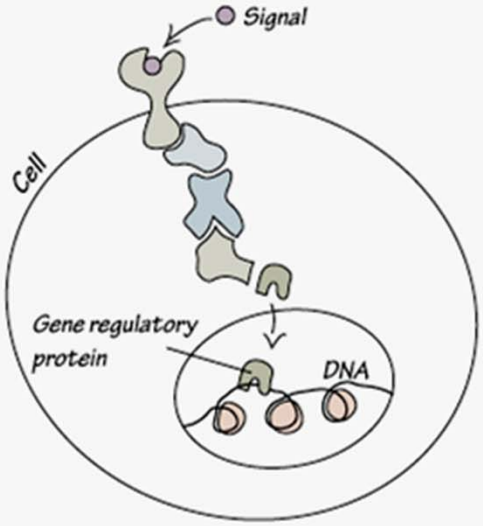
What you eat can change your gene expression.

Environmental signals can alter gene regulation through epigenetic changes

Proteins Carry Signals to the DNA

Once a signal reaches a cell, proteins carry information inside. Like runners in a relay race, proteins pass information to one another. The specifics of the proteins involved and how they work differ, depending on the signal and the cell type. But the basic idea is universal.

The information is ultimately passed to a gene regulatory protein that attaches to a specific sequence of letters on the DNA.

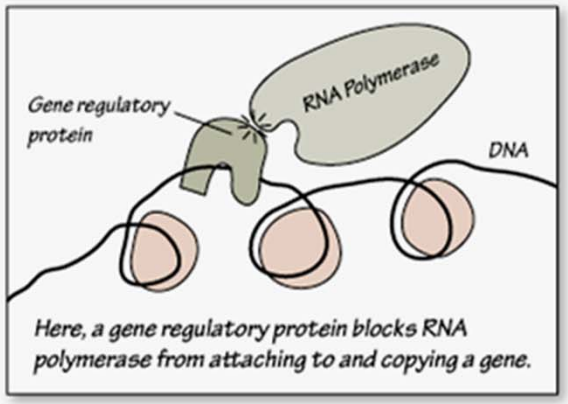


To learn more about how signals pass from protein to protein, visit The Inside Story of Cell Communication

Gene Regulatory Proteins Have Two Functions

1. SWITCH SPECIFIC GENES ON OR OFF

A gene regulatory protein attaches to a specific sequence of DNA on one or more genes. Once there, it acts like a switch, activating genes or shutting them down.

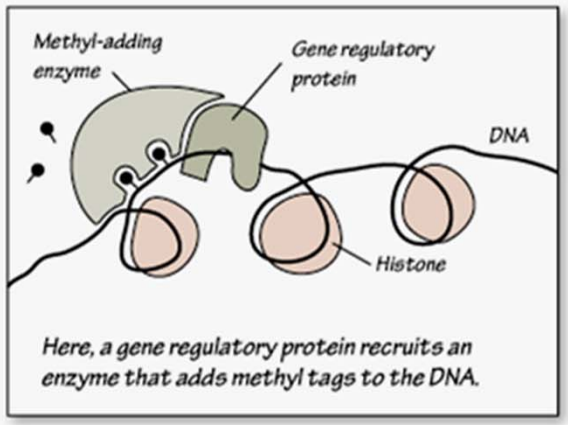


Here, a gene regulatory protein blocks RNA polymerase from attaching to and copying a gene.

2. RECRUIT ENZYMES THAT ADD AND REMOVE EPIGENETIC TAGS

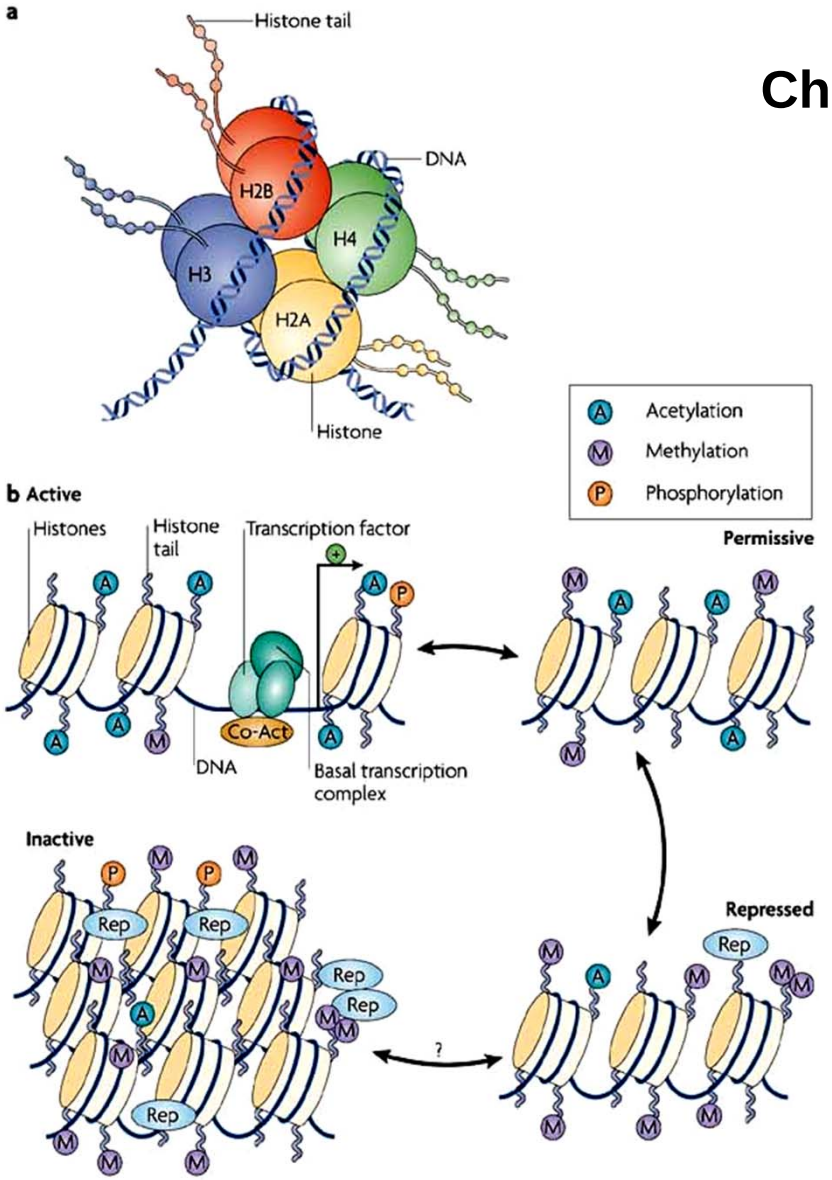
Gene regulatory proteins also recruit enzymes that add or remove epigenetic tags. Enzymes add epigenetic tags to the DNA, the histones, or both.

Epigenetic tags give the cell a way to "remember" long-term what its genes should be doing.



Here, a gene regulatory protein recruits an enzyme that adds methyl tags to the DNA.

http://learn.genetics.utah.edu/content/epigenetics/epi_learns/



Chromatin remodeling helps turn genes on & off

a. A nucleosome showing a DNA strand wrapped around a histone octamer

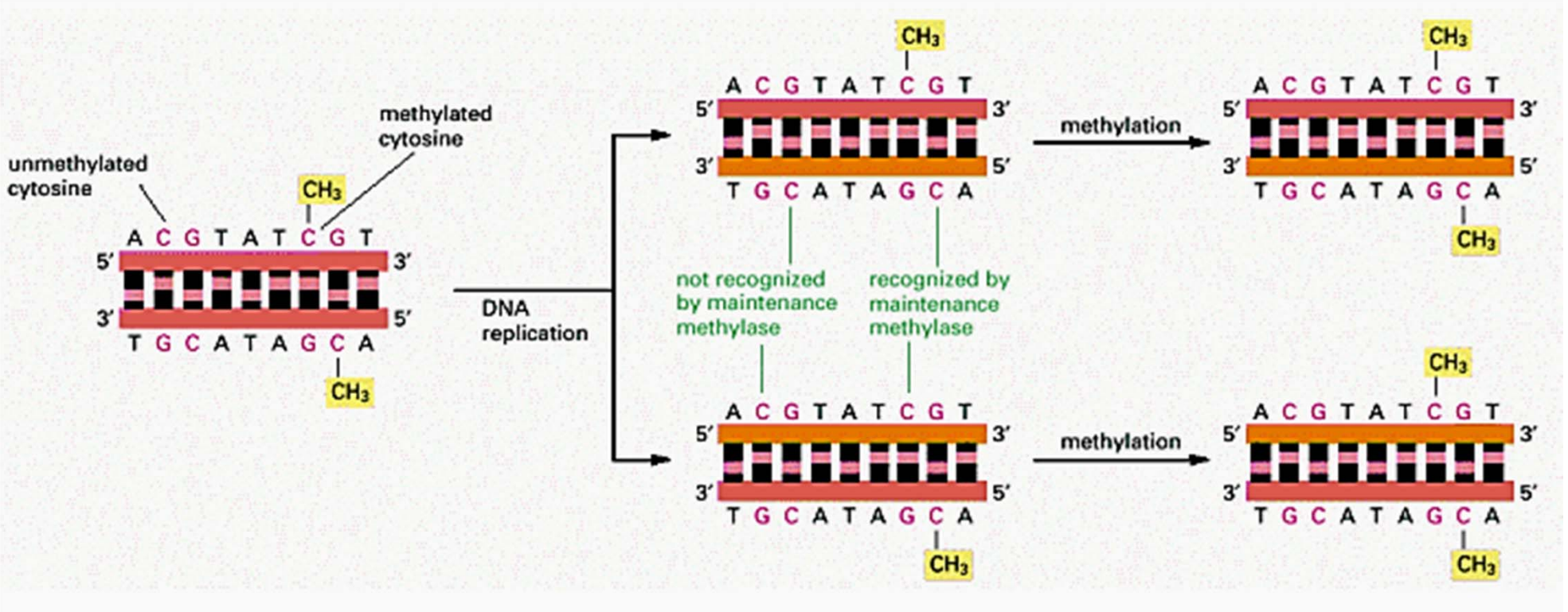
b. Chromatin can be conceptualized as existing in two primary structural states:

- as active, or open, (top left) in which histone acetylation (A) is associated with opening the nucleosome to allow binding of the basal transcriptional complex and other activators of transcription; or

- as inactive, or condensed, where all gene activity is permanently silenced (bottom left) associated with histone methylation.

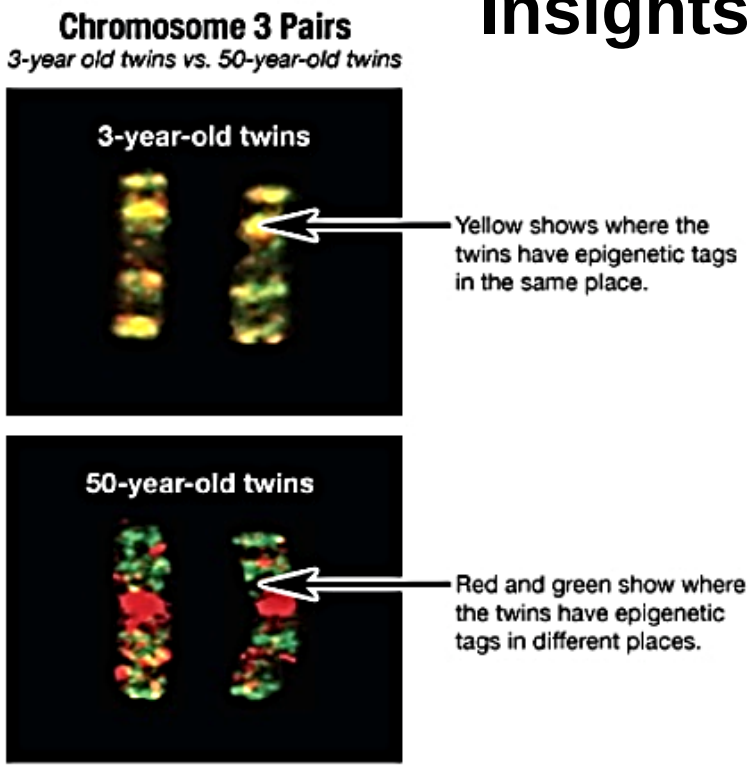
- In reality, chromatin exists in a continuum of several functional states (active; permissive (top right); repressed (bottom right); and inactive). Enrichment of histone modifications such as acetylation and methylation (M) at histone tails and related binding of transcription factors and co-activators (Co-Act) or repressors (Rep) to chromatin modulates the transcriptional state of the nucleosome.

How DNA methylation patterns are faithfully inherited.

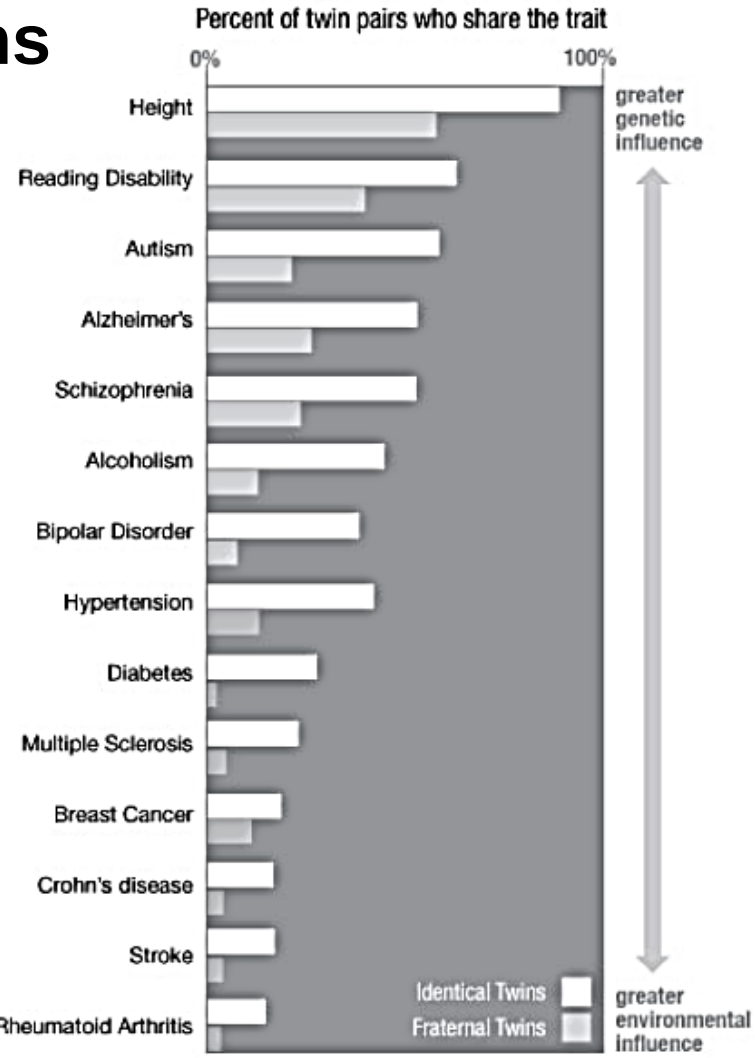


In vertebrate DNA, a large fraction of the cytosine nucleotides in the sequence CG are methylated. Because of the existence of a methyl-directed methylating enzyme (maintenance methylase), once a pattern of DNA methylation is established, each site of methylation is inherited in the progeny DNA, as shown.

Insights from Twins

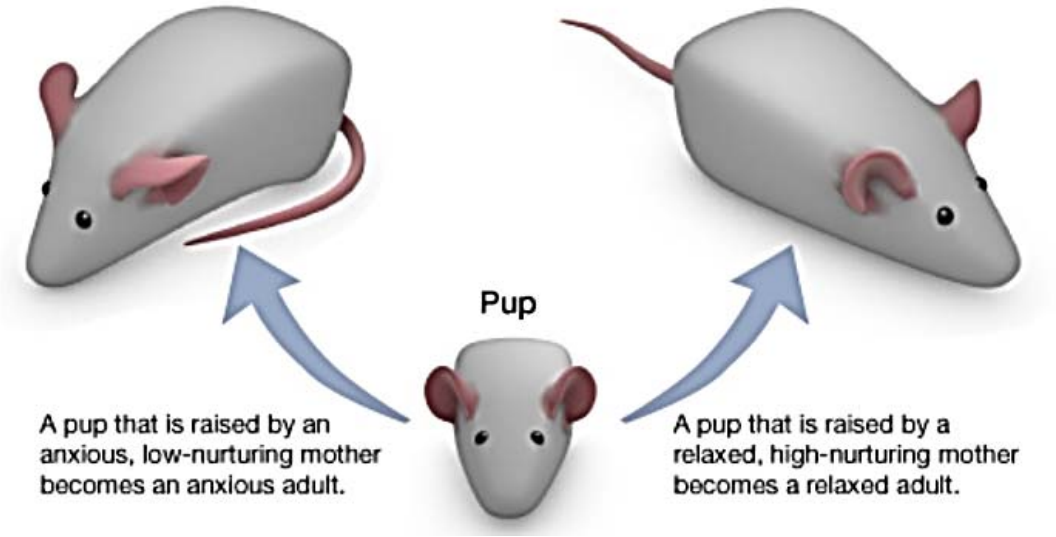


Chromosome 3 pairs in each set of twins are digitally superimposed. One twin's epigenetic tags are dyed red and the other twin's tags are dyed green. When red and green overlap, that region shows up as yellow. The 50-year old twins have more epigenetic tags in different places than do 3-year-old twins.



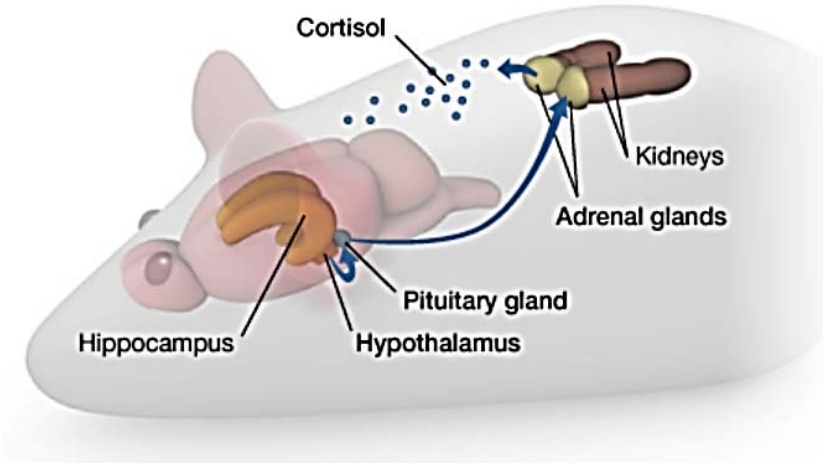
http://learn.genetics.utah.edu/content/epigenetics/twins/

Check out : Lick your rats!



High-nurturing mothers raise high-nurturing offspring, and low-nurturing mothers raise low-nurturing offspring. This may look like a genetic pattern, but it's not. Whether a pup grows up to be anxious or relaxed depends on the mother that raises it - not the mother that gives birth to it.

http://learn.genetics.utah.edu/content/epigenetics/rats/



The Stress Circuit -- also called the HPA Axis (for Hypothalamus-Pituitary-Adrenal).

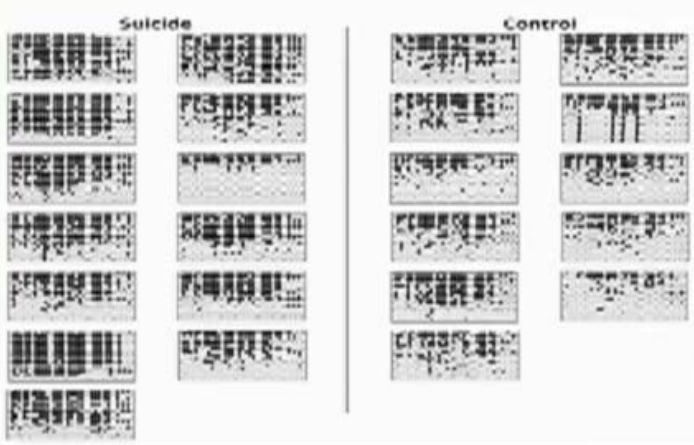
When cells in the hippocampus detect cortisol, which binds to the GR receptor, they send a signal to the hypothalamus that shuts down the stress circuit. Rats (and people) with higher levels of GR are better at detecting cortisol, and they recover from stress more quickly. Too much cortisol can lead to heart disease, depression, and increased susceptibility to infection.

Epigenetic and the human brain

Association between certain epigenetic patterns, suicide, and child abuse.

	Suicide (n = 13)	Additional Suicide (n = 5)	Control (n = 11)	Additional Control (n = 1)
Male/Female	13/0	5/0	11/0	1/0
Age (years)	36 ± 11	37 ± 11	33 ± 9	21
PMI (hours)	23 ± 6.2	23 ± 3.7	23 ± 6.4	24
pH	6.4 ± 0.2	6.6 ± 0.3	6.3 ± 0.2	6.42
Childhood Abuse/Neglect	13/13 100%	0/5 0%	0/11 0%	0/1 0%
Mood	9/13 69%	5/5 100%	3/11 27%	0/1 0%
Alcohol/drug dependence	9/13 69%	3/5 60%	5/11 46%	0/1 0%
Anxiety	3/13 23%	0/5 0%	1/11 9%	1/1 100%

The values are mean ± SD.



http://learn.genetics.utah.edu/content/epigenetics/brain/

People who commit suicide have less-active ribosomal RNA (rRNA) genes than people who die of other causes. In people who commit suicide, Methyl levels are higher on rRNA genes in a part of the brain called the hippocampus, which is important for learning and memory. More methyl means less rRNA production, which means fewer ribosomes, which means less protein production.

Child abuse is an environmental factor that leaves an epigenetic mark on the brain. In a comparison of suicide victims who were abused or not, only the abused victims had epigenetic tag on the GR gene. Interestingly, the GR gene receives a similar epigenetic tag in rat pups who receive low quality care from their mothers.

Findings and Social Implications

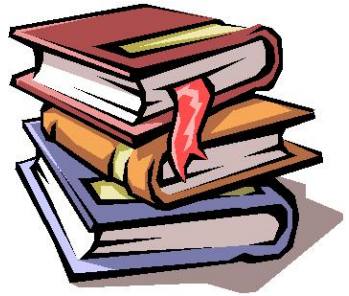
(check out for details http://learn.genetics.utah.edu/content/epigenetics/brain/)

- **Epigenetic changes can be caused by environmental or external signals. Social environment that can be affected by government policy may have affect on epigenetic changes in the population?**
- **The licking rat story tells us that through her licking behavior, a mother rat can write information onto her pups' DNA in a way that completely by passes eggs and sperm. The difference between a calm and an anxious rat is not genetic - it's epigenetic. The nurturing behavior of a mother rat during the first week of life shapes her pups' epigenomes. And the epigenetic pattern that mom establishes tends to stay put, even after the pups become adults.**
- **Child abuse is an environmental factor that leaves an epigenetic mark on the brain similar to in rat pups who receive low quality care from their mothers.**
- **People who commit suicide have less active ribosomal RNA (rRNA) genes due to higher methylation than people who die of other causes.**
- **Animal studies have shown that deficiency of methyl-donating folate or choline during late fetal or early postnatal development causes certain regions of the genome to be under-methylated for life. This can cause certain health-risk later in the adult life.**
- **Can we direct epigenetic changes for therapeutic purpose? Can these findings influence policies?**

Summary and Conclusion

- **Three important factors that drive evolution are variations (arising from mutation and recombination), natural selection (arising from environmental pressure) and time.**
- **A protein coded by a mutated gene may have harmful (associated with disease/disorder), neutral or even beneficial effects on the individual's capacity to function in the environment. Under selective pressure over a long time, this can change gene pool and contribute to evolution.**
- **Mutation in genes (alleles) encoding enzymes involved in neurotransmitter biosynthesis or neuro-receptors can affect the levels of neurotransmitters and the activity/function of neuro-receptors, respectively, hence affect transmission of neuro-signal and influence response and behavior.**
- **Mutation may cause susceptibility to addiction and mental illness. There are complex issues between drug addiction and drug treatment of mental illness as well as enhancement in mental performance.**
- **Epigenetic changes can caused phenotype change (and possibly inherited/passed on to the next generation) without changing the DNA sequence.**
- **Epigenetic changes are caused by addition/deletion of chemical tags (e.g. methyl group) on the DNA itself or the chromatin (complex of DNA, histones and non-histone proteins).**
- **Epigenome (sum total of chemical tags on the genome) is more susceptible to environmental cues than the genome, hence socio-environmental factors can caused epigenetic changes and affect individuals.**

Additional Enrichment Materials



- **Watch IVLE short movies : West Nile Virus-Animal to Humans; Selection of Super Rats; Strange Genes, Richly Tortured Minds**

Useful Weblinks:

- **Check out Variations, Selection & Time : http://learn.genetics.utah.edu/content/selection/**
- **Check out "The Science of Addiction: Genetics and the Brain":**
- **http://learn.genetics.utah.edu/content/addiction/**
- **Check out "Epigenetics": http://learn.genetics.utah.edu/content/epigenetics/**
- **Watch Short Version of "How nurture alters nature":** http://www.youtube.com/watch?v=fYMmwa2oWyQ&list=PLiIU8DltZbQoW0JXf5_YAeprl-C28y0ih&index=18
- **Long version:** https://www.youtube.com/watch?v=eS1-mz_c_GU
- **Read short article: "Is Your DNA Clock Running Fast? You May Die Sooner Than Later"**
- **Read short article: "Age-Related Epigenetic Changes Up the Cancer Risk"**