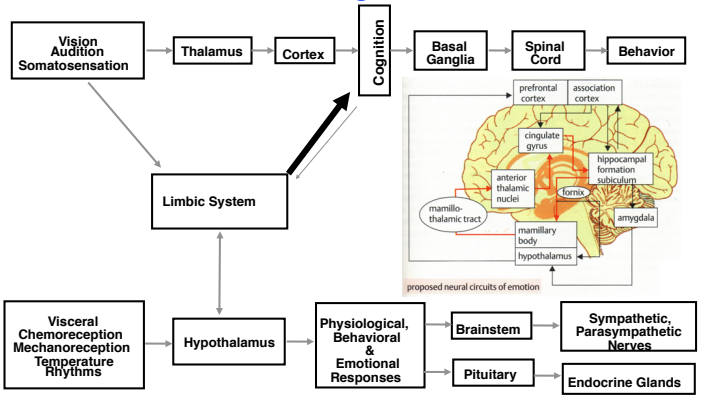
Depression

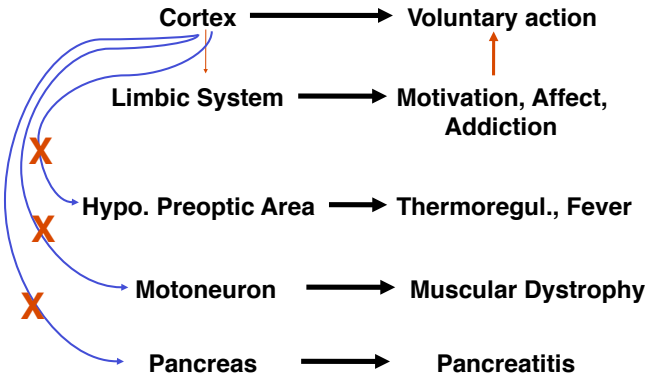
1. Definition and Relevance of Depression
2. Theories of Basis for Depression: Genetic, Monoaminergic, Stress
3. Antidepressant Treatments and their Mechanisms of Action
4. Animal Models of Depression
5. Bipolar Disorder

Example of depression as pathology and plasticity within the limbic system.

Limbic System as mediator between Visceral Neuraxis and Cognitive Neuraxis

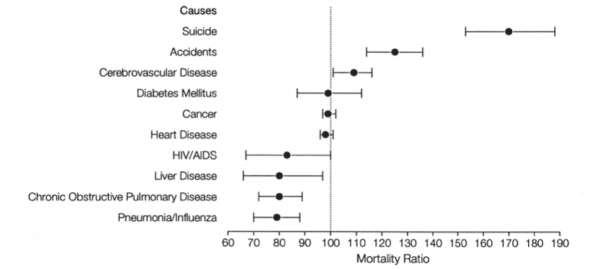


Mental Illness and "willpower" Is depression treated as a disease?



Increased Rate of Suicide in MDs (JAMA 6/18/03)

Figure. Proportionate Mortality Ratio for White, Male Physicians vs White, Male Professionals, 1984-1995



HIV indicates human immunodeficiency virus. *International Classification of Diseases, Ninth Revision*. Error bars indicate 95% confidence intervals. Data from Frank and Dingle.[32]

Epidemiology of Depression (JAMA 2003)

Structured interview of 9000+

Incidence of depression in US:

16% of population have major depression during lifetime

7% for 12-months or more

Socioeconomic status:

below poverty line: same lifetime risk, but 4x risk of 12-month episode.

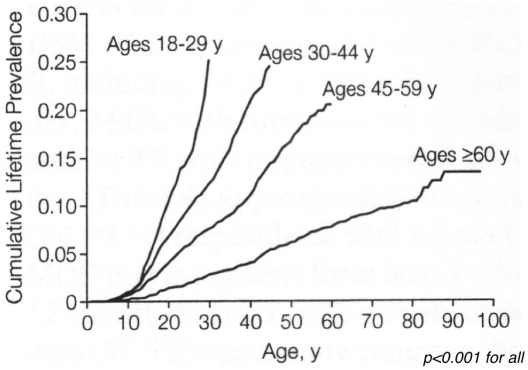
Co-moridity with:

psychiatric disorders, cardiac disease, stroke, HIV

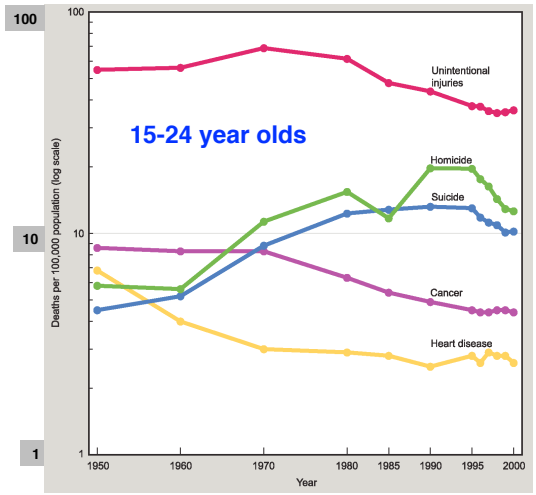
Risk factor for:

HIV progression, heart disease, overall mortality, etc

Cumulative Lifetime prevalence of Major Depression by Birth Cohort



p<0.001 for all



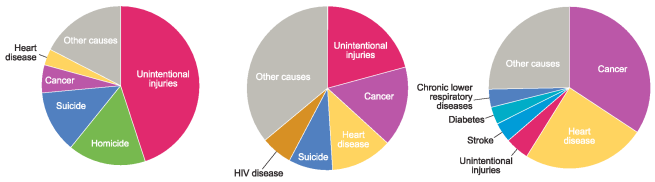
Infant mortality
3000 -> 500 per 100,000

Teen Heart Disease
8 -> 3 per 100,000

Teen Suicide
4 -> 10 per 100,000

"Health, United States 2003", HHS

Suicide: a Major Fatal Disease for ages < 44 yr



15-24 yr | 25-44 yr | 45-64 yr

"Health, United States 2003", HHS

Types of Depression

Major depression (unipolar)

Manic depression (bipolar disorder)

Criteria for Major Depressive Episode: DSM-5

Diagnostic and Statistical Manual, 5th revision

A. Five (or more) of the following symptoms have been present during the same 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.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

[see next slide]

B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C. 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).

- **Depressed mood** most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
- Markedly **diminished interest or pleasure** in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- Significant **weight loss** when not dieting or **weight gain** (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
- **Insomnia or hypersomnia** nearly every day.
- **Psychomotor agitation or retardation** nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- **Fatigue or loss of energy** nearly every day.
- Feelings of **worthlessness** or excessive or inappropriate **guilt** (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to **think or concentrate**, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- 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.

DSM IV criteria dropped from DSM V

Criteria for Major Depressive Episode

A. 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.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

B. The symptoms do not meet criteria for a Mixed Episode (see p. 335).

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. 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).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Rating Scales for Quantifying Symptoms

Hamilton Rating Scale for Depression

score 0 -4

1 Depressed mood
2 Guilt feelings
3 Suicide
4 Insomnia - early
5 Insomnia - middle
6 Insomnia - late
7 Work and activities
8 Retardation - psychomotor
9 Agitation
10 Anxiety - psychological
11 Anxiety - somatic
12 Somatic symptoms GI
13 Somatic symptoms -General
14 Sexual dysfunction - menstrual disturbance
15 Hypochondrias
16 Weight loss
17 Insight
18 Diurnal Variation
19 Depersonalization
20 paranoia
21 obsessional and compulsive

Rating Scales for Quantifying Symptoms

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)
   - **0=** Absent
   - **1=** These feeling states indicated only on questioning
   - **2=** These feeling states spontaneously reported verbally
   - **3=** Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
   - **4=** Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication
2. **FEELINGS OF GUILT**
   - **0=** Absent
   - **1=** Self reproach, feels he has let people down
   - **2=** Ideas of guilt or rumination over past errors or sinful deeds
   - **3=** Present illness is a punishment. Delusions of guilt
   - **4=** Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. **SUICIDE**
   - **0=** Absent
   - **1=** Feels life is not worth living
   - **2=** Wishes he were dead or any thoughts of possible death to self
   - **3=** Suicidal ideas or gesture
   - **4=** Attempts at suicide (any serious attempt rates 4)

Research Instruments are basis of Clinical Evaluation

e.g. Zoloft package insert

Clinical Trials
Major Depressive Disorder
The efficacy of ZOLOFT as a treatment for major depressive disorder was established in two placebo-controlled studies in adult outpatients meeting DSM-III criteria for major depressive disorder. Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 145 mg/day. Study 2 was a 6-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Overall, these studies demonstrated ZOLOFT to be superior to placebo on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement scales.

Major Depression (Unipolar)

Melancholic (60%)
depressed in a.m., insomnia, agitation, anorexia, anhedonia
later in life, phasic
sensitive to tricyclics, serotonin reuptake inhibitors, electroconvulsive shock

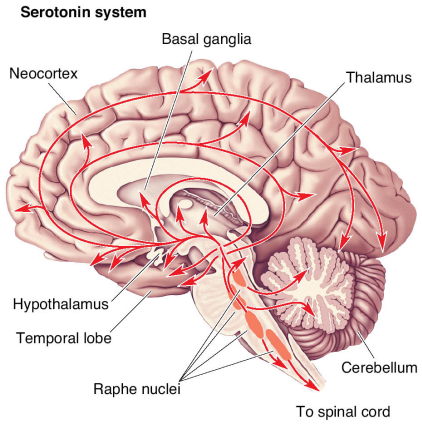
Atypical (15%)
depressed in p.m., oversleeping, overeating,anxious
early in life, chronic
sensitive to monoamine oxidase inhibitors (MAOIs)

Disthymia
persistent but milder

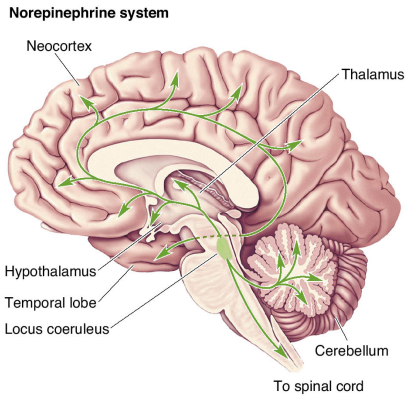
Theories of Depression

1. Monoamine
2. Genetic
3. Stress

Monoamine Theory of Depression: Serotonin



Monoamine Theory of Depression: Norepinephrine



Monoamine Theory of Depression

Serotonin (5HT) in the brain originates from midbrain raphe nuclei.

Norepinephrine (NE) from the locus ceruleus in pons.

Both systems project fibers widely throughout the brain, including hippocampus, hypothalamus, limbic system and cortex.

Both 5HT & NE have global effects on arousal, attention, and mood.

Decreased levels of monoamines, decreased numbers of monoamine receptors, or decreased sensitivity in the postsynaptic neuron leads to depressed mood.

Tryptophan Depletion-induced Depression

after drinking 15-amino acid shake without tryptophan (the precursor required for serotonin synthesis).

Placebo

	Tryptophan	Depression Score
8 am baseline	2.1 ± 0.5	7.0 ± 5.5
6 h postdrink	4.6 ± 1.0	6.7 ± 6.0
8 am next day	2.0 ± 0.3	7.9 ± 6.6

Tryptophan Depletion

	Tryptophan	Depression Score
8 am baseline	1.6 ± 0.5	6.9 ± 5.0
6 h postdrink	0.4 ± 0.2*	15.6 ± 6.9*
8 am next day	1.8 ± 0.2	12.3 ± 7.4*

7 out of 14 depleted subjects showed relapse
Bremner Arch Gen Psychiatry 54 (1997) 364

Genetic Theory of Depression

Major depression has a large heritable component.

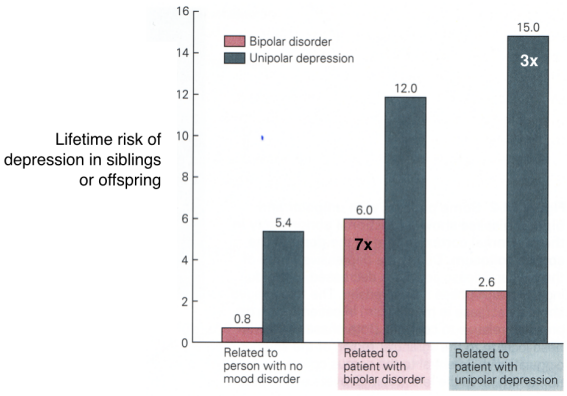
Suicide victims have increased 5HT-2 receptors, thought to be genetic difference.

Manic depression has also been linked to specific genes.

As with many polygenetic phenomena, genes may confer a predisposition to depression when an environmental stress is applied to the person.

(recall differences in stress response in genetically different rat strains)

Genetic Component to Depression

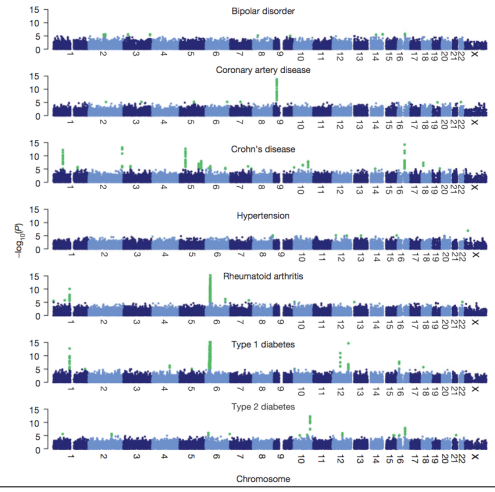


Bipolar disorder (BD). Bipolar disorder (BD; manic depressive illness[26]) refers to an episodic recurrent pathological disturbance in mood (affect) ranging from extreme elation or mania to severe depression and usually accompanied by disturbances in thinking and behaviour: psychotic features (delusions and hallucinations) often occur. Pathogenesis is poorly understood but there is robust evidence for a substantial genetic contribution to risk[27,28]. The estimated sibling recurrence risk (λ_s) is 7–10 and heritability 80–90%[27,28]. The definition of BD phenotype is based solely on clinical features because, as yet, psychiatry lacks validating diagnostic tests such as those available for many physical illnesses. Indeed, a major goal of molecular genetics approaches to psychiatric illness is an improvement in diagnostic classification that will follow identification of the biological systems that underpin the clinical syndromes. The phenotype definition that we have used includes individuals that have suffered one or more episodes of pathologically elevated mood (see Methods), a criterion that captures the clinical spectrum of bipolar mood variation that shows familial aggregation[29].

Genome wide screen of frequency of 500,528 single nucleotide polymorphisms in 2000 patients for each of 7 diseases vs. 3000 controls

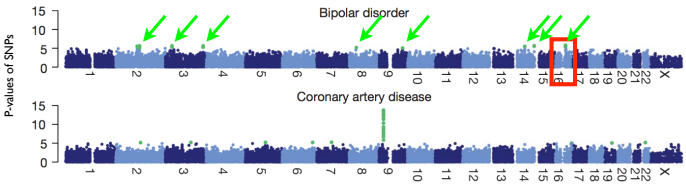
Nature, 447 (2007) 661

Genome wide screen of frequency of 500,528 single nucleotide polymorphisms in 2,000 patients for each of 7 diseases vs. 3,000 controls



Nature, 447 (2007) 661

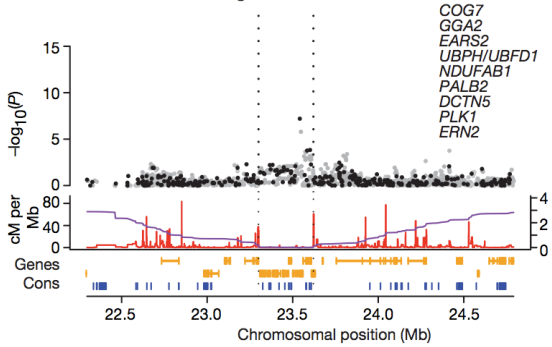
Genome wide screen of frequency of 500,528 single nucleotide polymorphisms in 2000 patients for each of 7 diseases vs. 3000 controls



Chromosome

Nature, 447 (2007) 661

BD hit region, chromosome 16



Prediction: You will be able to sequence patients genome to determine specific diagnosis and best treatment on an individual basis.

Nature, 447 (2007) 661

Stress Theory of Depression

Acute stress (normal condition)

activation of PVN in hypothalamus

-> acutely elevated glucocorticoids (cortisol)

-> energy mobilization, immune suppression for a short-term, focused adaptive response to stress

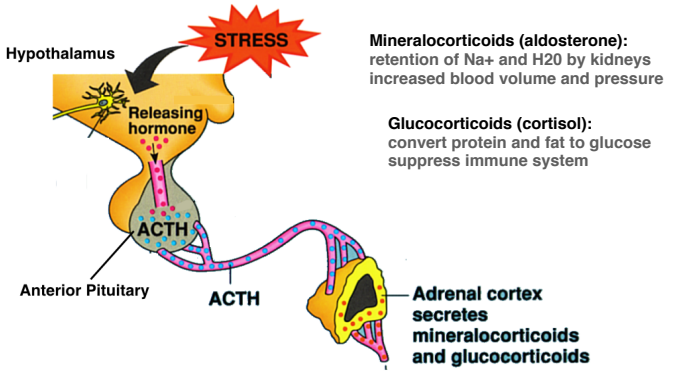
-> negative feedback regulation of CRH and ACTH release at the levels of hippocampus, hypothalamus, and pituitary

-> return to basal cort levels

Another feedback loop modulates limbic responses over time:

hippocampus produces brain-derived nerve growth factor (BDNF).
-> BNDF maintains 5HT, NE fiber innervation of the hippocampus.
-> 5HT, NE modulate limbic responses and maintain neuronal growth in the hippocampus.

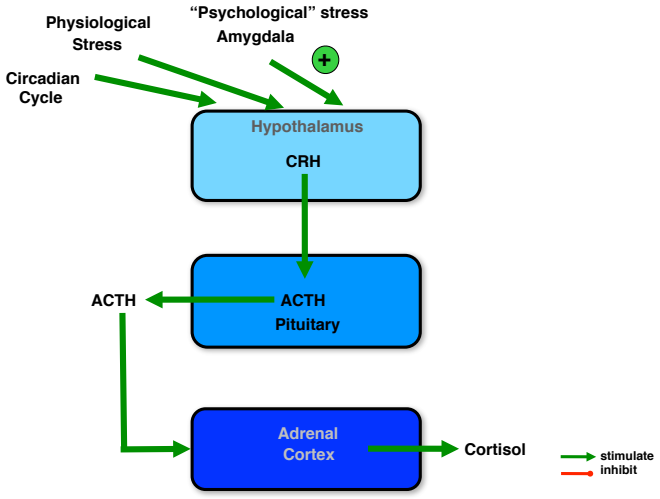
Long-Term Response to Stress:
secretion of mineralo- & glucocorticoids



Mineralocorticoids (aldosterone):
retention of Na+ and H20 by kidneys
increased blood volume and pressure

Glucocorticoids (cortisol):
convert protein and fat to glucose
suppress immune system

HPA axis: Positive Feed forward



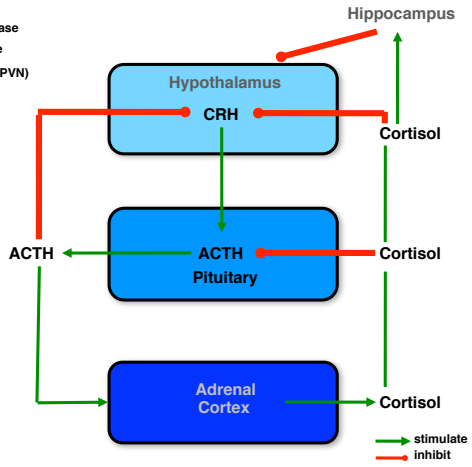
HPA axis: Negative Feedback

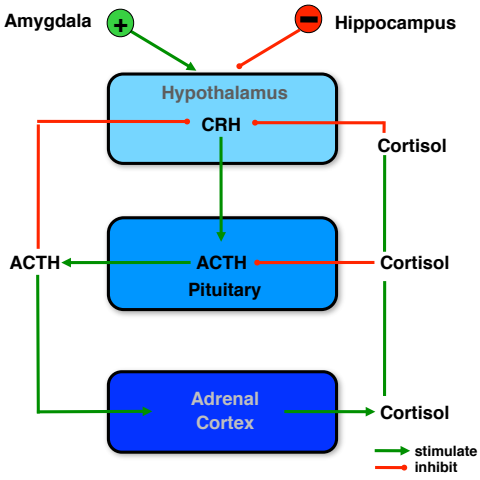
Cortisol feeds back to:

pituitary –> inhibit ACTH release

pcPVN –> inhibit CRH release

hippocampus –> fornix –> pcPVN)





Limbic stimulation -> cortisol release

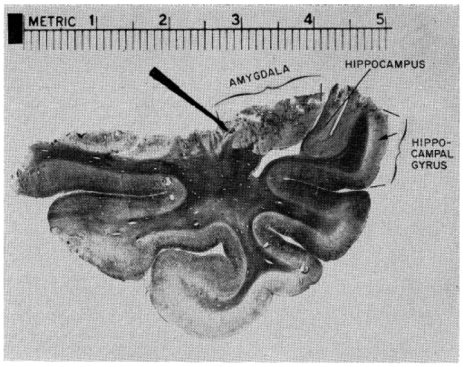


Fig. 1. Section of right temporal lobe, showing marker lesion (electrode tip) in basolateral amygdala. Lesion is the darker area at the immediate right of the pointer tip; Weil stain.

Science. 1966 Aug 12;153(737):767-8.

Amygdala stimulation -> cortisol release

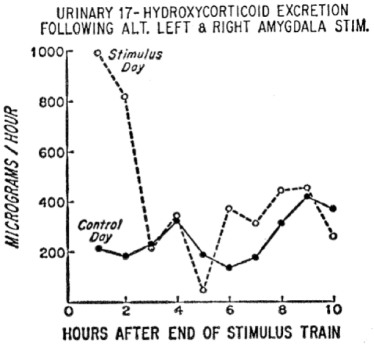
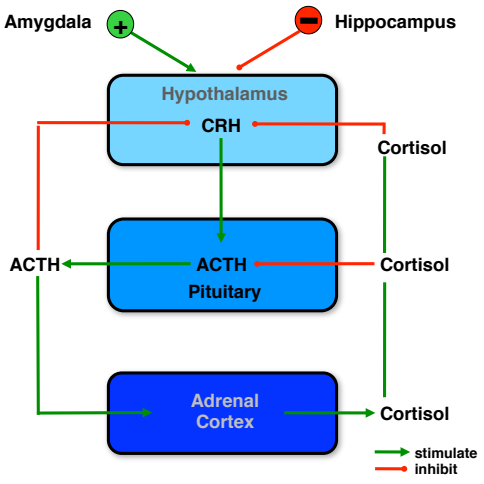


Fig. 2. Urinary 17-hydroxycorticoids after amygdala stimulation in patient 5.

Hippocampal Stimulation -> cortisol decrease
Amygdalar Stimulation -> cortisol increase

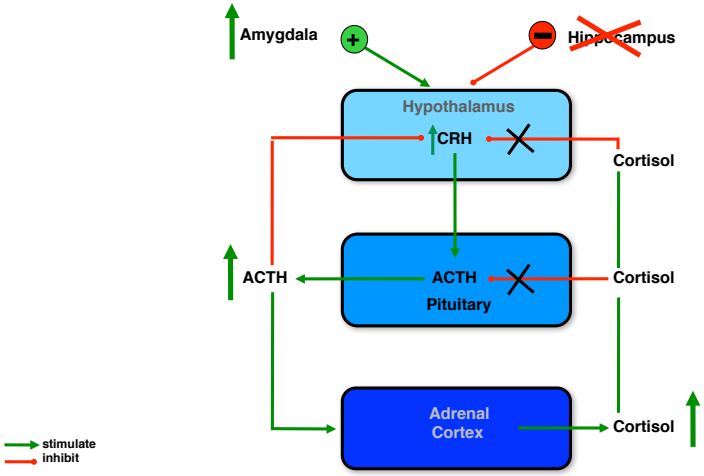
Patient	Location of stimulation	17-Hydroxy-corticoids in plasma: maximum change from control amount (%)
1	R-CA 2 hippocampus (histopath.)	−28
2	R-basolateral amygdala (histopath.)	+12
3	R-hippocampus (stereotaxic)	−88
3	L-subiculum hippocampus (histopath.)	−90
3	R-basolateral amygdala (stereotaxic)	+360
3	L-basolateral amygdala (histopath.)	+232
4	Anterior to L-amygdala (histopath.*)	+415
4	L-anterior hippocampus (histopath.*)	−18
4	L-CA 1 hippocampus (histopath.)	−100

* Unverified.



Stress Theory of Depression

-> disregulation at multiple levels, especially hippocampus

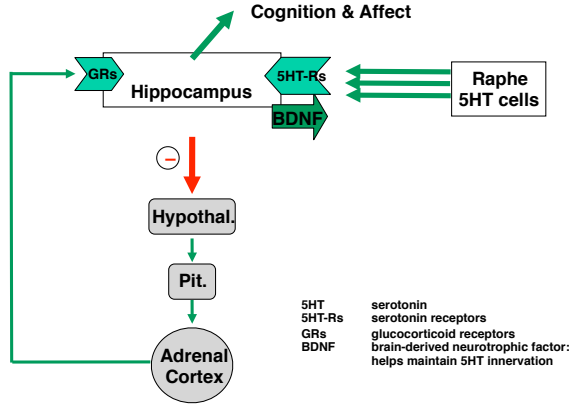


Mild Stress:

Glucocorticoids Feedback on Hippocampus to attenuate stress response

Serotonin helps maintain healthy hippocampus;

BDNF helps maintains serotonin input



Stress Theory of Depression

Chronic stress

chronically elevated glucocorticoids

–> death of hippocampal cells, and other cells in the limbic system (especially those receiving serotonin and norepinephrine inputs)

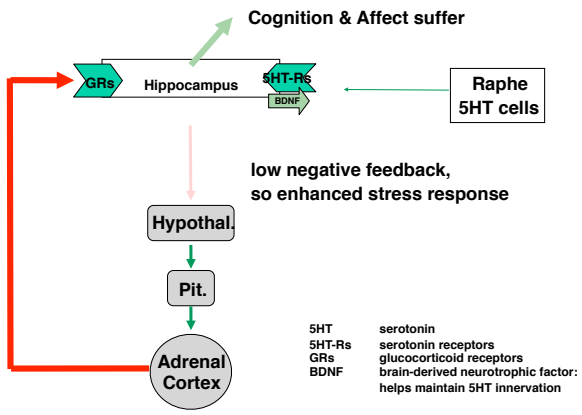
–> feedback cells killed, so glucocorticoids stay elevated

–> depression and other neural deficits.

–> antidepressants restore 5HT, NE, and BDNF levels.

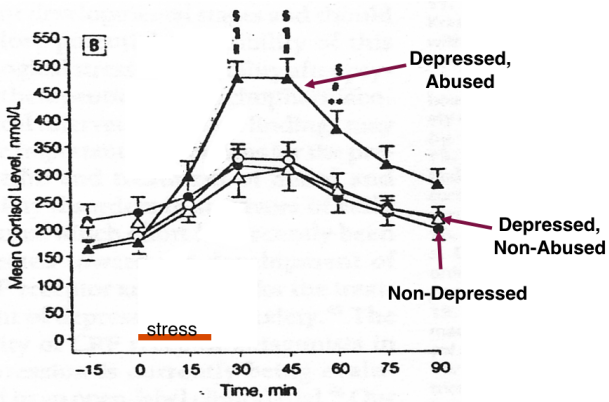
–> hippocampal growth & negative feedback restored.

Chronic High Stress:
High Glucocorticoids become toxic to Hippocampus
Negative Feedback and Serotonin Innervation decline



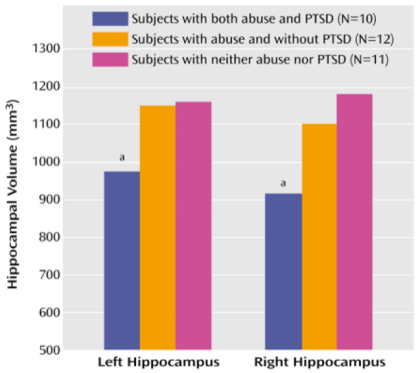
5HT	serotonin
5HT-Rs	serotonin receptors
GRs	glucocorticoid receptors
BDNF	brain-derived neurotrophic factor: helps maintain 5HT innervation

Decreased negative feedback after abuse
Depressed women with childhood abuse show enhanced stress response to social stress.



Many depressives fail the Dex-suppresion test…

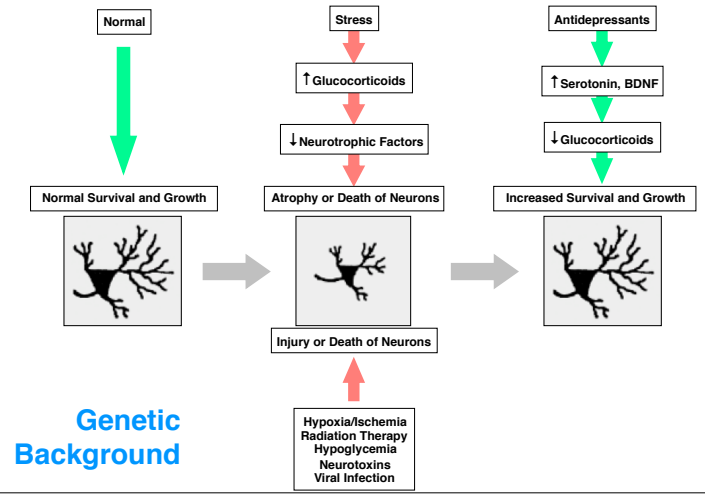
Effect of early abuse and PTSD on Hippocampus
abuse & PTSD cause decrease in hippocampal volume



Bremner JD & Charney, AJP, May 2003

Atrophy of Hippocampal Neurons can lead to Depression

Contributions from Genetics, Stress, and Insult



Treatments for Depression

Therapy

Serotoninergic and Noradrenergic Drugs

Electroconvulsive Therapy

Mechanisms of Antidepressants

Therapy & Behavior Modification vs. Drugs

Sensory Stimuli -> Limbic System

Psychotherapy may be as effective as medication in the treatment of mild to moderate depression

If there is no improvement after six to eight weeks of therapy, or if there is not complete resolution by 12 weeks, antidepressant medications are recommended

When patients do not respond to treatment, the most common cause is non-compliance with medication. A second important cause of treatment failure is inadequate dosing or duration of therapy

If there is no response to treatment by 4 weeks, or if there is a less than 50% response by 8 weeks, the clinician should either change to a different agent and/or consider referral to a psychopharmacologist.

[Brigham and Women's Hospital guidelines, 2006]

Antidepressant Drugs

Do not induce euphoria on their own, but correct depression.

So antidepressants are different from amphetamine, cocaine (which increase dopamine and norepinephrine) and ectasy (serotonin releasor) which have large, immediate effects on mood.

Antidepressants appear to upregulate serotonin and norepinephrine indirectly and slowly over weeks.

Antidepressant Drugs

Common property: take 2-12 weeks to achieve full efficacy.

Latency suggests a genomic or structural basis for effect.

All have unpleasant side effects: GI, salivary, vertigo, eating (+/-), sleep, irritability, etc. ***(5HT & NE are widespread both peripherally & centrally)***

Often a long course of treatment is required to titrate the appropriate dosage for each patient

A running battle between the side effects and the relief of depression.

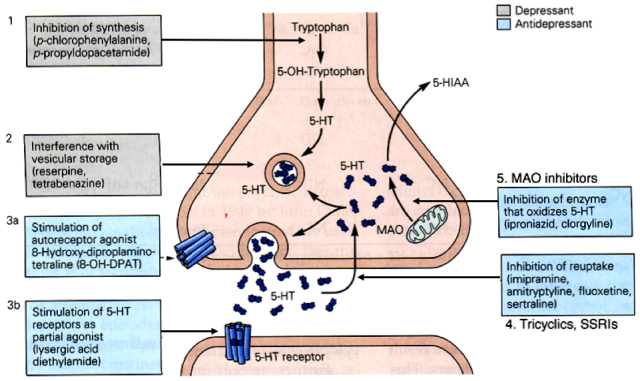
Cellular Mechanisms of Antidepressants

Increase 5HT and NorEpi levels in the synapse
block transporters, degradation, autoreceptors

Increase postsynaptic response to 5HT
via 5HT-4,6,7 receptors

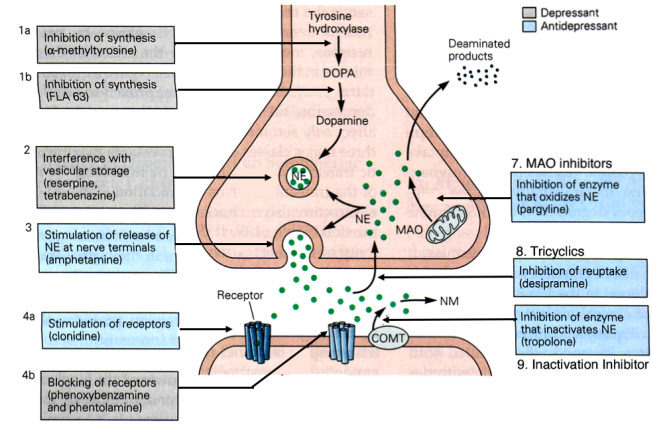
and Norepi
via beta-adrenergic receptors

The Serotonin (5HT) synapse



Kandel

The NE synapse



Kandel

Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs)

Block uptake or degradation of serotonin and norepinephrine, so increased recycling

–> higher vesicular concentration

–> more release at synapse.

TCAs have structure that looks similar to monoamines, so may compete at uptake mechanism.

MAOIs interfere with MAO enzyme function.

Selective Serotonin (and Norepinephrine) Reuptake Inhibitors (SSRIs & NRIs)

Blocks re-uptake of serotonin or norepinephrine from the synapse, so that effective concentration is increased and prolonged

SSRI:

fluoxetine (Prozac)
setraline (Zoloft)
paroxetine (Paxil)

NRI:

desipramine (Norpramine)
nortriptyline (Aventil)

SSRIs and drop in Suicide

1957-1986	**Suicide rate increased 31%**
1987	**SSRIs introduced**
1985 - 1999	**Antidepressant prescription rate increased 400%** **Suicide rate decreased 13.5%**

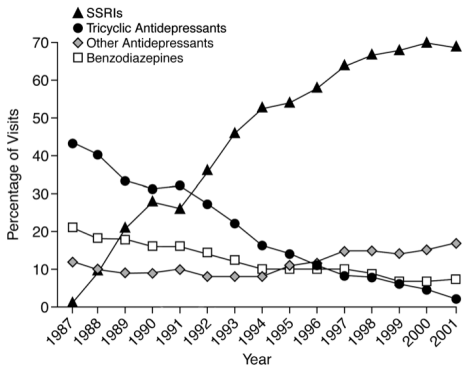
For every 10% increase in antidepressant prescriptions (15 million more), suicide rate decreased by 3% (968 fewer suicides).

1997-2000

Females:	**65-67% of antidepressant prescriptions** **22.5% drop in suicide**
Males:	**30-32% of antidepressant prescriptions** **12.8% decline in suicide**

Grunebaum 2004

Changes in Antidepressant Prescribing



Stafford, Primary Care Companion J Clin Psychiatry 3 (2001) 235

2005: 9.9 million prescriptions for all antidepressants < 20 y.o.

FIGURE 1. SSRI Prescription Rates in the United States, 2002–2005, Stratified by Age Group and Expressed as a Percentage of the 2003 Rate

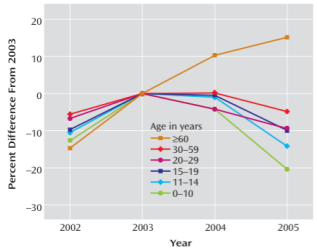
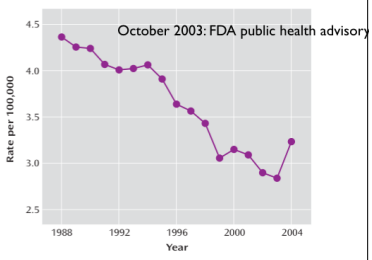


FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004



5-19 y.o.:
2003: 1737 suicides of 61.5 million
2004: 1985 suicides of 61.5 million, p <0.0001

2003-2005: 20% drop in SSRI prescriptions 0-15 y.o.

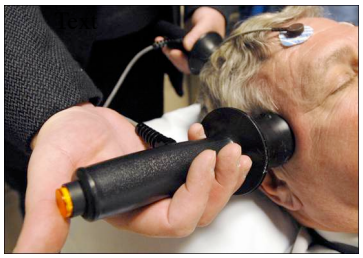
Gibbons et al., Am J Psychiatry 2007; 164:1356–1363

Electroconvulsive shock (ECS)

Electrical shock applied to anesthetized, paralyzed patient -> generalized seizures.

Unknown mechanism, but one of the best treatments.

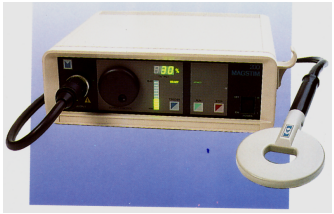
New version: focal transcranial magnetic stimulation of forebrain.

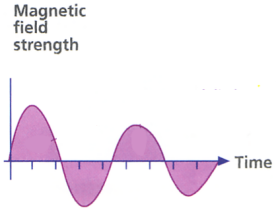


Dr. Serge D. Botsaris, acting chief of psychiatry at St. Vincent Hospital, demonstrates electroconvulsive therapy as he places two devices at the temple and back of a volunteer's head.

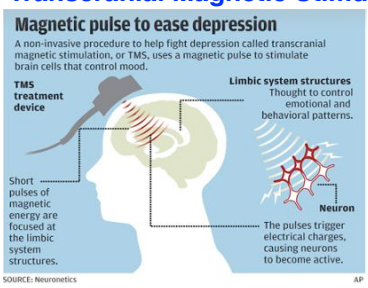
Telegram&Gazette 2006

Transcranial Magnetic Stimulation

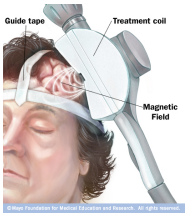




Transcranial Magnetic Stimulation

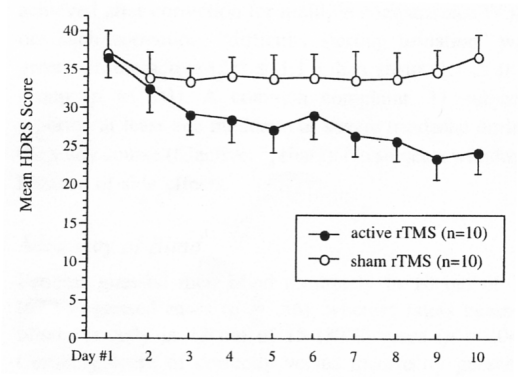


Neuronetics NeuroStar system



40 min Rx x 5/week x 6 weeks

Transcranial Magnetic Stimulation



Molecular Mechanisms of Antidepressants

increased 5HT & NE

–> increased stimulation of hippocampus

–> elevation of intracellular cAMP

–> elevation of the transcription factor CREB (cAMP-response-element binding protein)

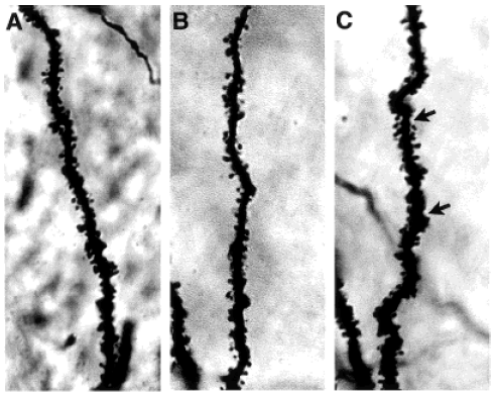
–> upregulation of neurotrophic factors (e.g. brain-derived neurotrophic factor, BDNF)

–> increased sprouting of serotonin fibers in the limbic system

–> increased survival of cells in the limbic system during stress.

Antidepressants Increase Spine Density on Dendrites

Control "Depressed" Antidepressant Rx



(Norrholm & Ouimet, 2001)

Striatum radiatum of hippocampus

Animal Models of Depression

Face validity
the symptoms of the model resemble the symptoms of depression

Predictive validity
the symptoms of the model are reversed by antidepressants with a similar profile to clinically used antidepressants in humans

Construct validity
the underlying cellular or molecular mechanisms in the model is homologous to the cause of human depression

Face Validity:

Isolation/separation depression in monkeys.

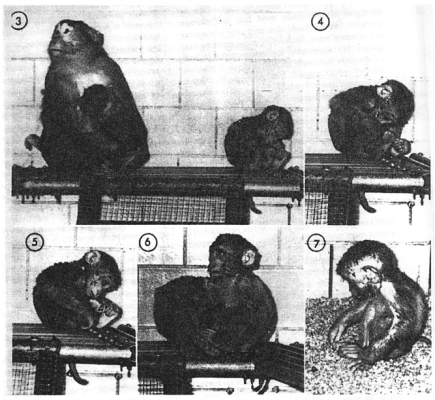


Figure 5–3. Depressed pigtail infant showing characteristic hunched-over posture with flexion throughout. He is completely disengaged from the mother and infant nearby who are in ventral-ventral contact.

Harlow expts

Predictive Models:

Olfactory bulb lesions

(Not caused by loss of smell.)

No obvious causal connection with human depression

hypoactivity, anhedonia, hyposerotonergic tone.

Reversed by SSRIs

Predictive model:

Forced swim-test

Place rats in cylinder of water from which they cannot escape.

Struggle for a while, then "give-up" trying to escape (never in danger of drowning; rats float well.)

Antidepressants reverse the "despair", and rats start struggling to escape again -- therefore have same 5HT/NE basis.

(Predictive, because clinical depression is usually not caused by unavoidable swimming.)

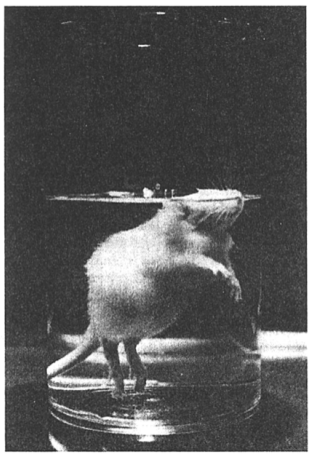


Figure 5–1. Rat showing characteristic posture of immobility.

Swim Test predicts anti-depressant effects

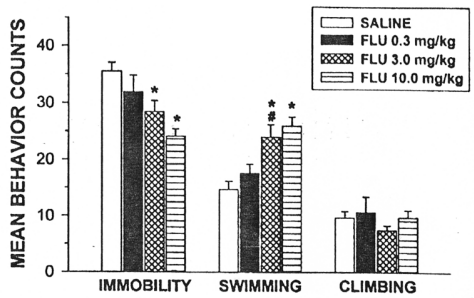


Fig. 4. The effects of treatment with fluoxetine in the FST. Bars represent the mean ± S.E.M. (n = 10/dose). ANOVA revealed a significant effect of dose on immobility [$F(3,45) = 6.46$, $P < .0001$] and swimming [$F(3,45) = 10.16$, $P < .0001$]. $*P < .05$ from saline, $\#P < .05$ from preceding dose.

(Hemby)

Construct models:

Reserpine-induced depression

prevents vesicles from storing monoamines, so monoamines remain in cytoplasm and are degraded.

drastic and sudden drop in brain 5HT and NE leading to depression-like syndromes.

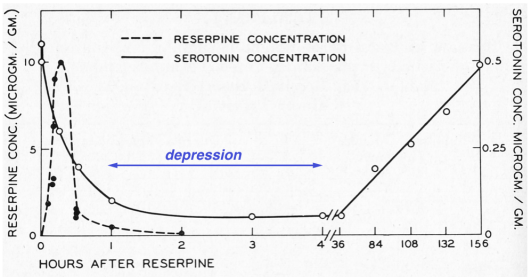


FIGURE 115. Concentrations of serotonin and reserpine in rabbit brain after injection of reserpine (from 1 to 5 mg./kg. I.V.).

Models in Drug Discovery

Take compounds from company library

↓

Screen against proteins, cells, lower organisms
e.g. with 5HTergic receptors, transporters, enzymes

Construct

↓

Screen against animal models
e.g. forced swim test, bulbectomy

Predictive

↓

Test in primates (mostly toxicology)

↓

Test in normal subjects (adverse effects)

↓

Test in patients (benefits and efficacy for indication)

Future of Depression Studies

Treatment of relapse & recurrence

More selective antidepressants.

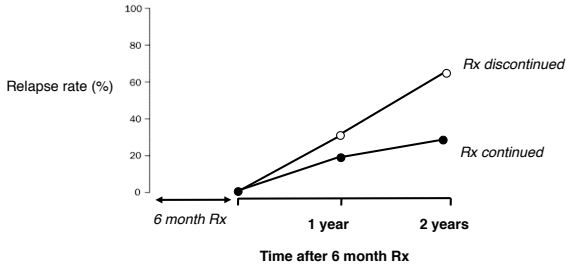
More targeted Rx of specific brain regions.

Biological markers
stress levels, sleep disorders, functional brain imaging

Better understanding of subtypes.

Better understanding of genetics.

Relapse after acute or prolonged antidepressant Rx



Patients received 6 months Rx with antidepressants:

When Rx was discontinued:
35% relapsed within 1 year
62% relapsed within 2 years

Continuous Rx cut the relapse rate in half.