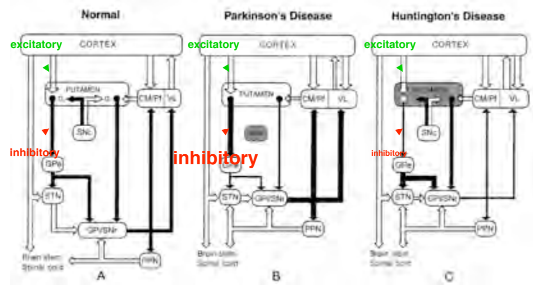
Lecture XIV.
Brain Diseases - II.
Mental Illness

Bio 3411

Friday

October 9, 2009



What this lecture is about:

- Widespread Systems
- Mood Disorders
  - Depression
  - Manic/Depressive Illness
- Schizophrenia
- Drugs

Brain Diseases II

NEUROSCIENCE

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References

†Breiter HC, Gollub RC, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Matrhew RT, Rosen BR, Hyman SE 1997 Acute effects of cocaine on human brain activity and emotion. Neuron 19:591-611.

†Buckley PF 1998 Structural brain imaging in schizophrenia. Psychiatric Clinics of North America. 21:77-

†Drevets WC 1998 Functional neuroimaging studies of depression: the anatomy of melancholia. Annual Reviews of Medicine. 49:341-61.

†Fu CHY, McGuire PK 1999 Functional neuroimaging in psychiatry. Phil Trans R Soc Lond B 354:1359-1379.

†Nemeroff CB 2006 The burden of severe depression: A review of diagnostic challenges and alternatives. J Psych Res doi:10.1016/j.jpsychires.2006.05.008.

†Sheline YI, Gado MH, Price JL 1998 Amygdala core nuclei volumes are decreased in recurrent major depression. NeuroReport 9:2023-2028.

†Articles/Abstracts posted on website.

Neuroscience, p 121

TABLE 6.1 Functional Features of the Major Neurotransmitters

Neurotransmitter	Postsynaptic effect*	Precursor(s)	Rate-limiting step in synthesis	Removal mechanism	Type of vesicle
ACh	Excitatory	Choline + acetyl CoA	CAT	AChEase	Small, clear
Glutamate	Excitatory	Glutamine	Glutaminase	Transporters	Small, clear
GABA	Inhibitory	Glutamate	GAD	Transporters	Small, clear
Glycine	Inhibitory	Serine	Phosphoserine	Transporters	Small, clear
Catecholamines (epinephrine, norepinephrine, dopamine)	Excitatory	Tyrosine	Tyrosine hydroxylase	Transporters, MAO, COMT	Small dense-core, or large irregular dense-core
Serotonin (5-HT)	Excitatory	Tryptophan	Tryptophan hydroxylase	Transporters, MAO	Large, dense-core
Histamine	Excitatory	Histidine	Histidine decarboxylase	Transporters	Large, dense-core
ATP	Excitatory	ADP	Mitochondrial oxidative phosphorylation; glycolysis	Hydrolysis to AMP and adenosine	Small, clear
Neuropeptides	Excitatory and inhibitory	Amino acids (protein synthesis)	Synthesis and transport	Proteases	Large, dense-core
Endocannabinoids	Inhibits inhibition	Membrane lipids	Enzymatic modification of lipids	Hydrolysis by FAAH	None
Nitric oxide	Excitatory and inhibitory	Arginine	Nitric oxide synthase	Spontaneous oxidation	None

*The most common postsynaptic effect is indicated; the same transmitter can elicit postsynaptic excitation or inhibition depending on the nature of the ion channels affected by transmitter binding (see Chapter 5).

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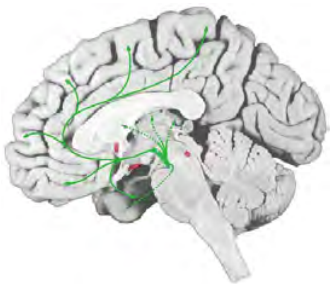
Dopaminergic Pathways



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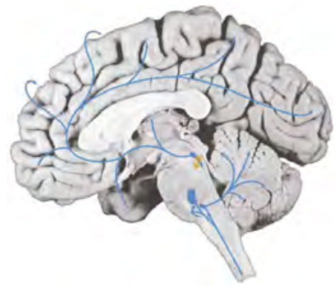
Serotonergic Pathways



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Noradrenergic Pathways

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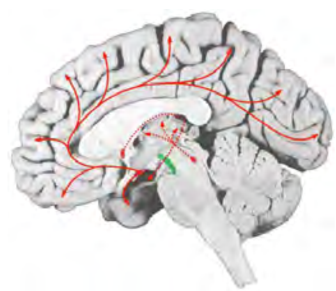
Cholinergic Pathways



Mood Disorder(s): Depressive (Unipolar) and Manic Depressive (Bipolar) Illness

- Sx: (Mood +/-): melancholic (black bile) thoughts, loss of interest in food and sex, sleep disturbances
- Prevalence: 10-15% lifetime
- Predisposition: Strongly genetic but may be multi-factorial
- Prevention: None
- Dx: Interview, suicidal actions.

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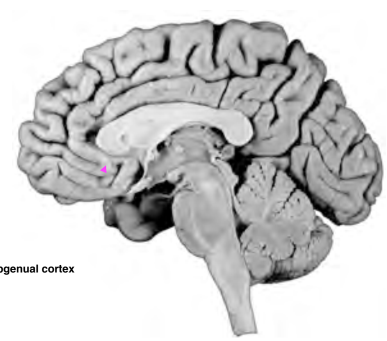
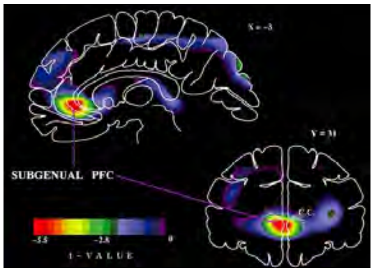


Subgenual cortex

Measurements of activity in persons with different forms of clinical depression demonstrate significant blood flow **reductions** in a region known as the subgenual (below the knee - genu - of the corpus callosum) cortex as compared to control subjects.



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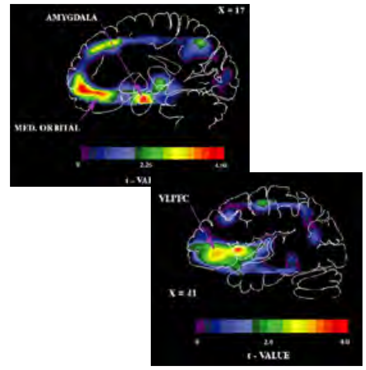
Measurements of activity in persons with different forms of clinical depression demonstrate significant blood flow **increases** in a regions of the frontal lobes, the amygdala, the thalamus (not shown) and the brainstem (not shown) as compared to controls.



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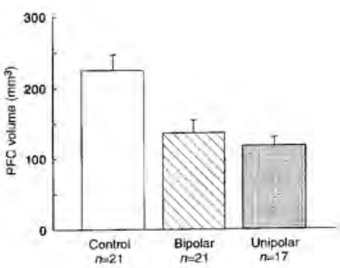
Measurements of the volumes of the subgenual cortex in individuals with different forms of clinical depression demonstrate significant reductions in this cortex as compared to control subjects.



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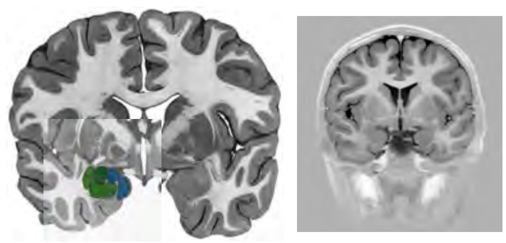
Amygdala (almond)



Central Nucleus

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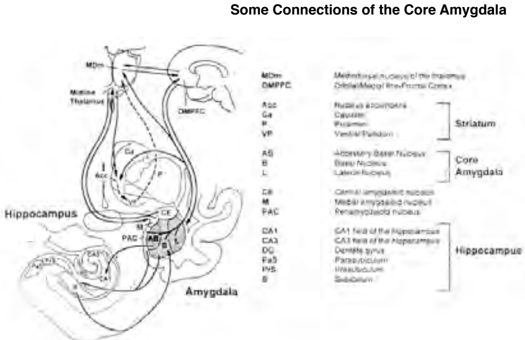
Some Connections of the Core Amygdala



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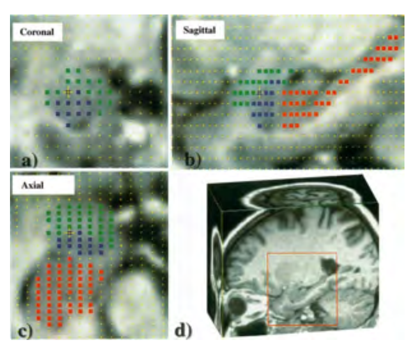
Measurements can be made from images of brain structures. The core of the **amygdala**, outlined here is smaller in persons with recurring depression.



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Structural Changes in Patients with Recurrent Major Depression

HAMD (Hamilton Rating Scale for Depression)

Table 1. Demographic and volumetric data

	Control (mean ± s.d.)	Depressed (mean ± s.d.)	Mean difference	p
Demographics				
Age (years)	53 ± 17	54 ± 18	0.25	0.80
Education (years)	16 ± 4	16 ± 3	0.06	0.93
Height (cm)	164 ± 6	162 ± 5	−2	0.22
HAMD score	1 ± 1	5 ± 4	4	0.0003 ◄
Volumes				
Core				
Left amygdala (mm^3)	620 ± 107	523 ± 97	-97	0.001 ◄
Right amygdala	593 ± 106	498 ± 91	-95	0.002 ◄
Non-core				
Left amygdala (mm^3)	1161 ± 241	1127 ± 302	−35	0.68
Right amygdala	1159 ± 250	1225 ± 314	67	0.39
Total				
Left amygdala (mm^3)	1782 ± 296	1650 ± 310	−131	0.16
Right amygdala	1752 ± 295	1724 ± 304	−28	0.74
Whole brain (cm^3)	1152 ± 125	1153 ± 116	1	0.97

- Pathophysiology: reduced activity in subgenual cortex; smaller volume; lower concentration of glia but not neurons; central amygdala
- Treatment: Antidepressants (aka minor tranquilizers). Current best class is selective 5HT re-uptake inhibitors (e.g., Prozac, Zoloft).
- General Strategies refer to the synapse - block breakdown of amines, stimulate receptors, inhibit uptake, increase release, deep brain stimulation.
- Long Term Changes: improvement with drugs and talk
- Brain Science: See schizophrenia.

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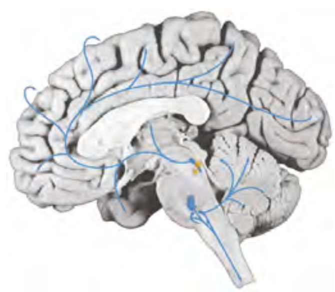
Serotonergic Pathways



Schizophrenia (split mind)

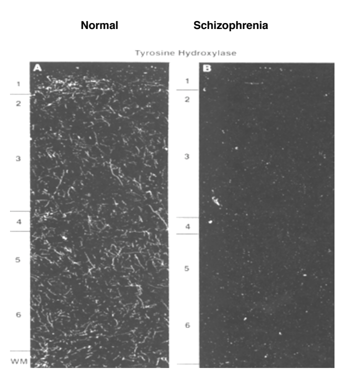
- Symptoms: (Schizophrenia +/-): + hallucinations (voices), delusions, schizophrenic thought; - withdrawal, autistic behavior
- Prevalence: ≈ 1% lifetime from early age (dementia praecox)
- Predisposition: Strongly genetic but may be multi-factorial
- Prevention: None

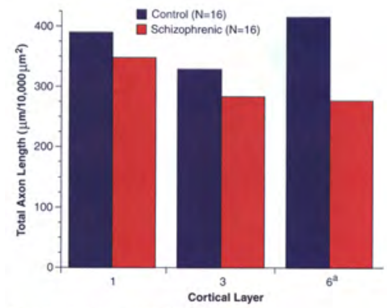
Table 1. STRUCTURAL BRAIN IMAGING STUDIES OF TEMPORAL LOBE PATHOMORPHOLOGY IN SCHIZOPHRENIA

Authors	Sample Patient/Control	Technique	Findings in Patients/Comments
Suddath et al. 1989	17/17	MRI	Smaller temporal lobe; amygdala, hippocampus
Andreasen et al. 1990	54/47	MRI	No temporal lobe abnormalities
Barta et al. 1990	15/15	MRI	Reduction in superior temporal gyrus correlated with auditory hallucinations
Suddath et al. 1990	15/15	MRI	Affected twins with schizophrenia have smaller left temporal lobe hippocampus
Breier et al. 1992	44/29	MRI	Reduced left amygdala and hippocampus
Shenton et al. 1992	15/15	MRI	Smaller left hippocampus; reduction in superior temporal gyrus correlated with thought disorder
Harvey et al. 1993	48/34	MRI	Reduction in temporal lobe attributable to generalized brain tissue loss
[illegible]	12/12	MRI	Normal superior temporal gyrus volume
Petty et al. 1995	14/14	MRI	Reversed asymmetry of the planum temporale
[illegible]	71/77	MRI	Abnormal temporal lobe asymmetry in deficit (negative symptom) subgroup
[illegible]	14/15	MRI	Temporal lobe volume reduction only in patient subgroups with positive symptoms
Jacobsen et al. 1996	21/11	MRI	No gross temporal lobe abnormalities in early onset of schizophrenia
[illegible]	[illegible]	MRI	First episode schizophrenia and temporal lobe epilepsy (TLE)* patients have smaller left hippocampal volumes than controls. TLE patients have bilateral hippocampus loss
Barta et al. 1997	24/22	MRI	Reversed planum temporale asymmetry, reduced gray matter thickness in the planum temporale
Frangou et al. 1997	[illegible]	MRI	Planum temporale asymmetry similar in patients, first degree relatives,† and controls

*Comparison group of patients with temporal lobe epilepsy.
†Comparison group of first degree relatives of patients with schizophrenia.

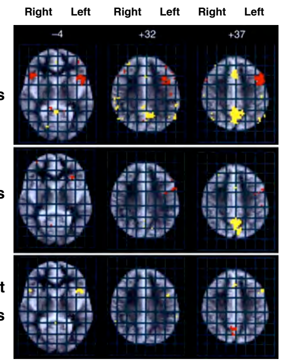
There are fewer serotoninergic fibers in the frontal cortex of the brains of schizophrenics.





a F=5.23, df=3, 10, p=0.02 (MANOVA).

Verbal Fluency (Hypofrontality)

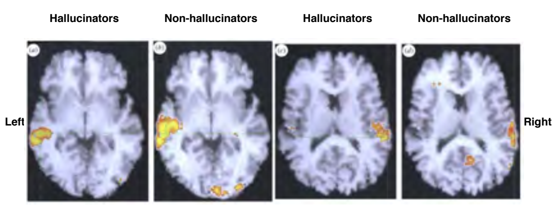


Controls

Schizophrenics

Significant Differences

Activation in an "auditory" verbal imagery task.



- Diagnosis: Interview, family and social history.
- Pathophysiology: enlarged ventricles, smaller hippocampus, possible reduction in cerebral asymmetries
- Treatment: Neuroleptic (aka, major tranquilizers); current best class is DA (D4) blockers
- Long Term Changes: improvement with drugs

Mental illness informs about function and changes are reported with imaging.

The discovery that certain antihistamines (allergy) and antimycotics (tuberculosis) reduced depression and psychosis respectively led to the discovery of central monoaminergic systems and focused discoveries in neurotransmitter pharmacology.

This led to the discovery of NE, 5HT & DA and many receptors involved in central brain pathway function(s).

The side effects of some of the drugs mimic Parkinsonism and suggest common mechanisms and common structures.

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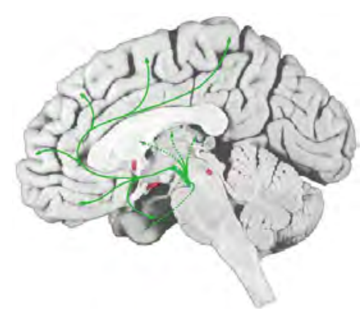
Dopaminergic Pathways



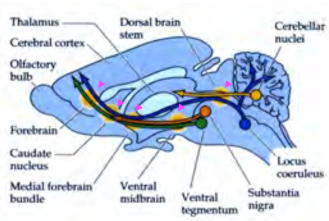
Machu Picchu

Widespread Systems Reward & Cocaine

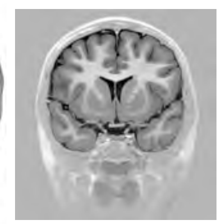
- Self stimulation and reward - the Olds experiment
- History - Incas and jungle conquest, coca leaves, local anesthetics.
- Cocaine shorter term - rush
- Cocaine longer term - craving
- Cocaine reduces DA and 5-HT uptake

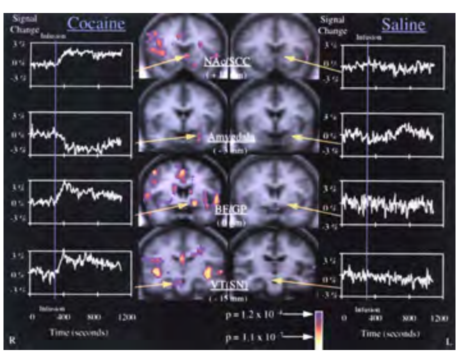
Sites of self stimulation in the rat (arrows)

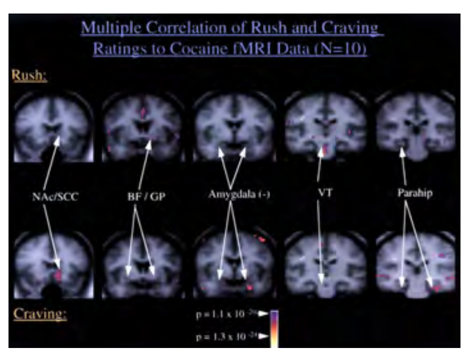
James Olds

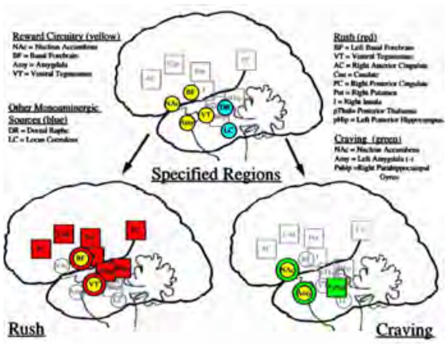


The Brain Atlas, 3rd ed pp 59, 60









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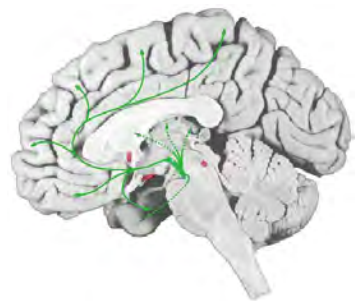
Dopaminergic Pathways



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Brain Diseases - Summary

- The brain like any organ has functions; input, output, “thought”, communication. *Brain diseases* interfere with these functions as heart disease interferes with pumping blood.
- Many brain diseases have a *strong genetic component*.
- The prevalence of *brain diseases* is high≈ 15-30%.
- The impact of *brain diseases* is distributed and often sustained, affecting individuals and their families, friends and co-workers profoundly.
- The cost of brain diseases exceeds $ Trillions annually.

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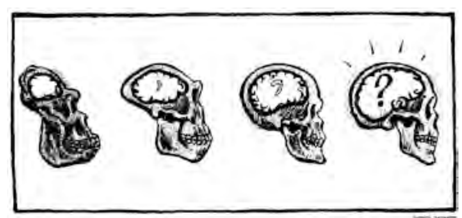

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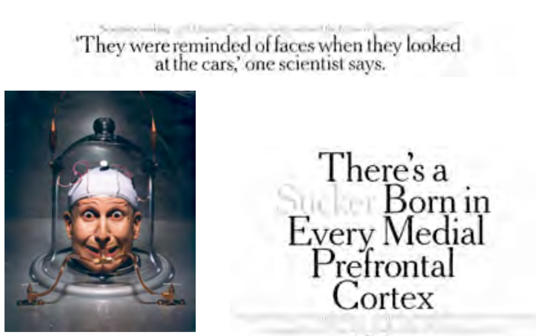

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