Neurobiology of Psychiatric Illness:

Review of functional neuroanatomy
Schizophrenia
Bipolar disorder
Major depression
Obsessive compulsive disorder
Post traumatic stress disorder

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Questions

Abnormal neuronal function in dysregulated neurocircuits can be caused by abnormalities in:

1. number of neurons or neuropil (glia)
2. density of connections between neurons
3. proteins that transduce neurotransmission (eg receptors)
4. gene expression
5. All the above

Questions

Schizophrenia can be understood as primarily

1. Inefficient cortical processing due to prefrontal cortical dysfunction
2. Dopamine neurotransmission abnormalities
3. A neurodegenerative process
4. Serotonergic and dopaminergic abnormalities
5. All the above

Questions

Bipolar illness is characterized by

1. A progressive illness course with greater time spent in the depressive phase of the illness, mixed episodes and rapid cycling ove time.
2. Decreased gray matter in prefrontal, temporal cortex and limbic structures.
3. Decreased temporal cortical thickness that correlates with the number of recent mood episodes, and cognitive impairment.
4. A BDNF polymorphism exaggerates these gray matter decrements.
5. All the above.

Questions

Major depression is

1. Primarily due to abnormal function in the noradrenergic and serotonergic neurotransmitter systems.
2. The result of a systems level dysregulation of multiple cortical, subcortical, and limbic neurociruits.
3. Not associated with volumetric abnormalities in any cortical or limbic structures.
4. The result of clear abnormal structure and functio of the mamillary bodies.
5. All the above.

Questions

Which of the following findings are seen in individuals with Obsessive Compulsive Disorder

1. Abnormalities in the noradrenergic system.
2. Hypermetabolism in the orbitofrontal cortex.
3. Decreased volume of the orbitofrontal cortex.
4. Prominent hypothalamic pituitary axis dysregulation.
5. All the above.
6. 1 and 2
7. 2 and 3

Questions

The following findings are found in individuals with Post-traumatic stress disorder.

1. Elevated CRF levels in CSF
2. Reduction in volume of the medial prefrontal cortex.
3. Abnormal connectivity between prefrontal cortical and limbic structures resulting in dysregulation of the hypothalamic pituitary axis and autonomic nervous system.
4. Reduced volume of limbic structures such as the hippocampus and amygdala
5. 1 and 3
6. All the above

Overview

Psychiatric illnesses are diagnosed by symptom clusters that are the result of abnormal brain tissue, or activity in specialized areas of the brain

Dysregulated circuitry results from abnormal neural function, or abnormal neural connections from one brain area to another

Symptoms in psychiatric illnesses are the consequence of dysregulated neurocircuitry

Neurocircuitry Dysfunction

Each psychiatric illness has uniquely dysregulated circuitry

Commonly implicated neurocircuits in psychiatric illness

1. Prefrontal cortical-striatal-pallidal-thalamic pathways
2. Prefrontal cortical-limbic pathways
3. Prefrontal cortical-aminergic feedback pathways
4. Paralimbic/limbic circuits
5. Diffuse innervation by biogenic amine nuclei in brainstem

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Systems level dysregulation in psychiatric illness

Abnormal neuronal function in dysregulated circuits can be caused by changes in:

1. number of neurons or neuropil (glia)
2. density of connections between neurons
3. receptor number or function
4. neurotransmitter release
5. proteins that transduce neurotransmission (eg receptors)
6. second messenger systems
7. gene expression

Background to understand the neurobiologyof pyschiatric illnesses

Neurocircuitry

- Frontal-subcortical circuits
- Frontal-limbic circuits

Prefrontal cortical and limbic structures

Neurotransmitters

- GABA
- Glutamate
- Role of monoamines 5HT, NE, DA

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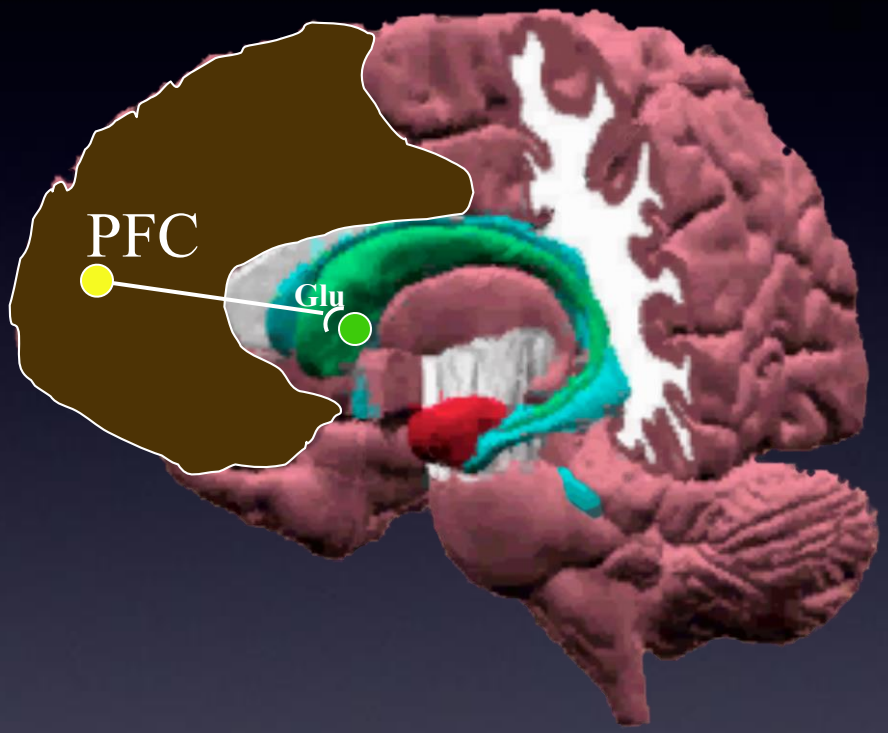
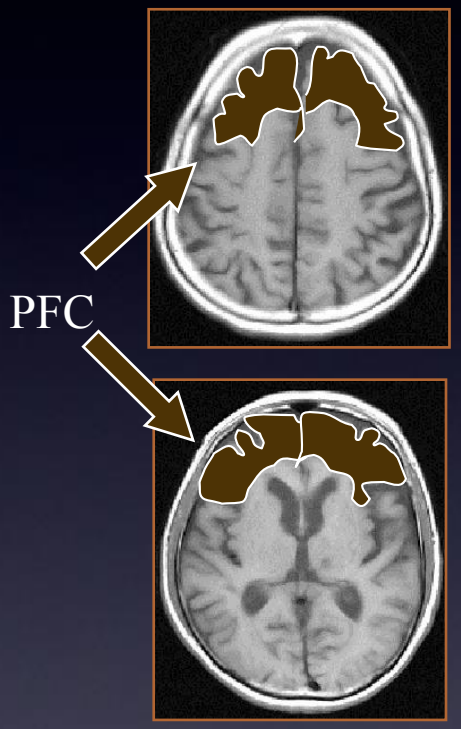
Cortical-striatal-thalamic circuitry simplified





- Prefrontal cortex
  Glutamatergic neurons project to the striatum

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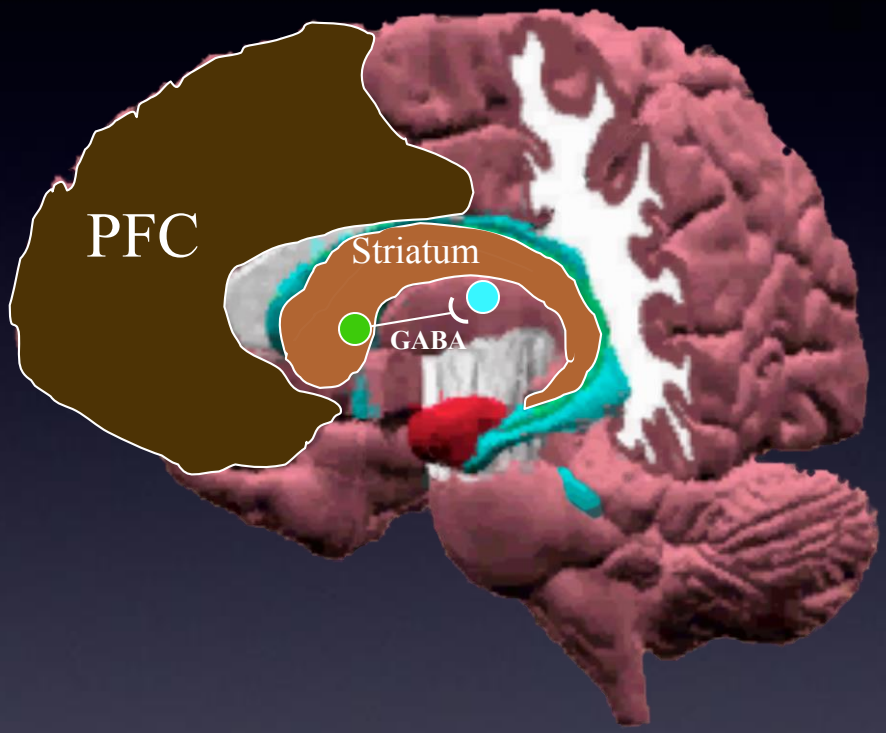
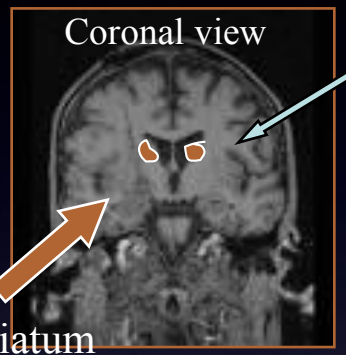
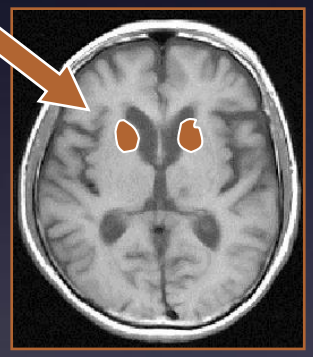
Cortical-striatal-thalamic circuitry simplified





Dorsal Striatum
(Caudate)



Horizontal view

- The striatum is made up of GABAergic neurons
- There are separate striatal structures: the dorsal striatum (caudate, putamen), and the ventral striatum (nucleus accumbens)

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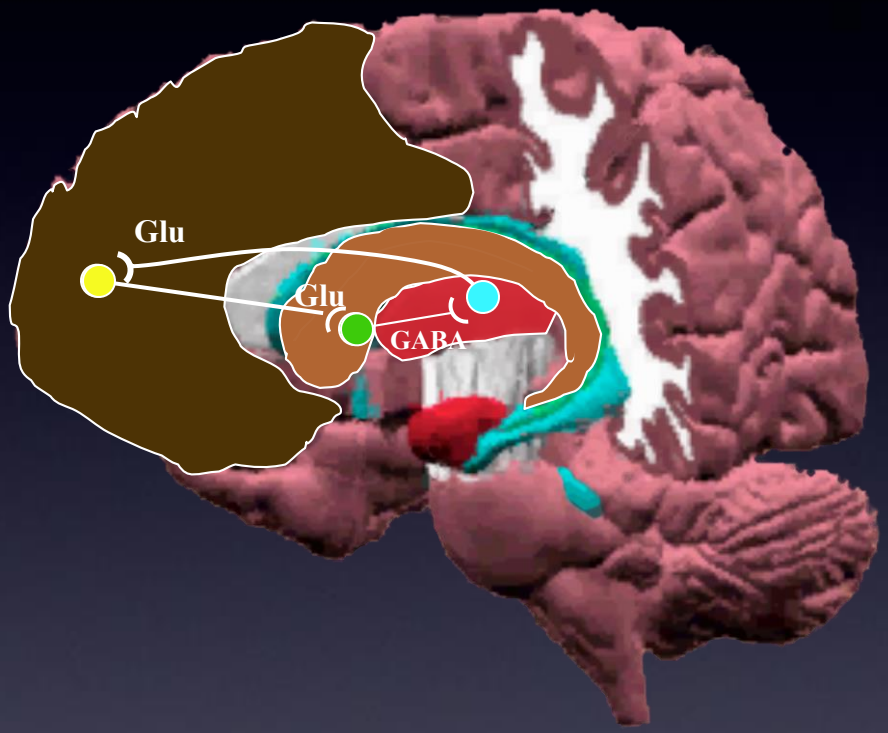
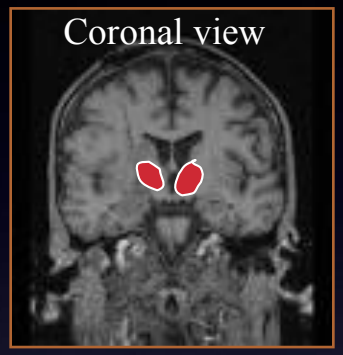
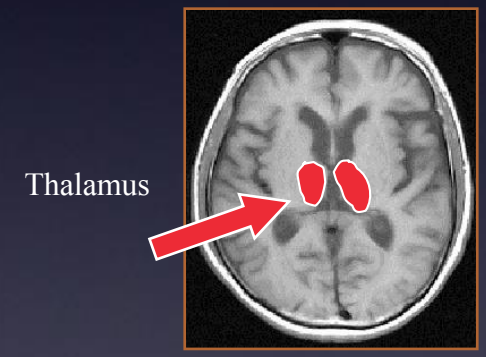
Cortical-striatal-thalamic circuitry simplified







- The thalamus is the final place prefrontal output is processed before it returns to back to the prefrontal cortex; it is glutamatergic

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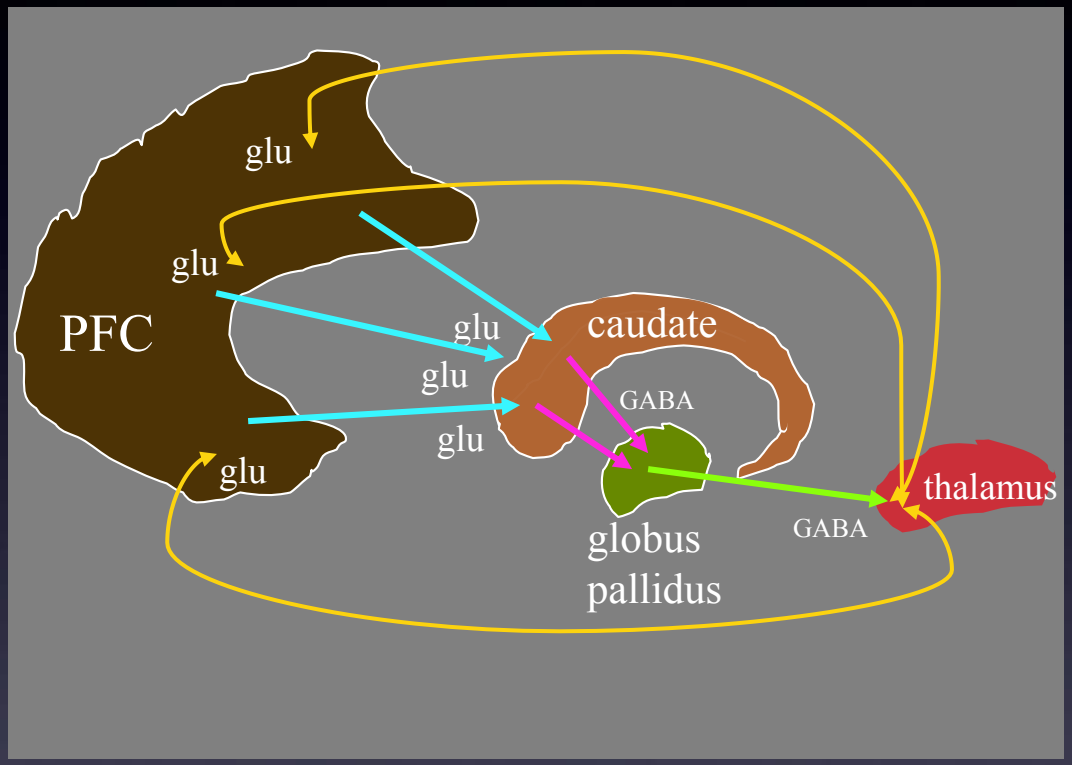
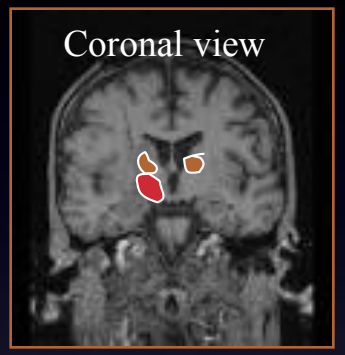
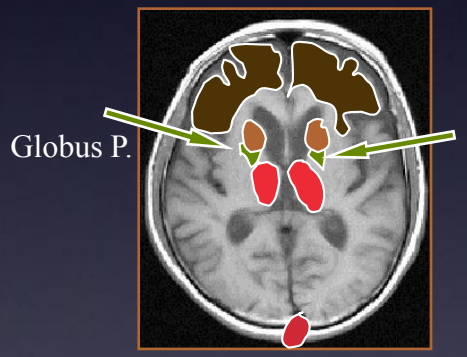
Cortical-striatal-pallidal-thalamic circuitry





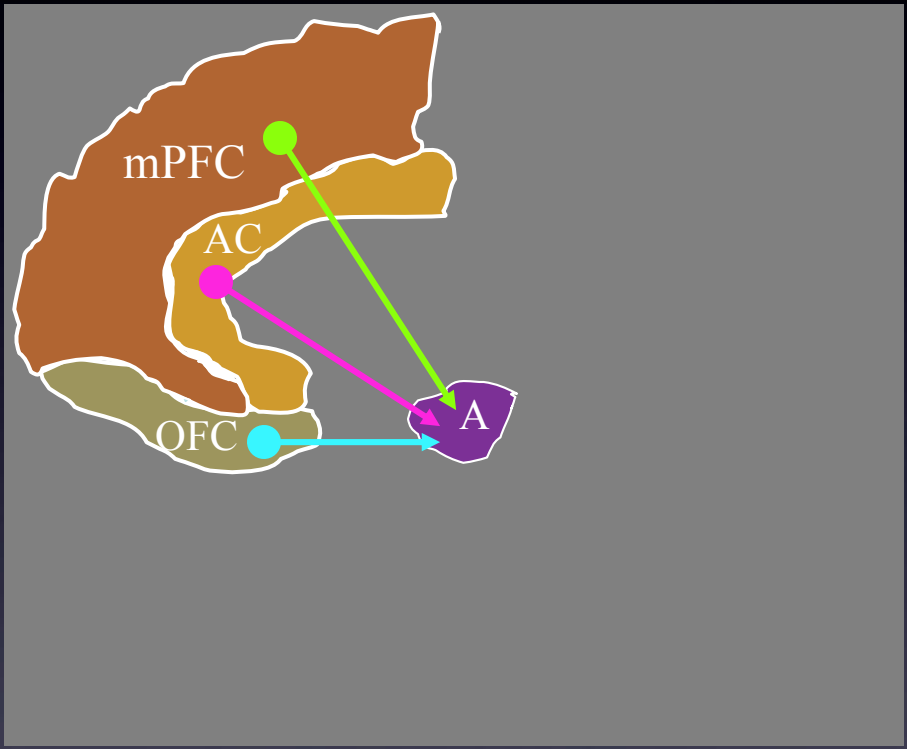


Horizontal view

This is an expanded view of the circuit with glutamate and GABAergic projections, the globus pallidus is here seen in green (not visible before).

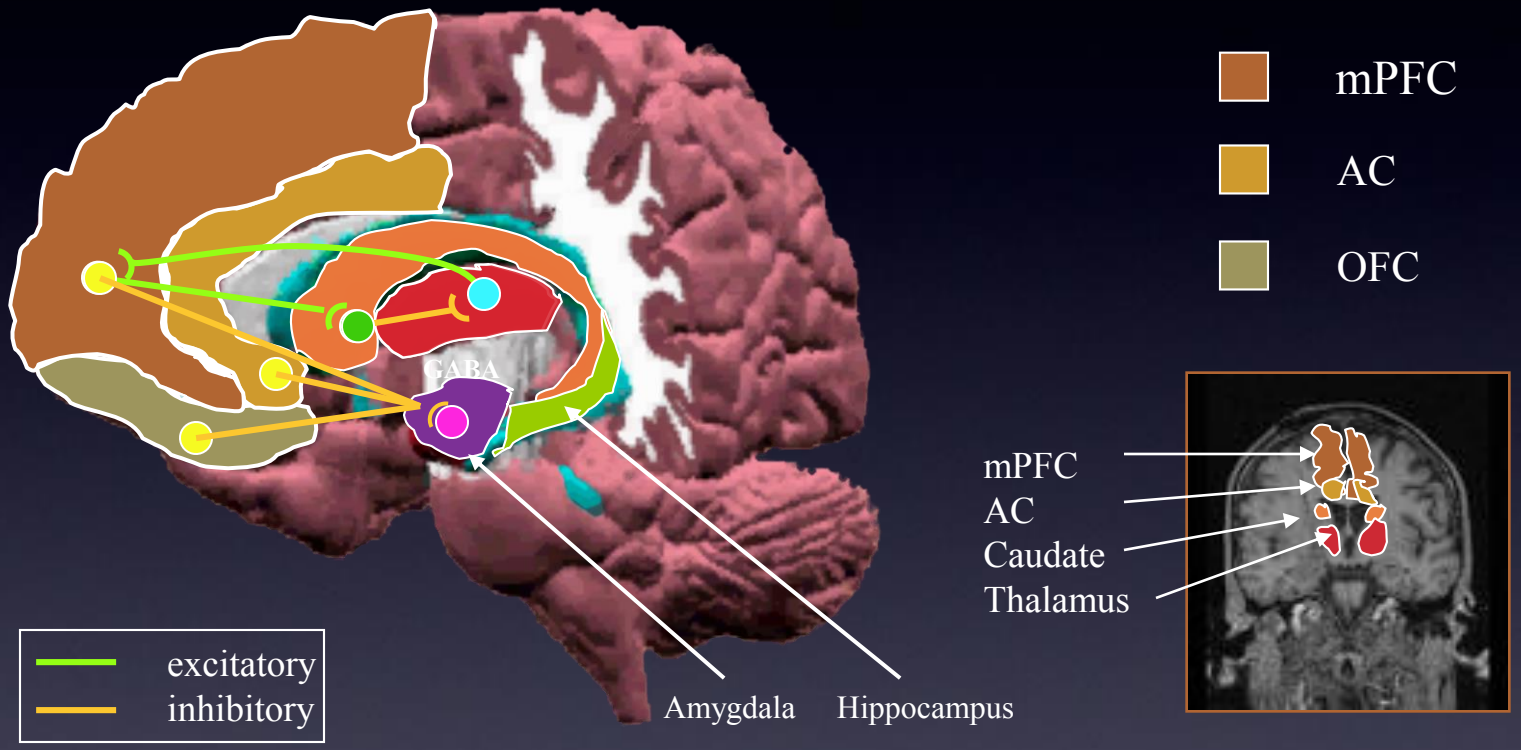
Pallidal projections are GABAergic and go to the thalamus.

Cortical and limbic connections: the prefrontal cortex inhibits the amygdala



- The mPFC, OFC, and AC all inhibit amygdalar activity
- When these structures are dysregulated, amygdalar activity is less modulated by the prefrontal cortex: anxiety and emotional responses are less controlled; fear may be more easily aroused.

Cortical and limbic connections



When prefrontal-striatal-thalamic processing is dysregulated, prefrontal function inhibition of hippocampus/amygdala will be disconnected resulting in:

- abnormal function in the mPFC, AC, and the OFC
- anxiety, autonomic arousal, hypothalamic pituitary axis (HPA) activation

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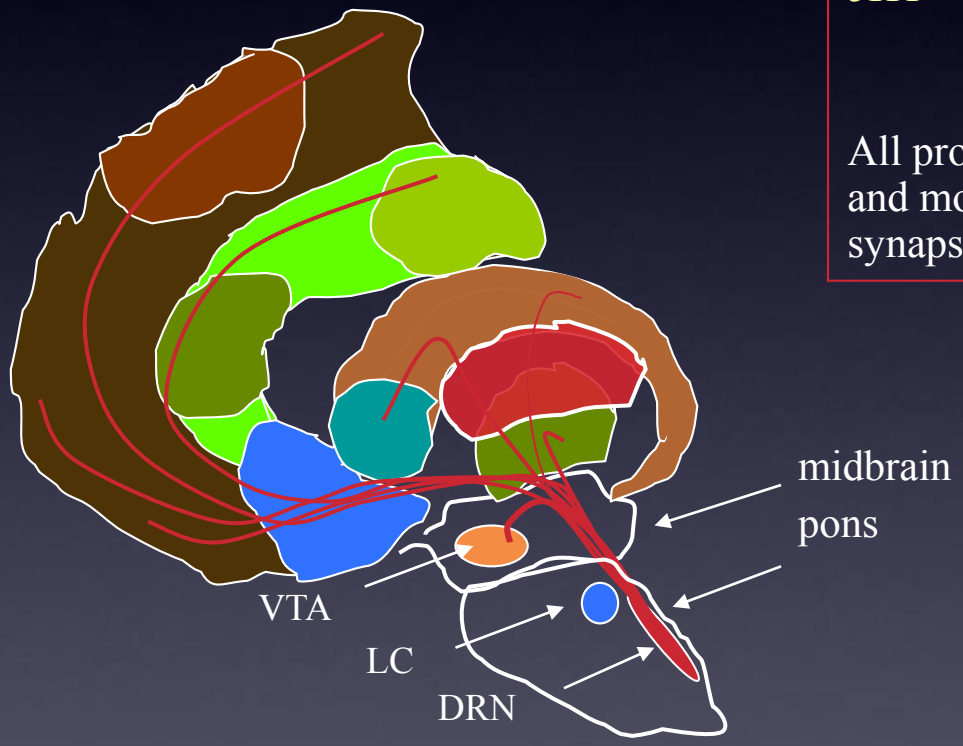
Cortical and limbic connections: role of monoamines (serotonin, norepinepherine, dopamine)

All monoamines have nuclei in the brainstem

DA	ventral tegmental area substantia nigra
NE	locus ceruleus
5HT	dorsal raphe nucleus median raphe nucleus

All project diffusely to all brain structures and modulate activity at GABA/glutamate synapses



Abbrev: dorsal raphe nucleus DRN; locus ceruleus LC; ventral tegmental area VTA; serotonin 5HT, glutamate glu,

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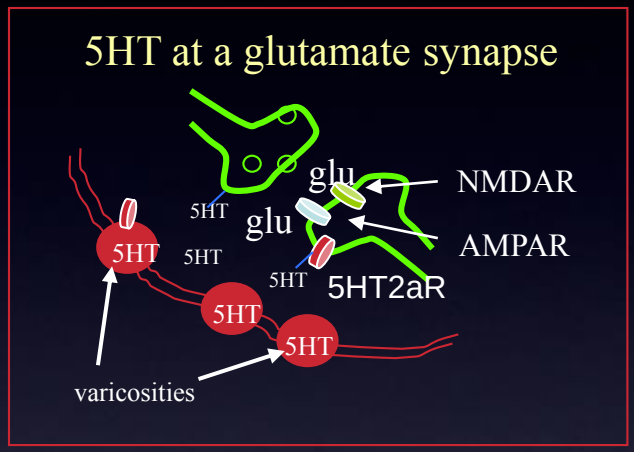
Cortical and limbic connections: role of monoamines (serotonin, norepinepherine, dopamine)

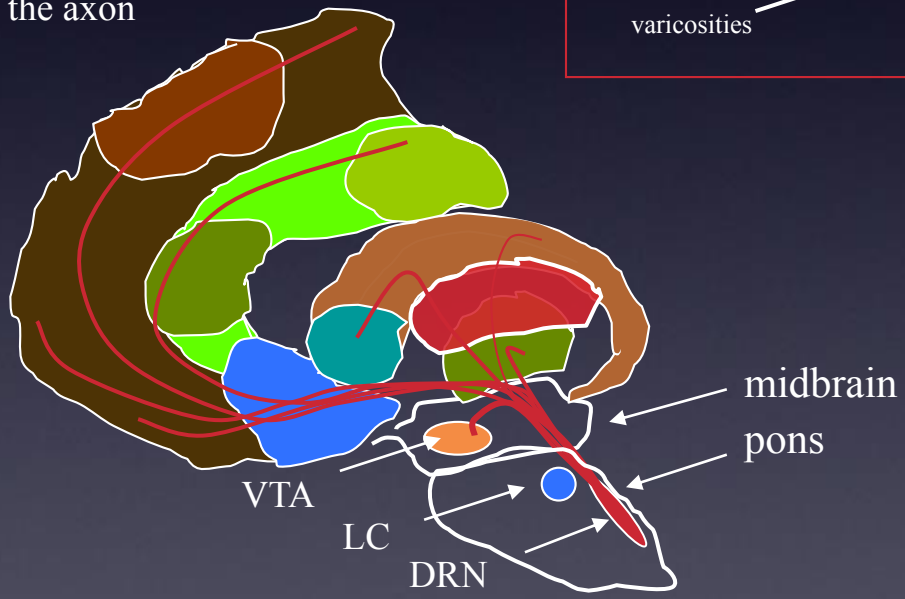
Example (see below and adjacent)

DA, NE and 5HT projections arise from brainstem nuclei

5HT modulates activity at glutamate and GABA synapses

5HT fibers bypass these synapses and release 5HT from varicosities along the axon





Abbrev: dorsal raphe nucleus DRN; locus ceruleus LC; ventral tegmental area VTA; dopamine DA, norepinepherine NE, serotonin 5HT, glutamate glu,

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Key points: Functional Neuroanatomy

Neurocircuitry important in understanding the neurobiology of psychiatric illness

- frontal-subcortical circuits
- frontal-limbic circuits

Prefrontal cortical structures regulate limbic areas

- amygdala
- hippocampus

Neurotransmitters found in these circuits

- GABA
- Glutamate

Monoamine neurotransmitters found in these circuits

- 5HT
- NE
- DA

Neurobiology of Psychiatric Illness:
Schizophrenia

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Overview:
Neurobiologic Abnormalities in Schizophrenia

Dopamine and glutamatergic hypothesis

Brain volume changes
- prefrontal cortex
- limbic structures

Working memory deficits: inefficient cortical processing

Genetic polymorphisms in schizophrenia
- COMT val-met polymorphism and effect on working memory

Postmortem molecular, cellular and structural abnormalities

Neurodevelopmental animal model of schizophrenia

Neurodevelopmental vs neurodegenerative models of schizophrenia

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Neurotransmitter Hypothesis: Dopamine, Glutamate, GABA

Dopaminergic hypothesis

Mesolimbic: hyperdopaminergic

- Mesolimbic structures
  Ventral striatum (Nucleus accumbens, olfactory tubercle),
  bed nucleus of stria terminalis, amygdala, lateral septal nucleus,
  dorsal striatum (caudate)

Mesocortical: hypodopaminergic

- Mesocortical structures
  Entorhinal cortex, Prefrontal cortex (PFC) including dorsolateral pfc,
  orbitofrontal pfc, and anterior cingulate

Results in overactive limbic areas

Poor prefrontal/executive function

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Neurotransmitter Hypothesis: Dopamine, Glutamate, GABA

Hypoglutamatergic hypothesis

Consequence of hypofunctional glutamatergic neurons in the prefrontal cortex

- abnormal cortical feedback to ventral tegmental area (VTA) disinhibits the VTA causing increased dopamine release in limbic areas
- disinhibits substantia nigra, causing increased dopamine release in dorsal striatum

Results in abnormal regulation of both cortical glutamate and GABA

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Neurotransmitter Hypothesis: Dopamine, Glutamate, GABA

Hypoglutamatergic hypothesis

During neurodevelopment, this hypoglutamergic state results in abnormal connectivity and function of prefrontal cortex and limbic areas resulting in inefficient cortical processing and both positive and negative sx

Pharmacologic model of schizophrenia

Negative and positive symptoms are mimicked by the NMDA glutamate receptor antagonist ketamine

Supports hypoglutamatergic hypothesis

Multiple structures of the brain are reduced in volume in schizophrenia

Prefrontal cortex

Temporal cortex

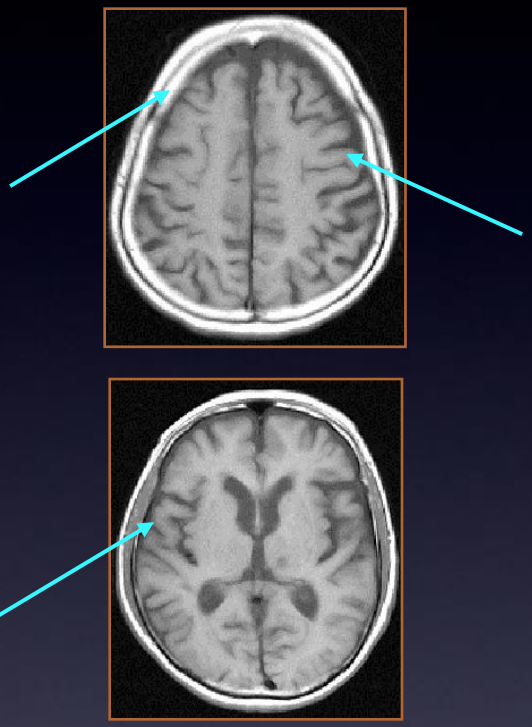
Entorhinal cortex

Parahippocampal cortex

Hippocampus

Cortical and limbic structural abnormalities in schizophrenia

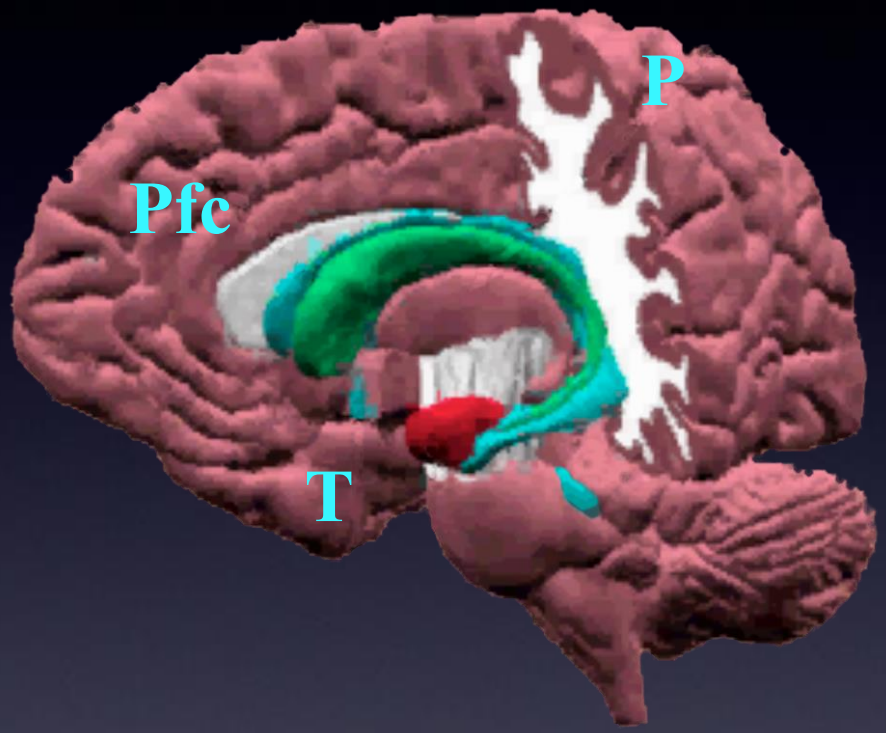
Area of reduced gray matter volume

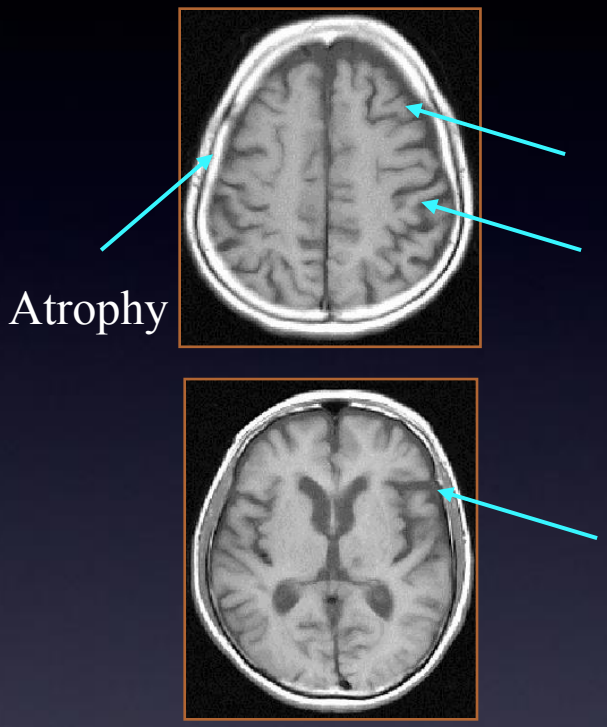


- Decreased total gray matter volume
  Overall 7%, regionally-frontal (Pfc), parietal (P), temporal (T)

Davatzikos C et al. Arch Gen Psychiatry 62:1218-1227 (2005). Pfefferbaum A,et al. Arch Gen Psychiatry 45(7): 633-640 (1988).

Cortical and limbic structural abnormalities in schizophrenia

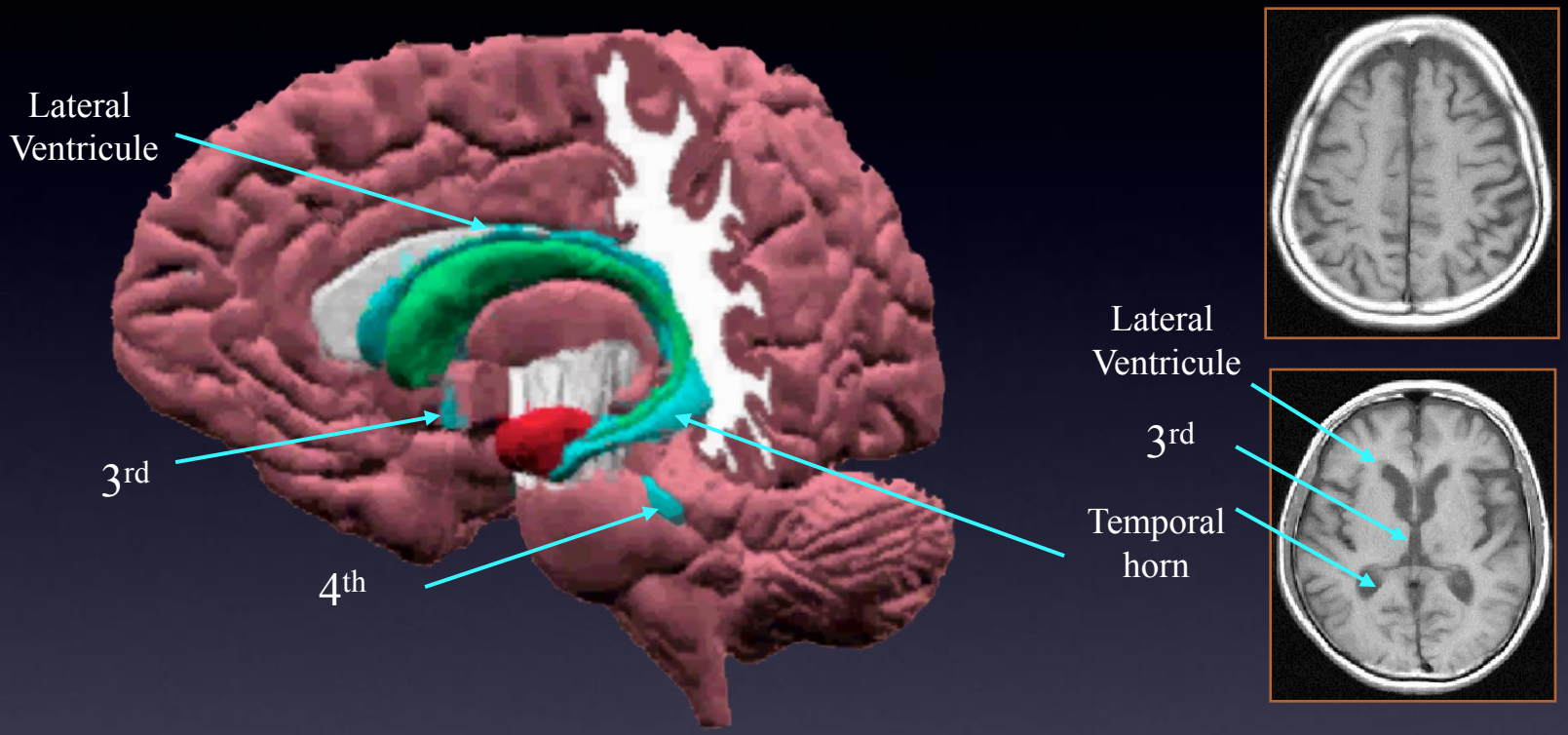




- Reduced total brain volume
  Increased sulcal sizes, increased sylvian fissure

Davatzikos C et al. Arch Gen Psychiatry 62:1218-1227 (2005). Pfefferbaum A,et al. Arch Gen Psychiatry 45(7): 633-640 (1988).

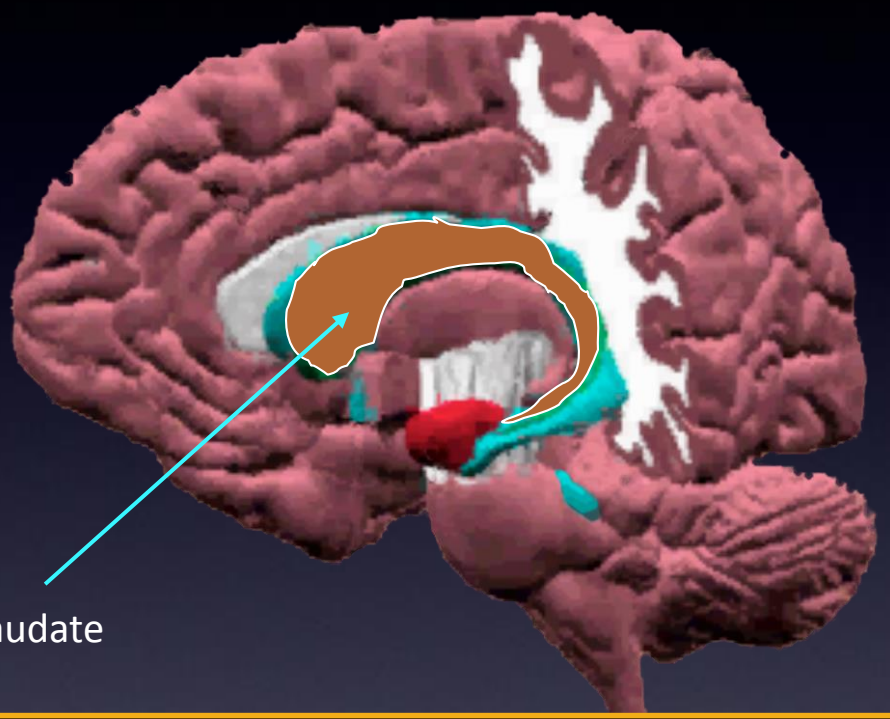
Cortical and limbic structural abnormalities in schizophrenia

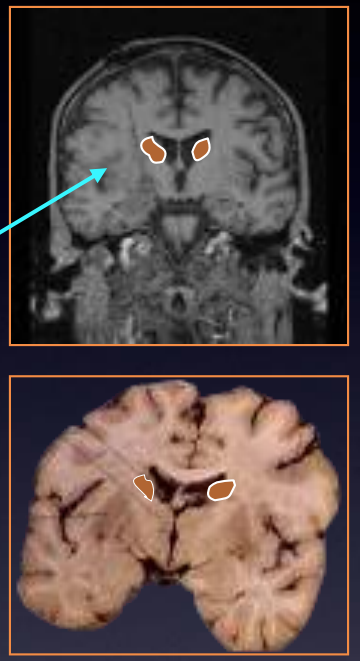


- Ventriculomegaly
  Enlarged lateral ventricle, temporal ventricular horn, 3rd and 4th ventricles, septum pellucidum

Davatzikos C et al. Arch Gen Psychiatry 62:1218-1227 (2005). Pfefferbaum A,et al. Arch Gen Psychiatry 45(7): 633-640 (1988).

Cortical and limbic structural abnormalities in schizophrenia





- **Caudate**
  Neuroleptic naïve decreased, but increased with typical antipsychotics
  May not be increased with atypical antipsychotics
  (with possible exception of risperidone)

Lang D et al. Am J Psychiatry 161(10):1829-1836 (2004). Massana G et al. J Clin Psychopharm 25(2):111-117 (2005).
Glenthoj A et al. Psychiatry Res. 154(3):199-208 (2007).

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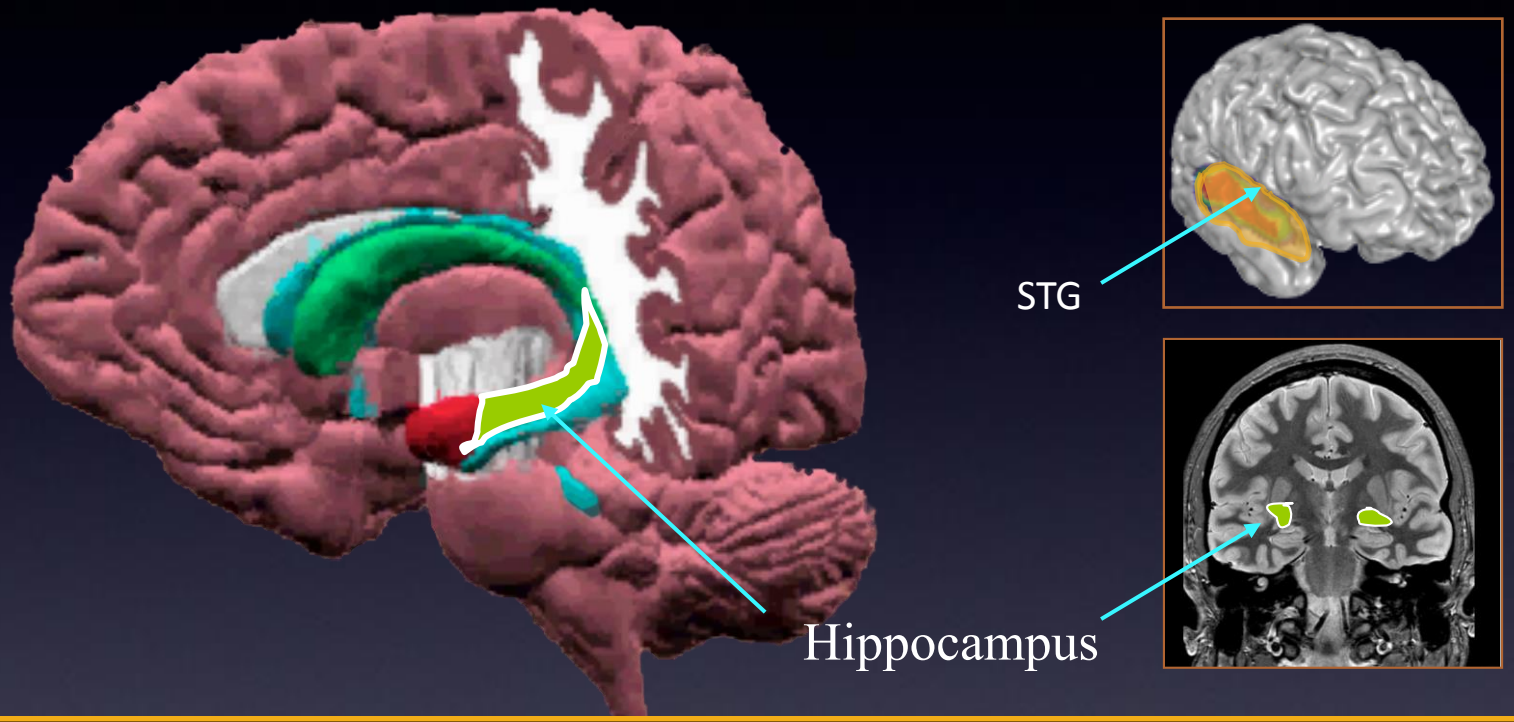
Cortical and limbic structural abnormalities in schizophrenia



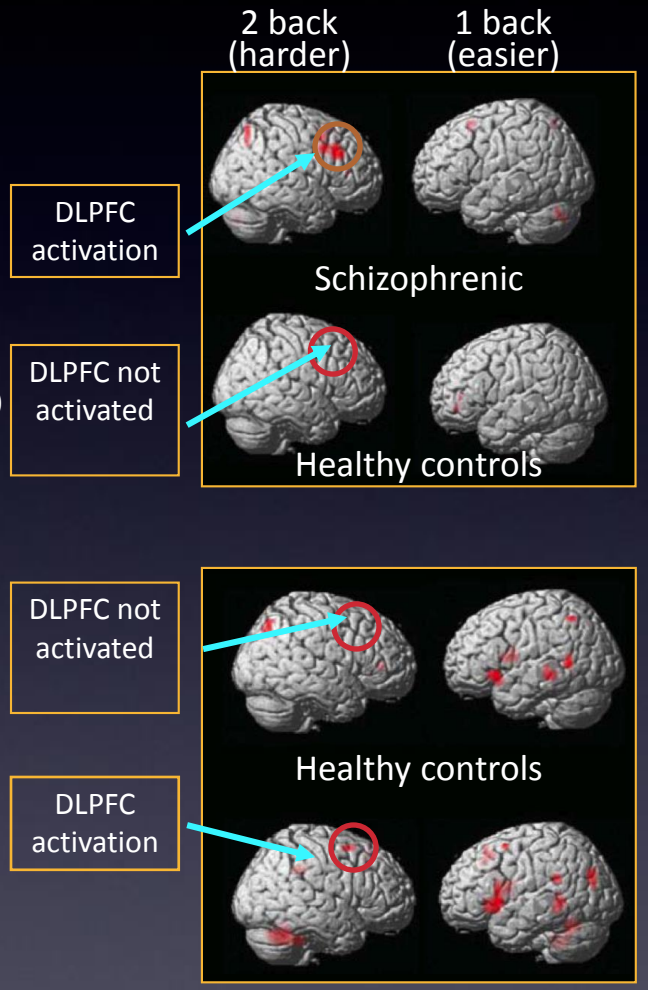
Temporal lobe decreased volume found in:

- Superior temporal gyrus (STG) planum temporale
- Mesial temporal structures - hippocampus, entorrhinal cortex, parahippocampus cortex

Takahashi T et al. Schizophr Res 83(2-3): 131-143 (2006). Yamsaki S et al. Eur Arch Psychiatry Clin Neurosci 257(6):318-324 (2007).

Working memory deficits in schizophrenia:
Dysfunction of the DLPFC and abnormal prefrontal connectivity

- 'N-back test' examines executive function (specifically 'working memory') which depends on activation of the DLPFC
- Schizophrenic subjects had a greater increase of metabolic activity in the DLPFC as the difficulty increased (their brain had to work harder to do the same as controls)
- This difference is still seen when controlling for equal performance between the controls and schizophrenic subjects
- This indicates that schizophrenic subjects have inefficient prefrontal activation in an executive function task (working memory)



Tan H-Y, et al.. Am J Psychiatry 163:1969-1977 (2006).Glahn D et al.. Human Brain Mapp 25:60-69 (2005).

Polymorphism of the catecho-O-methyl transferase (COMT) associated with prefrontal cortical dysfunction in schizophrenic subjects

Inefficient prefrontal cortex processing

Working memory (WM) impairment observed in schizophrenia

COMT metabolizes dopamine and norepinepherine at the synapse

COMT polymorphism at position 158: val to met

Val-val genotype has increased enzymatic activity, hence lower dopamine (DA) levels at synapse (DA more rapidly cleared than val-met or met-met)

Met-met genotype has less enzymatic activity, and dopamine levels at the synapse are higher (DA more slowly cleared from synapse)

DA levels act to 'fine tune' glutamate release and prefrontal cortical processing to maximize performance during working memory tasks

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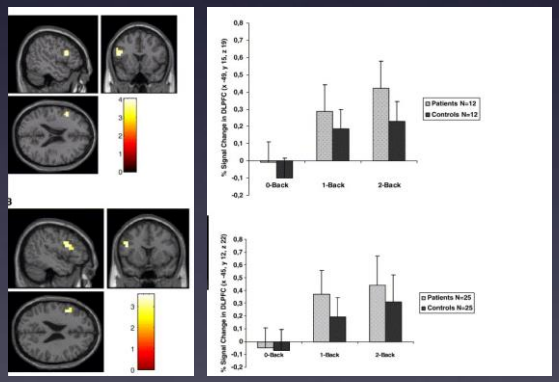
Polymorphism COMT gene associated with inefficient prefrontal processing as well as volumetric reductions In multiple brain structures

Val-val polymorphism associated with more hypermetabolism with working memory task than controls, even after controlling for performance (equally performing schizophrenic subject's brain compensates for inefficient processing by working harder eg are hypermetabolic)

Val-val polymorphism associated with greater volume reduction in schizophrenic subjects in prefrontal and limbic areas

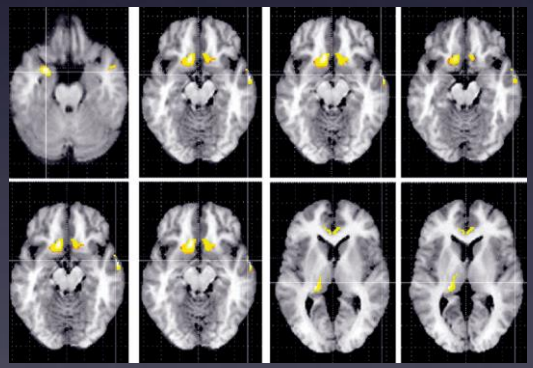
Overall importance: these data connect DA and GLU neurotransmitter hypotheses and observations of volumetric reductions in prefrontal and limbic structures resulting in abnormal circuitry and inefficient processing

Inefficient prefrontal processing



Val-val: cortex more hypermetabolic than met-met[21],and has poorer WM performance

Volumetric reduction



Areas reduced in volume: val-val associated with greater volume reductions than met-met[22]

Ohnishi T, et al.. Brain 129:399-410 (2006). Bertolino A, et al. Psychiatry Res 147(2-3) 221-228 (2006).

Post-mortem studies

Increased cell number, reduced gray matter, increased neuropil: prefrontal and auditory cortex, caudate, lateral nucleus of amygdala

Abnormal migration of cortical pyramidal cells in development found deep in white matter; remnant of migrating cells in developing brain

Abnormalities in oligodendrocytes

Abnormalities affecting neuronal maturation, survival, plasticity, synaptic integrity (synaptophysin, growth associated protein-GAP43)

Abnormalies in glutamate synapses in DLPFC: decreased binding kainate receptors, decreased mRNA of GluR5, glucocorticoid receptor

Abnormalities in GABA, Glu, DA neurotransmitter systems or synapses, in DLPFC and elsewhere: presynaptic GAD67, and reuptake channels; neuropeptideY, CCK; GABAA receptor subunits $\alpha 1$, $\alpha 3$, $\alpha 2$

Selemon LD,.Biol Psychiatry 45:17-25 (1999. .Kreczmanski P,et al. Brain 130:678-692 (2007) Knable M et al. Mol Psychiatry 7(4):392-404 2002
Hashimoto Tet al. Molec Psychiatry epub 1 May (2007). Flynn S et al. Mol Psychiatry 8(9):811-820 (2003). Weickert C et al. Cereb Cortex 11(2): 136-47 (2001).
Scarr E et al. Neuropsychopharmacology 30(8):1521-1531.

Neurodevelopmental vs Neurodegenerative Processes in Schizophrenia

Higher risk due to prenatal, perinatal or postnatal exposure to neuronal insult such as, infection, hypoxia, hypoglycemia, hypercortisolism,or genetic vulnerability

Abnormalities noted early in life cognitive/motor/social . Large prospective studies have confirm

Ventriculomegaly in twin studies: blinded raters can predict twin with schizophrenia by degree of *:* correlated to premorbid motor and social abnormalities, poor cognitive function

Reduced prefrontal gray matter volume over time,as well as reduced N-acetyl aspartate (NAA- a marker of neuronal number/viability) may be a neurodegenerative process due to excitotoxic glutamatergic activity

Lysaker P et al.. J Psychosoc Nurs Ment Health Serv 45(7):24-30 (2007). Lewis DA et al. Annu Rev Neruosci 25:499-532 (2002).
Isohanni M et al. World Psychiatry 5(3):168-171 (2006).Baare WF et al. Arch Gen Psych 58(1):33-40 (2001).
Van Haren N et al. Neuropsychopharmacology 32 (10):2057-2066 (2007) Abbot C et al. Curr Opin Psychiatry 19:135-139 (2006).

Key Points: Neurobiology of Schizophrenia

Marked cognitive impairment is a key feature of schizophrenia
- reduced prefrontal gray matter volume
- lower DA levels in COMT genotype val-val

Post-mortem abnormalities in brain structures, neurotransmitters etc.
- decreased volume in prefrontal, limbic, and subcortical structures
- abnormal migration during fetal development of cortical neurons

Schizophrenia may be due to
- neurodevelopmental abnormalities
- neurodegenerative abnormalities
- both, in at least some individuals

Lewis D et al. Annu Rev Neruosci 25:499-532 (2002).

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Olney J, Farber NB. Glutamate receptor dysfunction and schizophrenia. Arch Psychiatry 52:998-1007 (1995).

Cummings JL. Frontal-subcortical circuits and human behavior. Arch Neurol 50 (8):873-80 (1993).

Davatzikos C, Dinggang S et al. Whole-brain morphometric study of schizophrenia revealing a spatially complex set of focal abnormalities Arch Gen Psychiatry 62:1218-1227 (2005).

Pfefferbaum A, Zipursky RB et al. Computed tomographic evidence for generalized sulcal and ventricular enlargement in schizophrenia. Arch Gen Psychiatry 45(7): 633-640 (1988).

Van Haren NE, Pol HE et al. Progressive volume loss in schizophrenia over the course of illness: Evidence of maturational abnormalities in early adulthood. Biol Psychiatry 63(1):106-113 (2008).

Lang DJ, Kopala LC et al. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. Am J Psychiatry 161(10):1829-1836 (2004).

Massana G, Salgado-Pineda P et al. Volume changes in gray matter in first-episode neuroleptic-naïve schizophrenic patients treated with risperidone. J Clin Psychopharm 25(2):111-117 (2005).

Glenthoj A, Glenthoj BY et al. Basal ganglia volumes in drug-naïve first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypcial antipsychotic drug. Psychiatry Res. 154(3):199-208 (2007).

Kim JJ, Kim DJ et al. Volumetric abnormalities in connectivity-based subregions of the thalamus in patients in patients with chronic schizophrenia. Schizophr Res. 97(1-3):226-235epub Oct 30 (2007).

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Neurobiology of Psychiatric Illness:
Bipolar Disorder

Hugh Brent Solvason PhD MD
Associate Professor
Stanford University
Department of Psychiatry

Overview:
Neurobiologic Abnormalities in Schizophrenia

Illness course

Volumetric studies
- prefrontal cortex
- limbic structures

Functional imaging studies

Genetic polymorphisms in schizophrenia
- BDNF (brain derived neurotrophic factor)

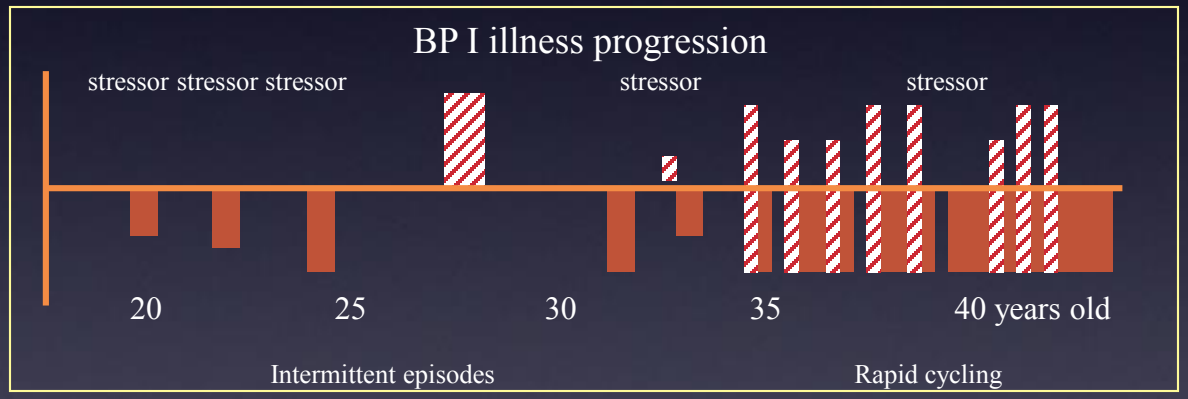
Neuronal metabolic abnormalities

Gene expression glycogen synthase kinase 3 (GSK-3)

Illness progression in bipolar disorder

Key Points : progressive change in illness over 20 years

- Dysphoric/mixed episodes more than euphoric mania
- Rapid cycling
- Well interval decreased



Adapted from R.Post http://www.medscape.com

Volumetric studies in mood disorders

Unipolar	(+studies)	Bipolar	(+studies)
↑ ventricles	(2/2)	↑ ventricles	(10/16)

Best replicated finding

Cortical volume		Cortical volume	
↓ temporal lobe	(0/1)	↓ temporal lobe	(10/20)
↓ prefrontal lobe	(6/9)	↓ prefrontal lobe	(4/8)
↓ orbitofrontal pfc	(9/13)	↓ orbitofrontal pfc	(7/10)
↓ dorsolateral pfc	(0/0)	↓ dorsolateral pfc	(4/6)
↓ subgenual pfc	(1/2)	↓ subgenual pfc	(2/4)
↓ anterior cingulate	(3/3)	↓ anterior cingulate	(7/9)

Konarski et al. Bipolar Disorder 10:1-37 (2008)

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Volumetric studies in bipolar disorder

Postmortem: amygdala volume decreased

Lateral nucleus	total volume
	total neuron number
	neuron density
Accessory basal nucleus	total neuron number

MRI: progressive decrease in gray matter prospectively over 4 years

hippocampus
temporal lobe
cerebellum

cognitive decline: correlates with verbal and performance IQ
illness course: correlates with number of mood episodes in 4 yr follow up period
Lithium treatment: increases hippocampal/amygdalar volume

Frazier, J. A. et al. Schizophr Bull 2008 34:37-46; doi:10.1093/schbul/sbm120.
William T Biol Psych 62: 894-090 2007
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Functional imaging studies in Bipolar disorder

Frontal subcortical neural network dissconnected in euthymic subjects

- euthymic bipolar and healthy control subjects identifying sad affect during fMRI
- Controls: processing negative affect activate cortical-subcortical network
- BP: activate hippocampal/amygdalar (subcortical) without cortical activation
- BP: lamotrigine increases cortical activation, decreases overactivity in temporal lobe

Cortical structures showed abnormal activation pattern in two tasks

- euthymic bipolar I vs healthy controls with fMRI
- N-back test shows abnormal DLPFC activation; increased parietal cortex activation
- gambling task (assess ventral pfc function) showed decreased pfc activation
- Bipolar subjects had increased activation of the temporal cortex and temporal pole

Lagopoulos J, Malhi GS.. Neuroreport 18(15): 1583-7 2007
Frangou S Kington J et al. Eur Psychiatry epub Jul;24 2007
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Genetic polymorphism in bipolar disorder

BDNF val^{66}met polymorphism

Met allele associated with:

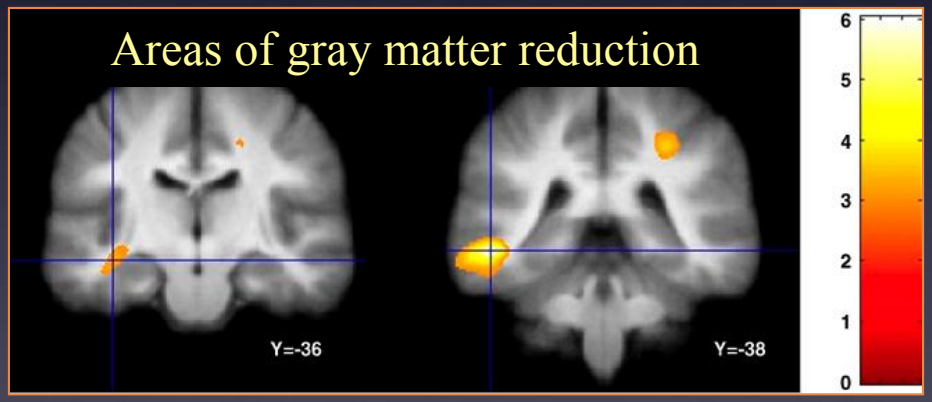
hippocampal function poorer for episodic memory

hippocampal activation abnormal

BP subjects with met allele (vs. no met-allele subjects)

progressive reduction in temporal lobe gray matter over 4 years

progressive hippocampal (left lateral area) volume reduction over 4 years



McIntosh A Moorhead T, McKirdy J, Sussman J, Hall, J, Johnstone E, Lawrie S. Temporal gray matter reductions in bipolar disorder are associeated iwtht eh BDNF val66met polymophism. Molecular Psychiatary 12:902-3 2007

Mechanism of action:valproate (VPA)/ lithium (Li)

Lithium and VPA are mood stabilizers

- Mechanism of action include effects on inositol metabolism, apoptotic enzymes
- GSK-3 is an enzyme that has profound effects on cell viability and metabolism
- GSK-3 activity is associated with poor viability and neuron death; inhibition improves survival

Mechanism of Li and VPA effect on GSK-3

- Lithium and VPA inhibit GSK-3,
- Li through its direct effect inhibiting the enzyme,
- VPA changes gene expression, acts as histone deacetylase (HDAC) antagonist,
  Opens 1-2% of genome, increasing expression of proteins such as BDNF.

Li and VPA effect on GSK-3

- Tested in in-vitro model of glutamate excitotoxicity with cerebellar granule cells
- Combination treatment was neuroprotective via effects on GSK-3 in rats
- Lithium also increases BCL-2, preventing programmed cell death in vitro
- Lithium increased hippocampal volume in prospective 2-4 year trial in human subjects

Leng Y, et al. J Neurosci 28(10):2576-88 2008
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Key Points: Neurobiology of Bipolar Disorder

Progressive gray matter loss may explain illness progression

- characteristics of mood episodes
- less well time
- response to treatment
- cognitive impairment over time

Post-mortem abnormalities support loss of gray matter in limbic structures

Lithium and VPA

- may have therapeutic effects in bipolar disorder by inhibiting GSK-3, thus promoting neuronal viability and survival
- Lithium has direct inhibitory effects on GSK-3
- VPA is a histone deactylase antagonist ,changes gene expression indirectly

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Post R http://www.medscape.com

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Yucel K, McKinnon M, Taylor V et al. Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. Psychopharmacology epub 20 Aug 2007

Neurobiology of Psychiatric Illness:

Major Depression

Hugh Brent Solvason PhD MD
Associate Professor
Stanford University
Department of Psychiatry

*

Multisystem dysregulation in depression

"Converging clinical, biochemical, neuroimaging, and postmortem evidence suggests that depression is unlikely to be a disease of a single neurotransmitter system. Rather, it is now generally viewed as a systems-level disorder affecting integrated pathways linking select cortical, subcortical and limbic sites, and their related neurotransmitter and molecular mediators"

Mayberg H, Lozano A, Voon V, et al 2005. Deep brain stimulation for treatment resistant depression. Neuron 45:651-60 2005

Overview

SgACC dysregulated in mood disorders

- depressive symptoms correlate with hypermetabolism of the sgACC
- volumetric studies: sgACC reduced in size
- postmortem studies: abnormalities primarily in glia

Limbic structures

- volumetric studies: abnormalities in hippocampus
- postmortem studies: abnormalities in hippocampus

Brain Derived Neurotrophic Factor (BDNF)

- stress decreases BDNF, causes dendritic atrophy
- all antidepressants normalize BDNF levels

Illness course: influence of prior mood episodes on neurobiology

- higher number of prior mood episodes associated neurobiologic abnormalities
- cytoarchitectural abnormalities
- volumetric reduction of prefrontal/limbic areas

Antidepressant treatments

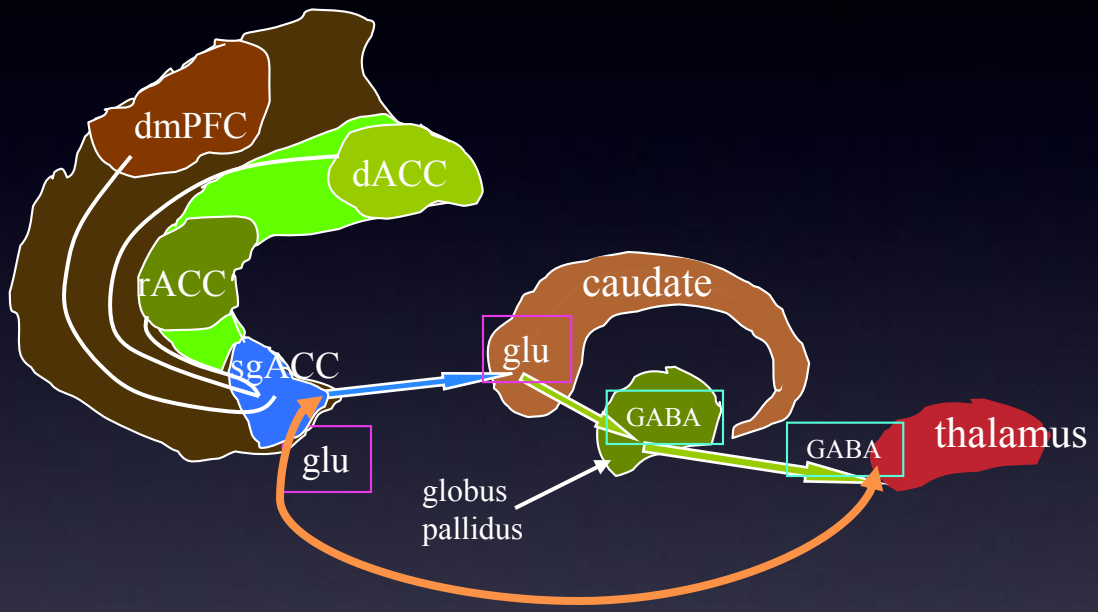
- normalize activity withthin the sgACC
- normalize BDNF levels

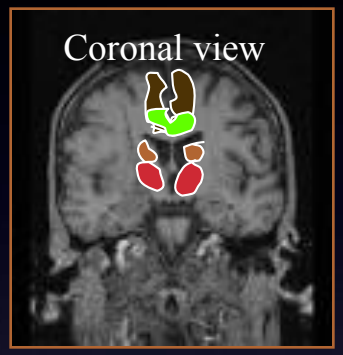
Neurocircuitry Dysfunction in depression

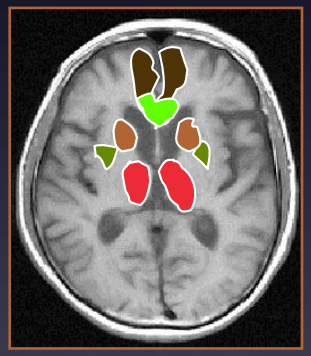
Dysregulated circuits in major depression

- Prefrontal cortical-striatal-pallidal-thalamic pathways
- Prefrontal cortical-limbic pathways
- Prefrontal cortical-aminergic feedback pathways
- Paralimbic/limbic circuits
- Diffuse innervation by biogenic amine nuclei in brainstem

Cortical-striato-pallidal-thalamic circuitry:
sgACC is processed by subcortical structures as well







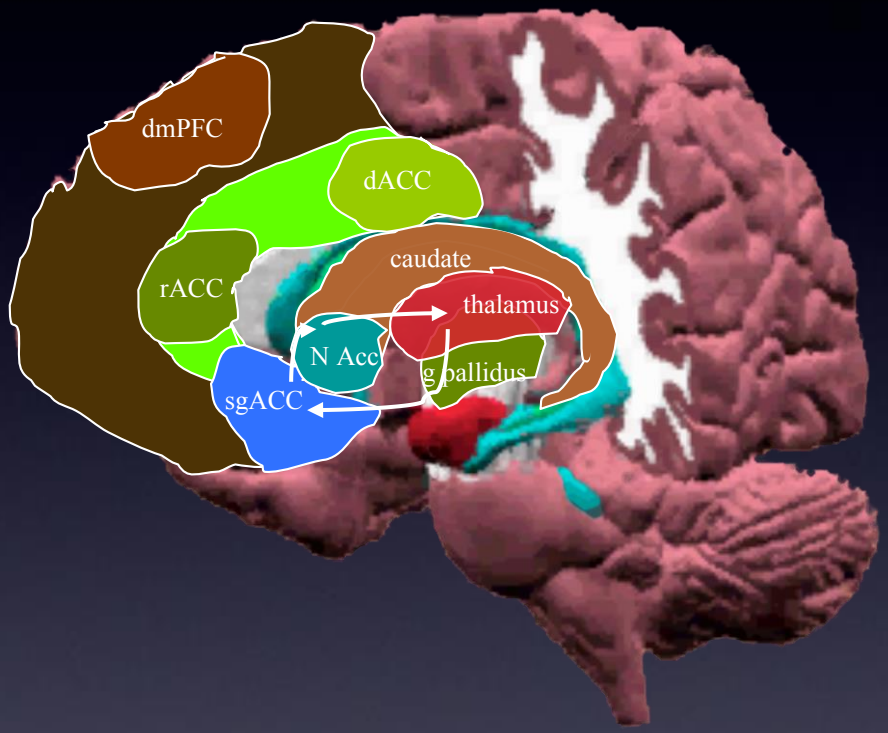
Horizontal view

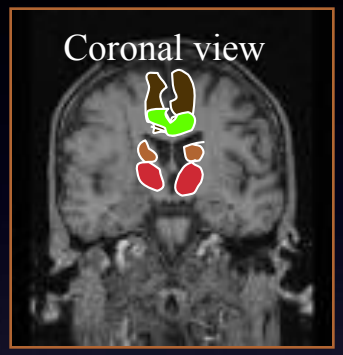
mPFC structures implicated in MDD and connected to the sgACC

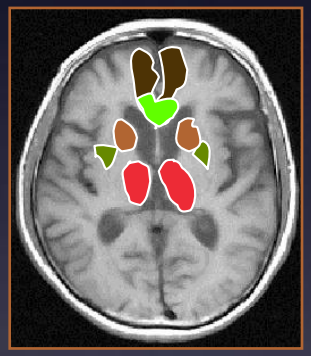
dorsomedial PFC (dmPFC); dorsal ACC (dACC), rostral ACC

subgenual ACC (sgACC) glu glutamatergic synapse GABA gabaergic synapse

Functional neuroanatomy of the mPFC structures







Horizontal view

Function of mPFC structures

dmPFC: self referential processing of emotion

sgACC: sadness, autonomic/endocrine response to stress; appraisal aversive/rewarding stimuli

rACC: emotional stroop (distinguishing emotional affect with distractor)

dACC: more cognitive appraisal of aversive/rewarding stimuli

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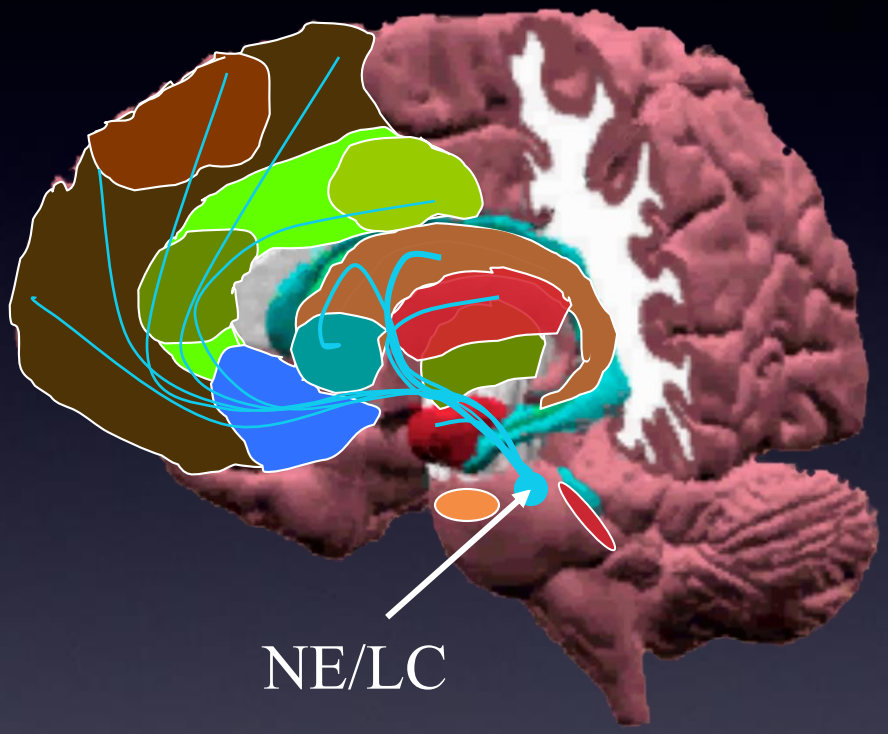
How do monoamines work? Powerful modulaters of GABA and glutamate synapses in cortical-striato-thalamic and limbic circuits



Monoamines/nuclei	
NE	LC
DA	VTA
5HT	DRN/MRN

All nuclei are found in the pons/midbrain.

They project diffusely throughout cortical, subcortical, and limbic areas.

They powerfully modulate activity at glutamate and GABAergic synapses.

Monoaminergic modulation of these synapses can re-regulate neural networks

Abbrev. DRN dorsal raphe nucleus. MRN median raphe nucleus. LC locus ceruleus. VTA ventral tegmental nucleus. NMDAR glutamate receptor, AMPAR glutamate receptor

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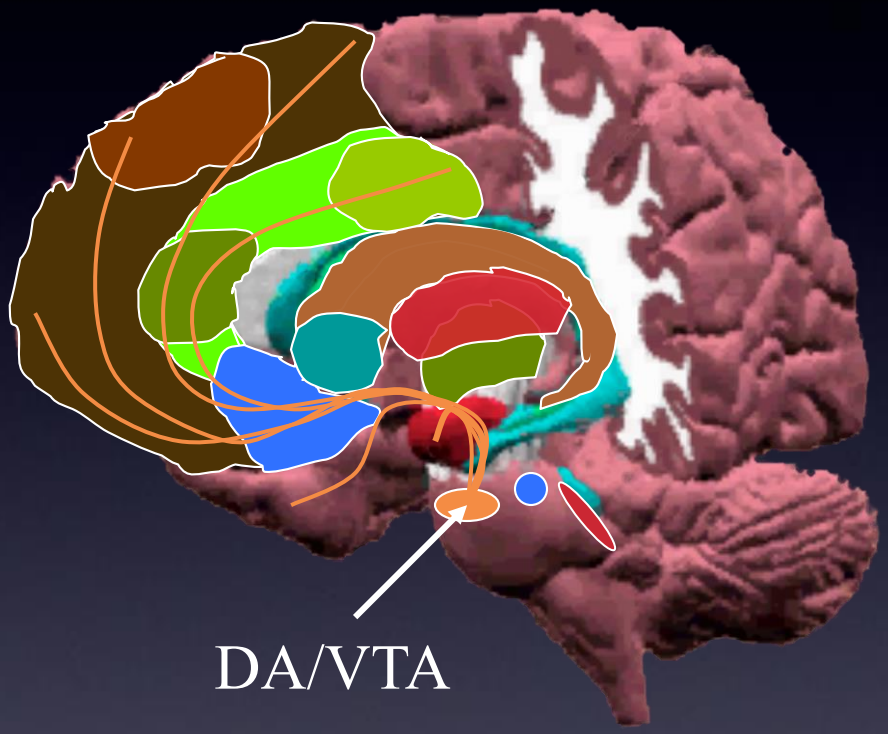
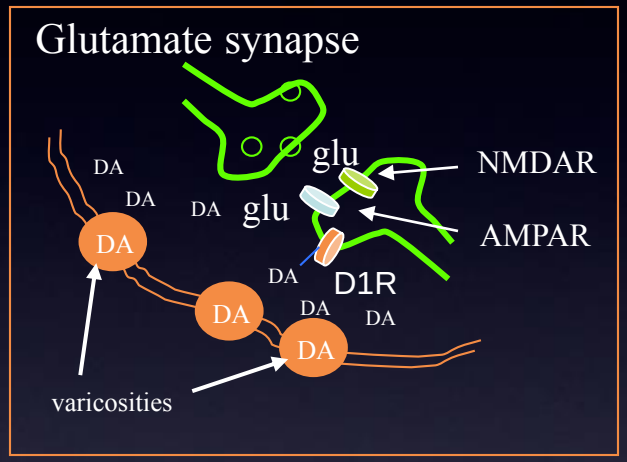
Monoamines: powerful modulaters of GABA and glutamate synapses in cortical-striato-thalamic and limbic circuits



DA/VTA

Dopaminergic system



NE synapses also appear like this

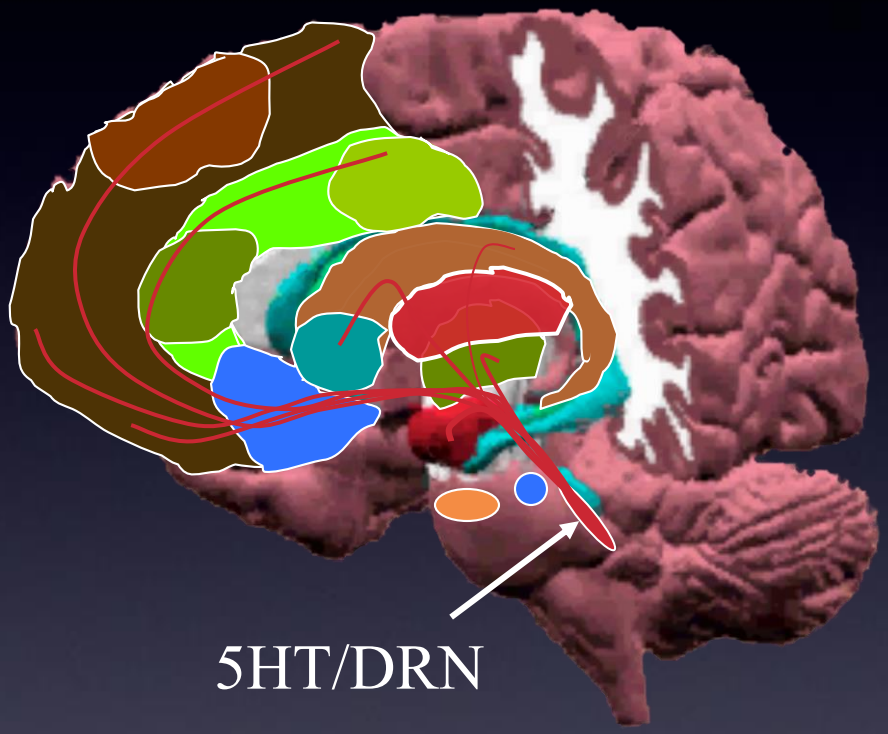
Above: DA fiber projecting from VTA to pyramidal neurons in pfc

D1R is postsynaptic, augments the effect of glutamate neurotransmission

Abbrev. DRN dorsal raphe nucleus. MRN median raphe nucleus. LC locus ceruleus. VTA ventral tegmental nucleus. NMDAR glutamate receptor, AMPAR glutamate receptor

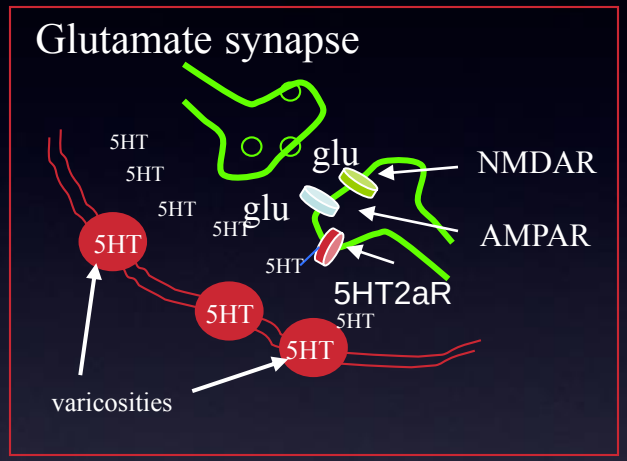
*

Monoamines: powerful modulaters of GABA and glutamate synapses in cortical-striato-thalamic and limbic circuits



5HT/DRN

Serotoninergic system



Above: 5HT fiber projecting from DRN to pyramidal neurons in pfc

5HT2a is postsynaptic, augments the effect of glutamate neurotransmission

Abbrev. DRN dorsal raphe nucleus. MRN median raphe nucleus. LC locus ceruleus. VTA ventral tegmental nucleus. NMDAR glutamate receptor, AMPAR glutamate receptor

mPFC: Cortical-limbic and cortico-cortical circuitry

What is the impact of dysregulation of mPFC/sgACC?
(mPFC highly connected to limbic, paralimbic and other cortical structures)

hypothalamus

regulates CRH release, mPFC dysregulates the hypothalamic pituitary axis

nucleus accumbens

mPFC can dysregulate the dopamine reward system causing anhedonia

ventral striatum

mPFC output dysregulated, not processed normally by ventral striatum

amygdala

mPFC regulates activation of the central nucleus, which is responsible for the neuroendocrine and autonomic response driven by the amygdala

fornix

pathway for communication of mPFC to hippocampus and amygdala

mPFC: Cortical-limbic and cortico-cortical circuitry

What is the impact of dysregulation of mPFC/sgACC?
(mPFC highly connected to limbic, paralimbic and other cortical structures)

hippocampus
- dysregualtion of information/memory processing

orbitofrontal cortex
- alters behavioral and visceral responses to punishing and hedonic stimuli

ventrolateral pfc
- would impair integration of stimuli with emotional salience

rostral and middorsal ACC
- impair sense of understanding of emotional information about self and others

dorsomedial pfc
- would impair integration of self referential information, understanding the state of mind and behavior of others

periaqueductal gray
- dysregulation of pain and affective behaviors

Cortical-limbic and cortico-cortical circuitry impact of dysregulation of these circuits

Impairment of function

mPFC and its sub-structures (sgACC, dmPFC, rACC) in depression.

Impact on insight

appraisal, comprehension, integration and action related to self and others situations where dynamic change occurs in rewarding or punishing situations

Key point:

- insight in recurrent MDD appears to be progressively impaired in some patients.
- impairment in insight into interpersonal relationships and ability to function at work has broad ramifications.
- poor decision making creates more stressful situations and higher risk of relapse

Functional imaging in depression: dysfunction in the medial PFC

Medial PFC dysregulated in depression

- hypermetabolism:
  - sgPFC
  - ventrolateral/dorsomedial PFC
- hypermetabolism in default network
  - correlated with illness duration
  - also showed abnormal connectivity with other structures

Hypermetabolism in sgPFC normalizes with antidepressant treatment, also:

- CBT causes decreases in:
  - anterior sgPFC,
  - ventrolateral and dorsomedial PFC
- venlafaxine causes decreases in:
  - posterior sgPFC
  - ventrolateral PFC, (temporal cortex)
- ECT/SSRI's cause decreases in:
  - sgPFC
- Deep brain stimulation
  - decreases sgPFC metabolism in responders

Kennedy S et al. Am J Psychiatry 164:778-788 2007: Mayberg H et al. Neuron 45:651-60 2005;
Greicius M et al. Biol Psychiatry 62(5): 429-37 2007 e pub

Volumetric studies of brain structures in depression

Meta analysis

	(Number of positive studies)
Ventricle/brain ratio increased	
most robust finding	(2/2)
Cortical volume decreased	
temporal lobe	(0/1)
prefrontal lobe	(6/9)
orbitofrontal pfc	(9/13)
dorsolateral pfc	(0/0)
subgenual pfc	(1/2)
anterior cingulate	(3/3)

Key point:

- Decreased structural volumes suggest widespread brain dysfunction in depression

Konarski et al. Bipolar Disorder 10:1-37 (2008)

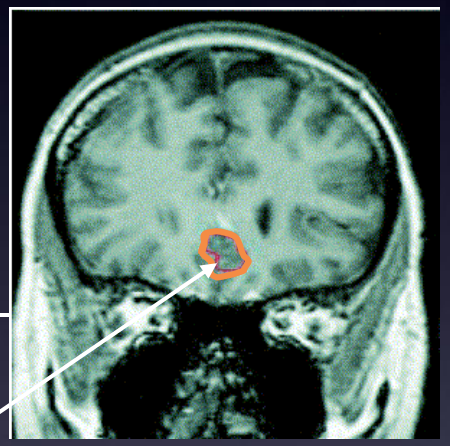
Metanalysis: volumetric studies of subgenual PFC

Meta analysis bipolar and unipolar MRI volumetric studies: 10 studies

Results: Mood disorders all together

sgPFC decreased but sub-analyses showed:
no significant findings in BPD
no significant findings in non-familial MDD

Familial MDD
left sgPFC volume decreased, trend right
no relationship between age and volume



Non-Familial MDD (single report n=15 MDD/21 HC)
reduced medial orbitofrontal cortex (31%) without change in sgPFC
medial OFC closely related, and adjacent to sgPFC

Hajek T et al. J Psychiatry Neurosci 33(2):91-99 2008;
Bremner J, et al. Biol Psychiatry 51(4): 273-79 2002

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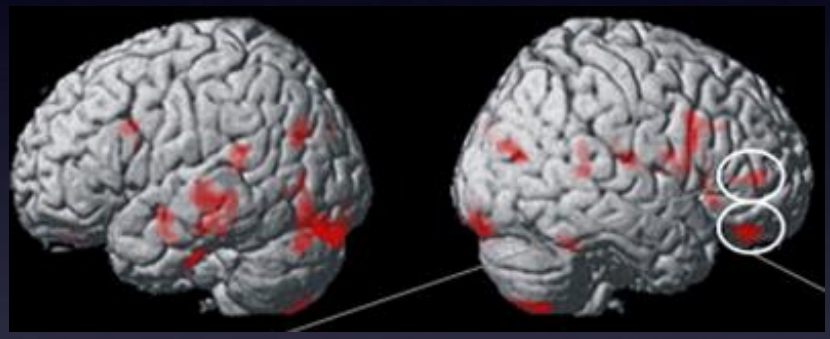
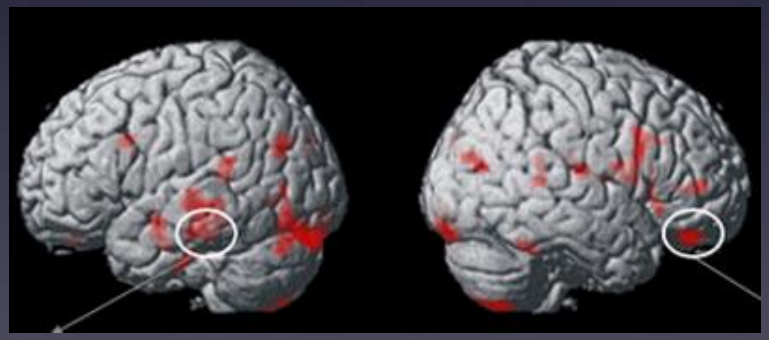
Metanalysis: volumetric studies of other prefrontal and cortical structures

Results: red highlighted areas have significant gray matter thinning in depressed subjects correlating with:

Cognition: circled areas-- where gray matter reduction correlated with performance on the Wisconsin Card Sorting Test





Severity:circled areas -- where gray matter reduction correlated with severity of depression by MADRS

Vasic N, et al.. J Affective Disorders epub 10 Jan 2008

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Post-mortem studies: volumetric abnormalities in depression

Subgenual PFC

- gray matter decrease (38-40%)
- cell number decreased
- neuron cell bodies reduced in size (but not decreased in number)
- glial cell number decreased (not neurons)
  - familial MDD reduced by 24%/BPD reduced by 41%

Lateral orbitofrontal cortex

- gray matter decrease (12-15%)
- pyramidal neurons decreased number lamina II

Dorsolateral PFC

- neuron cell packing and cell bodies reduced
- pyramidal neurons number decreased in lamina II & V

Amygdala

- dendritic branching decreased

Thalamus

- neuron number increased in limbic areas of thalamus (mediodorsal and ventralanterior nuclei)

Ongur et al. Proc Natl Acad Sci 95:13290-95 1998; Rajkowska G et al. Biol Psychiatry 45:1085-98 1999; Drevets et al. Nature 386:824-27 1997
Young K, et al. Am J Psychiatry 161(7(:1270-7 2004

*

Hippocampal atrophy: a highly replicated finding

Hippocampal atrophy highly replicated finding

Degree of atrophy in depression correlated with:

- duration of current episode
- duration of depressive illness
- duration untreated depression

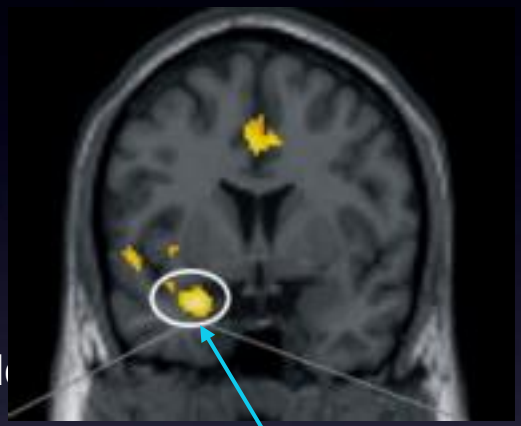
(smaller hippocampi: longer duration/less treatment)

First episode depression atrophy correlates with:

- number of stressful experiences prior to 1st episod

Cognition Negatively affected

- Impaired cognition on Wisconsin Card Sorting Test (WCST) coorrelates with reduced hippocampal volume



hippocampus

Key points:

- reduced hippocampal volume appears to result from both stress and episodes of depression, and negatively impacts mood/cognition
- untreated depression may allow for progressive neurodegenerative changes

Vasic N, et al. Affective Disorders epub 10 Jan 2008. Sheline Y, et al. Proc Natl Acad Sci 83(9):3908-13 1996
Sheline Y, Mokhtar H, Gado M. et al. Am J Psychiatry 160:1516-18 2003. Kronmuller KT, et al. J Affective Disorders epub Mar 5 2008;

Postmortem abnormalities in gene expression of the dorsolateral prefrontal cortex in depression

Intracellular

- signalling abnormalities
  - WNT, phosphoCREB, PKC pathway
  - changes would decrease cell viability

Extracellular

- signalling abnormalities
  - affecting metabolism and signalling of glu/GABA
  - affects cellular adhesion, extracellular matrix

Cell death

- apoptosis
  - would increase caspace activation
  - increase likelihood of programmed cell death

Epigenetic:

- histone deacytlase (HDAC) 9 and 5 decreased
  - HDAC controls chromatin opening--open=gene expression
  - HDAC 5 antagonism is molecular target of antidepressants
  - HDAC antagonism is molecular target of valproate

Note: these are from non-suicide postmortem samples

Kang J et al. J Neurosci 27(48):13329-40 2007

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Key Points:
Volumetric and postmortem findings

Gray matter volume reductions are widespread and affect cognition

- correlate with symptom severity, degree of cognitive impairment
- subgenual PFC affected in familial depression
- orbitofrontal cortex reduction not limited to familial depression
- reproducible findings showing reduced volume of hippocampus

Postmortem data confirm gray matter volume reductions

- cortical and limbic structures
- glial cells decreased not neurons

Gene expression is broadly abnormal affecting:

- extracellular signalling
- intracellular signalling
- neuron viability
- epigenetic effects on gene expression

*

Neuroendangerment hypothesis in depression: brain derived neurotrophic factor (BDNF)

BDNF

stimulates growth and neuronal viability

- hypothesized risk factor for depression/anxiety
- correlates with neuroticism/vulnerability to depression
- stress decreases BDNF in animal models
- all antidepressant treatments increase BDNF
- may reverse injury to hippocampus after stress/depression

BDNF polymorphisms

- BDNF promoter region polymorphisms
  - val-met substitution at position 66
  - met/met and met/val genotypes have decreased BDNF

met allele correlates with (in non-psychiatric subjects):

- poor performance on California Verbal Learning Test (CVLT)
- correlates with smaller hippocampal volume

Kronmuller KT, Pantel J, Gotz B et al. Life events and hippocampal volume in first episode major depression. J Affective Disorders epub Mar 5 2008

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Genetic polymorphisms in depression: 5HTTLPR the serotonin reuptake channel gene

5HTTLPR

- serotonin promoter region polymorphisms
  - two forms: short (s) and long (l)
  - hypothesized as risk factor for depression/anxiety-- results mixed
  - correlates with neuroticism-predictive of vulnerability to depression

5HTTLPR

- gene x environment interaction
  - prospective study
  - 3 or more stressors in prior year increase probability of MDE
  - s/s genotype markedly increases risk for depressive symptoms, depression, and suicidality
- hippocampus
  - l/l genotype associated with smaller hippocampus in MDD subjects

Kendler K, et al. Arch Gen Psychiatry 62(5): 529-35 2005. Caspi A, et al. Science 301(5631) 386-9 2003. Fordl T et al. Arch Gen Psychiatry 61(2):177-83 2004. Munafo M et al. Neuropsychobiology 53(1):1-8 2006..

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Genetic polymorphisms in depression: glucocorticoid receptor

Glucocorticoid receptor (GR) polymorphisms

- GR in high density in the brain
  - hippocampus
  - amygdala
  - prefrontal cortex
- two polymorphisms: rs10052957 and rs1866388 are genetic elements that control transcription of the GR gene
  - rs10052957 is upstream from the GR gene
  - rs 1866388 is in the 2nd intron (introns are not transcribed)
- these polymorphisms
  - are associated with depression
  - correlate with degree of hippocampal volume reduction

Zobel et al. American Journal Medical genetics Part B: Neuropsychiatric Genetics epub 19 Feb 2008.

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Key Points: Genetic polymorphisms in depression

BDNF

- BDNF function promotes normal cognitive function/hippocampal volume
- antidepressant treatment may be key to reverse decreased BDNF level
- thus improve neuronal viability, connectivity, and function

5HTTLPR

- serotonin transporter promoter area has two versions s and l.
- s/s genotype interacts with number of stressors to create vulnerability for depression compared with l/l genotype

Glucocorticoid receptor

- GR polymorphisms affect vulnerability for depression, and correlate with hippocampal volume.
- high cortisol levels, hippocampal neuron cell death or impairment, and hippocampal atrophy due to a genetic variant would increase risk of depression
- results support neuroendangerment hypothesis of depression

Zobel et al. American Journal Medical genetics Part B: Neuropsychiatric Genetics epub 19 Feb 2008.

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Key Points: Neurobiology of Depression

Depression is a systems level disorder of the brain

- cortico-striato-pallido-thalamic circuits
- cortical-limbic circuits

Neural circuitry is dysregulated due to abnormalities which impair

- neuronal function
- connectivity to other neurons

Dysregulated cortical-limbic and cortical-subcortical circuits result in:

- poor processing of cognitive and emotional stimuli
- consistent with cognitive impairment and mood changes in depression

Findings contributing to dysregulated circuits and neuronal function

- decreased cortical and limbic gray matter volume
- impaired functional connectivity between hippocampus and PFC
- cytoarchitectural abnormalities
- changes in neurotransmission and 2nd messengers systems
- changes in gene expression

Major depression references

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Johansen-Berg H, Gutman D, Behrens T, et al.Anatomical Connectivity of the Subgenual Cingulate Region Targeted with Deep Brain Stimulation for Treatment-Resistant Depression.Cerebral Cortex epub 10 Oct 2007

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Mayberg H, Lozano A, Voon V. et al. Deep brain stimulation for treatment resistant depression. Neuron 45:651-60 2005

Konarski et al. Volumetric neuroimaging investigations in mood disorders: bipolar and. depressive disorder Bipolar Disorder 10:1-37 2008

Hajek T, Kozeny J, Kopecek M et al. Reduced subgenual cingulate volumes in mood disorders: meta-analysis. J Psychiatry Neurosci 33(2):91-99 2008

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Munafo M, Clark T, Roberts K, Johnstone E. Neuroticism mediates the associateion of the serotonin transporter gene with lifetime major depression. Neuropsychobiology 53(1):1-8 2006..

Neurobiology of Psychiatric Illness:
Obsessive Compulsive Disorder

Hugh Brent Solvason PhD MD
Associate Professor
Stanford University
Department of Psychiatry

Overview:
Obsessive compulsive disorder (OCD)

Orbitofrontal cortex processing by subcortical structures

Neuroimaging findings in OCD

Hyperglutamatergic hypothesis of OCD

Genetic polymorphisms

What symptoms are associated with dyregulation in the following medial prefrontal structures?

Orbitofrontal cortex (OFC)

Poor understanding of nonverbal social cues
Impulsive/aggressive

Anterior cingulate cortex (ACC)

apathy
poor concentration

Medial prefrontal cortex mPFC

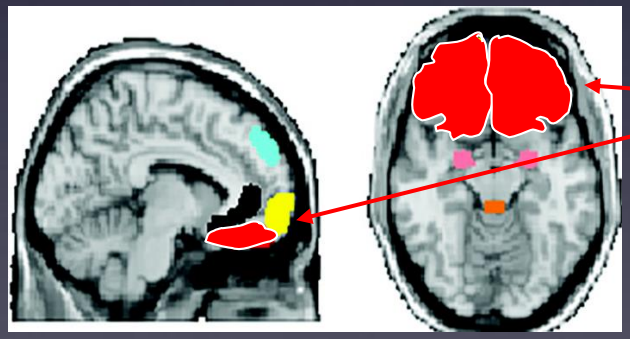
Self and other awareness

Subgenual ACC (sgACC)

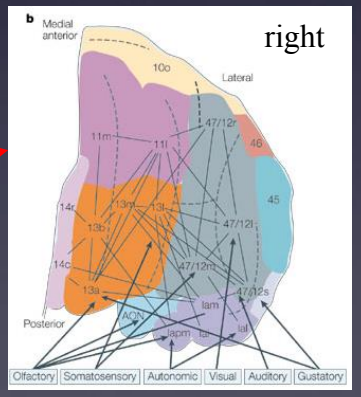
Depressed mood/sadness

Overview: orbitofrontal cortex (OFC)

- OFC lays just above the temporal petrus bone of the skull, overlying orbits
- Divisible into multiple Broadman areas that are highly interconnected (see below)
- Receives visceral/sensory input, as well as multimodal sensory input
- Extensive visceral motor, sympathetic and parasympathetic output
- Primitive cortex-more visceral/emotional regulation moving medial and caudal
- Important in hedonic and negatively reinforced responses
  Medial = updates reward value and assesses hedonic stimuli for behavioral response
  Lateral = updates punishment value and assesses negatively reinforcing stimuli for response



OFC
Broadman areas
highly interconnected



Johansen-Berg H, et al. Cerebral Cortex epub 10 Oct 2007

Kringelback M. Nature Rev Neurosci 6;691-702 2005

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Injury to the OFC: insights into its function

Phineas Gage: destroyed left OFC; medial right OFC; mPFC

- irritable
- Impulsive/violent
- lost social skills
- poor decision making

Cognitive impairments difficult to identify following injury

- OFC injury results in difficulty updating the rewarding or punishing value of task
- gambling task: two decks of cards, deck A is highly rewarding initially, then reward switches to deck B
  - -- healthy controls shift to deck B as the value of choosing B improves
  - -- injury to lateral OFC: inability to shift from rewarding deck after it ceased being rewarding

Clinical example successful business man, following brain injury to OFC

- Irritable, easily frustrated
- loses ability to understand social behaviors, appears disinhibited
- persists at tasks that have lost value -- unable to work,
- can't adapt behavior in dynamic relationship -- divorced,
- all cognitive testing was normal

Abbrev orbitofrontal OFC, medial prefrontal cortex mPFC

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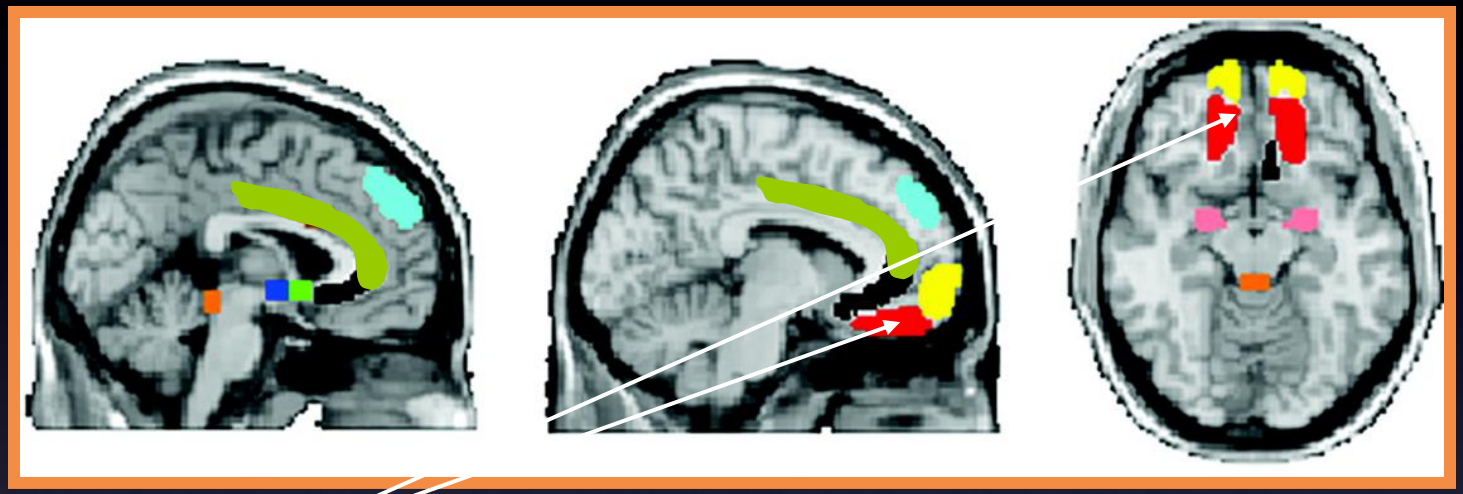
Connectivity of OFC to medial prefrontal cortical and limbic structures



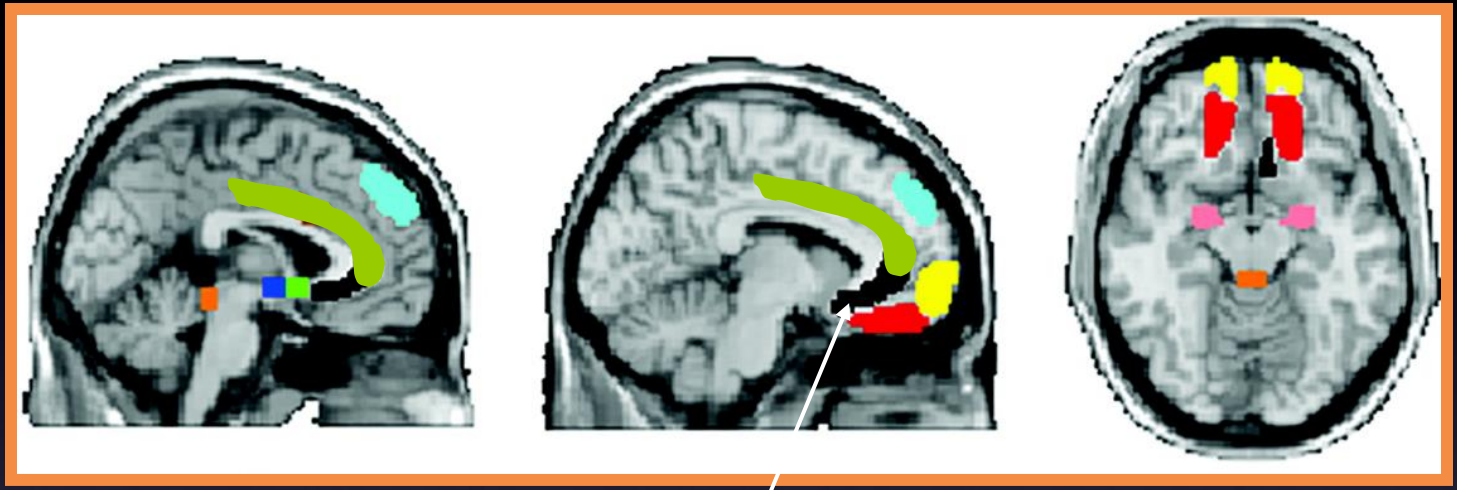
OFC

connects extensively to:

Subgenual PFC
Anterior cingulate
Amygdala
Hippocampus
Hypothalamus

Johansen-Berg H, et al. Cerebral Cortex epub 10 Oct 2007

Connectivity of OFC to medial prefrontal cortical and limbic structures



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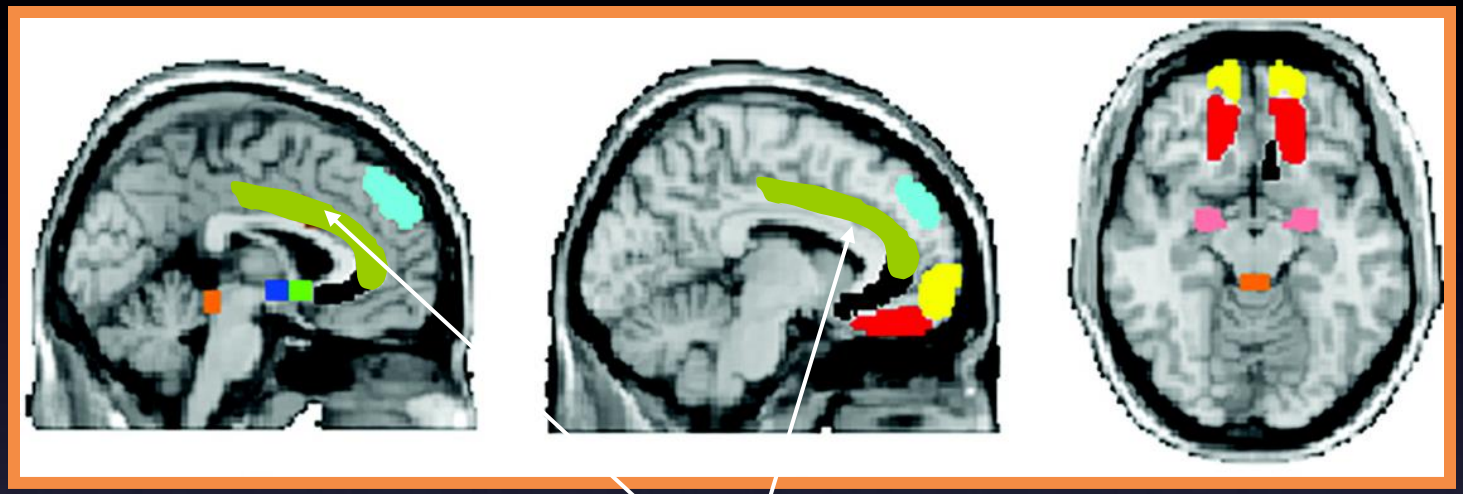

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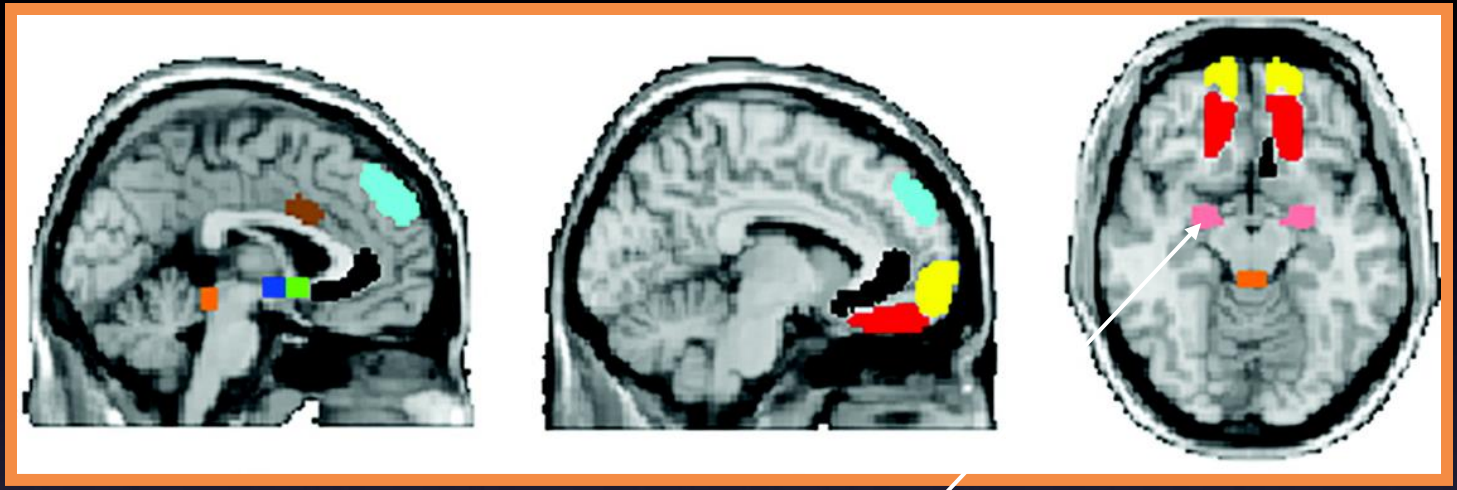

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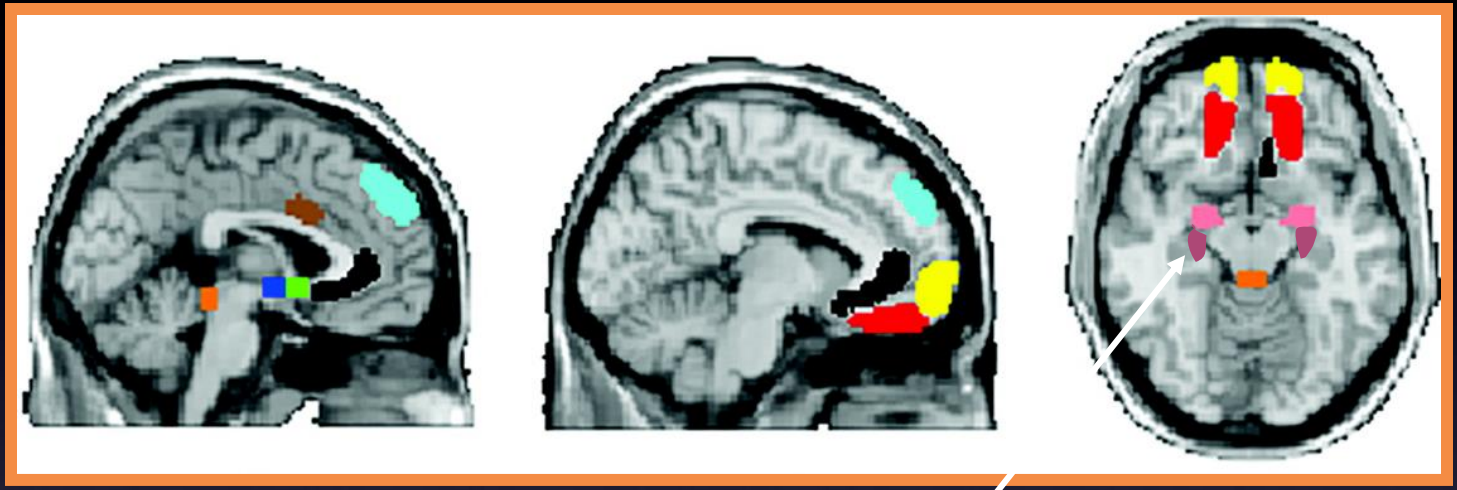

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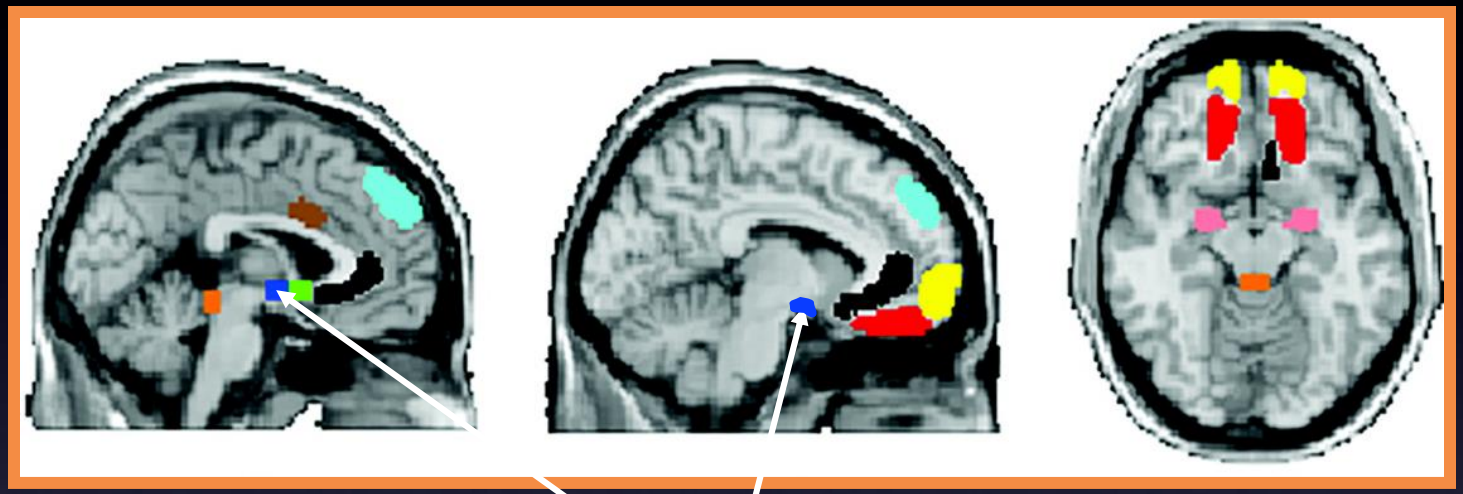

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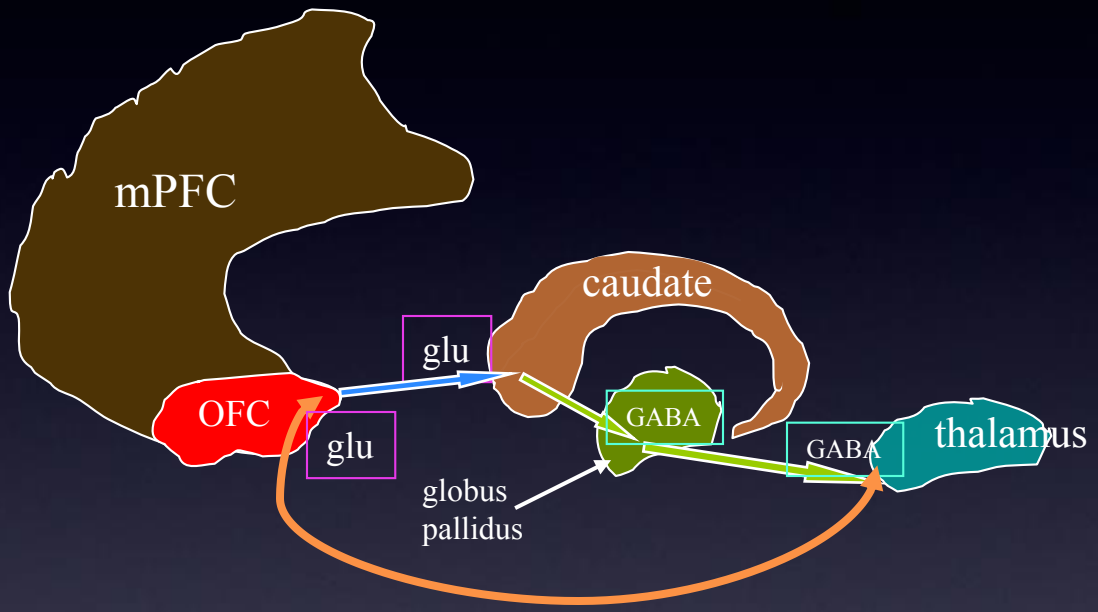
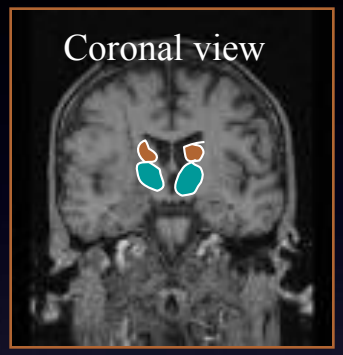
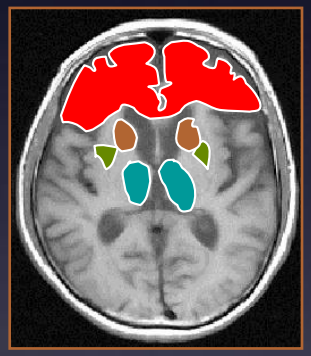
Johansen-Berg H, et al. Cerebral Cortex epub 10 Oct 2007

Cortical-striato-pallidal-thalamic circuitry: mPFC output is processed via subcortical structures







Horizontal view

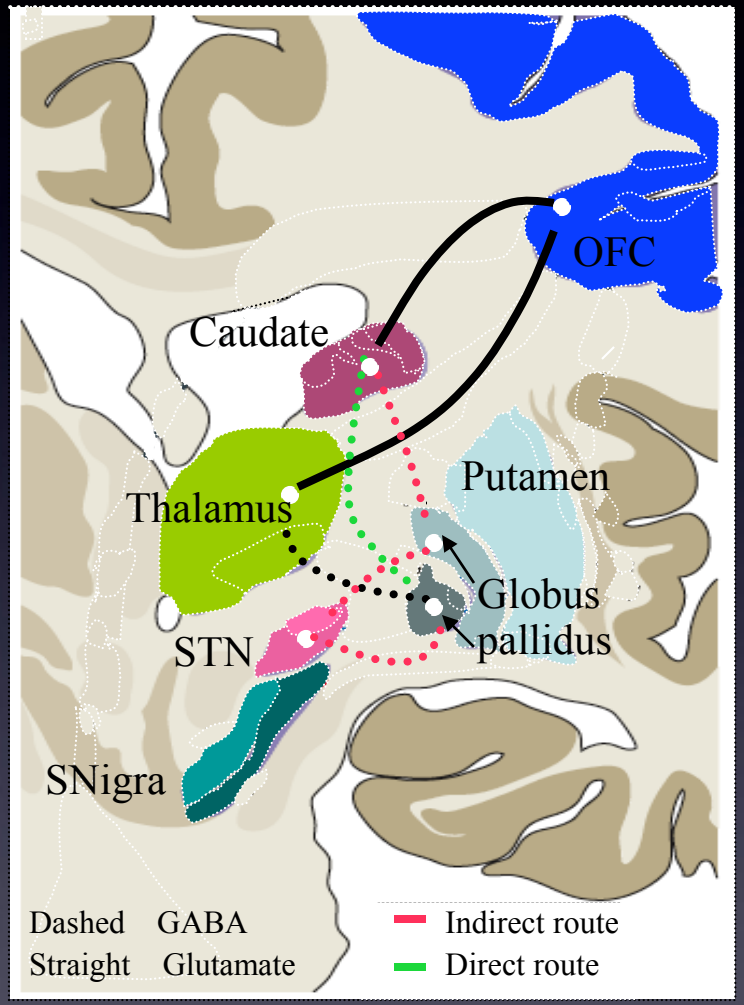
OFC output is processed via multiple subcortical structures

(subthalamic nucleus and indirect pathway not shown)

glu — Glutamatergic synapse: OFC to caudate, thalamus to OFC

GABA — GABAergic synapse: caudate to g.pallidus, g palllidus to thalamus

mPFC-striatal-pallidal-thalamic circuitry



OFC output is processed via 2 pathways in subcortical structures

Direct: D1 dependent (green)
Indirect: D2 dependent (red)

See diagram

activation of direct pathway causes excess glutamatergic firing in the OFC, thalamus, and caudate

Direct and indirect pathways
OCD can be conceptualized as pathologic dominance of the direct pathway
This results in hypermetabolism in OFC, commonly seen in functional imaging

Adapted from Breakefield X et al. Nature Neurosci Rev 9:222-234 2008

Abbrev. subthalamic nucleus STN; substantial nigra SNigra

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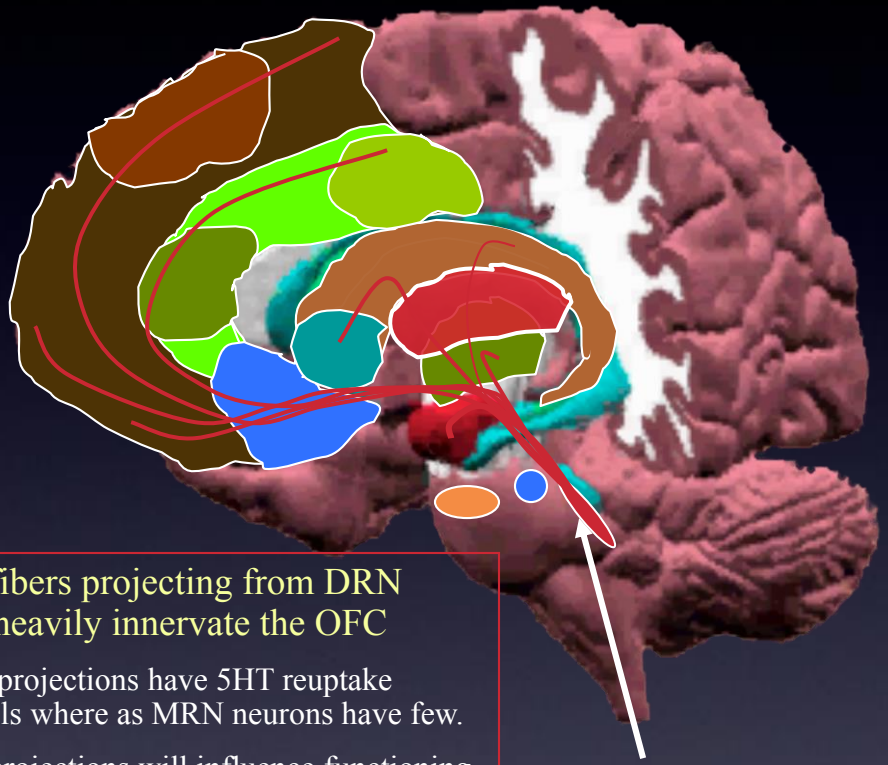
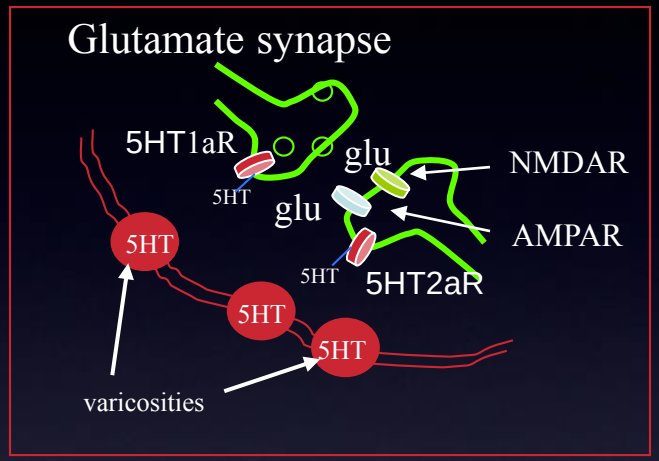
5HT powerfully modulates of GABA and glutamate synapses in OFC-striato-thalamic and limbic circuits



5HT/DRN



5HT fibers projecting from DRN most heavily innervate the OFC

- DRN projections have 5HT reuptake channels where as MRN neurons have few.
- 5HT projections will influence functioning in the OFC more than other monoamines.
- SRI's will therefore be more effective at eliciting a treatment response.

5HT fibers project from the DRN to pyramidal neurons in prefrontal cortex

- 5HT2a is postsynaptic receptor; augments the effect of glutamate neurotransmission
- 5HT1a is presynaptic heteroreceptor, inhibits serotonin release but also glutamate

Abbrev. DRN dorsal raphe nucleus. MRN median raphe nucleus. LC locus ceruleus. VTA ventral tegmental nucleus. NMDAR glutamate receptor, AMPAR glutamate receptor, serotonin 5HT

Wedzony K et al. J Physiol Pharmacol. 58(4): 611-24 2007

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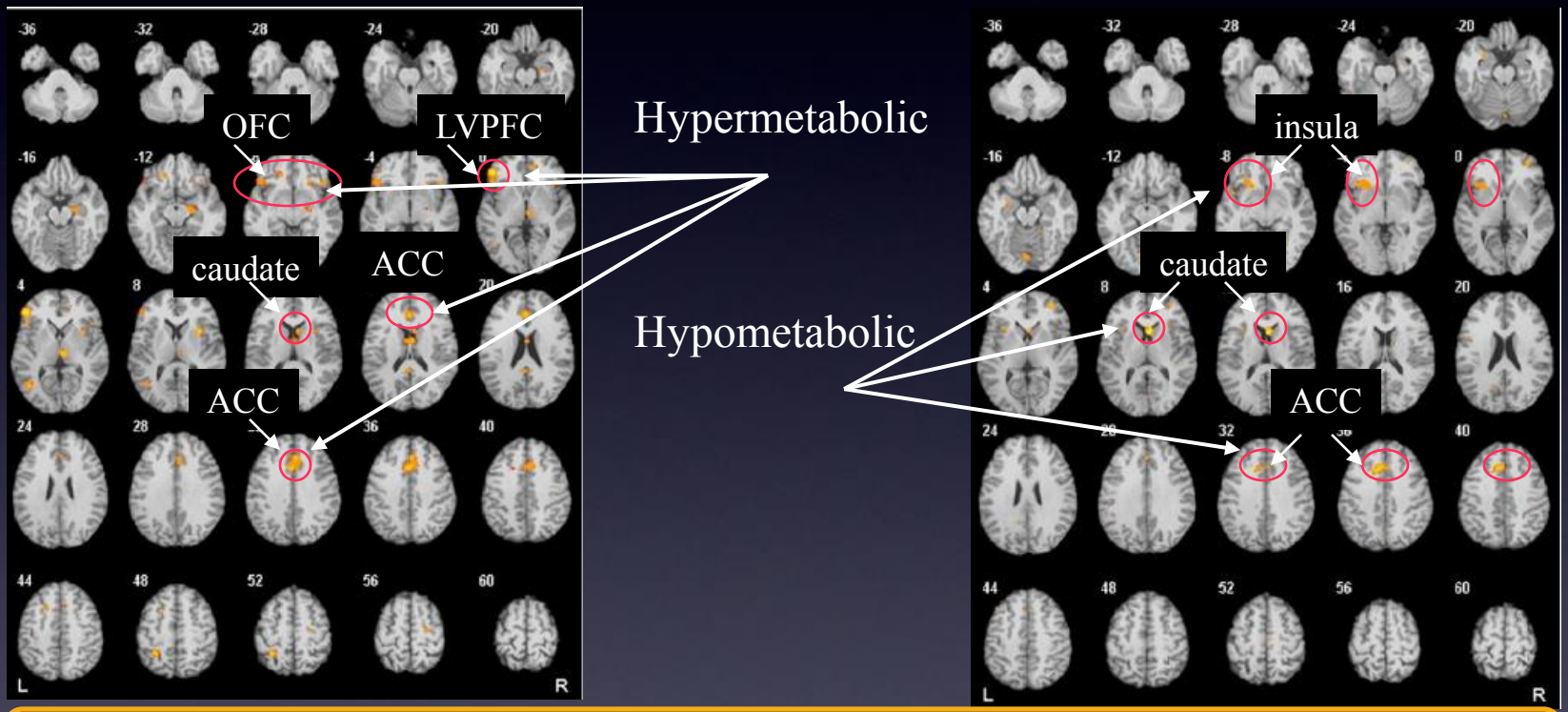
OCD functional imaging study summary

Orbitofrontal-ACC-striatal abnormalities in metanalysis

10 studies, 114 OCD subjects, 148 healthy controls (HC) total



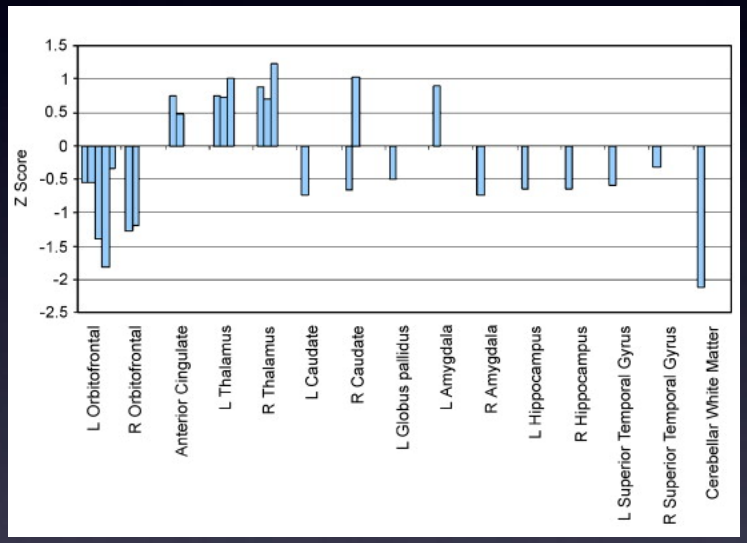
Key point Functional imaging studies show multiple cortical, subcortical, and limbic structures are abnormally activated in OCD, notably the OFC

Menzies L et al. Neurosci Behaviroal Rev. 32(3) 525-49 2008 **Abbrev. ACC anterior cingulate cortex; LVPFC ventral lateral prefrontal cortex**

OCD structural imaging study summary

Orbitofrontal-ACC-striatal abnormalities in metanalysis

10 studies, 114 OCD subjects, 148 healthy controls (HC) total



Structure volume changes OCD v HC

OFC volume decrease most consistent finding

ACC/thalamus R caudate increased volume

Temporal structures and cerebellum decreased

Limbic structures decreased in volume

Key point

Multiple cortical, subcortical, and limbic structures are smaller in those with OCD

Menzies L et al. Neurosci Behaviroal Rev. 32(3) 525-49 2008

Abbrev. OFC orbitofrontal cortex; ACC anterior cingulate cortex; LVPFC ventral lateral prefrontal cortex

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Cognitive abnormalities in OCD summary

- Prepotent response inhibition (inhibiting usual response to stimulus to match new instructions) impaired
- Deficits in changing strategies when reward is shifted to another outcome
- Attentional deficits in set shifting
- Planning impairment
- Decision making

Key point

These findings are possibly dependent on multiple neurocircuits, however these data imply that abnormalities in the OFC and lateral OFC and possibly DLPFC result in cognitive impairment in OCD subjects

Adapted from: Menzies L et al. Neurosci Behaviroal Rev. 32(3) 525-49 2008

Abbrev. OFC orbitofrontal cortex; ACC anterior cingulate cortex; LVPFC ventral lateral prefrontal cortex

Key Points: Neurobiology of OCD

OFC-subcortical circuits
- dysregulated in OCD
- OFC dysregulation a consistent finding
- striatum, insula, and anterior cingulate cortex also implicated

Cognitive impairment implies abnormal function in
- OFC
- lateral prefrontal cortex
- dorsolateral prefrontal cortex

Glutamate and GABA mediate neurotransmission in these networks
- serotonin modulates activity at the glutamate/GABA synapse in OFC-striatal-thalamic circuits
- dopamine affects processing in subcortical pathways

Serotonin and dopamine's role in the OFC-striatal-thalamic circuit suggest a mechanism for SRI and D2 antagonists' role in the treatment of OCD

OCD references

Kringelback M. The human orbitofrontal cortex: linking reward to hedonic experience. Nature Rev Neurosci 6;691-702 2005

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Neurobiology of Psychiatric Illness:
Post Traumatic Stress Disorder

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Overview: PTSD

Fear pathways

Structural and functional imaging studies in PTSD

Hypothalamic pituitary axis dysregulation

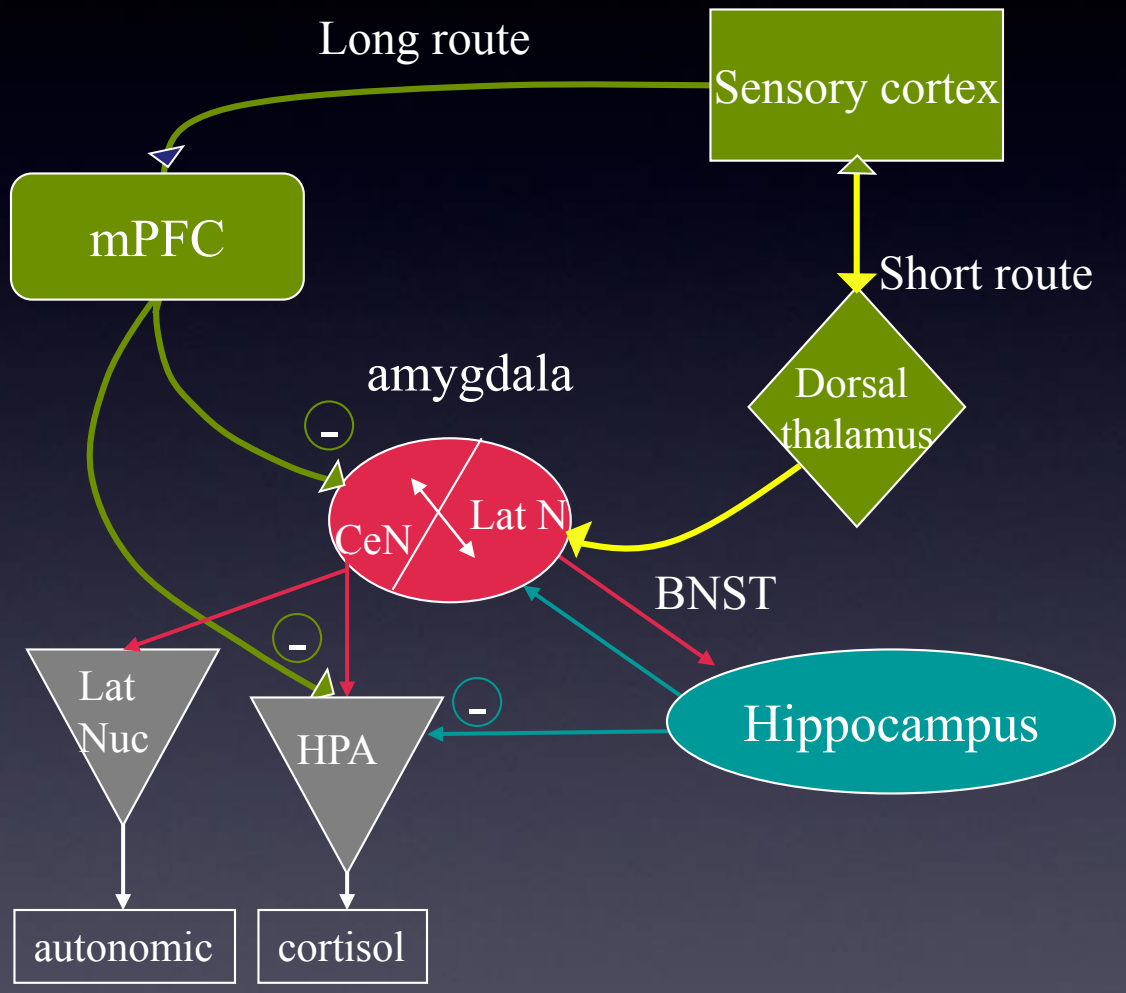
PTSD and fear circuitry

Fear network

Sensory cortex: context and cues
CeN/Lat N amygdala response
Sympathetic and cortisol response

Learned association
Adaptive avoidance behavior

Network overactive in PTSD
Sensory cues over-generalized
Failure to extinguish non-adaptive avoidance behavior



Abbrev. Lateral nucleus of the amygdala LNA, central nucleus of the amygdala CeN, lateral nucleus of the hypothalamus Lat Nuc. Hypothalamic pituitary axis HPA, bed nucleus of the stria terminalis BNST, medial prefrontal cortex mPFC

PTSD and fear circuitry

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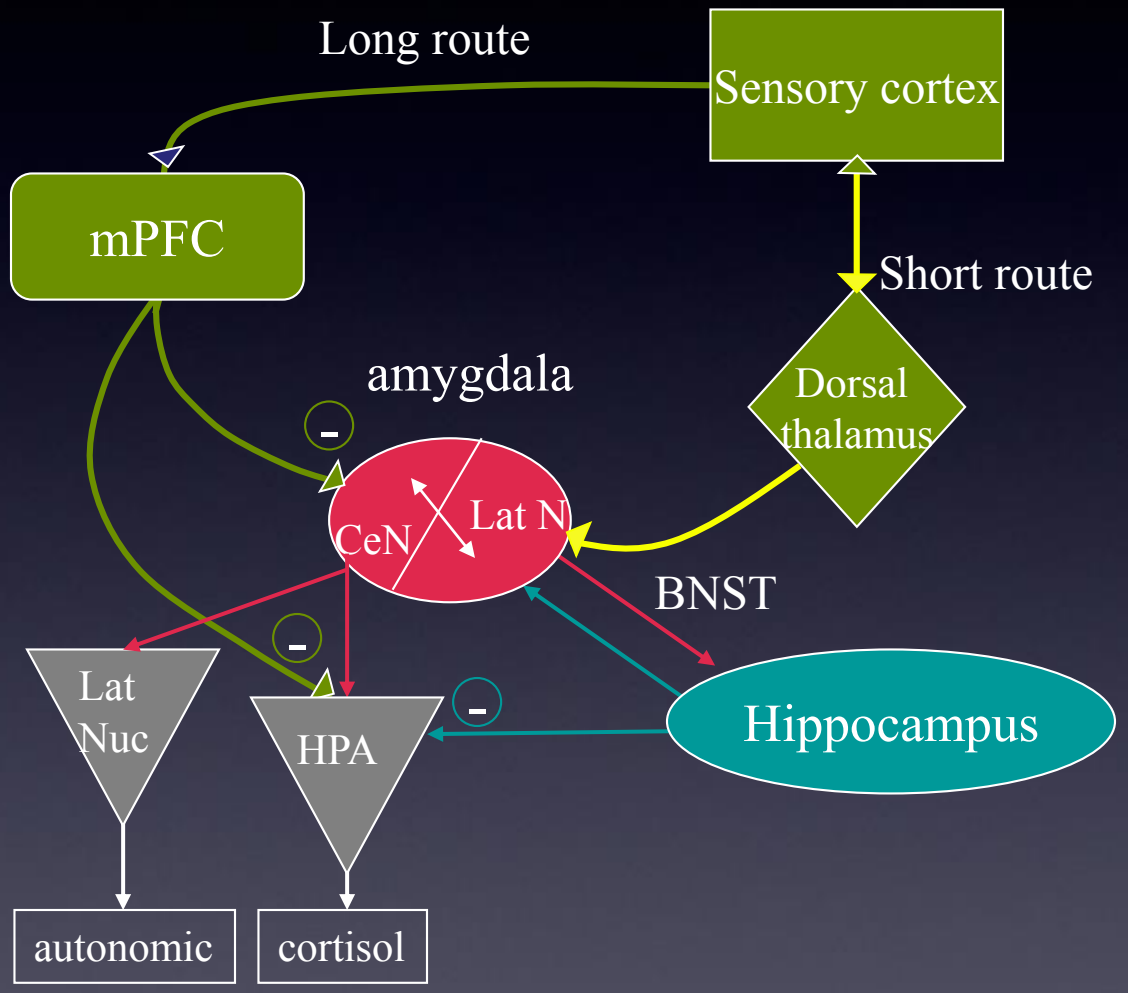

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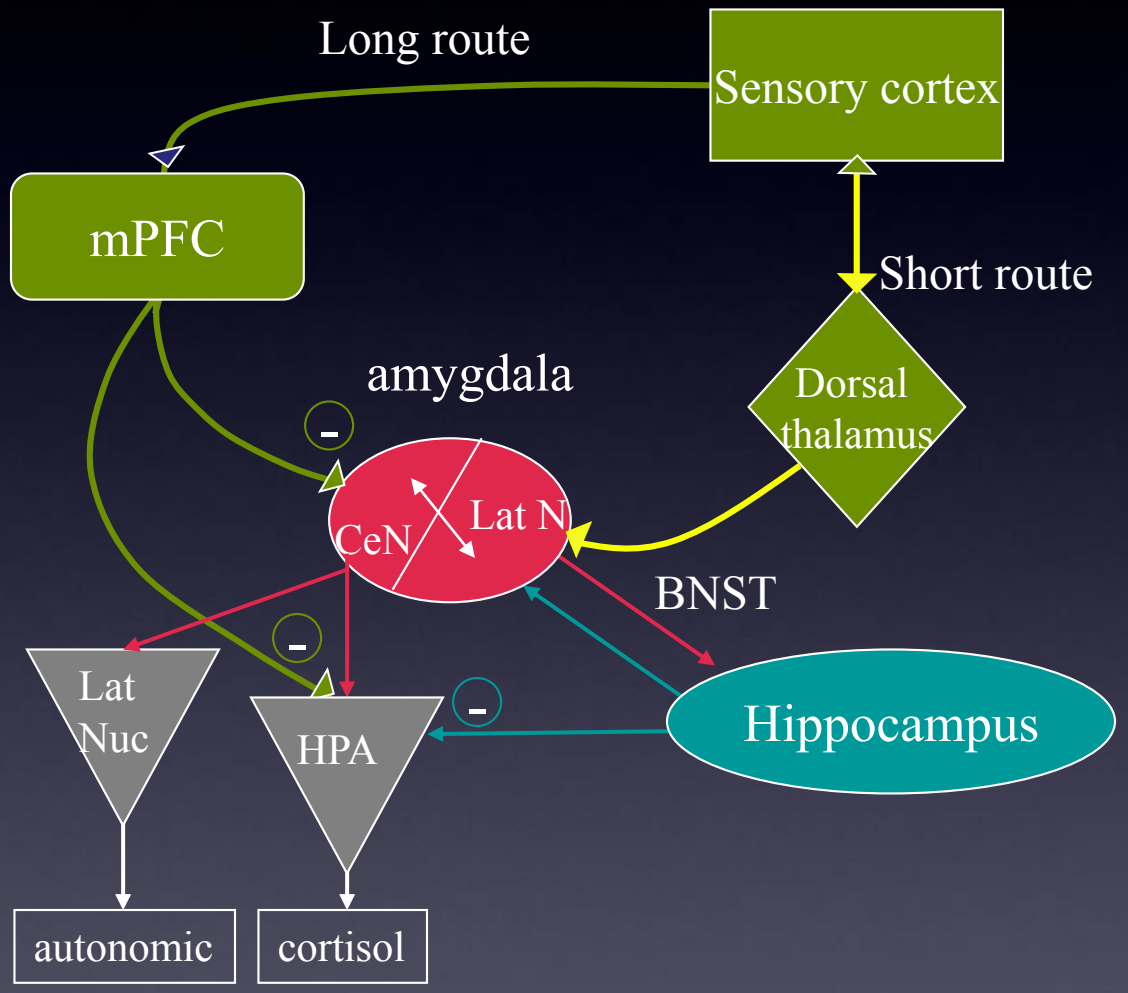

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PTSD and fear circuitry

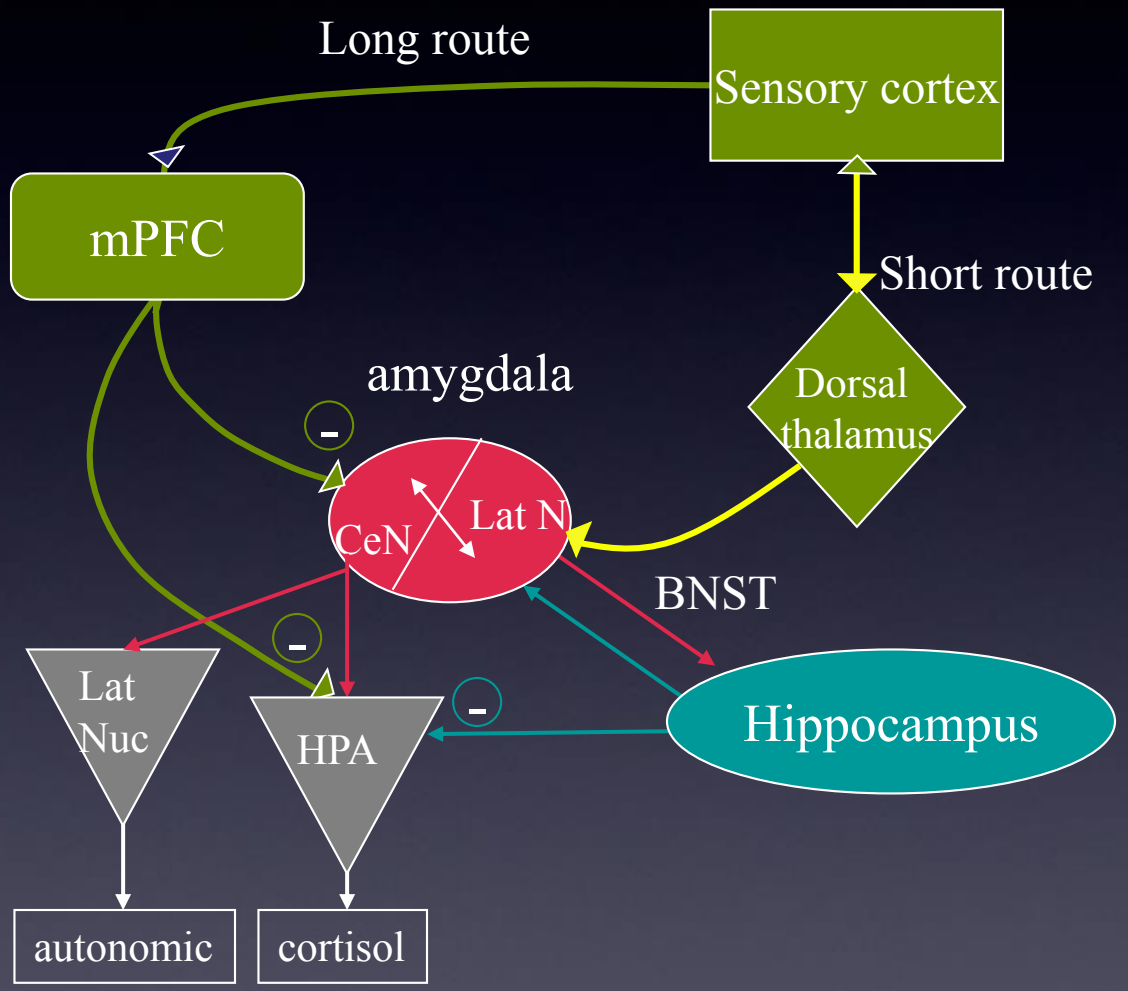
Fear network

Short route

Fast, reactive

Bodily response to a cue

No conscious component



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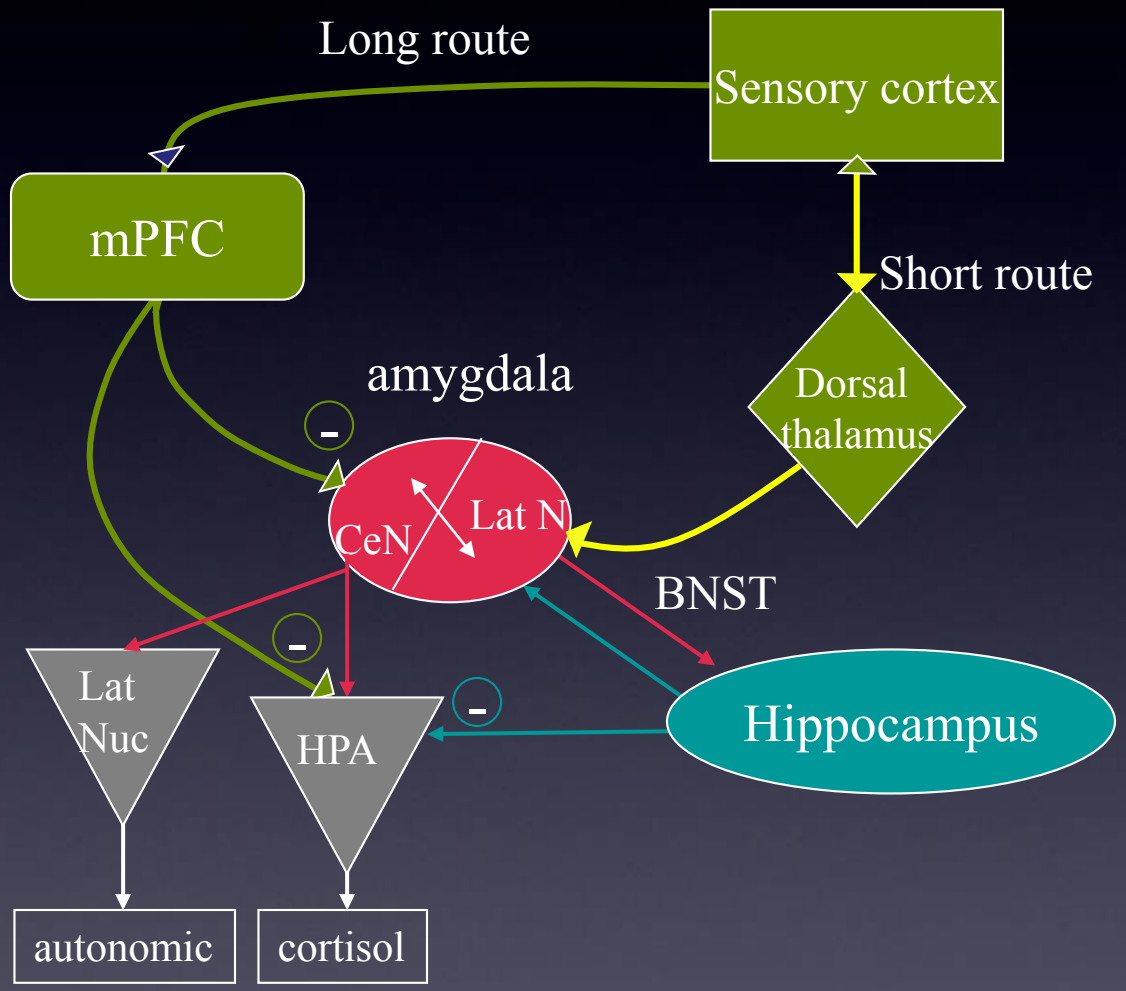
PTSD and fear circuitry

Fear network

Long route via mPFC

cognitive processing of cue

mPFC may inhibit non-adaptive amygdalar response



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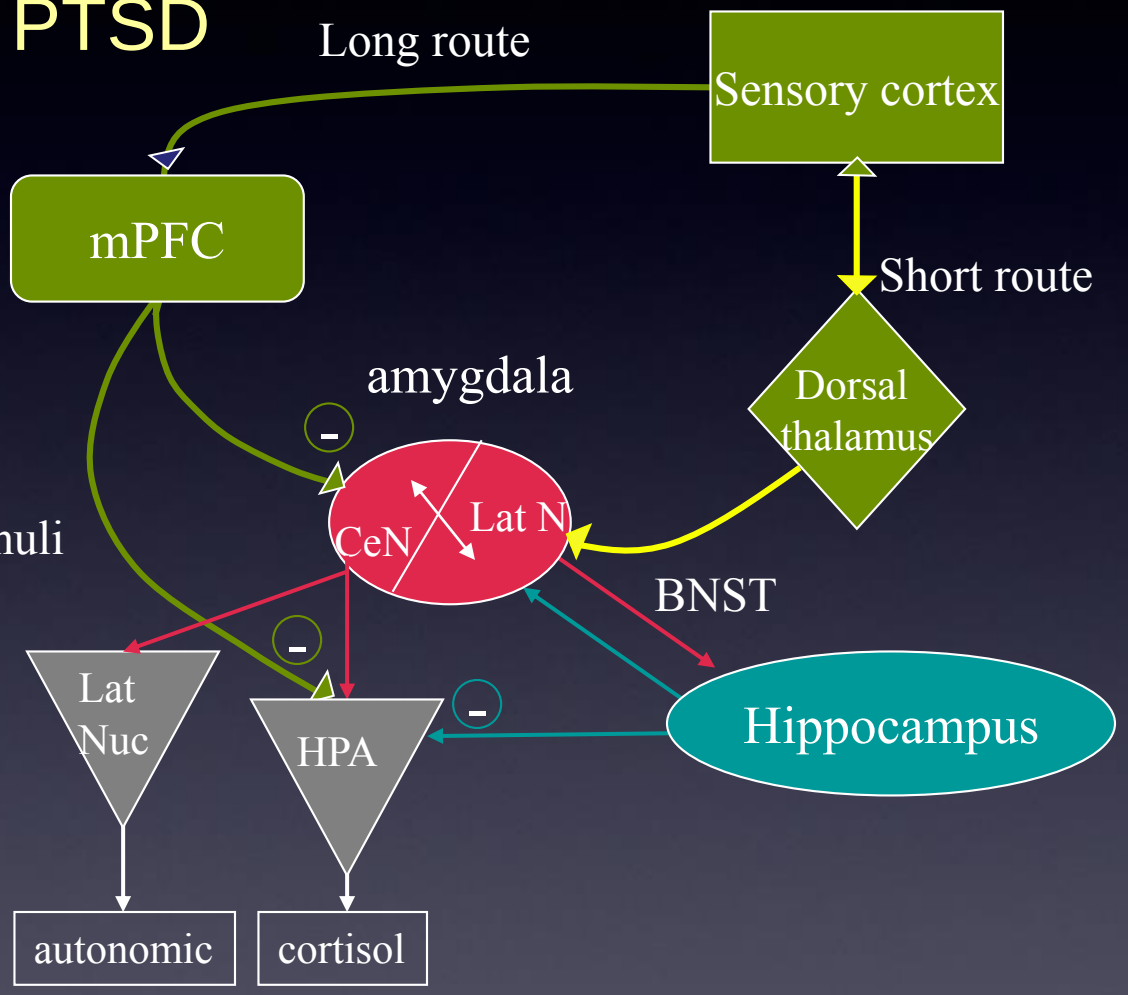
PTSD and fear circuitry

Anatomical basis of PTSD

- Fear response
  - CeN activation
    - sympathetic response
    - cortisol increases
- Behavioral sensitization
  - LNA/mPFC
    - learned response to fearful stimuli
    - avoidance behavior
- Fear extinction
  - mPFC/LNA
    - failure to extinguish
    - non-adaptive fear responses



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PTSD and fear circuitry

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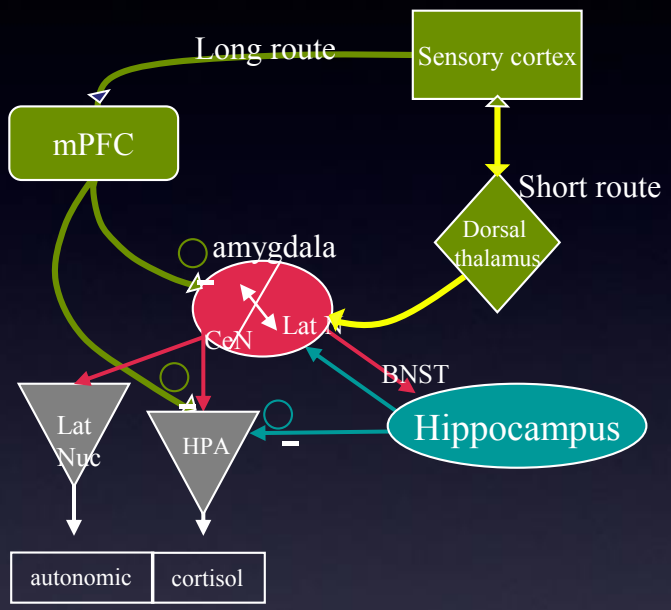


Key points

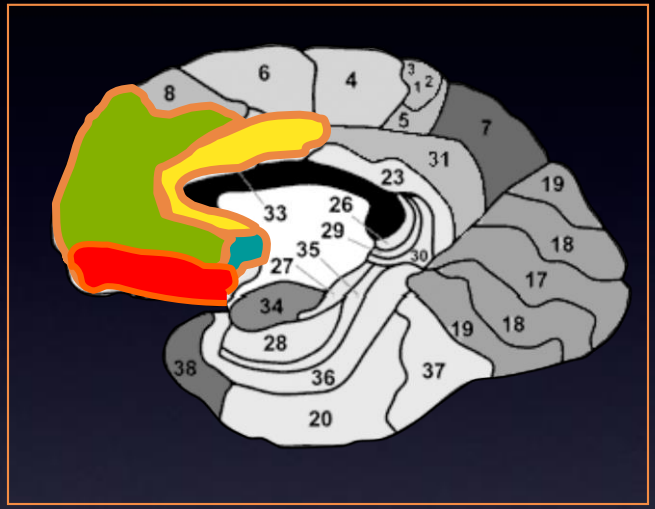
- Increased arousal, avoidance, and re-experiencing can be understood
- as dysregulation of the fear network
- Abnormal function in the amygdala, mPFC and hippocampus are especially implicated

Medial Prefrontal cortical structures; Where are they and what do they do?

Orbitofrontal cortex (OFC)

Anterior cingulate cortex (ACC)

Medial prefrontal cortex mPFC



Medial prefrontal structures and their functions

- Regulate the autonomic response to stress
- Regulate emotional state and response to stimuli
- Regulate the HPA response to stress
- Self knowledge (self attributes)
- Knowledge of others (theory of mind-what others may feel, what they may do)

*

Structural imaging abnormalities in PTSD

Decreased volume in hippocampus
- PTSD vs trauma exposed subjects
- PTSD vs healthy controls
- non-ptsd trauma exposed subjects vs healthy controls

Decreased volume
- medial prefrontal cortex
- amygdala
- OFC (cancer survivors)

Moderators
- age and sex; medication treatment; severity

Key points
- Hippocampal and amygdalar volume changes may dysregulate the stress response, autonomic reactivity, and result in avoidance behavior
- mPFC and OFC atrophic changes impair limbic regulation, also implicated

Karl A et al. Neurosci Biobehavioral Rev 30(7):1004-31 2006. Bremner J. Clin Neurosci 8(4): 445-61 2006. Bremner J, et al. Prog Brain Res 157z:171-86 2008, Kakamata Y, et al.. Neurosci Res 59(4) 383-89 2007.

Abbrev medial prefrontal cortex mPFC, orbitofrontal cortex OFC

Functional imaging abnormalities in PTSD

Summary of SPECT findings in PTSD

Increased

- R hemisphere CBF
- R cuneus
- Cerebellum
- L hemisphere CBF
- PFC
- L amygdala

Decreased

- Medial frontal gyrus
- R STG,fusiform gyrus
- PFC distribution volume
- Superior frontal cortex
- R caudate
- mPFC
- Cerebellum
- thalamus

Key points

- SPECT findings limited by relatively poor resolution
- Medial prefrontal and superior temporal cortex appear to be hypometabolic
- Subcortical (caudate) and limbic (amygdala) abnormalities identified

Francati V, et al. Depression Anxiety 24:202-18 2007

Abbrev CBF cerebral blood flow; prefrontal cortex PFC, STG superior temporal gyrus

Functional imaging abnormalities in PTSD

Summary of PET/fMRI findings in PTSD

Increased	Decreased
Amygdala	mPFC/ ACC
Parahippocampal cortex	mPFC/OFC
	Hippocampus
	Thalamus

Key points

- PET/fMRI have better resolution of activation than SPECT
- Ventral and medial prefrontal cortical structures hypometabolic
- Subcortical (thalamus) and limbic (amygdala/hippocampus) abnormalities

Francati V, et al. Depression Anxiety 24:202-18 2007

Abbrev CBF cerebral blood flow; medial prefrontal cortex mPFC, ACC anterior cingulate cortex, OFC orbitofrontal gyrus

Functional imaging of emotion provocation in PTSD: Amygdala and medial prefrontal cortical structures

PET/fMRI of response to emotional stimuli

- Increased response to emotional faces (fearful, happy, neutral)
  Amygdala
- Decreased response to emotional faces (fearful, happy, neutral)
  mPFC

- Abnormal connectivity between structures using autobiographical scripts
  Areas controlling visceral and autonomic emotional responses abnormal
  Amygdala hyperactive
  ACC hyperactive

Key points

- Emotion provocation paradigms reflect functional connectivity abnormalities
- Implicate medial prefrontal (mPFC and ACC) and amygdala dysfunction

Francati V, et al. Depression Anxiety 24:202-18 2007

Abbrev medial prefrontal cortex mPFC,, anterior cingulate gyru ACCs

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*

Imaging findings in PTSD

Key points

Structural and functional abnormalities in PTSD converge on
- mPFC, amygdala, and hippocampus

Amygdala shows increased sensitivity to fearful stimuli
- Evoked by combat sounds, images, emotional faces and words, traumatic autobiographical scripts
- Appears to represent activation of the fear network by the amygdala
- Possible reason for lack of extinction of response to fearful stimuli

mPFC (and OFC) show decreased activation to stimuli

mPFC, OFC both inhibit amygdalar responses
- Findings may represent disinhibition of amygdala due to hypofunction of the mPFC

mPFC and hippocampus inhibit the HPA
- Findings may reflect etiology of HPA/cortisol abnormalities in PTSD

Francati V, et al. Depression Anxiety 24:202-18 2007

Abbrev medial prefrontal cortex mPFC, orbitofrontal cortex OFC, anterior cingulate cortex ACC, hypothalamic pituitary axis HPA.

Hypothalamic Pituitary Axis (HPA) Abnormalities in PTSD

Hypothesis: HPA and arousal mechanisms abnormal in PTSD

- baseline cortisol levels lower than controls
- CRF levels in CSF elevated
- suggests following model:
  CRF increased in CSF; ACTH response to CRF,and cortisol response to ACTH blunted

Exposure to stress or trauma related conditions

- increased autonomic response to combat noise compared to controls
- increased cortisol response in anticipation and during
  negative feedback in arithmetic challenge and personalized trauma script

CRH challenge: expect CRH receptor downregulation, blunted ACTH response

- elevated CRH in CSF of subjects with PTSD
- blunted ACTH response as predicted

ACTH challenge: measures adrenocortical responsiveness, expected blunted cortisol response

- increased cortisol noted in PTSD group (not as predicted based on earlier study)

Dexamethasone suppression test: expect increased suppression of post dex cortisol

- increased cortisol noted in PTSD group (not as predicted based on earlier study)

Bremner, M. *et al*., Biological Psychiatry 54:710–18 2003. Bremner J, et al. Psychoneuroendocrinology 28 (2003), pp. 733–750. Liberzon I, et al. Neuropsychopharmacology 21: 40–5 1999. Elzinga B et al, Neuropsychopharmacology 28:1656–166 2003. de Kloet et al.. J Psychiatric Res 40(6); 550-56 2006.

Key Points: Neurobiology of PTSD

PTSD is a persistent state of trauma related neurobiologic abnormalities

Volumetric studies show decreased volume in limbic and paralimbic cortex: mPFC, OFC, hippocampus and amygdala;
these structures regulate autonomic response and the HPA/cortisol axis

Functional imaging studies show abnormal activation and abnormal connectivity between these limbic and cortical structures to trauma-related and unrelated stimuli

The HPA/cortisol axis and autonomic response is abnormally regulated

These findings suggest exposure to trauma in some individuals may cause marked changes in structures and function of the brain that persist, leading to behavioral abnormalities and hyperarousal

Abbrev medial prefrontal cortex mPFC, orbitofrontal cortex OFC, anterior cingulate cortex ACC, hypothalamic pituitary axis HPA.

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Questions

Abnormal neuronal function in dysregulated neurocircuits can be caused by abnormalities in:

1. number of neurons or neuropil (glia)
2. density of connections between neurons
3. proteins that transduce neurotransmission (eg receptors)
4. gene expression
5. All the above

Questions

Schizophrenia can be understood as primarily

1. Inefficient cortical processing due to prefrontal cortical dysfunction
2. Dopamine neurotransmission abnormalities
3. A neurodegenerative process
4. Serotonergic and dopaminergic abnormalities
5. All the above

Questions

Bipolar illness is characterized by

1. A progressive illness course with greater time spent in the depressive phase of the illness, mixed episodes and rapid cycling ove time.
2. Decreased gray matter in prefrontal, temporal cortex and limbic structures.
3. Decreased temporal cortical thickness that correlates with the number of recent mood episodes, and cognitive impairment.
4. A BDNF polymorphism exaggerates these gray matter decrements.
5. All the above.

Questions

Major depression is

1. Primarily due to abnormal function in the noradrenergic and serotonergic neurotransmitter systems.
2. The result of a systems level dysregulation of multiple cortical, subcortical, and limbic neurociruits.
3. Not associated with volumetric abnormalities in any cortical or limbic structures.
4. The result of clear abnormal structure and functio of the mamillary bodies.
5. All the above.

Questions

Which of the following findings are seen in individuals with Obsessive Compulsive Disorder

1. Abnormalities in the noradrenergic system.
2. Hypermetabolism in the orbitofrontal cortex.
3. Decreased volume of the orbitofrontal cortex.
4. Prominent hypothalamic pituitary axis dysregulation.
5. All the above.
6. 1 and 2
7. 2 and 3

Questions

The following findings are found in individuals with Post-traumatic stress disorder.

1. Elevated CRF levels in CSF
2. Reduction in volume of the medial prefrontal cortex.
3. Abnormal connectivity between prefrontal cortical and limbic structures resulting in dysregulation of the hypothalamic pituitary axis and autonomic nervous system.
4. Reduced volume of limbic structures such as the hippocampus and amygdala
5. 1 and 3
6. All the above