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# How Stress Produces Major Depressive Disorder

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*[www.MindMatters.ws](http://www.MindMatters.ws)*

*[www.Hippocampus.us](http://www.Hippocampus.us)*

*[www.BellevuePsychiatry.com](http://www.BellevuePsychiatry.com)*

# Conflicts of Interest Statement

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- This presentation contains many references to medications. I should note that I am neither a “pill pusher” nor a “therapy pusher.”
- Additionally, I have no financial interest in any medical supply or pharmaceutical company, nor do I accept or utilize medication samples in my practice. I do not allow myself to visit with or be influenced by drug company representatives and I receive no gifts or other benefits from any pharmaceutical company.

# Acknowledgments

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- I am not a research scientist.
- Data, concepts and other material presented in this lecture come primarily from research papers and writings that are posted on the Internet.
- I particularly acknowledge a colleague in Corvallis, Oregon, Jim Phelps, M.D., who is responsible for a very informative Web site at [PsychEducation.org](http://PsychEducation.org).

# Objectives of Presentation

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- Learn new acronyms..... heehee... CRF, HC, BDNF, SSRI, and others!
- Learn long “chemical” names like brain derived neurotrophic factor
- Understand neurotransmitter function
- Learn about significant aspects of the biological basis of major depression
- Learn about sunny, pink, and blue people

# What Major Depression is Not

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- It's not a bad hair day....
- It's not your average reaction to a minor loss, which is more short-lived.
- It's not usually part of a more major loss, or the grieving process associated with it.

# Depression as a Symptom

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- The mood of depression can exist in many disorders including:
  - Major Depressive Disorder
  - Bipolar Disorder
  - Posttraumatic Stress Disorder
  - Dysthymia
  - Adjustment Disorder
  - Substance abuse disorders
  - Other medical conditions (diabetes, hypothyroidism, Parkinson's, etc.)

# What is Major Depression?

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- Major Depressive Disorder (MDD) is described and defined in a book called the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM4).
- In the DSM4, there are several MDD Disorder categories such as single episode, recurrent, mild, moderate and severe. Severe may have psychotic features.

# What is Major Depression?

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- The diagnosis of MDD requires
  - Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either
    - (1) depressed mood or
    - (2) loss of interest or pleasure.

# 5 needed (nearly every day)

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- (1) depressed mood most of the time, most every day
- (2) markedly diminished interest or pleasure in daily activities
- (3) significant weight loss when not dieting or weight gain, or appetite loss
- (4) insomnia or hypersomnia
- (5) psychomotor agitation or retardation (observable by others)
- (6) fatigue or loss of energy
- (7) feelings of worthlessness or excessive or inappropriate guilt
- (8) diminished ability to think or concentrate
- (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

# In Addition, for MDD, Note:

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- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- The symptoms are not better accounted for by bereavement. MDD can be a result of the shock of a significant loss and is thought of as “complicated bereavement” as opposed to a “simple bereavement.” MDD symptoms that persist for about 2 months or longer and are characterized by continuing functional impairment constitute complicated bereavement.

# Serendipity and Research

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- Note: Much of what we have learned about the biological bases of depression and antidepressants originated “accidentally.”
- One early antidepressant was iproniazid (an MAOI), originally developed to treat tuberculosis.
- Then came MAOIs, tricyclics, SSRIs, and SNRIs.

# Threat Response System

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- “Flight or Fight” response to a threat
- Human threat (stressor) response:
  - The brain releases CRF (corticotropin releasing factor)
  - CRF travels to pituitary and triggers release of ACTH (adrenocorticotrophic hormone) which travels to the adrenal glands
  - Adrenal glands secrete cortisol, epinephrine (adrenaline), and norepinephrine

# Epinephrine and Cortisol

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- Epinephrine increases heart rate and stroke volume, dilates the pupils, and constricts arterioles in the skin and gut while dilating arterioles in leg muscles.
- Cortisol increases blood pressure and blood sugar levels among other things. Unlike epinephrine, it can be damaging to the central nervous system.

# The Relaxation Response

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- After a perceived danger has passed, our body attempts to return to normal. Sometimes, this is not so easy and there is evidence that it becomes more difficult with age. Although the sympathetic nervous system jumps into action immediately, it is very slow to shut down and allow the tranquilizing parasympathetic nervous system to calm things down. Cortisol can stick around longer than needed.

# CRF, Cortisol, Hippocampus

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- Perceived threats (stress) stimulate CRF. CRF not only produces the needed human emergency response by getting messages to the adrenals, but it also stimulates other parts of the brain.
- Cortisol has been shown to be directly toxic to hippocampus nerve cells.

# Cortisol Damages HC

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- Studies in rats have shown that the hippocampus of stressed rats are on average smaller and microscopic examination reveals that there are far fewer dendrites and synapses than normal.

# Importance of HC

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- Hippocampus (HC) helps with:
  - Consolidation of new memories
  - Processing emotions, especially emotional memory
  - Navigation
  - Spatial orientation

# Emotion and Memory

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- Emotion and memory are closely related. For instance, after going to a party, whose faces do you remember most? The person who made you laugh, made you embarrassed, complimented you, etc. -- in other words, the ones that had an emotional impact.

# Known HC Damage

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- In Alzheimer's disease -- one of the first regions to suffer damage resulting in memory problems (especially new memory) and disorientation.
- Evidence shows that the hippocampus in chronically depressed humans and depressed rats is damaged.

# HC's Home -- Limbic System

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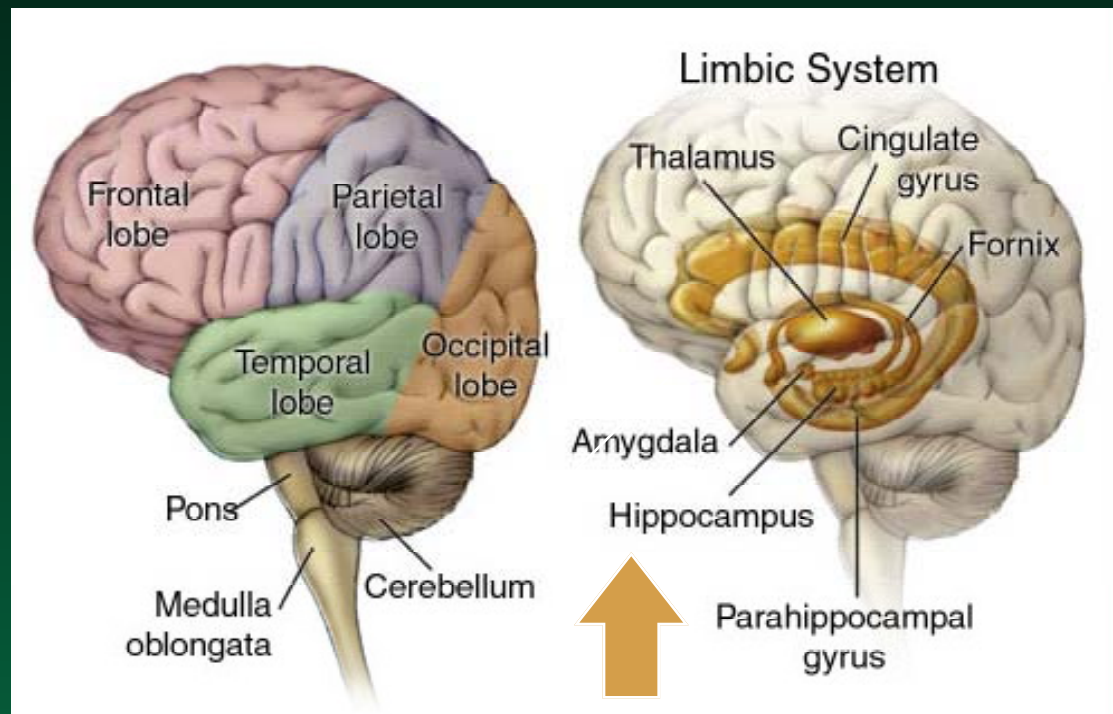
- The limbic system (sometimes called the emotional system) includes the structures in the human brain involved in emotion, motivation, and emotional association with memory.
- Limbic system “old” part of brain, in all mammals and many reptiles

# Some Limbic Components

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- Amygdala: Involved in aggression, jealousy, and fear
- Cingulate gyrus: Autonomic functions (heart rate, blood pressure), cognitive and attentional processing
- Hippocampus: Required for formation of long-term memories (emotional memories)
- Hypothalamus: Regulates autonomic system (blood pressure, heart rate, hunger, thirst, sexual arousal, and sleep/wake cycle)
- Nucleus accumbens: reward, pleasure, addiction
- Parahippocampal gyrus: formation of spatial memory
- .... and there is more... skip for now...

# Limbic System and HC



The brain has two hippocampus areas just inside each temporal lobe on each side of the brain. Together they are the hippocampus.

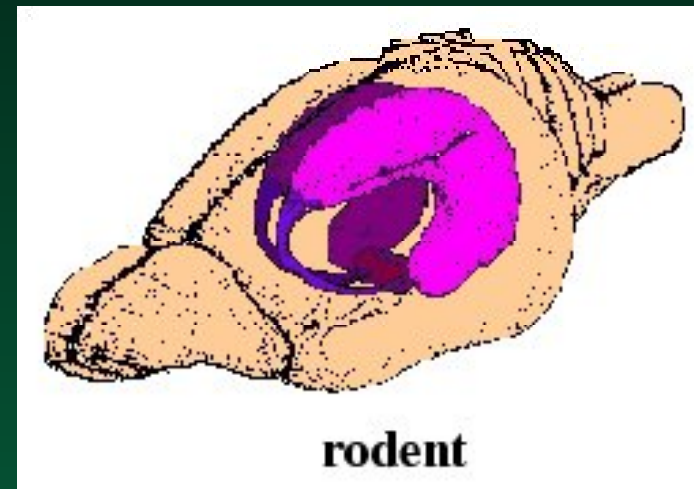
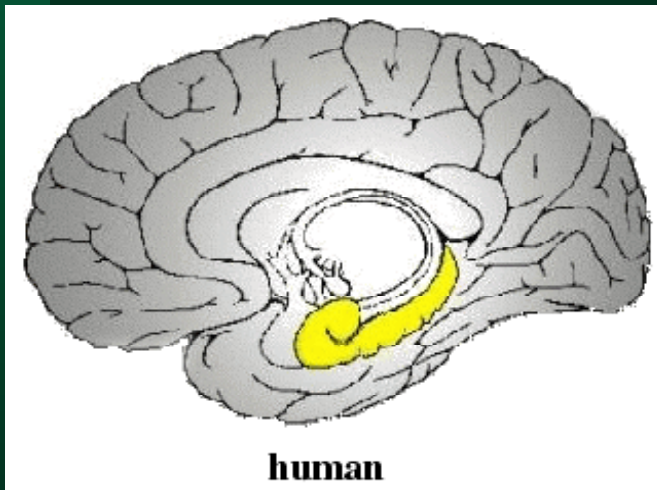
# Lobotomy Evidence

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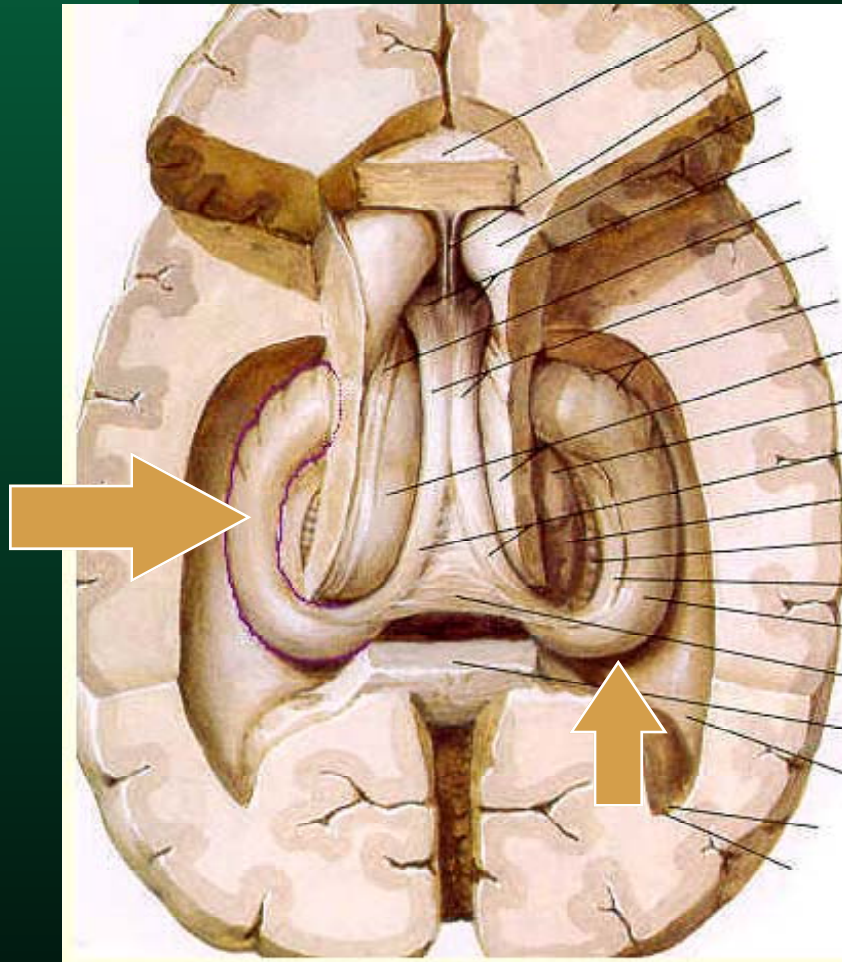
- Limbic system is tightly connected to prefrontal cortex. A very outdated method to cure severe emotional disorders, the “lobotomy,” was a surgical procedure that severed the connection. Post-operative patients often became passive, lacking all motivation. Many scientists concluded the limbic connection to the cortex produces the pleasure humans obtain from solving problems (a very human trait).

# Human & Rat Hippocampus

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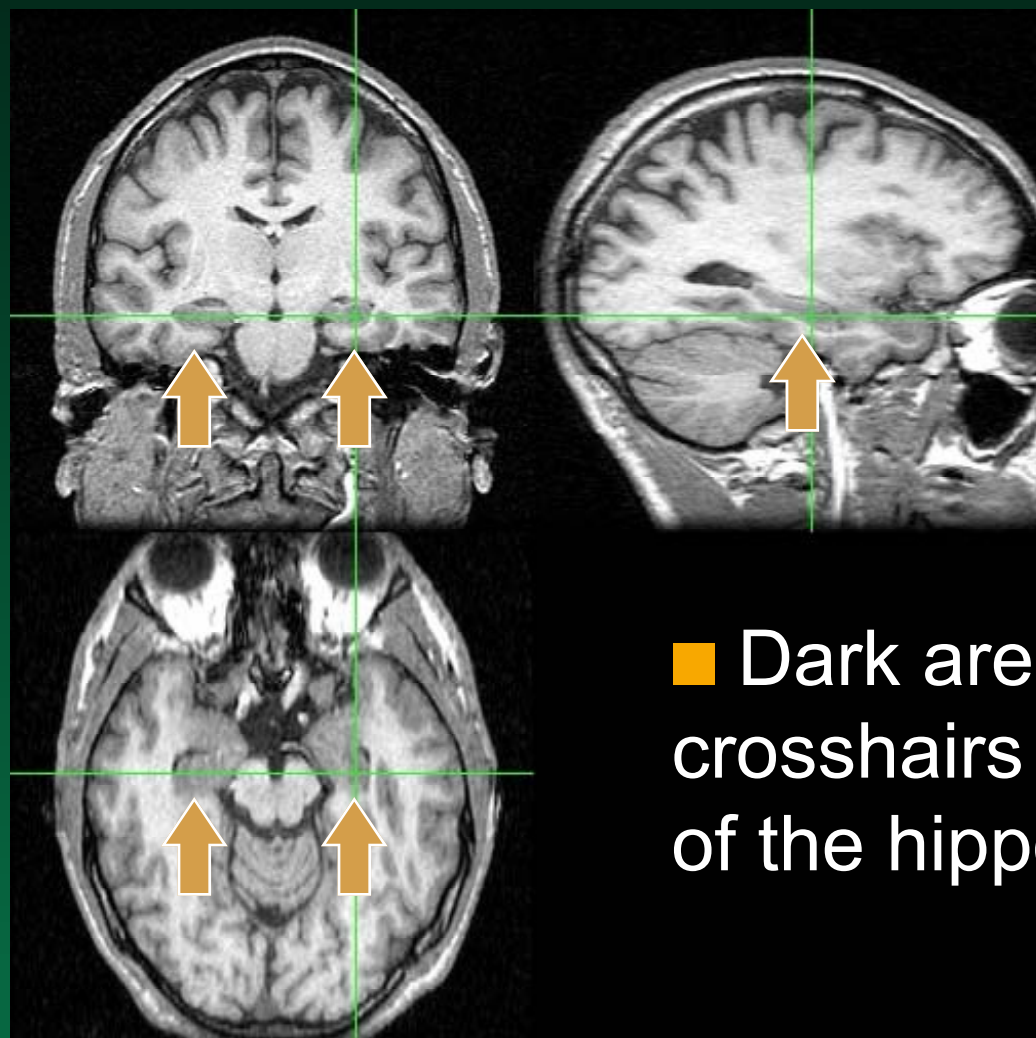


# Dissection Showing Bilateral HC



- There are two HC structures -- one on each side of the brain, just inside the temporal lobes. Together they are the hippocampus. (This view is looking down into the brain from above.)

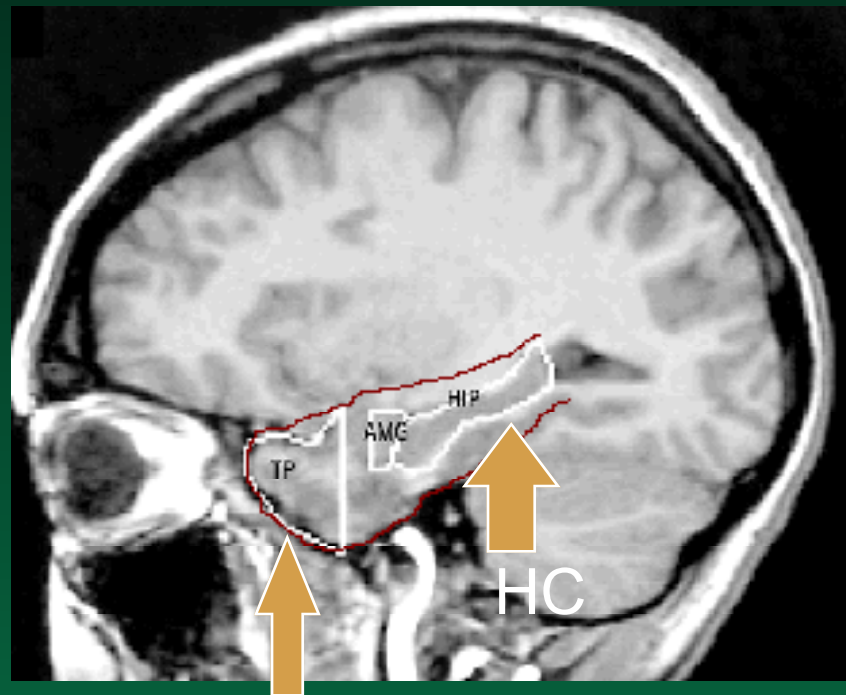
# MRI - 3 Views of HC



- Dark areas at green crosshairs are the body of the hippocampus

# MRI -- Temporal Lobe, HC

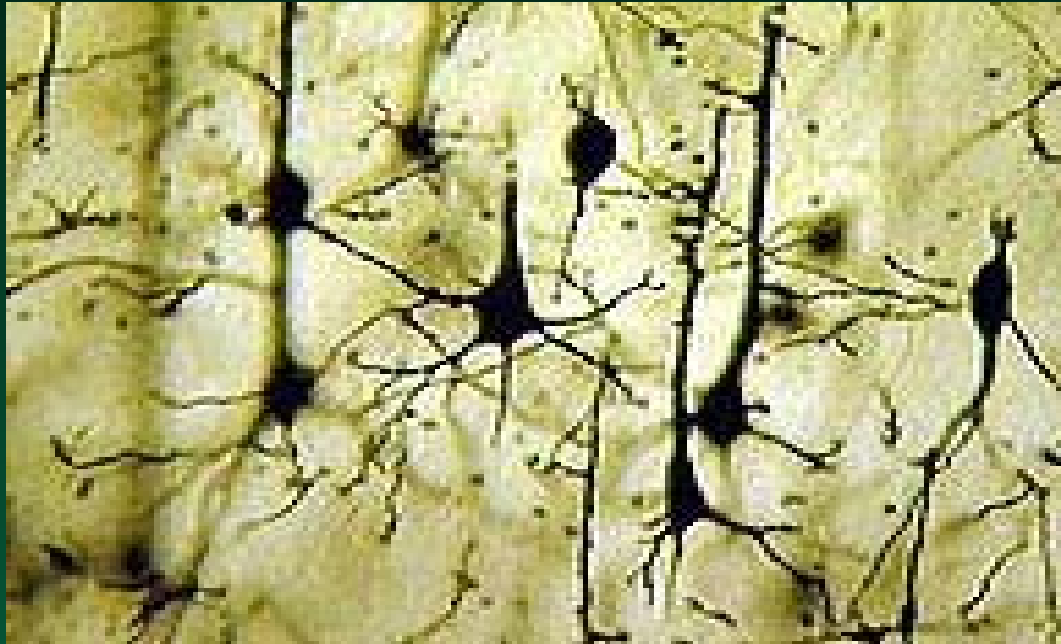
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Temporal lobe outlined in red

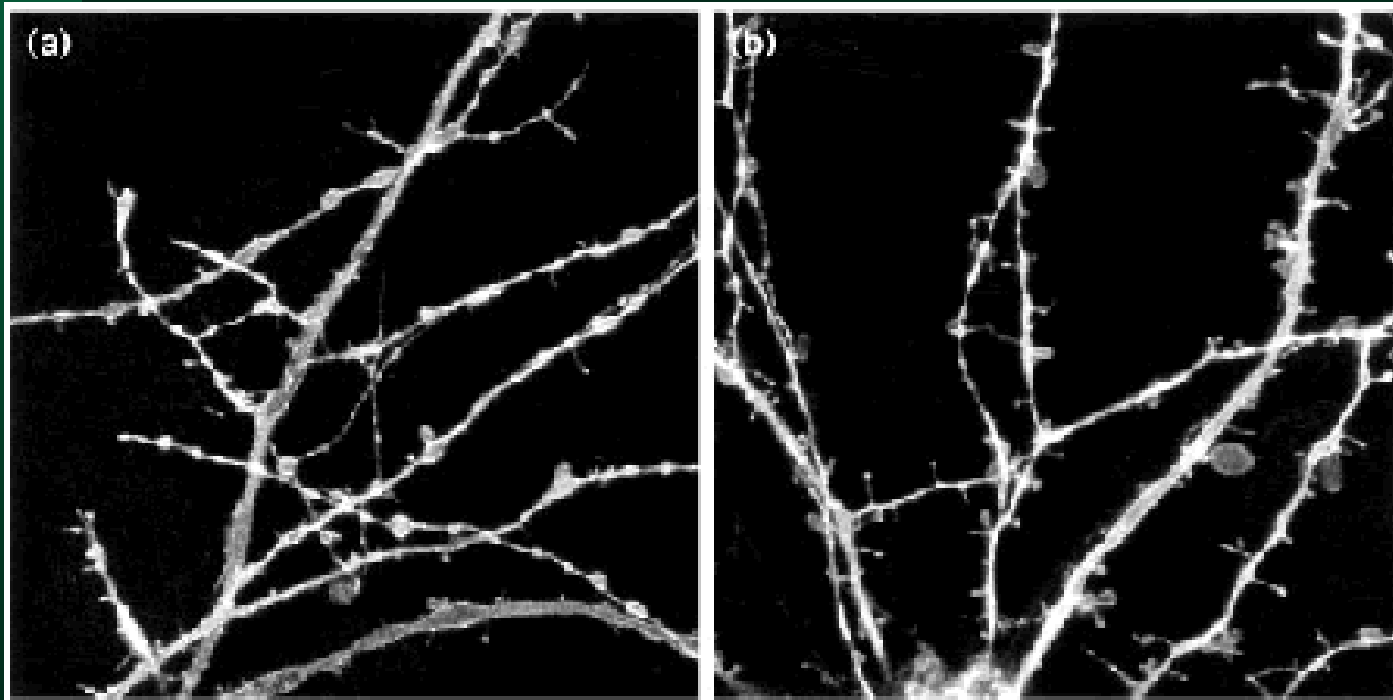
# Neurons, Axons, Dendrites

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A neuron has a cell body with a central area (the large bulb) with larger stems which are called axons and there are branches from both the body and the axons called dendrites. Synaptic areas where nerve cells connect to each other can be found mostly on the dendrites.

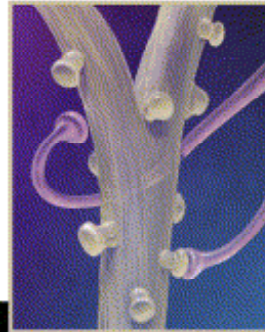
# Dendrites -- before and after



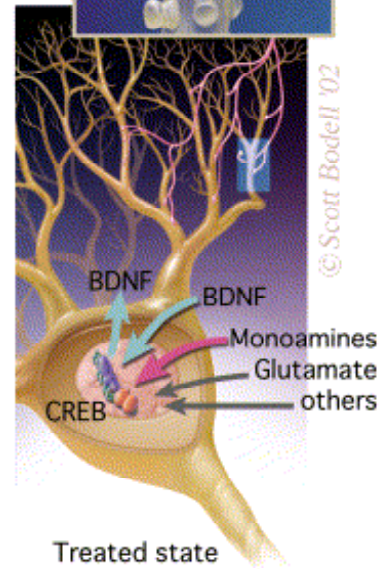
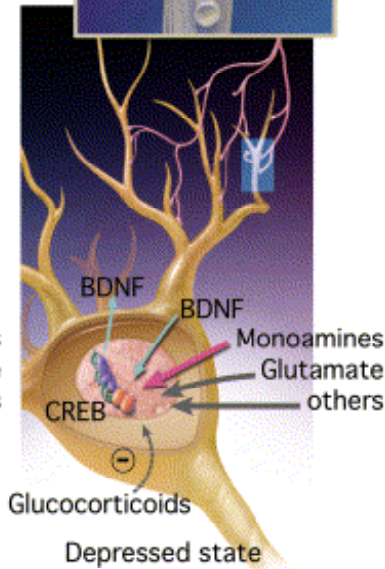
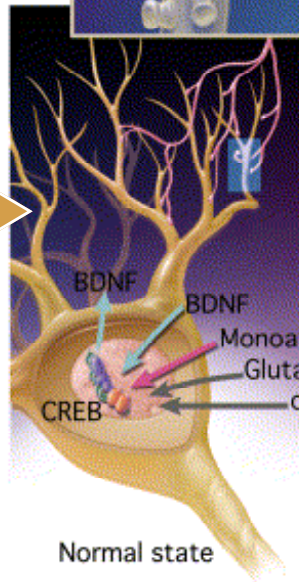
Picture of rat hippocampus dendrites, before and after. The right picture shows more spikes or buds off of the dendrites. This is from a research study of estrogen effects on rat hippocampus dendrites.

# Dendrites and Synapses

Synapses



Dendrites



© Scott Bodell '02

# Vulnerability to CRF, Cortisol

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- Some people are more vulnerable to stress than others
- Some rats are more vulnerable to the stress than others
- We can study the rat hippocampus much more easily. What do we know?

# Rats, Prozac, and Exercise

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- You can't stress damage the hippocampus of a rat on Prozac
- You can't stress damage the hippocampus of a rat who gets consistent exercise
- You can repair a damaged rat hippocampus with Prozac
- Not clear if exercise alone can repair a damaged hippocampus

# How does repair take place?

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- The hippocampus is one of the very few parts of the brain where nerve cells can repair and regrow (neurogenesis)
- Repair can be stimulated by many antidepressants (not just Prozac) but no other medications that we yet know
- Repair is mediated by an intracellular hormone called brain derived neurotrophic factor (BDNF)

# BDNF

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- Discovered during neural development studies in animals
- Assists survival of existing neurons, and encourages growth and differentiation of new neurons and synapses
- Known to be higher in rats who are given Prozac or who exercise consistently
- Lower in humans with MDD
- Protects hippocampus nerve cells from damaging effects of CRF and cortisol

# BDNF -- Vulnerability Factor?

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- High BDNF produced by ingestion of Prozac or exercise protects against stress-related damage
- Individual variation of BDNF may be one key to understanding why some people are more vulnerable to stress-induced hippocampus damage (MDD)

# CRF Cortisol Dysfunction Exists

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- Early trauma such as abuse leads to apparent permanent changes
  - Increased number of CRF neurons are produced
  - Hypersensitive and increased CRF and cortisol responsiveness
  - Thus, even mild stress can lead to exaggerated CRF and cortisol responses
  - Chronic exposure to above-normal cortisol levels leads to hippocampus damage
  - Hippocampus damage positively correlated to MDD

# What About Serotonin?

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- As you may know, Prozac and many other modern antidepressants are called SSRIs - Selective Serotonin Reuptake Inhibitors
- They increase serotonin in spaces outside nerve cells by preventing nerve cells from reabsorbing the serotonin
- Nerve cells produce their own serotonin (mostly in synaptic areas)
- It is a neurotransmitter

# What is a Neurotransmitter?

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- It is a chemical bridge between nerve cells
- It relays, amplifies and/or modulates electrical signals between a neuron and another cell, usually another neuron (nerve cell)
- Many types of neurotransmitters
- Very specialized and often located only in certain parts of the brain
- Serotonin concentrated in limbic system

# Types of Neurotransmitters

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- Serotonin - memory, emotions, wakefulness, sleep and temperature regulation
- Norepinephrine - wakefulness or arousal
- Dopamine - voluntary movement and emotional arousal
- Acetylcholine - voluntary movement of the muscles
- ... and there is more... skip for now...

# Neurotransmitter Pathways

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- Diseases may affect specific neurotransmitter pathways. For example, Parkinson's disease is at least in part related to failure of dopamine producing cells to produce dopamine in the substantia nigra. Treatments which increase dopamine can alleviate some symptoms (but have many side effects because not all the “ingested” dopamine gets into the nerve cells)

# “Reuptake” - What is it?

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- Once a neurotransmitter transmits the electrical signal from one neuron to the next neuron(s) it is reabsorbed by the surrounding nerve cells so it can be recycled and so it quits transmitting
- For serotonin, the system is called the Serotonin Transporter System
- There are two genes that control the Serotonin Transporter

## 2 versions of transporter gene

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- Long gene and short gene
- Long gene has more potent manufacturing signal -- in other words, it tells serotonin producing nerve cells to make lots of it. The short gene is not as powerful.
- This leads to three groups of people -- yellow ["sunny"] (two long genes), pink (one long, one short) and blue (two short)

# Sunny, Pink, Blue... hmmm..

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- Research shows that it takes a lot of stress to depress a sunny person (two long genes) and not as much to depress a pink or blue person
- Obviously, if you don't produce serotonin well, you won't have it available to process information with -- transmissions will break down, chemical bridges will be out

# Do Meds Fix Low Production?

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- Probably not.
- So, why does putting a lot of serotonin in the space between limbic nerve cells help? Wouldn't that just confuse neurons? -- Disorganized, chaotic transmission, rather than targeted?
- It does -- many side effects of SSRIs probably relate to that situation

# So, What do SSRI Meds Fix?

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- Most significant - many antidepressants (not just SSRIs) increase BDNF levels
- Increased BDNF repairs, grows, and protects neurons from stress damage AND create more dendrites/synapses (increased sites of serotonin production)
- Probable reason why SSRIs don't produce significant changes for many weeks or months (repair is slow).

# BDNF and Production Probs

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- The Serotonin production system is controlled by genes -- you either have good or poor production
- However, nerve cells produce most of their serotonin in dendritic (synapse) areas of neurons
- Guess what, BDNF increases dendrite and synapse density, so, production is increased by having more sites for production (inefficient but numerous)

# Medication for MDD

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- Making the right choice is complex process. I can't cover all aspects in one presentation.
- It used to be that we thought the significant action of an SSRI, like Prozac, was to increase serotonin levels -- a good thing, but if so, why didn't symptoms improve more rapidly? Now we know... repair takes time.

# Role of Psychotherapy?

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- Can you think yourself out of a major depression? Probably not. It's like being in a hole where more work produces more stress which then produces more damage (used to be treatment consisted of long vacation at local sanitarium or similar)
- Understanding dynamics of MDD is important -- psychoeducation

# Role of Psychotherapy?

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- Once MDD is appropriately being treated with appropriate medication (no mean task), then work on learning how to reduce perceived stress (BIG role for psychotherapy!)
- No MDD yet? If strong family history, psychotherapy might be very important unless you just want to deal with the MDD when it arrives with medication

# Risk of Waiting for MDD

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- When it arrives, it can be lethal
- When it arrives, it can really cause lots of problems -- financial, marital, you name it...
- Prevention, as they say, is 9/10ths of the law (or is that possession?)... well, you know what I mean. A stitch in time saves nine...

# Conclusions

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- Likely that individual baseline BDNF is genetically determined (vulnerability)
- Low baseline BDNF may determine higher vulnerability to stress-induced hippocampus damage (MDD)
- Fix baseline vulnerability to stress damage by increasing BDNF (several antidepressants and exercise do it)

# Conclusions

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- Serotonin production system has significant genetic control -- sunny, pink, and blue people
- Don't have a way to increase efficiency of production but have a way to increase sites of production
- Lots of serotonin in space between neurons creates side effects (must be tolerated to get the desired effect -- increased BDNF)

# The End. Some Books?

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- Since much of this information is from recent research, a lot of it is not showing up in books yet, except profession-related textbooks.
- Your best bet is to search at Amazon.com using “neurobiology of depression” and choose the most recent books.