Neurobiology of Psychiatric Illness:

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

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Neurobiology of Psychiatric Illness:

Addendum Slides: found at the end of the slide set

Monoaminergic Systems and Prefrontal-Subcortical and Prefrontal-Limbic Neurocircuits

Hypothalamic Pituitary Axis

Neuroendangerment and Neuroprotection in depression

Genetic Polymorphisms in Psychiatric Illness

Brief review of the molecular biology of plasticity in the brain

Brief review of the molecular biology of gene expression

Instructions for the lecturer

- There are 5 sections in this slide set. One on schizophrenia, bipolar disorder, major depression, ocd and ptsd in that order.

- I have put an overview for the lecturer before each of the 5 sections. The overview slide is intended for your use only. It will provide you with a sense of the major points that are covered in that section.

- Key teaching points are highlighted frequently through the slide set. With the overview for the lecturer at the beginning of the slide set, and these key points, it should help you focus the residents attention to the major teaching points.

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 over 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 best understood as:

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 neurocircuits.
3. Not associated with volumetric abnormalities in any cortical or limbic structures.
4. The result of clear abnormal structure and function 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

Neurobiology of Psychiatric Illness:
Review of functional neuroanatomy

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For the lecturer: Functional neuroanatomy

- An understanding of shared neuroanatomic networks and their function lays the ground work for developing coherent models for the neurobiology of psychiatric illness.
- To understand symptoms as the manifestation of a dysregulated circuit is primary to understanding how neurobiologic abnormalities, from gene expression, neurotransmitters, and plasticity at synapses, influence processing in the brain.
- The primary neuroanatomical circuits implicated in many psychiatric illnesses are the prefrontal-subcortical and prefrontal-limbic circuits, and these areas are the main focus of this section.
- These circuits are modulated by diffuse innervation by monoamines (NE, DA, 5HT) that have nuclei found in the brainstem and project broadly to limbic and prefrontal areas.
- The widespread innervation by monoamines regulate activity within neurocircuits primarily by their modulatory effects at GABA and glutamate synapses.

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

- Main prefrontal areas projections from: orbitofrontal, anterior cingulate, medial prefrontal cortices
- They project to: hippocampus, amygdala, hypothalamus

Neurotransmitters

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

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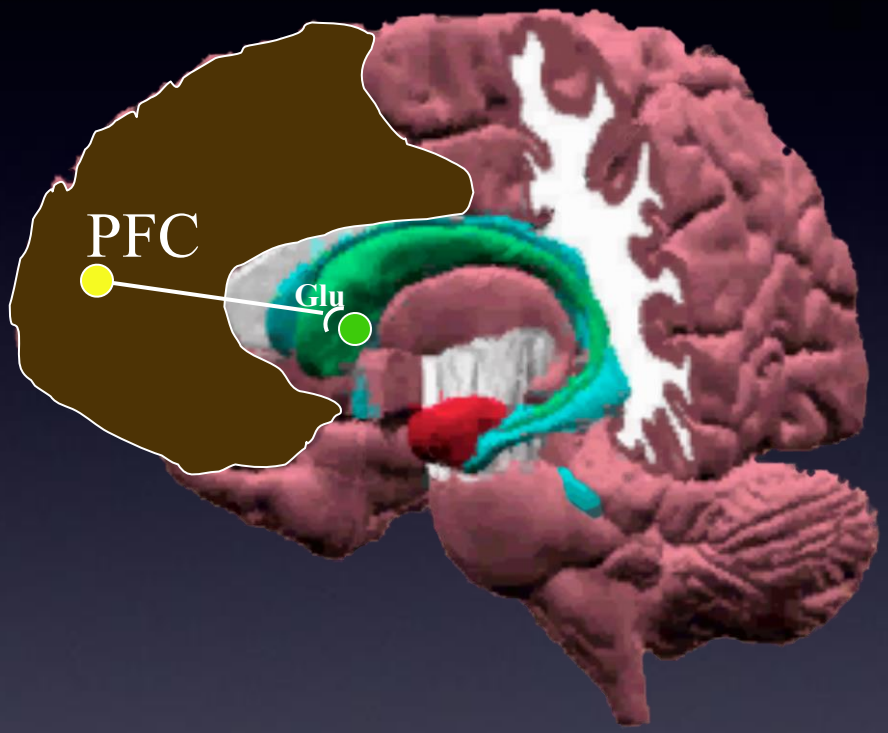
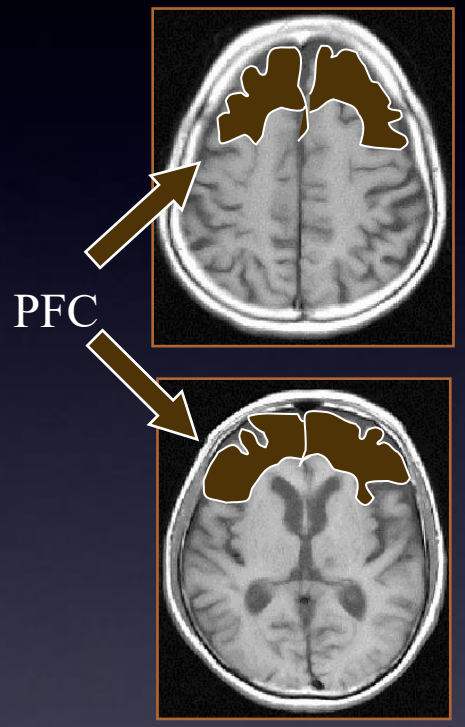
Cortical-striatal-thalamic circuitry simplified





- Prefrontal cortex
  Glutamatergic neurons project to the striatum

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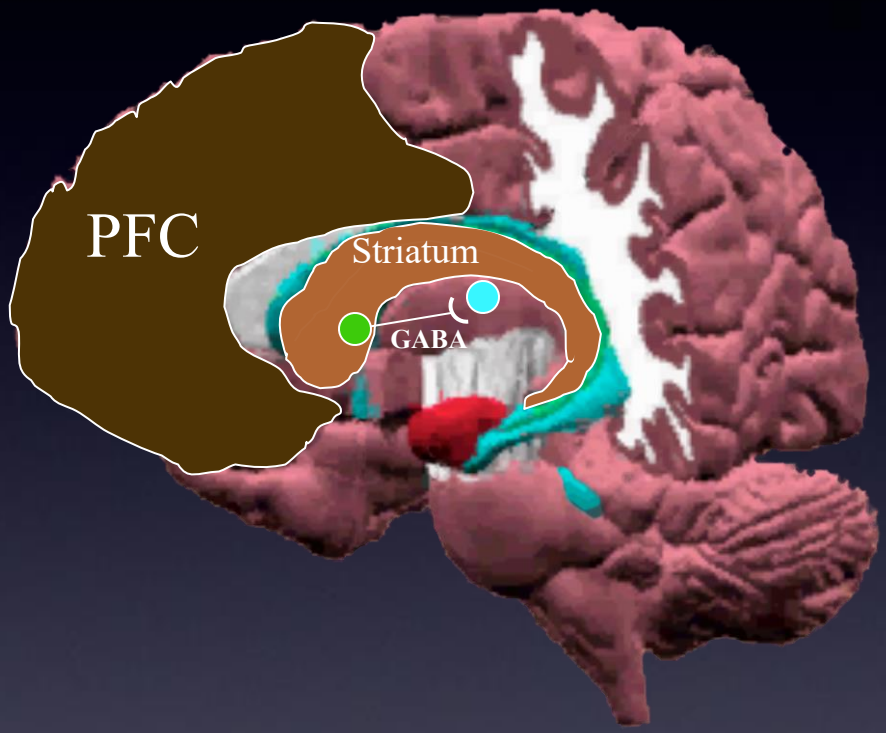
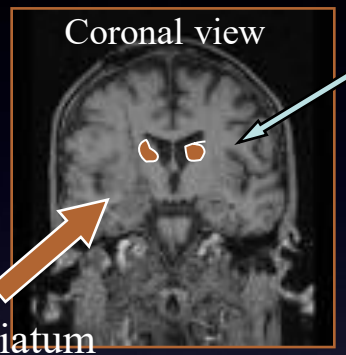
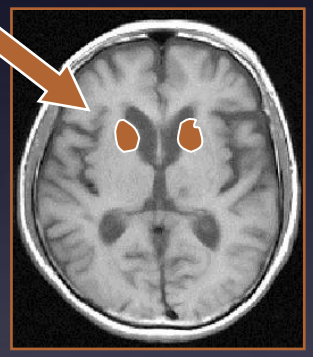
Cortical-striatal-thalamic circuitry simplified





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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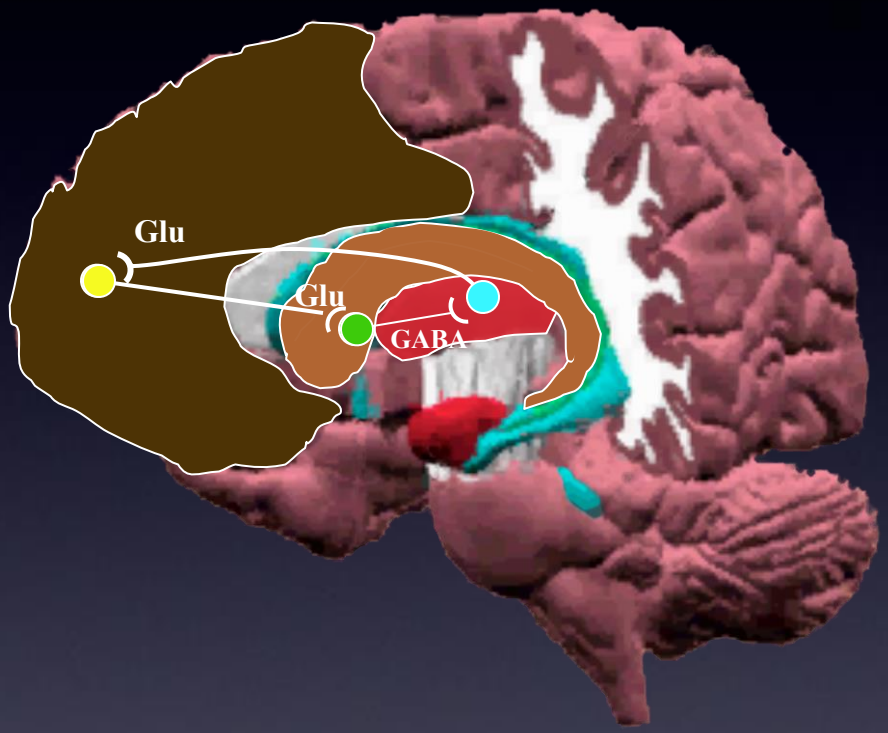
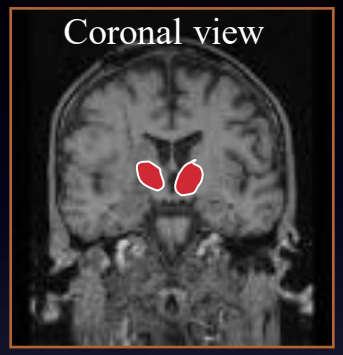
Cortical-striatal-thalamic circuitry simplified





- 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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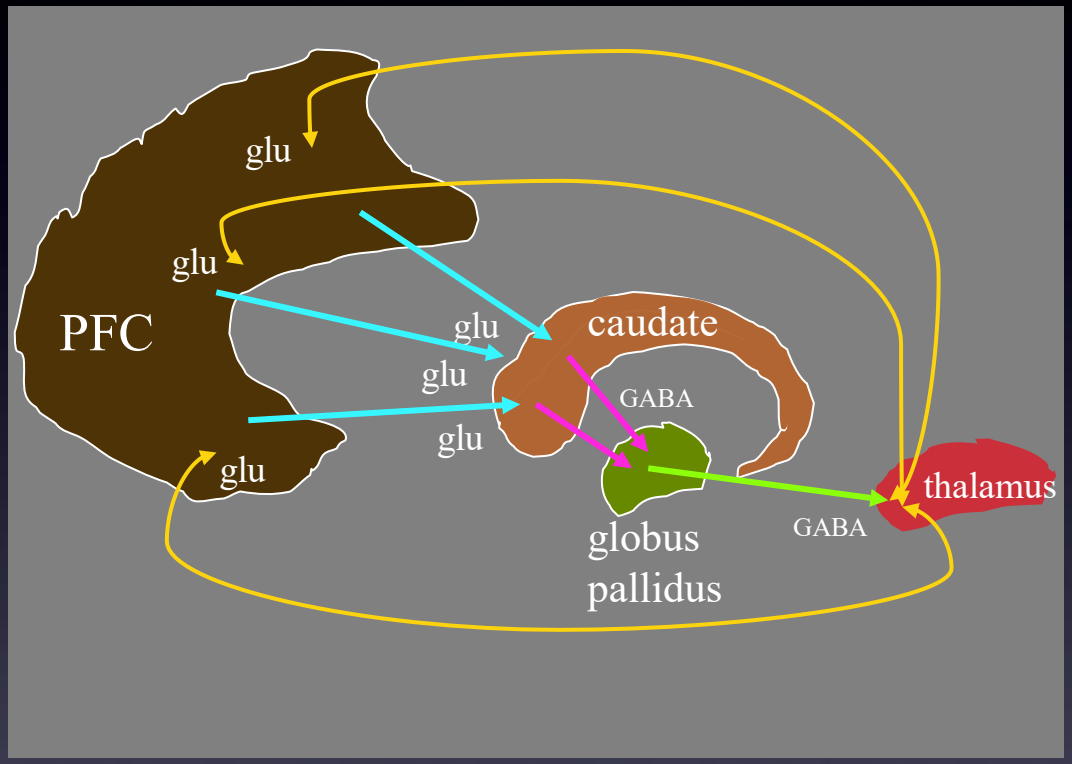
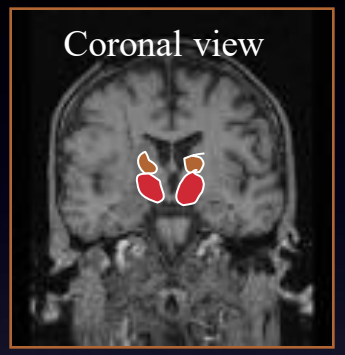
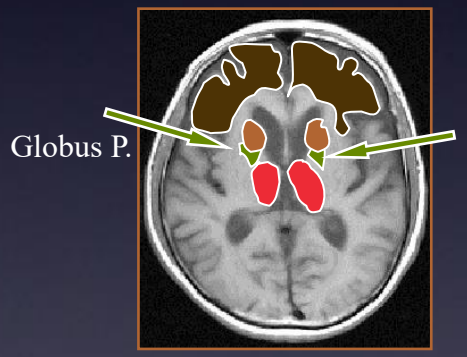
Cortical-striatal-pallidal-thalamic circuitry





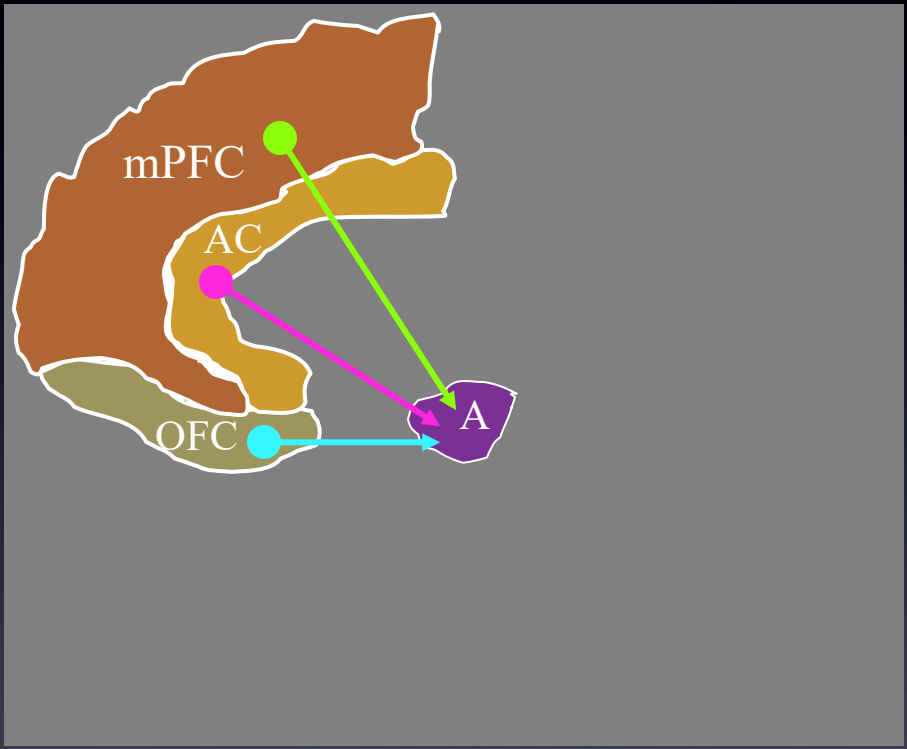


Horizontal view

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.

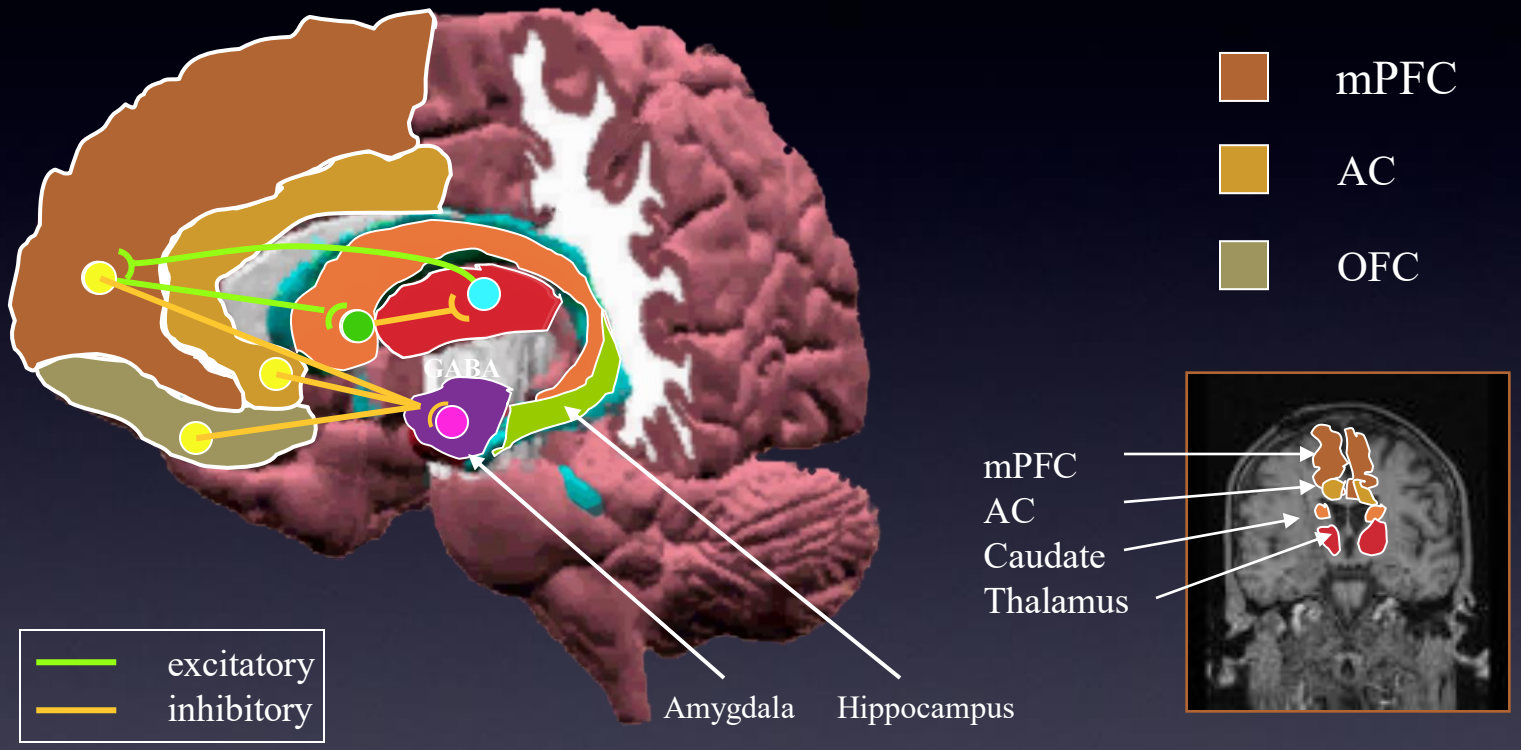
Cortical and limbic connections: the prefrontal cortex inhibits the amygdala



The mPFC, OFC, and AC Regulate 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 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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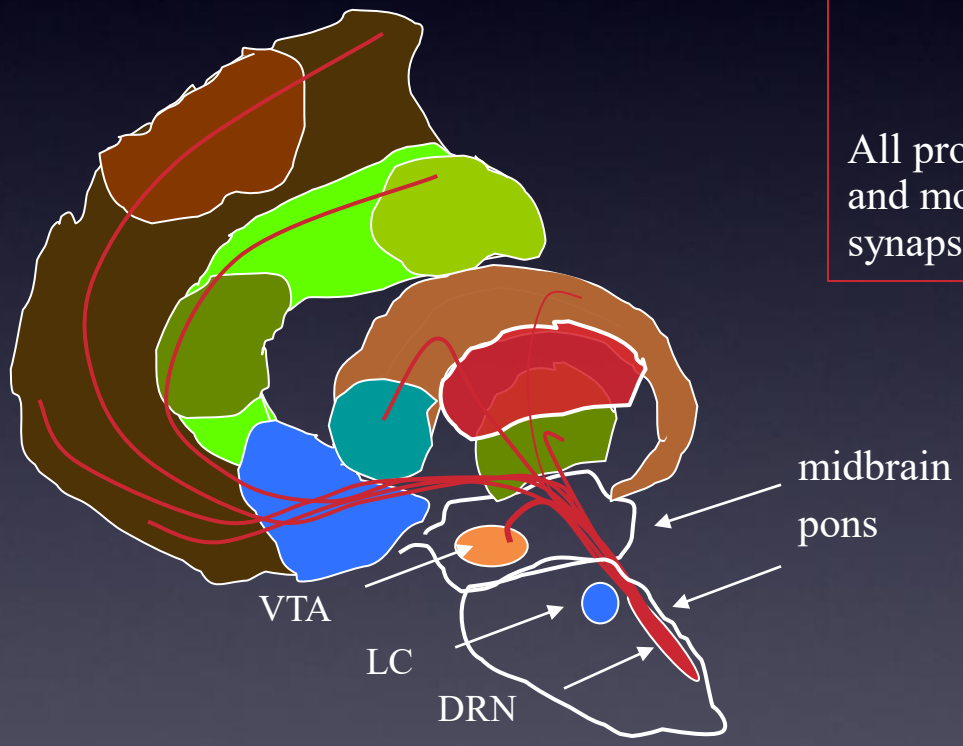
Cortical and limbic connections: role of monoamines (serotonin, norepinepherine, dopamine)

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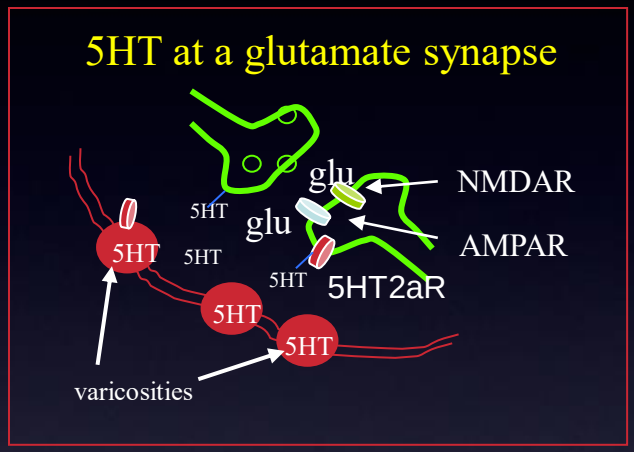
Cortical and limbic connections: role of monoamines (serotonin, norepinepherine, dopamine)

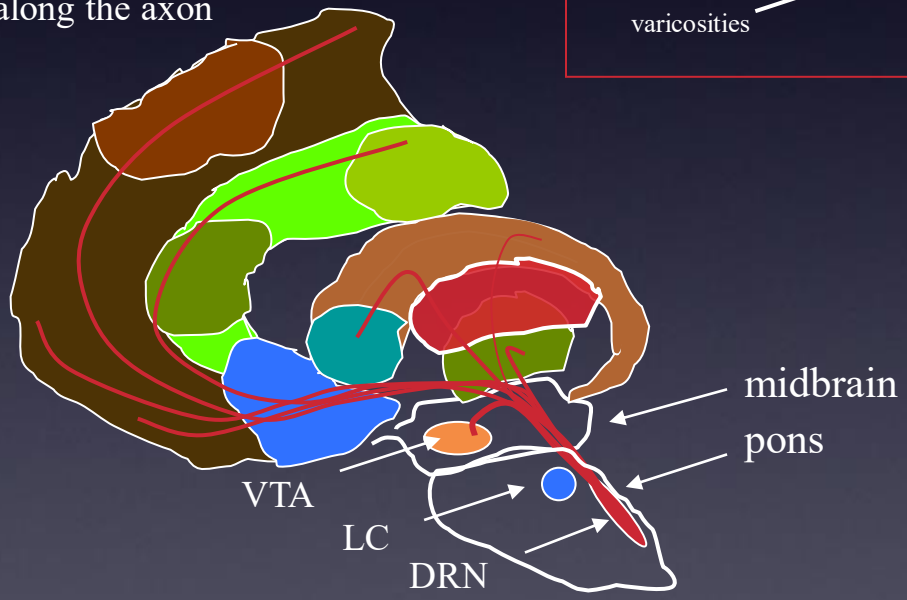
Example (see below and adjacent)

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

Hypothalamic-Pituitary axis (HPA)

Hypothalamic-Pituitary axis (HPA)

Addendum Slides: at the end of the slide set.
Hypothalamic Pituitary Axis

HPA axis: feedback regulation of cortisol

Hypothalamic nuclei → anterior pituitary regulating ACTH release
- CRH released from paraventricular nucleus
- AVP released from magnocellular elements
- chronic stress → AVP coreleased with CRH ⇈ ACTH

ACTH → adrenal cortex regulates cortisol release

Circulating cortisol → negative feedback inhibits cortisol release in:
- Paraventricular nucleus
- Anterior pituitary
- Hippocampus
- Medial prefrontal cortex

Other factors impacting cortisol response
- sympathetic activation,
- humoral factors derived from immune system,
- physiological variables affecting the adrenal cortex (‘exhaustion’)

HPA axis: dysregulation

Abnormal feedback at all points (hypothalamus, anterior pituitary, adrenal cortex, medial prefrontal structures)

Dysregulation of HPA is present in depression, most apparent in
- Psychotic depression HPA axis is most apparent
- Complex dysregulation of HPA
  - changes diural cycle of cortisol max (around 6am) and mimimum (8 pm)
  - may increase cortisol levers
  - CRH ,ACTH release is abnormal

Circulating cortisol negative feedback fails to inhibit cortisol release especially in the context of a stressor

Medial prefrontal structures have abnormal metabolism in the depressed state, and these mPFC structure, as well as the hippocampus normally tightly regulate cortisol levels in blood

Neuroendangerment & Neuroprotection

Addendum Slides: found at the end of the slide set
Neuroendangerment and Neuroprotection in depression

Neuroendangerment & Neuroprotection

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Neuroendangerment & Neuroprotection

Evidence from animal and human studies suggest that apoptotic mechanisms inducing cell death may have a role in several disorders

- Major Depression
- Bipolar Disorder
- PTSD
- Schizophrenia

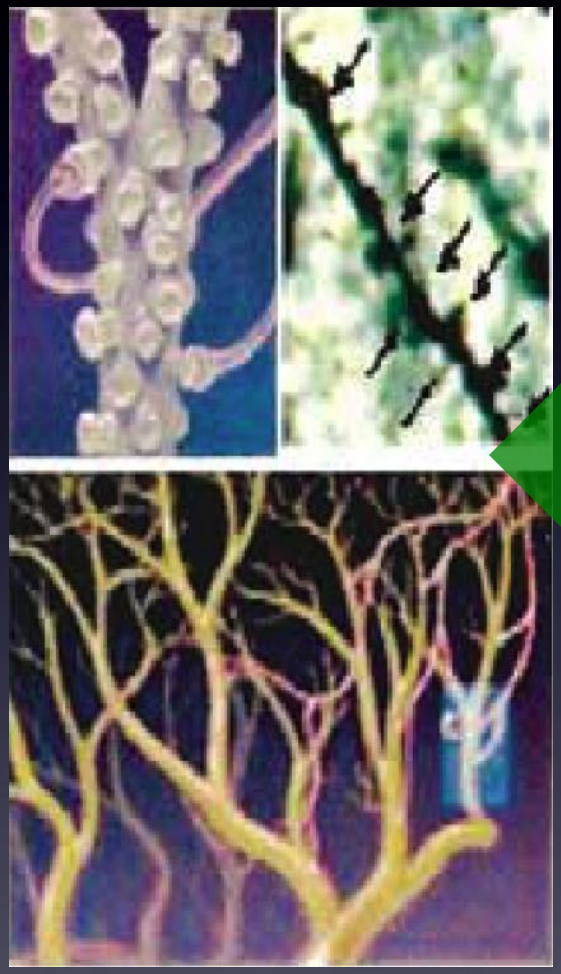
Hypothesized mechanisms

- Reduced neuronal growth factors
- Reduced BCL-2 levels or increased pro-apoptotic proteins
- Increased activity of GSK-3β

Implicated factors leading to the above

- Hypo or hyper-glutamatergic activity
- Increased cortisol
- Additive effect of insults to cell including hypoxia, hypoglycemia

Neuroendangerment in a picture

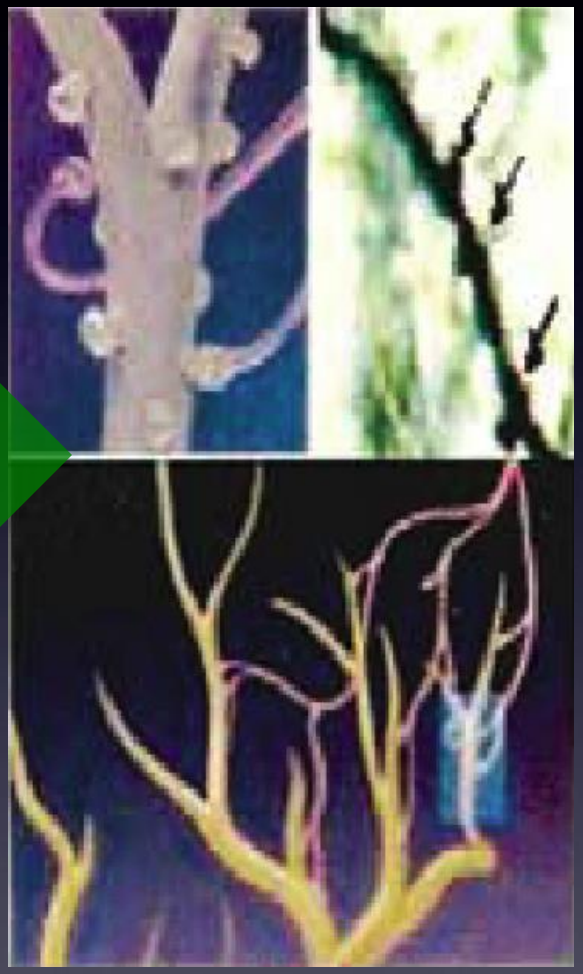


Plasticity goes both ways

Health

Illness

Effect of treatment in restoring dendrites and connectivity?



Neuroendangerment

Plasticity- not always a good thing

Psychiatric illness may cause persistent change to the brain

Neuronal insults lead to

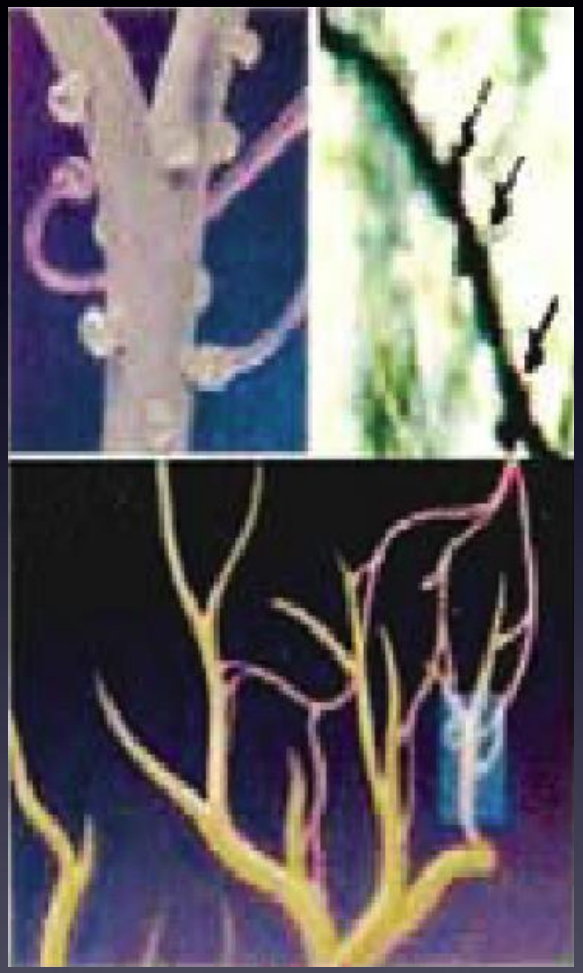
Loss of dendritic arborization, and spines

Loss of viability, and cell death?

This damage leads to decreased connectivity and results in

Dysregulated neurocircuitry

Emergence of symptoms



Dendritic spines are plastic

The synapse is at the dendritic spine

Each dendritic branch receives multiple inputs through the spines

Synaptic activity causes ultrastructural change of the spine

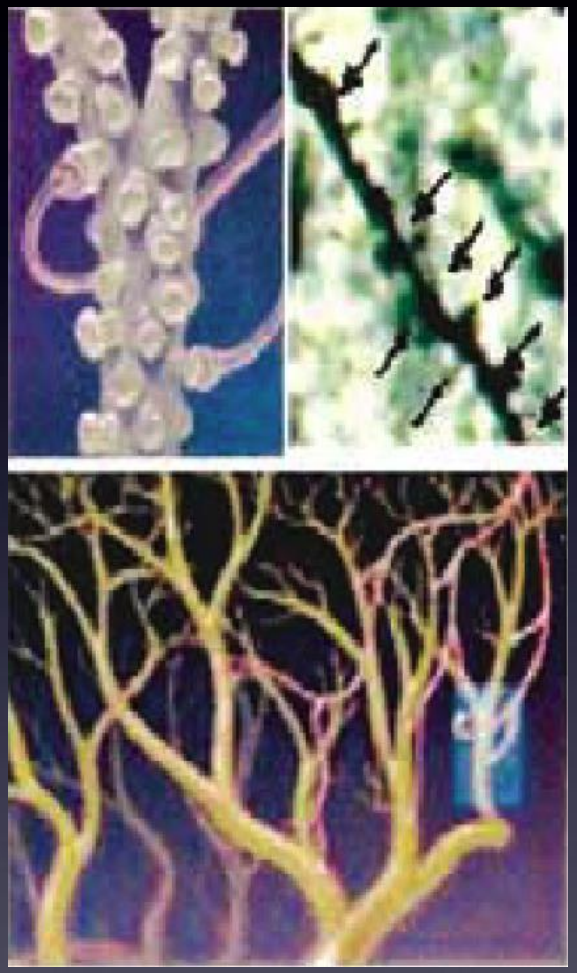
Glutamate receptors AMPA/NMDA

Brain derived neurotrophic factor (BDNF)

Ultrastructural change goes along with change in synaptic strength

Changes inter-neuronal (synaptic) connectivity and systems level connectivity

Re-establishes normal circuit behavior



Neuroprotection

Use of drug properties to promote viability and resist apoptosis

Mood stabilizers: Li, valproate, other AED?
Antidepressants, ECT, second generation antipsychotics

Drug induced epigenetic effects

Histone de-acetylase antagonists: valproate, and antidepressants
Opens 2-3% of genome resulting in increased transcription of viability promoting and antiapoptotic proteins

Direct effect on kinase cascades to re-regulate gene expression

Lithium inhibits GSK-3β
Antidepressants increase P-CREB via effect on monoamine receptors
Both increase BDNF/TrkB, and BCL-2 expression

Slowing of progression of illness in mood disorders:

Biochemical: ↑ NAA, ↑ P-CREB, ↑ BCL-2, ↓ GSK-3β,
Restore structural changes due to loss of neurons, dendrites, and glia

Key Points: neuroendangerment

Neuroplasticity is both a response to neuropathophysiology of psychiatric illness as well as treatment

Neuronal responses to insults can impair viability and increase the likelihood that a neuron will go on to cell death

Some messenger cascades play a key role in maintaining neuronal viability

GSK-3β is a key regulatory enzyme and is an important target of lithium and may mediate its therapeutic effect

HDAC antagonists like antidepressants and valproate regulate gene expression through epigenetic effects

Neurobiology of Psychiatric Illness:

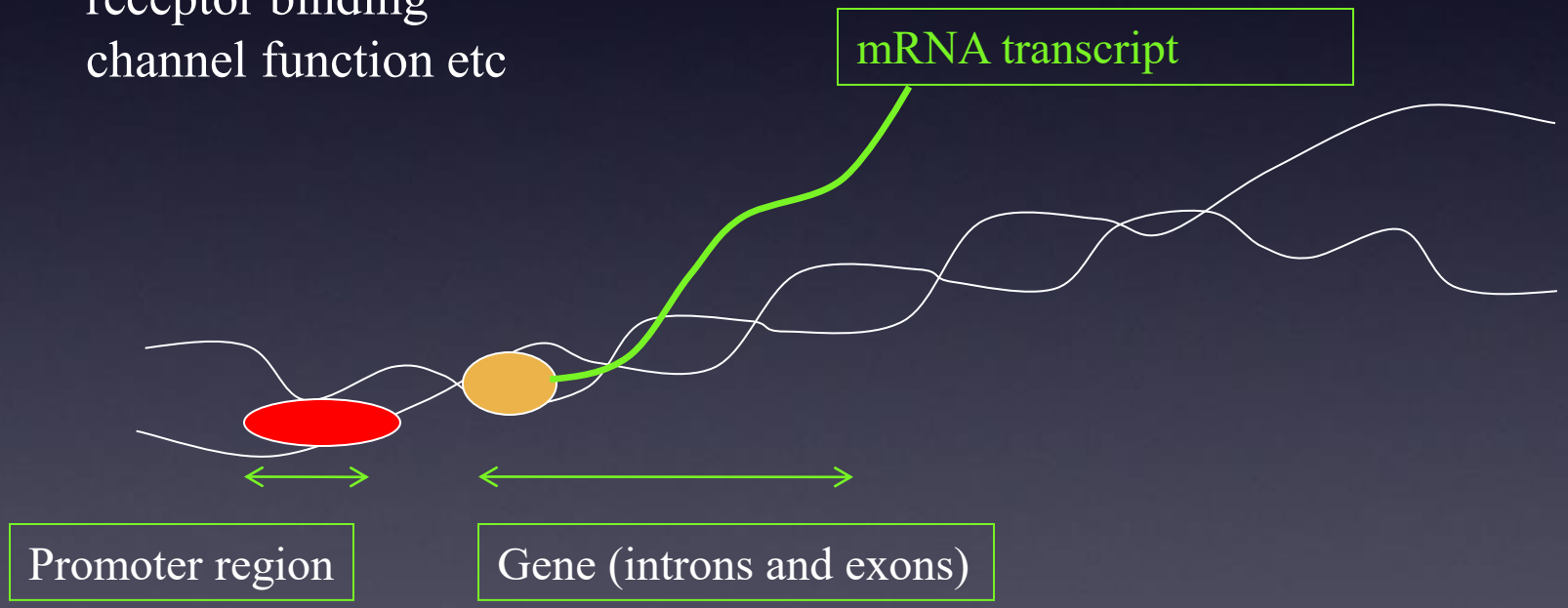
Genetic polymorphisms and psychiatric disorders

Addendum Slides: found at the end of the slide set
Genetic Polymorphisms in Psychiatric Illness

Gene expression

Genetic polymorphisms may occur in the:

- promoter area – influences gene expression
- gene introns – not always predictable
- gene exons – can change the translated protein affecting
  - enzymatic activity
  - receptor binding
  - channel function etc



Gene expression

Example of promoter polymorphism: 5HTTPRL
Upstream promoter areas regulate transcription

Examples of proteins binding to these upstream promoter areas

Bind to regulatory elements of large family of genes

CREB – in phosphoryated form goes into nucleus to bind DNA

AP-1 – important in many messenger cascades, regulate transcription of genes important in cell cycle

Example of exon polymorphism: BDNF

Background:

BDNF stimulates neuronal growth and viability

BDNF 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

Example of exon polymorphism: COMT

Background:

DA (via D1R) is thought to improve prefrontal processing

COMT metabolizes dopamine and norepinepherine at the synapse

Changes in COMT activity will alter DA levels at the synapse

Higher DA levels at the synapse improve prefrontal efficiency

Example of exon polymorphism: COMT

COMT polymorphism at position 158: val to met

Val haplotype has increased enzymatic activity

- clears DA from the synapse more rapidly
- results in lower DA levels at synapse

Met haplotype has less enzymatic activity

- DA more slowly cleared from synapse
- DA levels at the synapse are higher

Clinical impact:

- Val-Val genotype is associated with greater prefrontal cortical volume reduction in schizophrenia

Genetic polymorphisms in depression

5HTTLPR - the serotonin reuptake channel gene

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

- 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, major depressive episode, and suicidality

- hippocampus
  - l/l genotype associated with smaller hippocampus in MDD

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..

Key Points: Genetic polymorphisms

Can control gene expression

Can modify proteins that affect post-translational modification

Can affect the activity of enzymes and other proteins, some of which may significantly modulate cascade messenger systems, or affect synaptic plasticity (eg cytoskeleton)

Some of these will likely be found to play an important role in vulnerability to psychiatric illness, illness course, and changes in brain structure or plasticity

Not clear they will affect somatic treatment approaches

Neurobiology of Psychiatric Illness:
Schizophrenia

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For the lecturer: Schizophrenia slides

- Schizophrenia can best be understood as the complex of both positive and negative symptoms that result from inefficient prefrontal cortical processing.

- Inefficient or dysregulated prefrontal cortical processing will impact cortical function, as well as limbic activity. Prefrontal cortical dopamine is important in fine tuning prefrontal activity, by increasing the difference between signal and noise, and improving the efficiency of the prefrontal cortex.

- The most often studied marker of inefficient cortical processing in schizophrenia is called working memory. Its hallmark is the need to remember something in the present, compare it to something in the past, and then make decisions about what to do. This is studied using the N-back test described in the slides.

- Performance on the N-back test is most impaired in schizophrenic individuals, but is also impaired in unaffected siblings, being intermediate to the schizophrenic individual and healthy controls. This impairment is also seen in functional imaging studies. Schizophrenic brains work harder to accomplish the same task, and fail earlier than do the brains of healthy controls.

For the lecturer: Schizophrenia slides

- Impaired prefrontal cortical processing can be explained through abnormalities of dopamine networks (hyper in limbic areas, hypo in prefrontal areas) or through abnormalities of the glutamate system- hypoglutamatergic activity in the prefrontal cortex. (GABA abnormalities have been described as well, but no ‘coherent’ model of schizophrenia has been put forward based on GABA abnormalities)

- Impaired prefrontal processing can also be understood to be the consequence of structural brain abnormalities in prefrontal cortex, temporal lobe structures, and limbic areas. Generally, decreased brain volume is noted in these studies, or decreased gray matter. It is interesting to note that the decreased gray matter seen in the brains of schizophrenics is not due to fewer neurons, but less supporting tissue around neurons.

- There are good supporting data for a neurodevelopmental hypothesis of schizophrenia, as well as a neurodegenerative process. The neurodevelopmental data derive from a variety of studies showing increased risk of schizophrenia with pre, peri and post natal insults, and in an animal model of medial temporal lobe lesions in the first week of life in rats. Neurodegenerative changes in gray matter volume in specific brain structures are apparent in schizophrenic brains over time. This loss of brain volume and gray matter may be slowed or arrested with effective treatment.

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 symptoms

Pharmacologic model of schizophrenia

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

A drug-induced hypoglutatergic neurotransmission

Supports hypoglutamatergic hypothesis

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Multiple structures of the brain are reduced in volume in schizophrenia

Prefrontal cortex

Temporal cortex

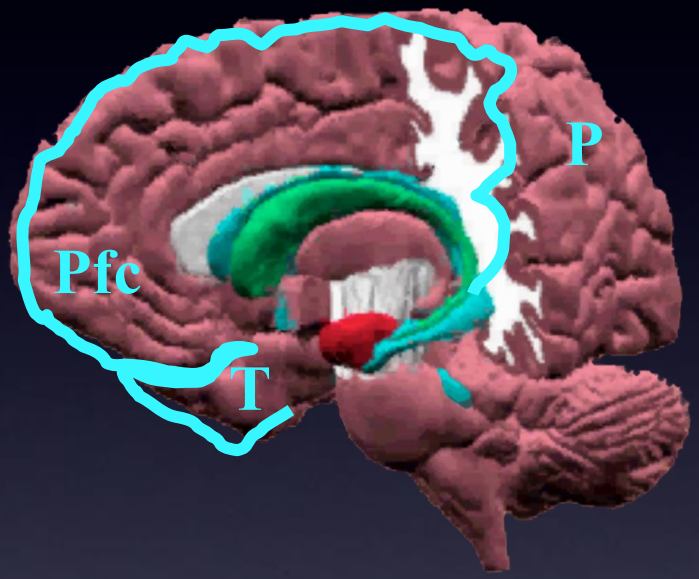
Entorhinal cortex

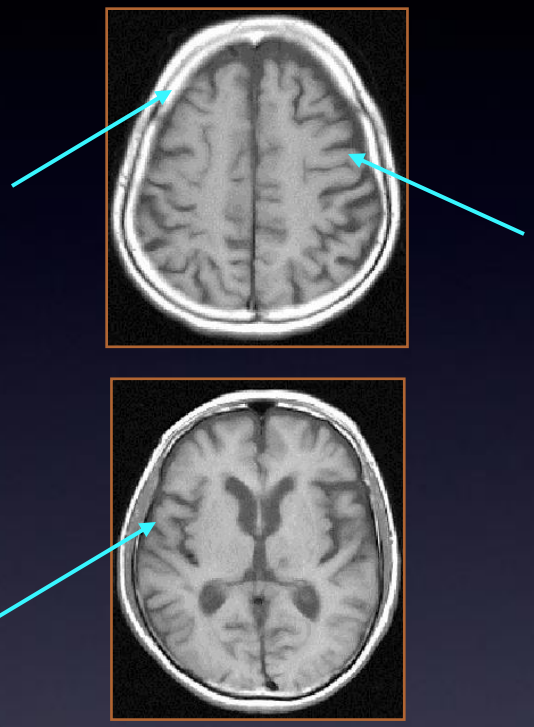
Parahippocampal cortex

Hippocampus

Cortical and limbic structural abnormalities in schizophrenia

Decreased total gray matter volume



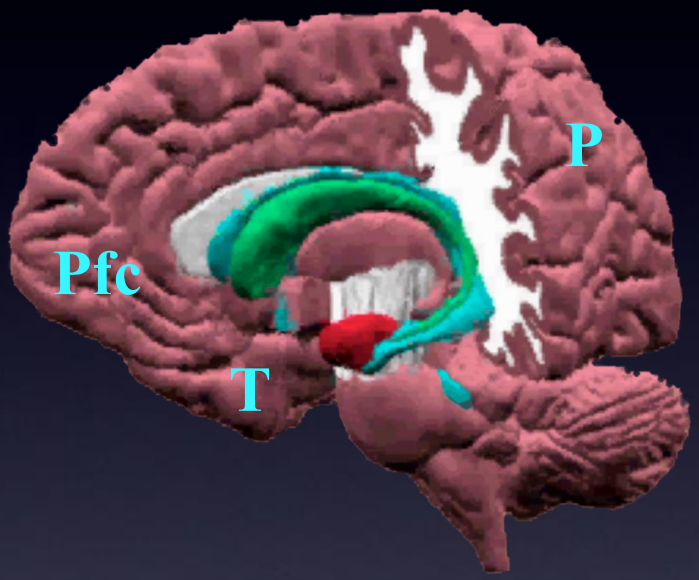


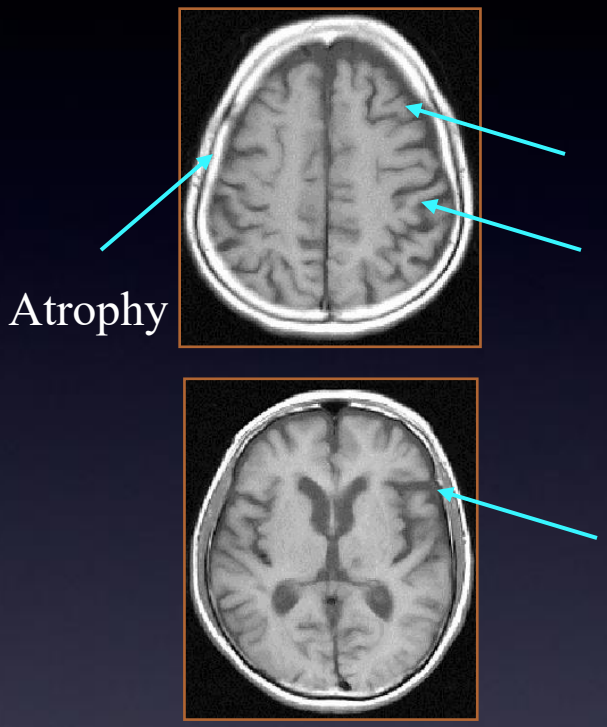
Area of reduced gray matter volume

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).

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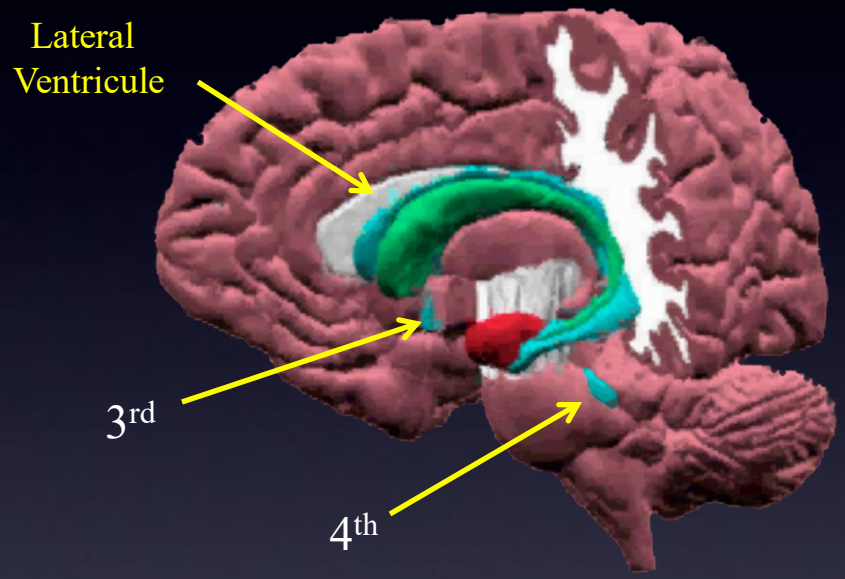
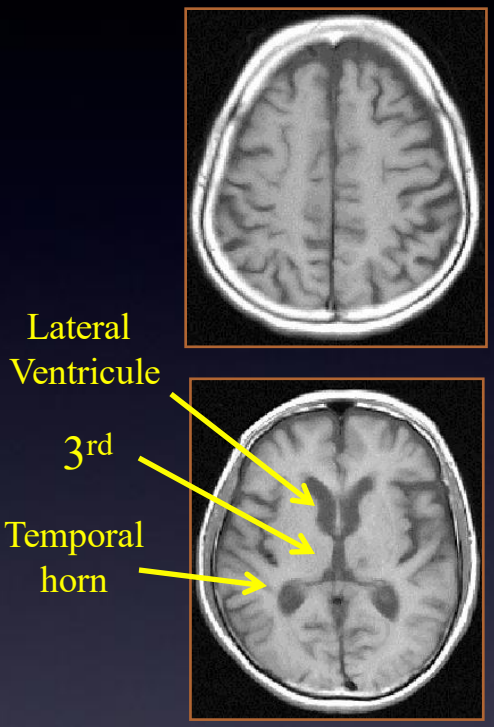
Cortical and limbic structural abnormalities in schizophrenia

Ventriculomegaly



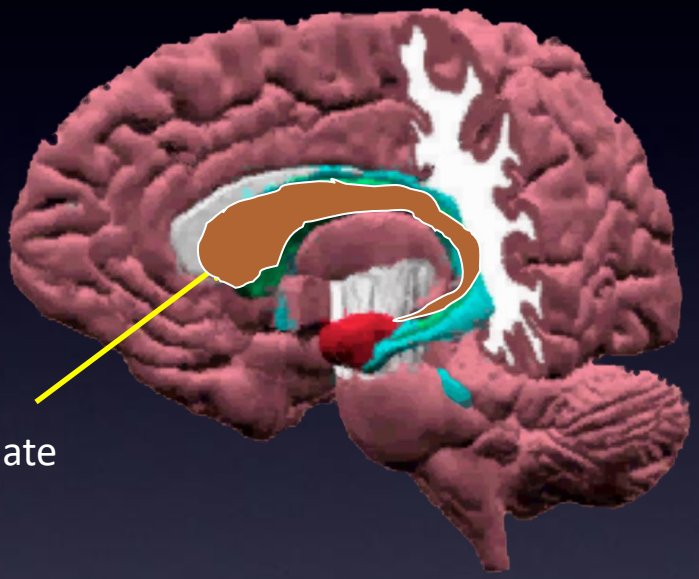


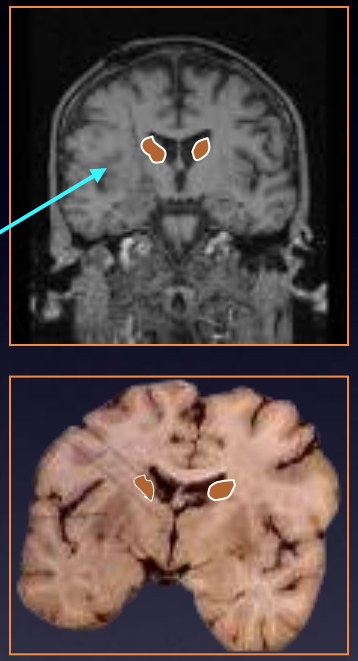
Enlarged lateral ventricle, temporal ventricular horn, 3rd and 4th ventricles, septum pellucidum

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 in volume,
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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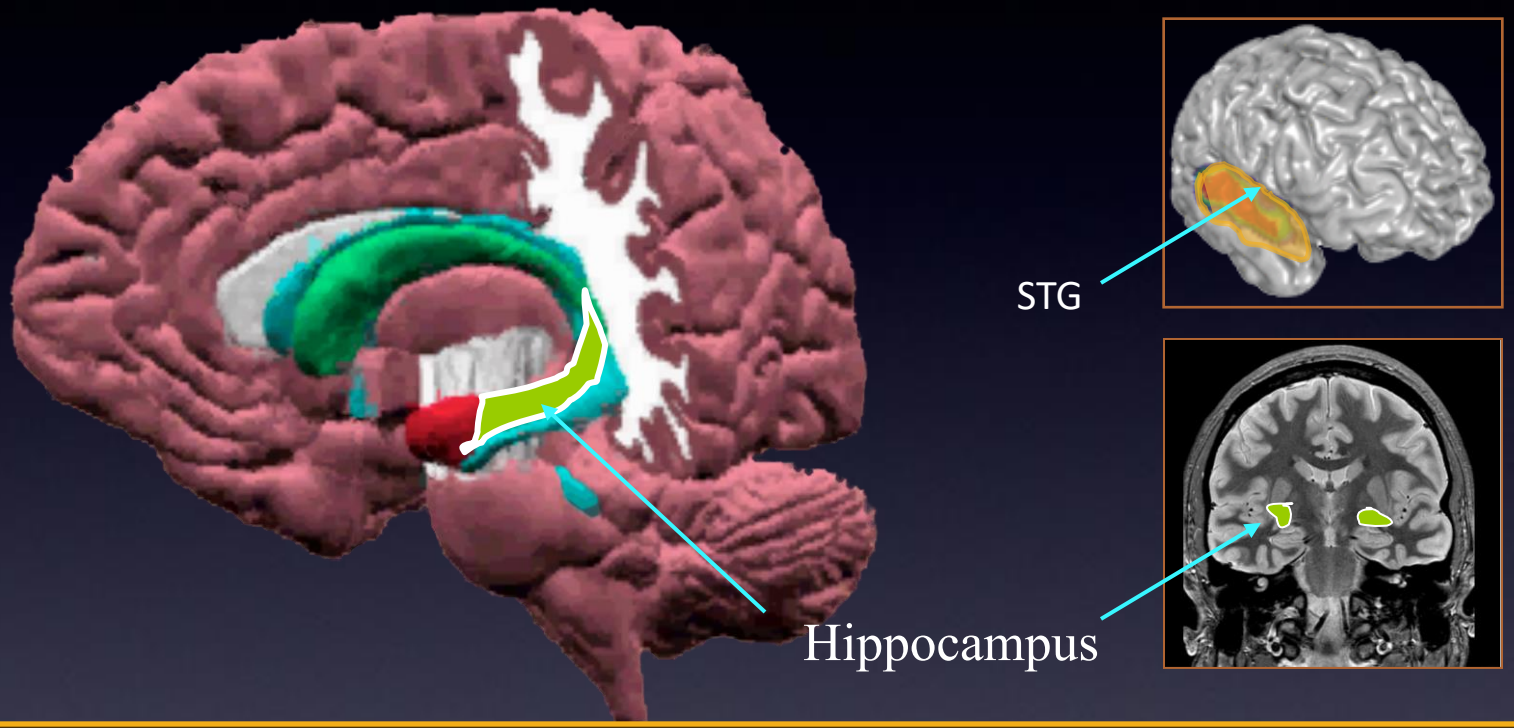
Cortical and limbic structural abnormalities in schizophrenia



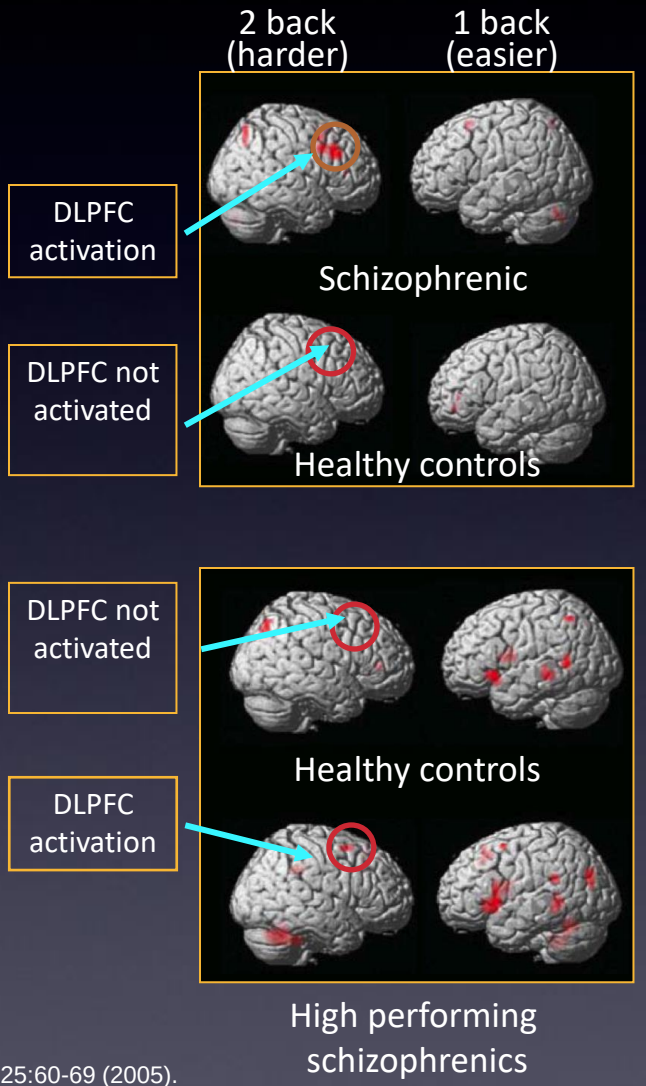
Temporal lobe decreased volume found in:

- 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' the prefrontal cortex

- Modulates glutamate release and prefrontal cortical processing to maximize performance during working memory tasks.
- More DA (as happens with met-met) improves prefrontal processing.

Back to genetic section

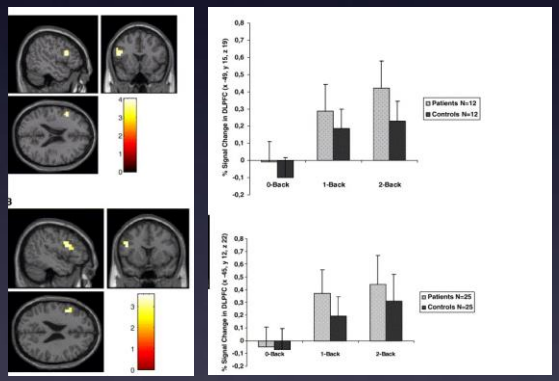
*

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 (inefficient pfc processing compensated by making the brain work harder eg is hypermetabolic). This is presumably due to lower DA levels at the synapse.

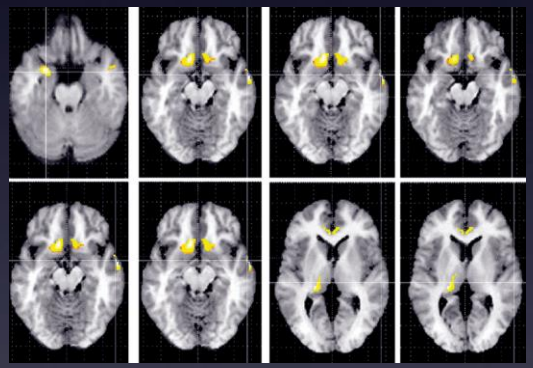
Val- val polymorphism associated with greater volume reduction in schizophrenic subjects in prefrontal and limbic areas, presumably the consequence of low pfc DA.

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]

Key point: These data connect DA and GLU neurotransmitter hypotheses and observations of volumetric reductions in prefrontal and limbic structures in schizophrenia.
Both the DA and GLU contribute to abnormal circuitry and inefficient prefrontal cortical processing.

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, decreased neuropil (neurons more tightly packed) seen in prefrontal, auditory ctx, caudate, lat nuc 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 (white matter)

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; $GABA_A$ 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 of schizophrenia associated with pre, peri or postnatal exposure to neuronal insult such as, infection, hypoxia,hypoglycemia, hypercortisolism, or due to a genetic vulnerability (like COMT val-val)

Abnormalities noted early in life
involves cognitive, motor, and social behaviors.
large prospective studies confirm these findings multiple times.

Ventriculomegaly (VM) in twin studies:
blinded raters can predict twin with schizophrenia by degree of VM.
correlated to premorbid motor and social abnormalities, poor cognition

Reduced prefrontal gray matter volume over time
reduced N-acetyl aspartate, a marker of neuronal number and viability
possible neurodegenerative process

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 by cortical neurons

Key points: schizophrenia may be due to
- neurodevelopmental abnormalities
- neurodegenerative abnormalities
- or both, in at least some individuals

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

Addendum Slide: Imaging studies support the dopamine and glutamate hypotheses of schizophrenia:
vulnerability polymorphism COMT val158met plays a role

D2 receptors over expressed in schizophrenic subjects after DA depletion

- Presynaptic DA depletion, compared baseline to post-DA depletion D2 receptor number
- SPECT and D2 binding radioligand
- Under these conditions, schizophrenic subjects had increased D2 receptors in striatum
- Supports DA dysregulation hypothesis of schizophrenia

COMT val158met polymorphism associated with high D1 receptors

- val/val genotype results in highest DA degradation at synapse: → low DA levels
- PET measured D1 availability, D1 receptors high in cortex of schizophrenic subjects
- High D1 receptors an adaptation to chronically low DA in cortex
- Correlates with poor working memory

Ketamine abusers: COMT val/val associated with high D1 receptors as well

- Ketamine blocks glutamate NMDA receptor, abusers chronically lower GLUR activity
- PET measured D1 availability, D1 receptors high in cortex of ketamine abusers
- High D1 receptors means low DA in cortex of people with chronically blocked GLUR
- Indicates GLUR/D1 receptor coregulated in cortex
- Ties glutamate hypothesis (low GLU in cortex) and DA hypothesis (low DA in cortex)

Key point

These data support both the glutamate and dopamine hypotheses of schizophrenia. It also provides data indicating that GluR activity influences DA release in cortex, This causes executive dysfunction as seen in individuals with schizophrenia.

Abi-Dargham Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):8104-9. Abi-Dargham.J Neurosci. 2002 May 1;22(9):3708-19.
Slifstein M.Mol Psychiatry. 2008 Mar 4. [Epub ahead of print]

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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).

Khorram B, Lang DJ et al. Reduced thalamic volume in patients with chronic schizophrenia after switching from typical antipsychotic medications to olanzapine. Am J Psychiatry 163(11):2005-2007 (2006).

Harris MP, Wang L et al. Thalamic shape abnormalities in individuals with schizophrenia and their nonpsychotic siblings. J Neurosci 27(50):13835-1842 (2007).

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Yamsaki S, Yamasue H et al. Reduced planum temporale volume and delusional behavior in patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci 257(6):318-324 (2007).

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Joyal CC, Lasko MP et al. A volumetric MRI study of the entorhinal cortex in first-episode neuroleptic naïve schizophrenia. Biol Psychiatry 51(12):1005-1007 (2002).

Prasad KM, Rohm BR, Keshavan MS. Parahippocampal gyrus in first episode psychotic disorders, a structural magnetic resonance study. Prog Neuropsychopharm Biol Psychiatry 28(4):651-658 (2004).

Tan H-Y, Sust S et al. Dysfunctional prefrontal regional specialization and compensation in schizophrenia. Am J Psychiatry 163:1969-1977 (2006).

Glahn DC, Ragland DJ et al. Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory inn schizophrenia. Human Brain Mapp 25:60-69 (2005).

Bertolino A, Caforio G et al. Prefrontal dysfunction in schizophrenia controlling for the Val158Met genotype and working memory performance. Psychiatry Res 147(2-3) 221-228 (2006).

Ohnishi T, Hashimoto R et al. The association between the Val158Met polymorphism of the COMT gene and morphologic abnormalities of the brain in schizophrenia. Brain 129:399-410 (2006).

Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia.Biol Psychiatry 45:17-25 (1999).

Kreczmanski P, Heinsen H, et al. Volume, neuron density and total neuron number in five subcortical regions in schizophrenia. Brain 130:678-692 (2007).

Goldman AL, Pezawas L et al. Heritabiity of brain morphology related to schizophrenia: A large scale automated magnetic resonance imaging study. Biol Psychiatry Aug 27(epub) (2007).

Heinz A, Saunders R, et al. Striatal Dopamine Receptors and Transporters in Monkeys with Neonatal Temporal Limbic Damage. Synapse 32: 71-79 (1994).

Flynn SW, Lang DJ et al. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with anlaysis of oligodendrocyte proteins. Mol Psychiatry 8(9):811-820 (2003).

Weickert CS, Webster MJ et al. Reduced Gap-43 in dorsolateral prefrontal cortex of patients with schizophrenia. Cereb Cortex 11(2): 136-47 (2001).

Scarr E, Beneyto M et al. Cortical glutamatergic markers in schizophrenia. Neuropsychopharmacology 30(8):1521-1531.

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Knable MB, Barci BM, et al. Molecular abnormalities in the major psychiatric illnesses: Classification and regression tree analysis of post-mortem prefrontal markers Mol Psychiatry 7(4):392-404 2002

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Schneider M, Koch M. Behavioral and morphological alterations following neonatal excitotoxic lesions of the medial prefrontal cortex in rats. Experimental Neurology 195:185-198 (2005).

Flores G, Alquicer G. Alterations in dendritic morphology in prefrontal cortex and nucleus accumbens neurons in post-pubertal rats after neonatal excitotoxic lesions of the ventral hippocampus. Neuroscience 133:463-470 (2005).

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Lewis DA Levitt P. Schizophrenia is a disorder of neurodevelopment. Annu Rev Neruosci 25:499-532 (2002).

Isohanni M, Miettunen J et al. Risk factors for schizophrenia. Follow up data from the Northern Finland 1966 cohort study. World Psychiatry 5(3):168-171 (2006).

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Van Haren NE, Huslhoff Pol HE et al. Focal gray matter changes in schizophrenia across the course of illness: a 5 year follow up study. Neuropsychopharmacology 32 (10):2057-2066 (2007)

Abbot C, Bustillo J. What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update. Curr Opin Psychiatry 19:135-139 (2006).

Abi-Dargham A, Rodenhiser J, Printz D. et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia.Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):8104-9.

Abi-Dargham A, Mawlawi O, Lombardo I. et al. Prefrontal dopamine D1 receptors and working memory in schizophrenia.J Neurosci. 2002 May 1;22(9):3708-19.

Slifstein M, Kolachana B, Simpson EH, et al. COMT genotype predicts cortical-limbic D1 receptor availability measured with [(11)C]NNC112 and PET.Mol Psychiatry. 2008 Mar 4. [Epub ahead of print]

Neurobiology of Psychiatric Illness:
Bipolar Disorder

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

For the lecturer: Bipolar slides

- Bipolar disorder, like unipolar depression, is a progressive illness. Overtime there is a qualitative change in mood episodes: fewer euphoric manias, more mixed symptoms, more time depressed, more chronic depression, greater likelihood of rapid cycling, decreased well interval.
- Kindling has been suggested as a model to understand how progressive changes in the brain,either in its structure or neurophysiology, may occur with each mood episodes. The consequence of these changes in the brain, is a change in the phenomenology of the illness time: eg there is an illness course in bipolar disorder. This presumed to represent changes in the brain over time.
- As in schizophrenia, there are cortical and subcortical regions that are reduced in volume in people with bipolar disorder. There is data to suggest that some of these structures continue to atrophy with time, indicating a possible neurodegenerative process. There is also evidence that the brain volume loss correlates with the number of mood episodes, and cognitive decline (IQ).
- There is a dysregulation of prefrontal and limbic connected networks in euthymic bipolar subjects indicating that whatever neurobiologic abnormalities exist in this disorder, they are present when the individual is symptom free as well as when they are symptomatic.
- Brain derived neurotrophic factor has a polymorphism that is associated with greater gray matter volume loss over time in individuals with bipolar disorder. Presumably, this could be a genetic marker for those most likely to have a more rapid progression of illness course.
- Lithium and valporate sodium share neuroprotective properties that may be important in their ability to reduce mood symptoms, and reduce the number of mood episodes, as well as to protect neurons from poor functioning and death. Overtime this is hoped to reduce or prevent gray matter volume loss in this illness.

Neurobiologic Abnormalities in Bipolar disorder

Illness course

Volumetric studies

- prefrontal cortex
- limbic structures

Functional imaging studies

Genetic polymorphisms in Bipolar disorder

- BDNF (brain derived neurotrophic factor)

Neuronal metabolic abnormalities

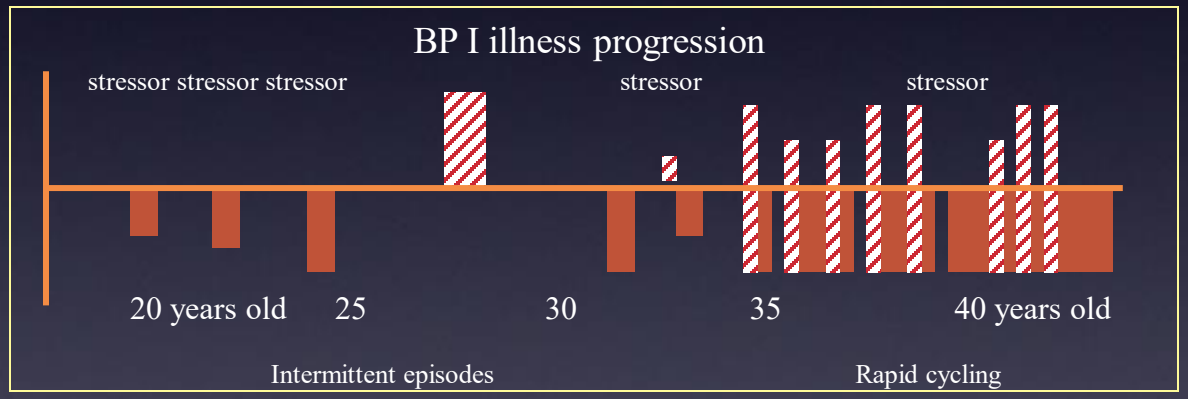
Gene expression abnormalities

- Glycogen synthase kinase 3β (GSK-3β)

Illness progression in bipolar disorder

Key Point : progressive change in illness over 20 years

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



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

Unipolar: Cortical volume		Bipolar: 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)

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: degree of gray matter loss correlates with verbal and performance IQ
illness course: also 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
Foland LC et al. Neuroreport 22:19(2) 2008 et al

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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
Jogia J, et al. Br J Psychiatry 192:197-201 2008

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Frangou S Kington J et al. Eur Psychiatry epub Jul;24 2007
Jogia J, et al. Br J Psychiatry 192:197-201 2008

Genetic polymorphism in bipolar disorder

BDNF val^{66}met polymorphism

Met allele associated with:

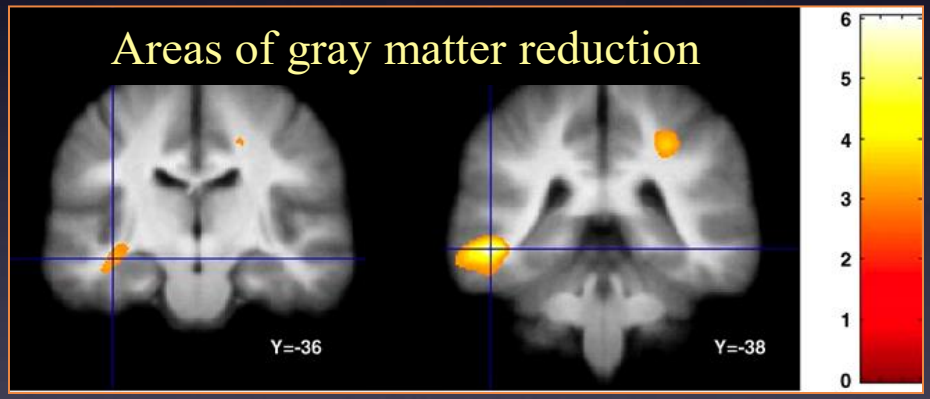
hippocampal function poorer for episodic memory

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



Key point

progressive reduction in temporal gray matter and hippocampal volume will impair selected cognitive functions even when euthymic, and it will presumably make relapse more likely.

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
Yucel et al. Psychopharmacology epub 20 Aug 2007

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- 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 Li+VPA was neuroprotective due to effects on GSK-3 activity (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
Yucel et al. Psychopharmacology epub 20 Aug 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,
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- Combination treatment was neuroprotective via effects on GSK-3 in rats
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- Lithium increased hippocampal volume in prospective 2-4 year trial in human subjects

Leng Y, et al. J Neurosci 28(10):2576-88 2008
Yucel et al. Psychopharmacology epub 20 Aug 2007

Key Points: Neurobiology of Bipolar Disorder

Progressive cortical gray matter loss may explain illness progression

- characteristics of mood episodes
- chronicity, decreased well-interval, mixed episodes, response to treatment
- cognitive impairment over time

Post-mortem findings 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

Addendum Slide: persisting cognitive deficits in lithium treated bipolar patients over two years

Euthymic bipolar patients have persisting cognitive impairment

- 44/106 subjects met criteria for study, BP I or II
- 33/44 seen at 2 year follow up
- Lithium only mood stabilizer, dose 400 - 1600/day, levels 0.43 to 0.95

Outcomes

- Major findings in executive function
  - Trails B
  - FAS verbal fluency of Controlled Oral Word Association Test-Categories
  - Stoop word-color interference test
  - Stroop inhibition test
- Processing speed
  - Trails A
  - Connors Continuous Performance Test II
- No effect on memory tasks

Key point

This data supports finding of cognitive impairment in euthymic bipolar subjects. These have also been treated with Lithium, which may reduce the rate at which such deficits may progress. The stability of cognitive impairment over 2 years supports the hypothesized neuroprotective effect of Lithium.

Mur et al. J Clin Psych 69 (5) 712-719 2008

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Post R http://www.medscape.com

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Benes FM, Kwok EW, Vincent SL, Todtenkopf MS: A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. Biol Psychiatry 1998; 44:88-97

Port J, Unal S, Mrazek D, Marcus S. Metabolic alterations in medication-free patients with bipolar diisorder: a 3T CSF-corrected magnetic resonance spectroscopy imaging study. Psych Res Neuroimaging 162(2):113-21 2008

Leng Y, Liang M, Ren M, et al. Synergistic neuroprotective effects of lithium and valproic acid or other histone deacetylase inhibitors in neurons: roles of glycogen synthase kinase-3 inhibition. J Neurosci 28(10):2576-88 2008

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

Mur et al. J Clin Psych 69 (5) 712-719 2008

Bipolar references

Benes FM, Kwok EW, Vincent SL, Todtenkopf MS: A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. Biol Psychiatry 1998; 44:88-97

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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

Mur M, Portella M, Martinez-Aran A, Pifarre J, Vieta E. Long term stability of cognitive impairment in bipolar disorder: a 2 year follow up study of lithium-treated Euthymic bipolar patients. J Clin Psych 69 (5) 712-719 2008

Neurobiology of Psychiatric Illness:

Major Depression

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

For the lecturer: Depression slides

- The symptoms of depression are the consequence of dysregulated circuits regulating mood, anxiety, interests, cognition etc.
- The subgenual prefrontal cortex may be a key area in understanding the dysregulation of the brain in depression. It is reduced in volume in familial depression, it is hypermetabolic in the depressed state, and appears to normalize its activity as symptoms improve with many antidepressant treatments, including ECT and DBS.
- Dysregulation of the subgenual prefrontal cortex has widespread implications for spreading dysregulation to other structures due to its intimate connections to multiple limbic and prefrontal cortical areas.
- Other prefrontal areas besides the subgenual cortex, have reduced volume and gray matter thinning. In one study, the degree of gray matter thinning appeared to be correlated with poor executive functioning, and the severity of depressive symptoms.
- Hippocampal atrophy is a highly replicated finding, and may be driven by the duration of illness, the duration of untreated depression, and genetic polymorphisms of the serotonin transporter gene.
- Post mortem studies show abnormalities in the volume of brain structures, the number of neurons, second messenger signaling abnormalities, and changed gene expression in the brains of individuals with depression.

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. 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
- nay normalize BDNF levels

Neurocircuitry Dysfunction in depression

Dysregulated circuits in major depression

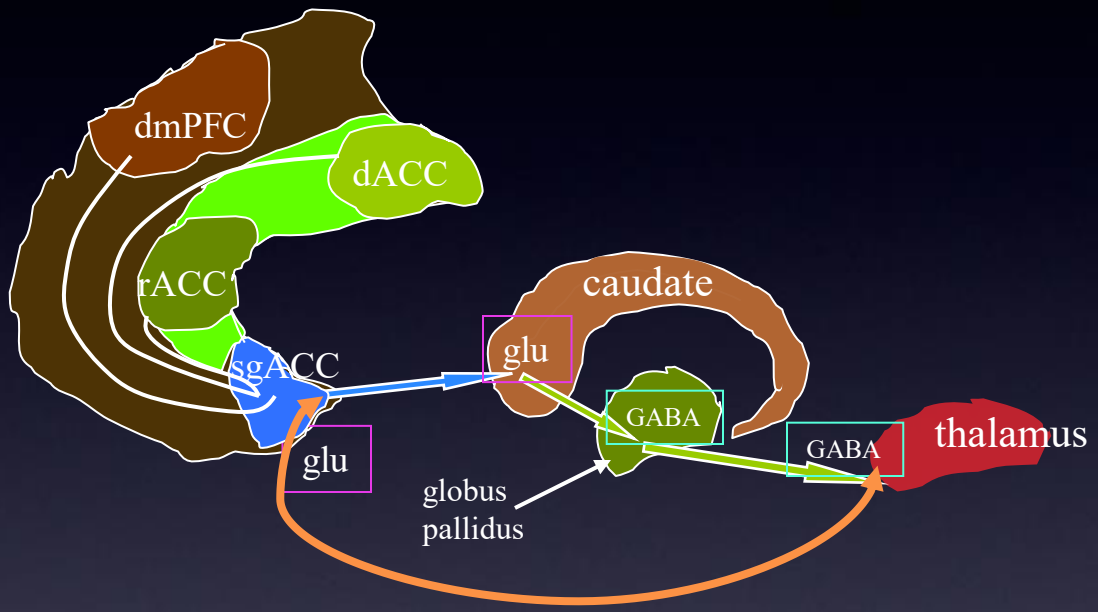
Prefrontal cortical-striatal-pallidal-thalamic pathways
Prefrontal cortex, dorsal and ventral striatum, globus pallidus, medial thalamus

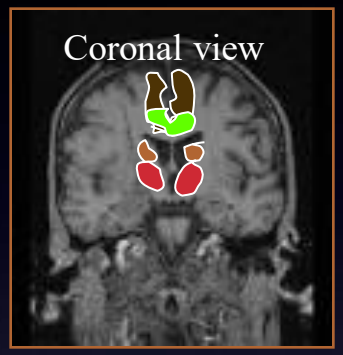
Prefrontal cortical-limbic pathways
Prefrontal cortex to hippocampus, amygdala, and hypothalamus

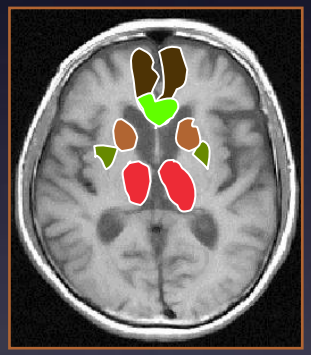
Prefrontal reciprocal cortical-aminergic feedback pathways
Prefrontal cortex to the dorsal raphe (5HT), locus ceruleus (NE), ventral tegmental area (DA)

Paralimbic areas with dense reciprocal innervation to limbic areas:
anterior cingulate, medial prefrontal, subgenual, orbitofrontal, entorhinnal cortex

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







Horizontal view

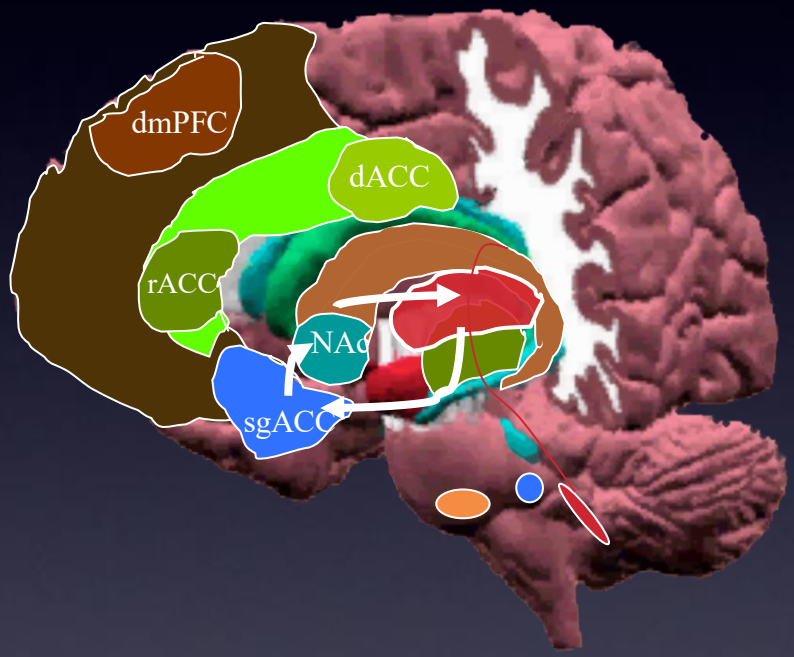
mPFC structures implicated in MDD and connected to the sgACC

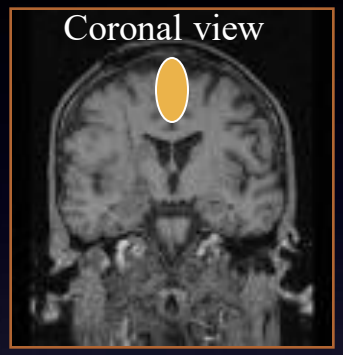
dorsomedial PFC (dmPFC); dorsal ACC (dACC), rostral ACC

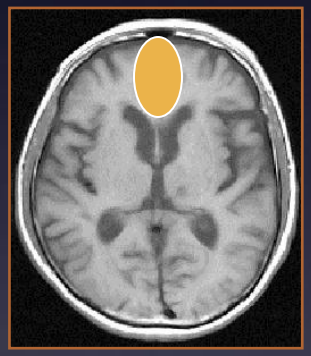
subgenual ACC (sgACC) glu glutamatergic synapse GABA gabaergic synapse

Functional neuroanatomy of the mPFC structures

Function of medial prefrontal cortical areas







dmPFC: self referential processing of emotion
sgACC: sadness, autonomic/endocrine response to stress; appraisal aversive and rewarding stimuli
rACC: emotional stroop (distinguishing emotional affect with distractor)
dACC: more cognitive appraisal of aversive/rewarding stimuli

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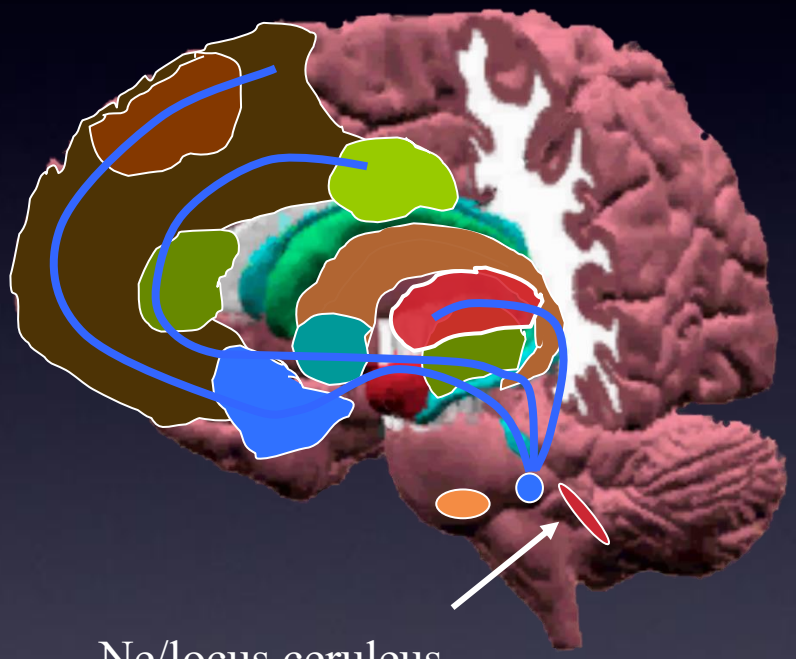
How do monoamines work? Powerful modulaters of GABA and glutamate synapses in cortical-striato-thalamic and limbic circuits

Noradrenergic system



Ne/locus ceruleus

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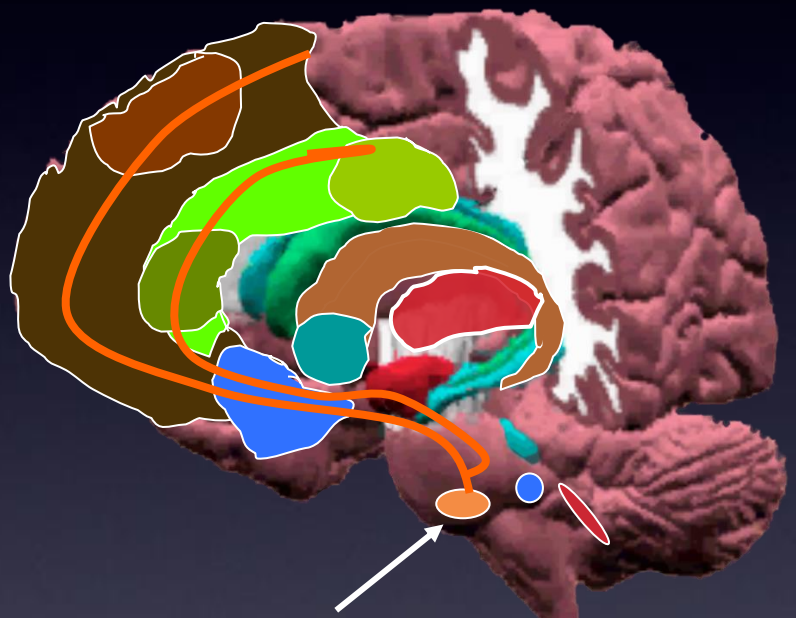
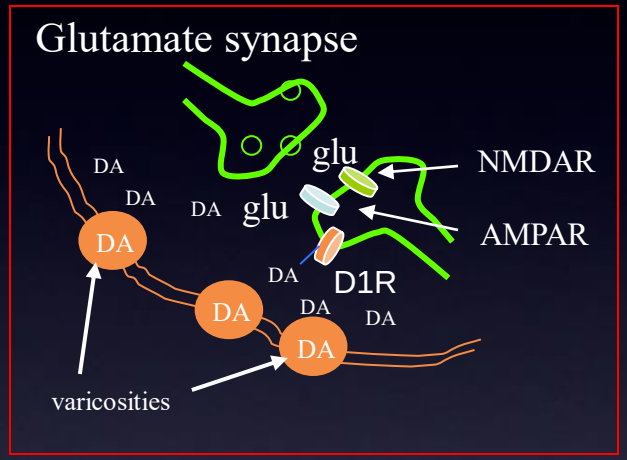
Monoamines: powerful modulaters of GABA and glutamate synapses in cortical-striato-thalamic and limbic circuits

Dopaminergic system



DA/Ventral tegmental area



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

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.

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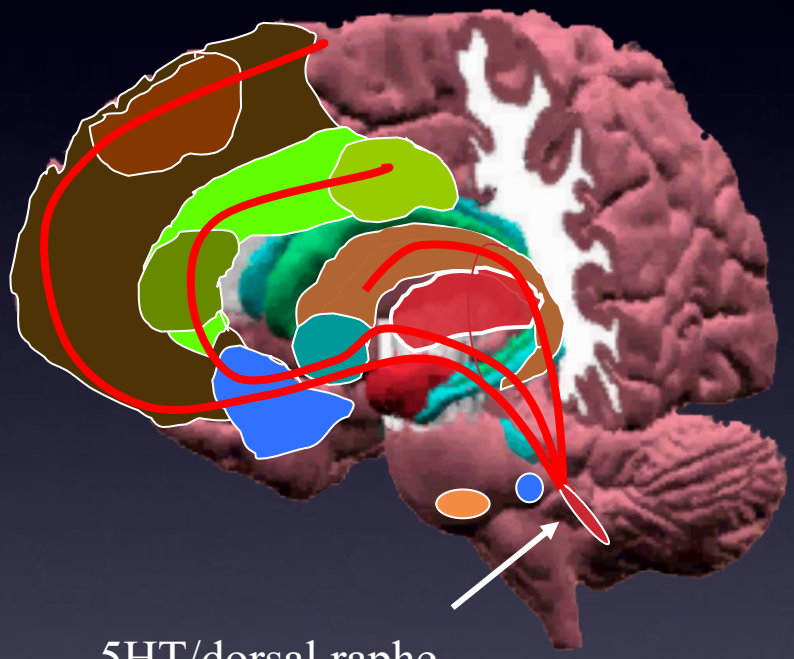
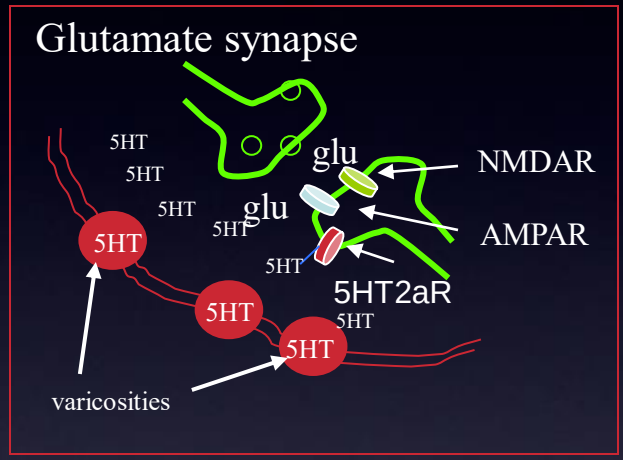
Monoamines: powerful modulaters of GABA and glutamate synapses in cortical-striato-thalamic and limbic circuits

Serotoninergic system



5HT/dorsal raphe



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?
(recall mPFC is highly connected to limbic, paralimbic and cortical structures)

hypothalamus

mPFC dysregulation disturbs the hypothalamic pituitary axis (CRH release)

nucleus accumbens (N Ac)

mPFC can dysregulate the dopamine reward system causing anhedonia

ventral striatum

imPFC output dysregulated, it will not be processed normally by N Ac

amygdala

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

fornix

pathway for communication of mPFC to hippocampus and amygdala

mPFC: Cortical-limbic and cortico-cortical circuitry

What is the functional impact of dysregulation of mPFC/sgACC?

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

rostral/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 for psychosocial well-being
- poor decision making creates more stressful situations and higher risk of relapse

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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:

CBT: decreases in ant sgPFC, ventrolateral & dorsomedial PFC

venlafaxine: decreases in post sgPFC, ventrolateral PFC,

ECT/SSRI's: 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:

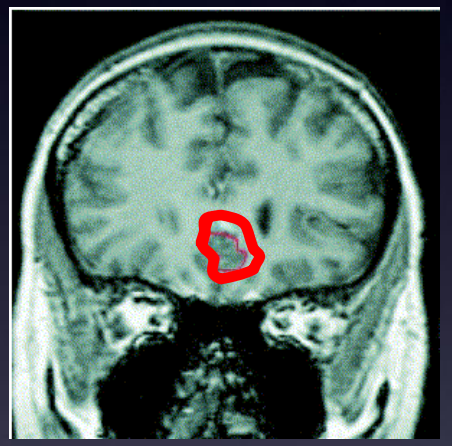
Decreased structural volumes suggest widespread brain dysfunction in depression

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

Metanalysis bipolar and unipolar MRI volumetric 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 healthy controls)
reduced medial orbitofrontal cortex (31%) without change in sgPFC
medial OFC closely related cortex, 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 cortical structures

Results:

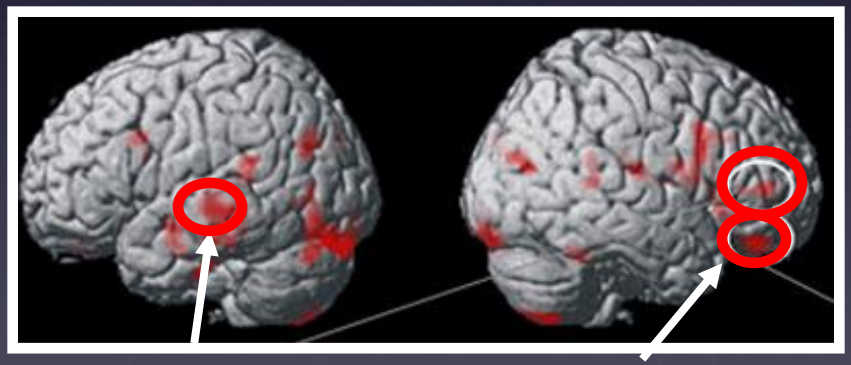
red highlighted areas have significant gray matter thinning in depressed subjects correlating with:

Impaired cognition:

gray matter reduction correlated with poor performance on Wisconsin Card Sorting Test

Severity:

gray matter reduction correlates with severity of MADRS scores



Temporal ctx

Ventrolateral pfc

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

Post-mortem studies:volumetric abnormalities

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 glia reduced by 24%/BPD reduced by 41%

Lateral orbitofrontal cortex

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

Dorsolateral PFC

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

Amygdala

- dendritic branching decreased

Thalamus

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

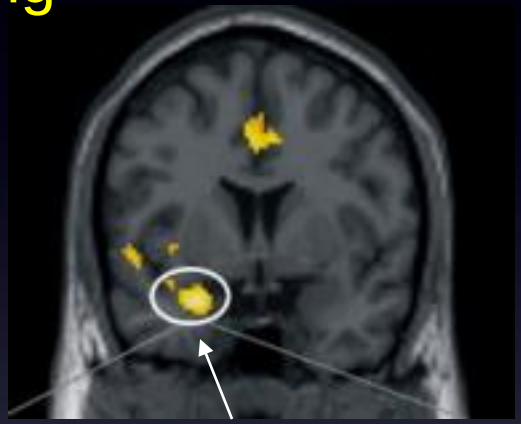
Ongur et al. Proc Natl Acad Sci 95:13290-95 1998; Rajkowska G et al. Biol Psychiatry 45:1085-98 1999; Drevets et al. Nature 386:824-27 1997
Young K, et al. Am J Psychiatry 161(7(:1270-7 2004

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)



hippocampus

First episode depression atrophy correlates with:

number of stressful experiences prior to 1st episode

Cognition Negatively affected

Impaired cognition on Wisconsin Card Sorting Test (WCST) performance coorelates with reduced hippocampal volume

Key points:

reduced volume is associated with more episodes of depression, untreated depression: 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;

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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
  - 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 is molecular target of antidepressants, antag. ↑ gene transcription
  - HDAC is molecular target of valproate, antag. ↑ gene transcription

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 ACC 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 in sgACC

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 neuronal growth and viability

↓ BDNF 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

Genetic 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 (CVL)
smaller hippocampal volume

Key points: BDNF promotes cognitive function/↑ hippocampal volume
Antidepressant treatment may be key to reverse decreased BDNF level
This will improve neuronal viability, connectivity, and function

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

- 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, major depressive episode, and suicidality

- hippocampus
  - l/l genotype associated with smaller hippocampus in MDD

Back to genetic section

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.

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.

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

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Neurobiology of Psychiatric Illness:
Obsessive Compulsive Disorder

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

For the lecturer: OCD slides

- OCD is an excellent example of a systems level dysregulation, primarily characterized by hypermetabolism in the orbitofrontal cortex (OFC).
- From this standpoint, we examine the important connections the OFC has with other structures. This helps to begin to understand the potential areas of associated dysregulation that could result from a primary orbitofrontal dysregulation.
- The consequence of this dysregulation has functional implications for specific neurotransmitter systems, especially glutamate and serotonin.
- Not surprisingly, there is apparent atrophy in the OFC, likely the result of prolonged hyperglutamatergic activity. Such volume loss over time may make individuals more treatment resistant and symptomatic.
- Because the OFC has the most dense innervation by serotonin fibers in the brain, and the subcortical processing network is highly modulated by dopamine, the pharmacologic basis for treatment with SRI's and D2 antagonists as an adjunctive strategy, begins to make some sense.

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
Impulsivity/aggression
suicidality

Anterior cingulate cortex (ACC)

apathy
poor concentration

Medial prefrontal cortex mPFC

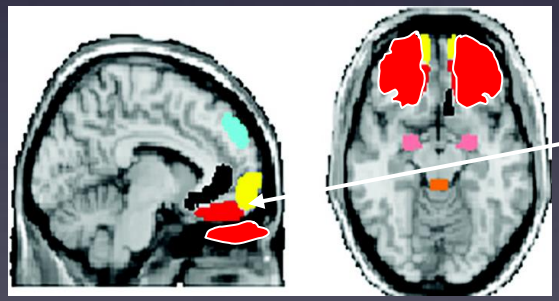
Self and other awareness

Subgenual ACC (sgACC)

Depressed mood/sadness

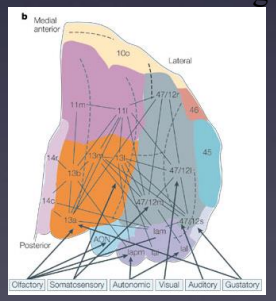
Overview: orbitofrontal cortex (OFC)

- 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 in medial, caudal part
- 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

right



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

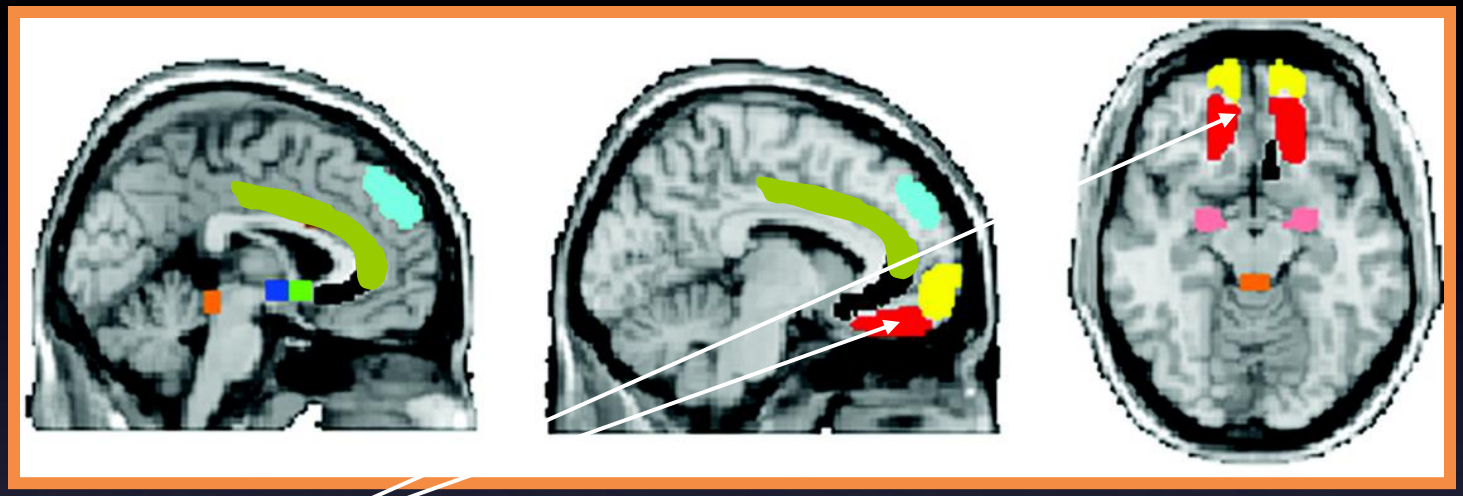
- OFC injury results in difficulty updating the rewarding or punishing value of task
- gambling task: two decks of cards, deck A is highly rewarding initially, then reward switches to deck B
  - -- healthy controls shift to deck B as the value of choosing B improves
  - -- injury to lateral OFC: inability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

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

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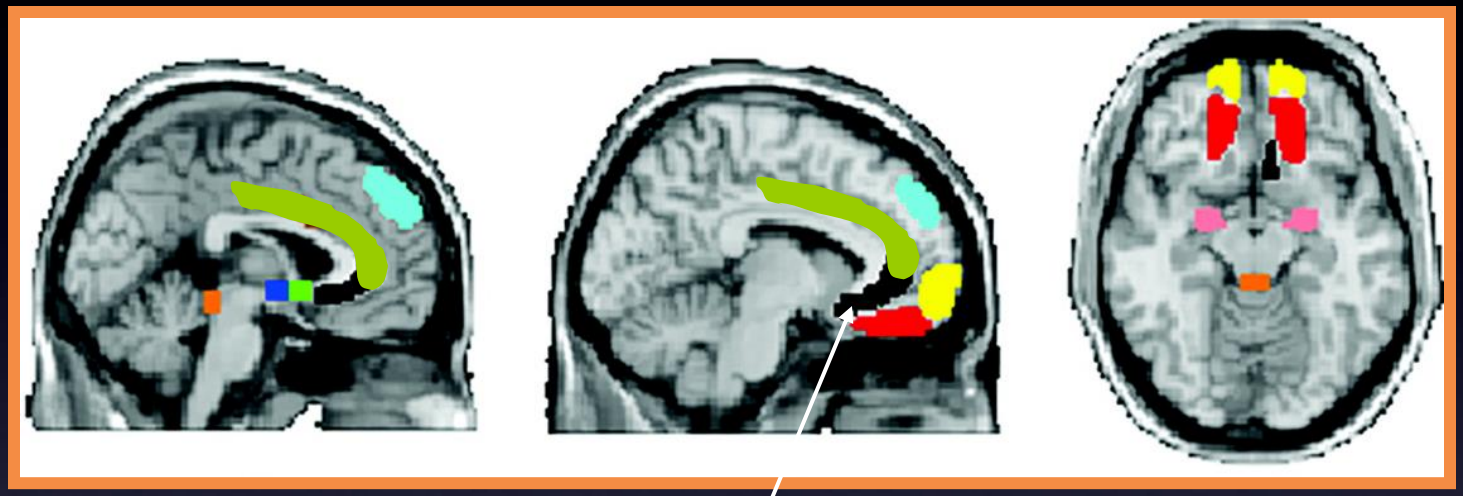

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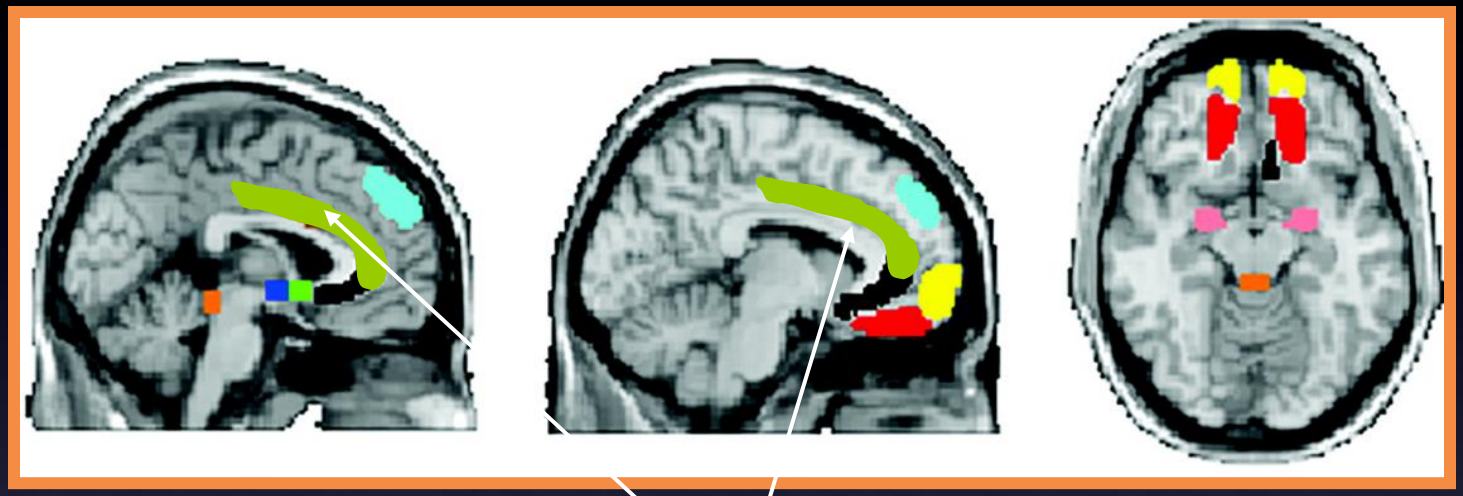

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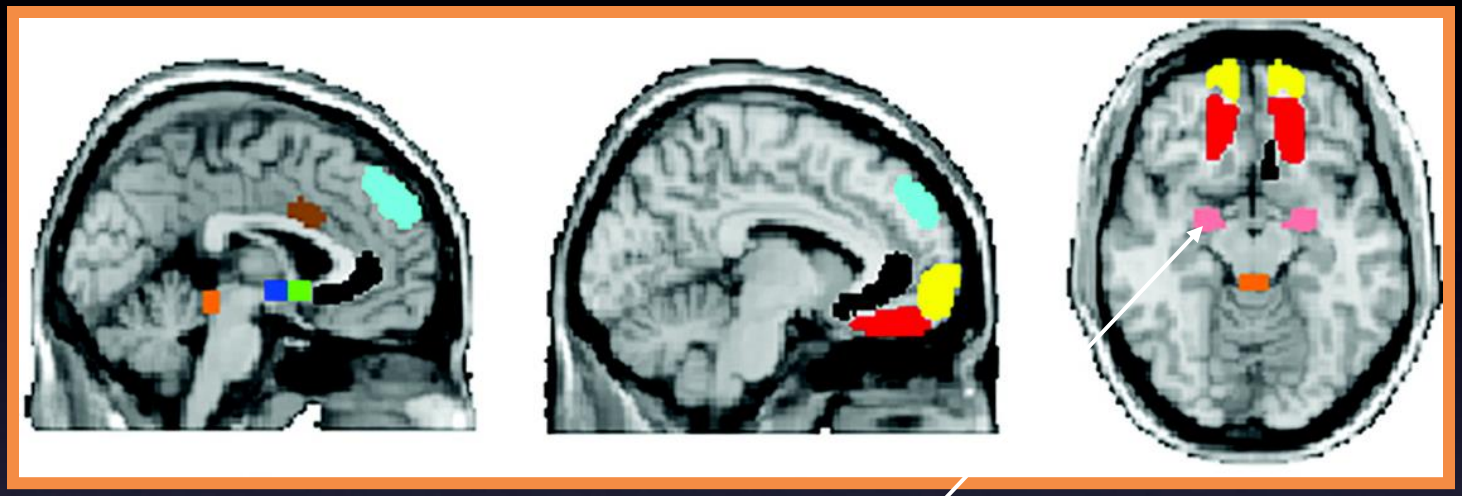

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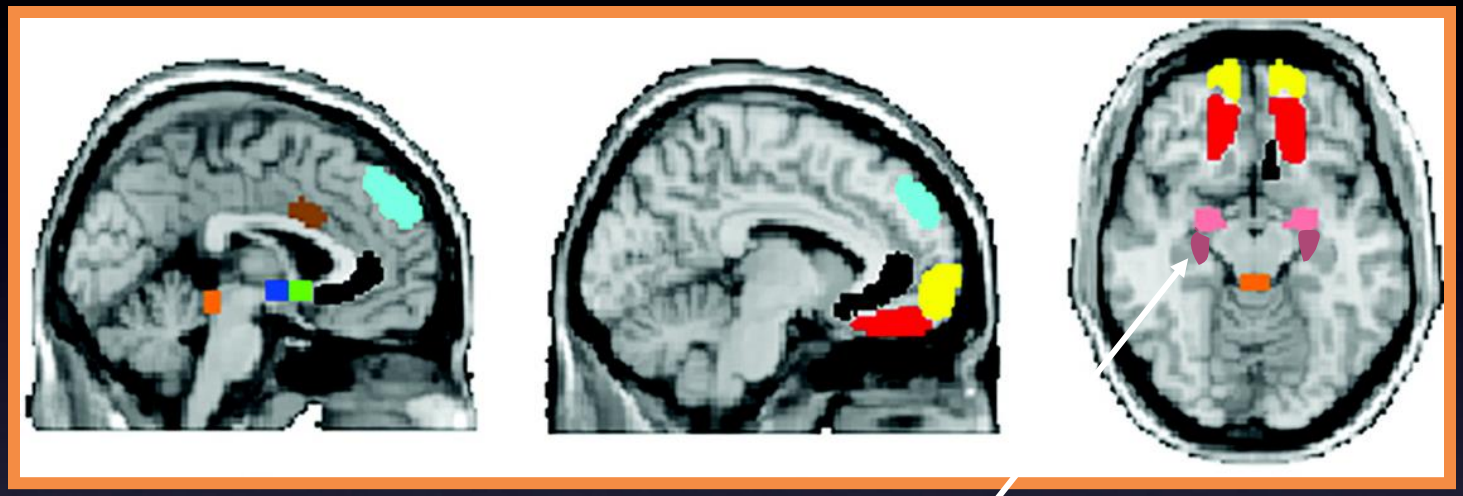

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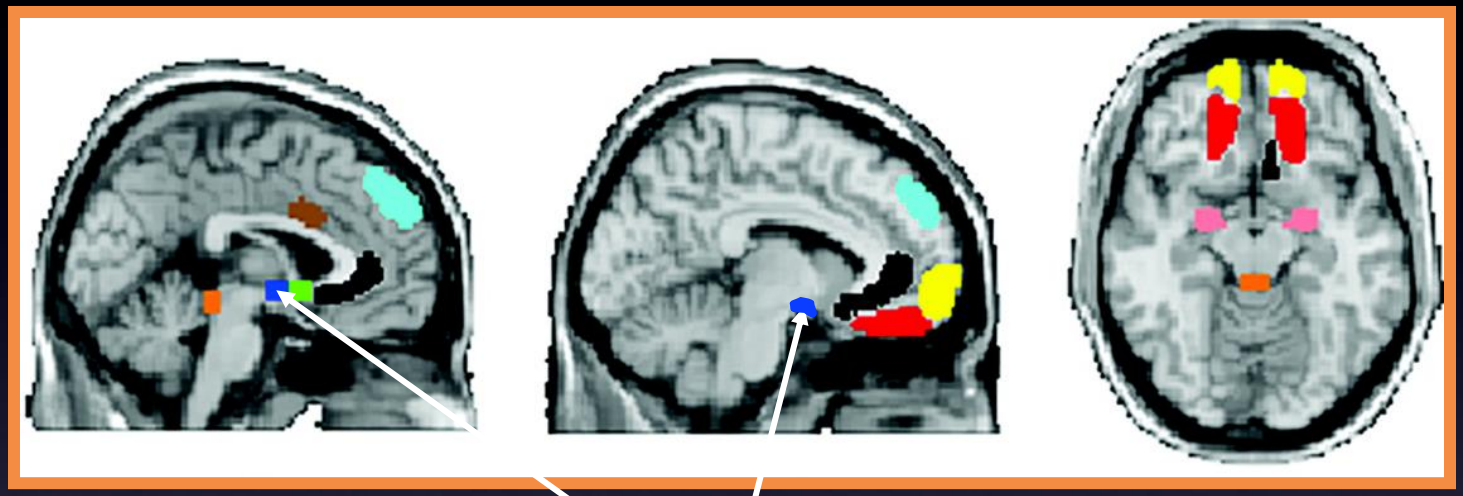

OFC

connects extensively to:

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Hypothalamus

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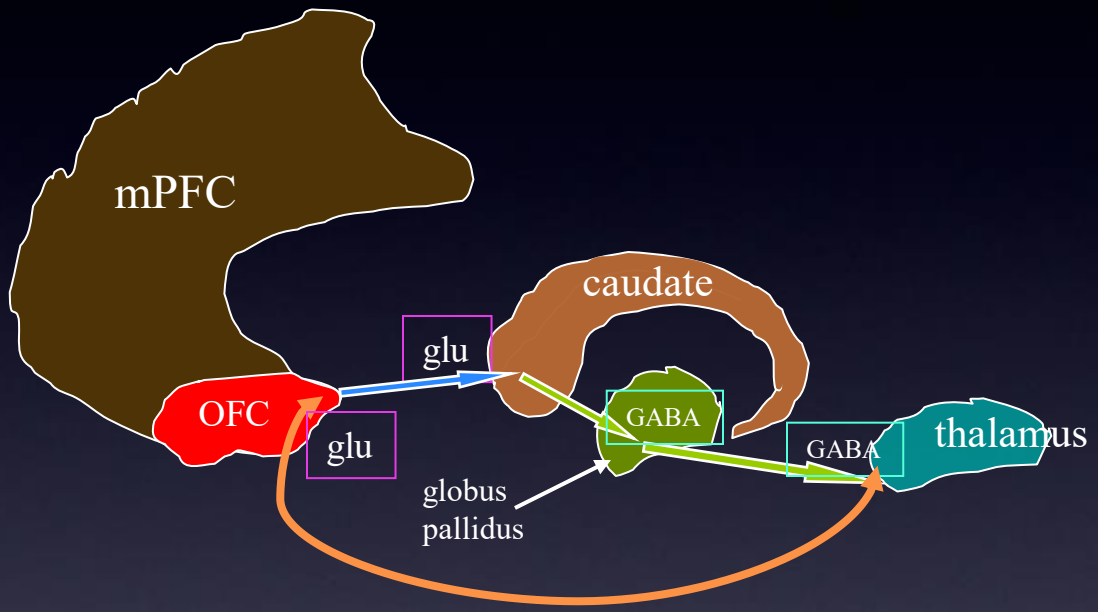
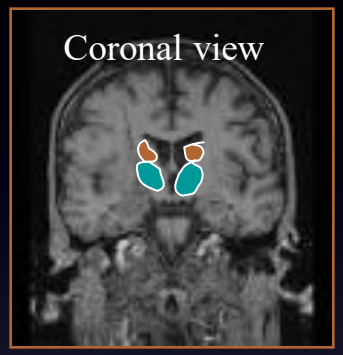
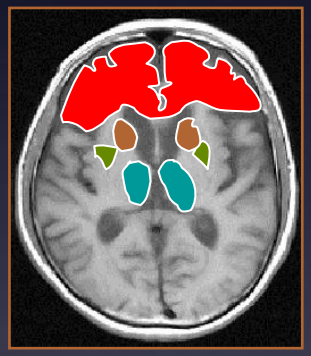
Cortical-striato-pallidal-thalamic circuitry: mPFC output is processed via subcortical structures







Horizontal view

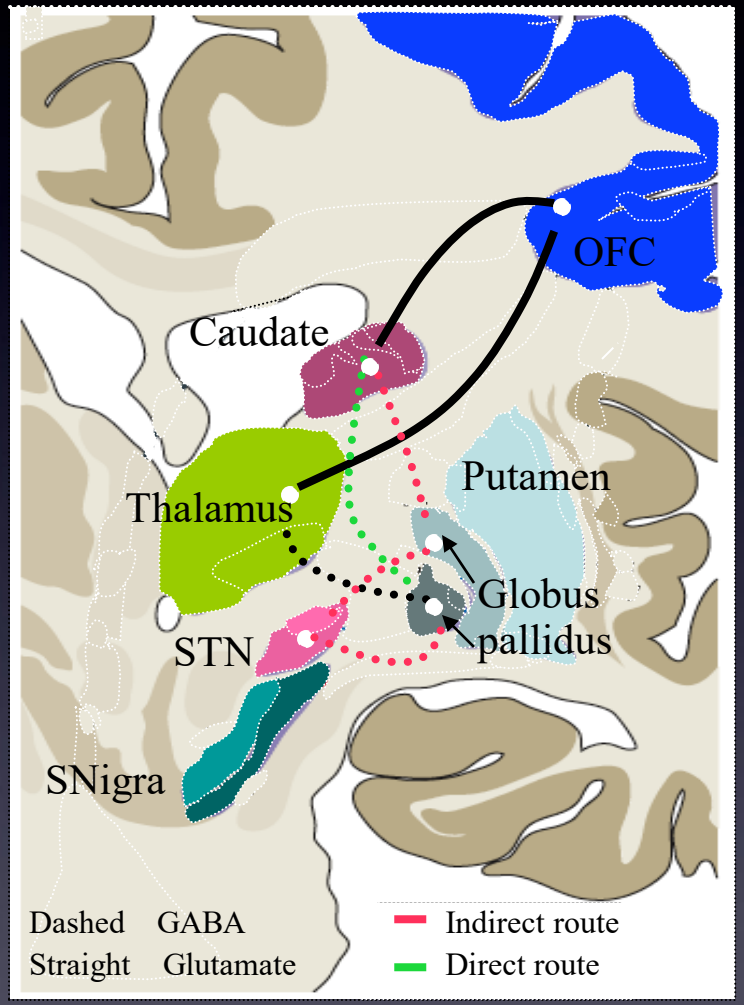
OFC output is processed via multiple subcortical structures

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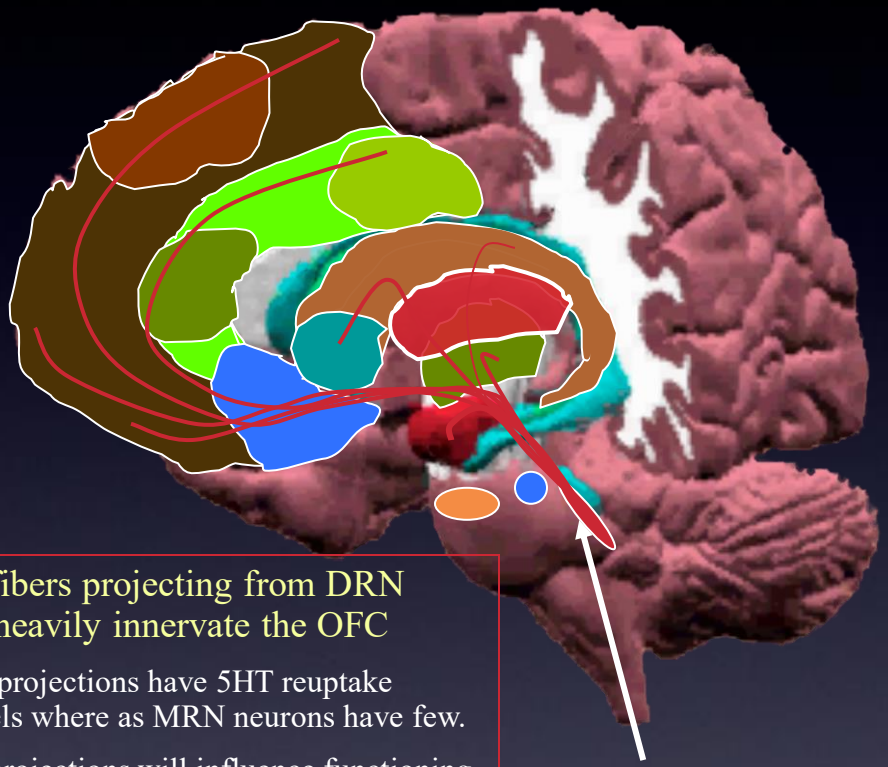
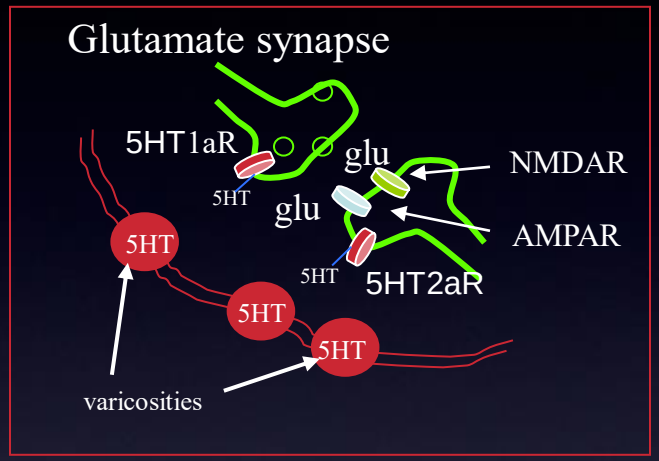
5HT powerfully modulates GABA and glutamate synapses in OFC-striato-thalamic and limbic circuits



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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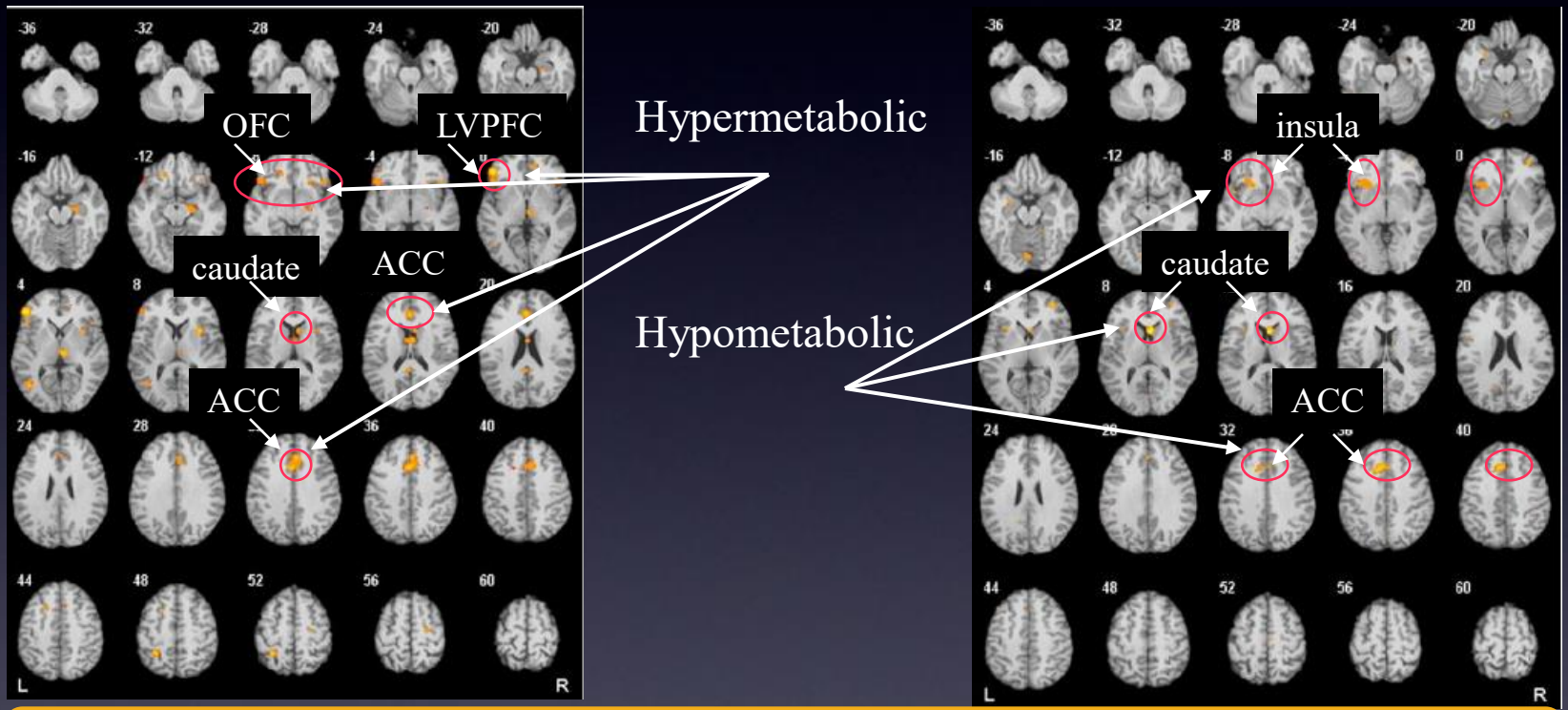
OCD functional imaging study summary

Orbitofrontal-ACC-striatal abnormalities in metanalysis

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



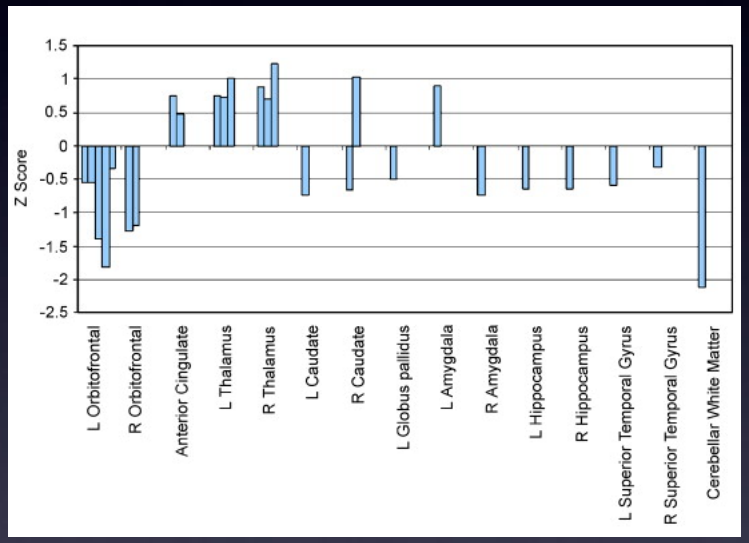
Key point Functional imaging studies show multiple cortical, subcortical, and limbic structures are abnormally activated in OCD, notably the OFC

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

*

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

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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Wedzony K Chocyk A, Mackowiak M. Glutamatergic neurons of the rat medial prefrontal cortex innervating the ventral tegmental area are positive for serotonin 5HT1A receptor protein. J Physiol Pharmacol. 58(4): 611-24 2007

Menzies L, Chamberlain S, Laird A, et al. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofrontal-straital model revisited. Neurosci Behaviroal Rev. 32(3) 525-49 2008

Neurobiology of Psychiatric Illness:
Post Traumatic Stress Disorder

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

For the lecturer: Post traumatic stress disorder

- PTSD is an excellent example of abnormal processing of experience with hyperactivation of the stress response, a conditioned fear response, and the consequent avoidant behavior.
- Medial prefrontal structures appear to be important in mediating some aspects of PTSD, and imaging studies confirm both structural abnormalities in this area, and metabolic changes that may be important in understanding the pathophysiology of this illness state.
- The amygdalar-based fear reaction network is reviewed to understand how the fear network connects to, and modulates other structures that are also dysregulated in PTSD. It is important to note that there are two pathways through the fear network. One is conscious, and is processed through the mPFC, the other unconscious, and has no prefrontal processing at all.
- Finally, prolonged activation of the fear network has implications for the stress hormone axis, which are not fully understood at this time, with data that at times appear conflicting.
- Putting the overall picture together: a conditioned fear response is elicited as a result of trauma. The fear pathway is activated, and has both a conscious and unconscious component. A conditioned association with the event and a fear reaction is formed. The conditioned fear response is normally inhibited by the mPFC if it is non-adaptive. Damage to the mPFC noted in reduced gray matter volume in people with PTSD, makes it harder for the system to extinguish the maladaptive conditioned fear response. As long as the fear pathway remains activated by triggers associated with the trauma (which tend to be overgeneralized), there will be ongoing symptoms of PTSD, and avoidant behaviors.

Overview: PTSD

Fear pathways

Structural and functional imaging studies in PTSD

Hypothalamic pituitary axis dysregulation

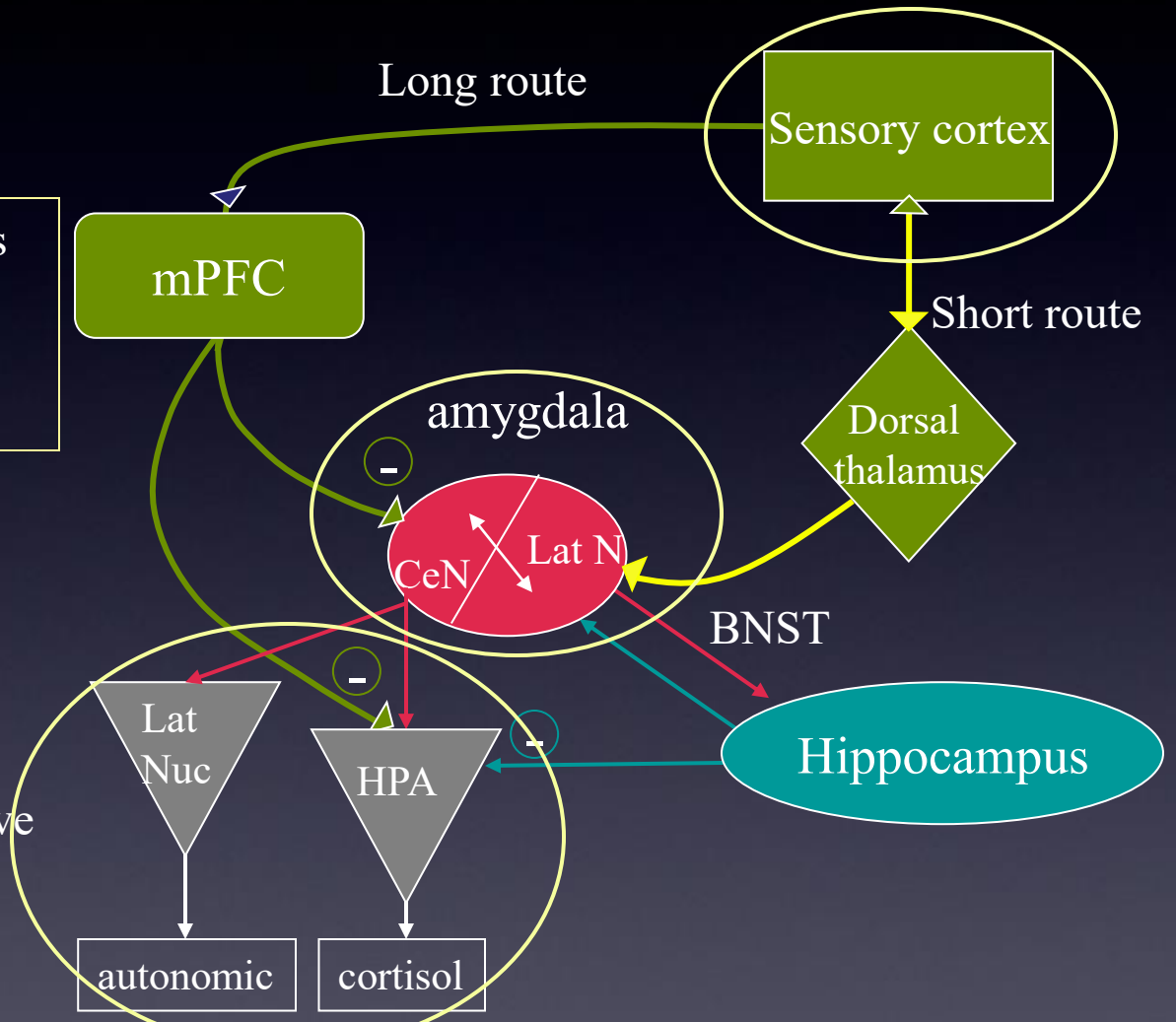
PTSD and fear circuitry

Fear network

Sensory cortex: context and cues
Fear network activated:
--CeN/Lat N amygdala
--Sympathetic NS and cortisol

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

Fear network

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

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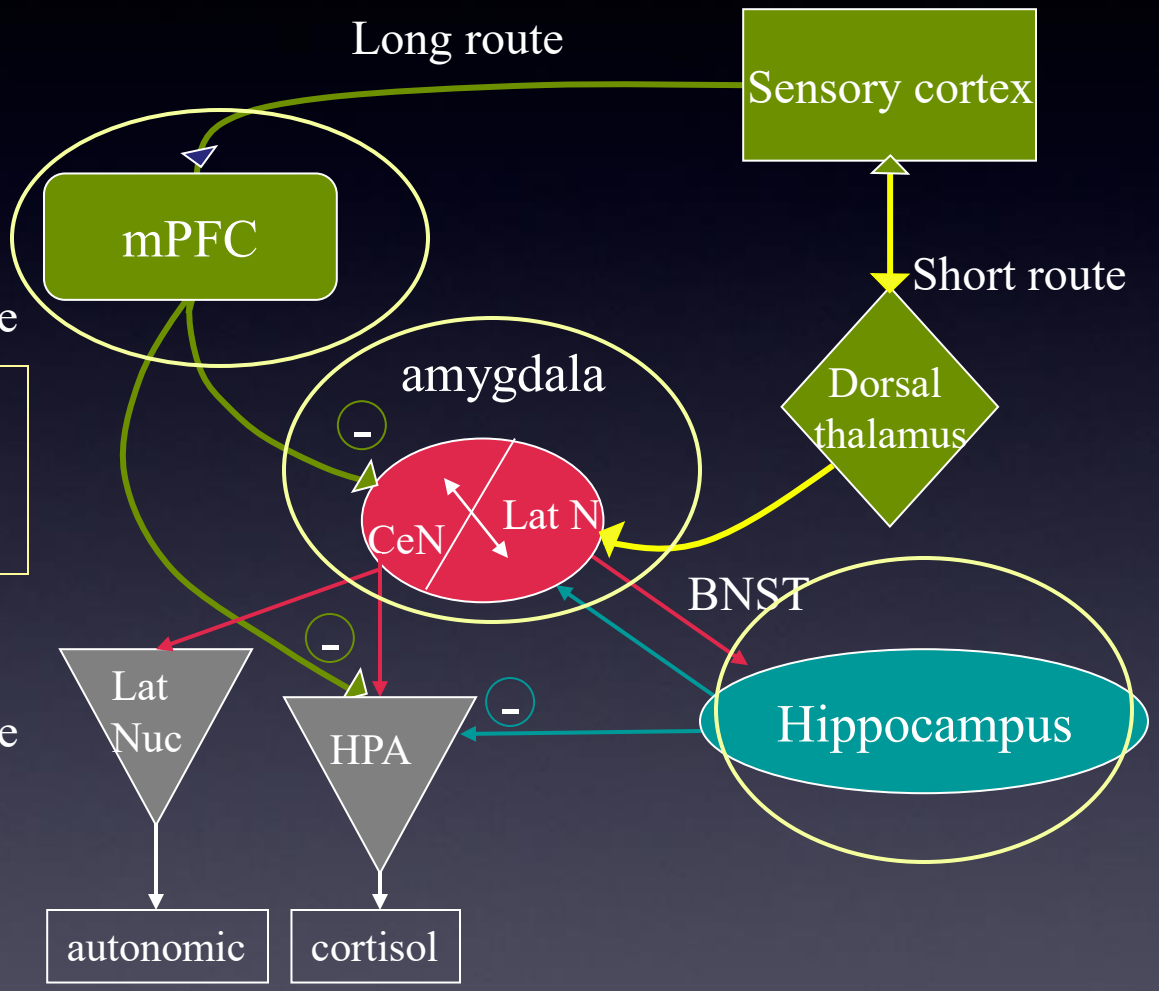
Network overactive in PTSD
Sensory cues over-generalized
Failure to extinguish non-adaptive avoidance behavior



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PTSD and fear circuitry

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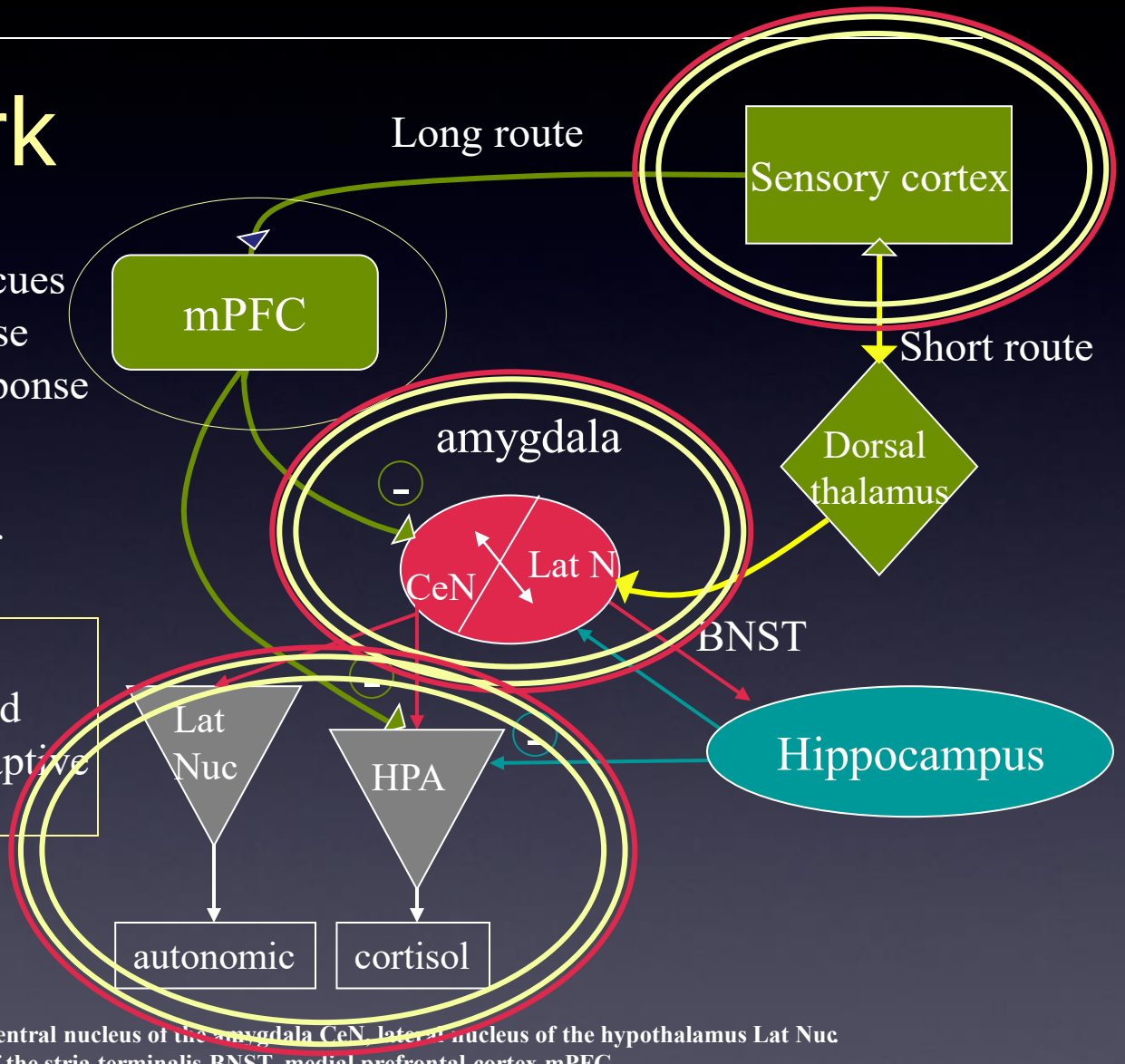

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PTSD and fear circuitry

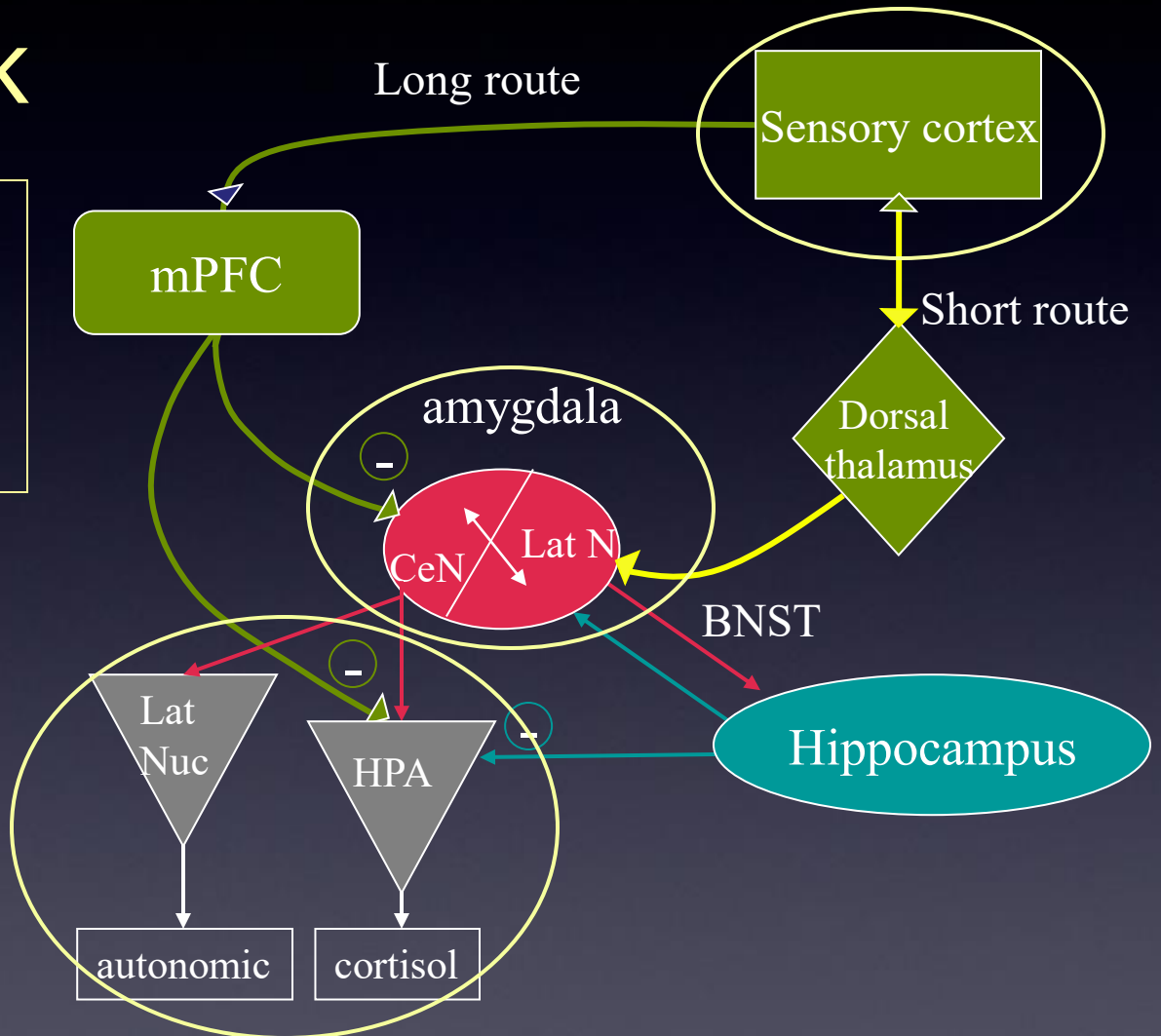
Fear network

Short route

Fast, reactive

Bodily response to a cue

No conscious component



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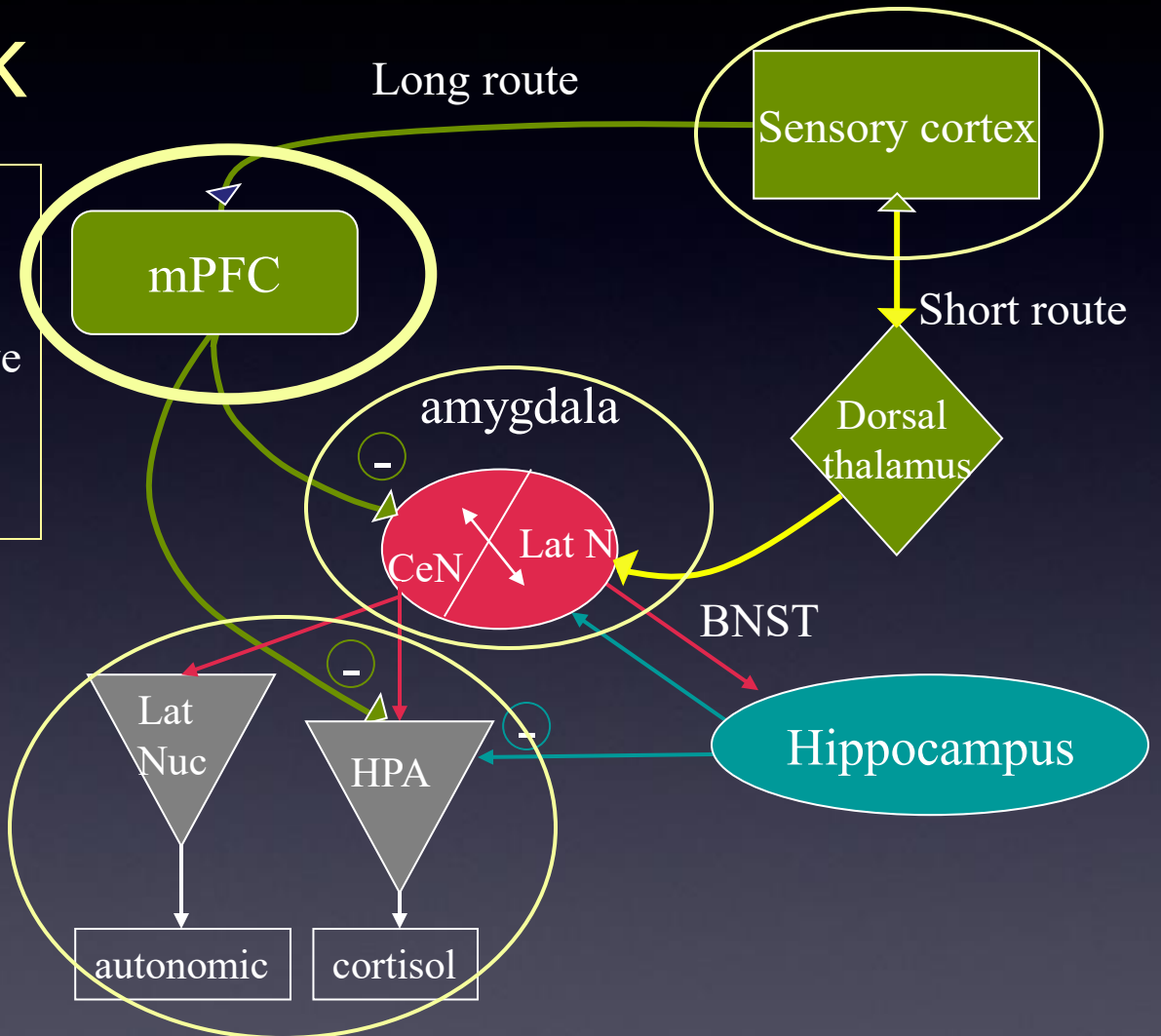
PTSD and fear circuitry

Fear network

Long route via mPFC

cognitive processing of cue

mPFC may inhibit non-adaptive amygdalar response when appropriate



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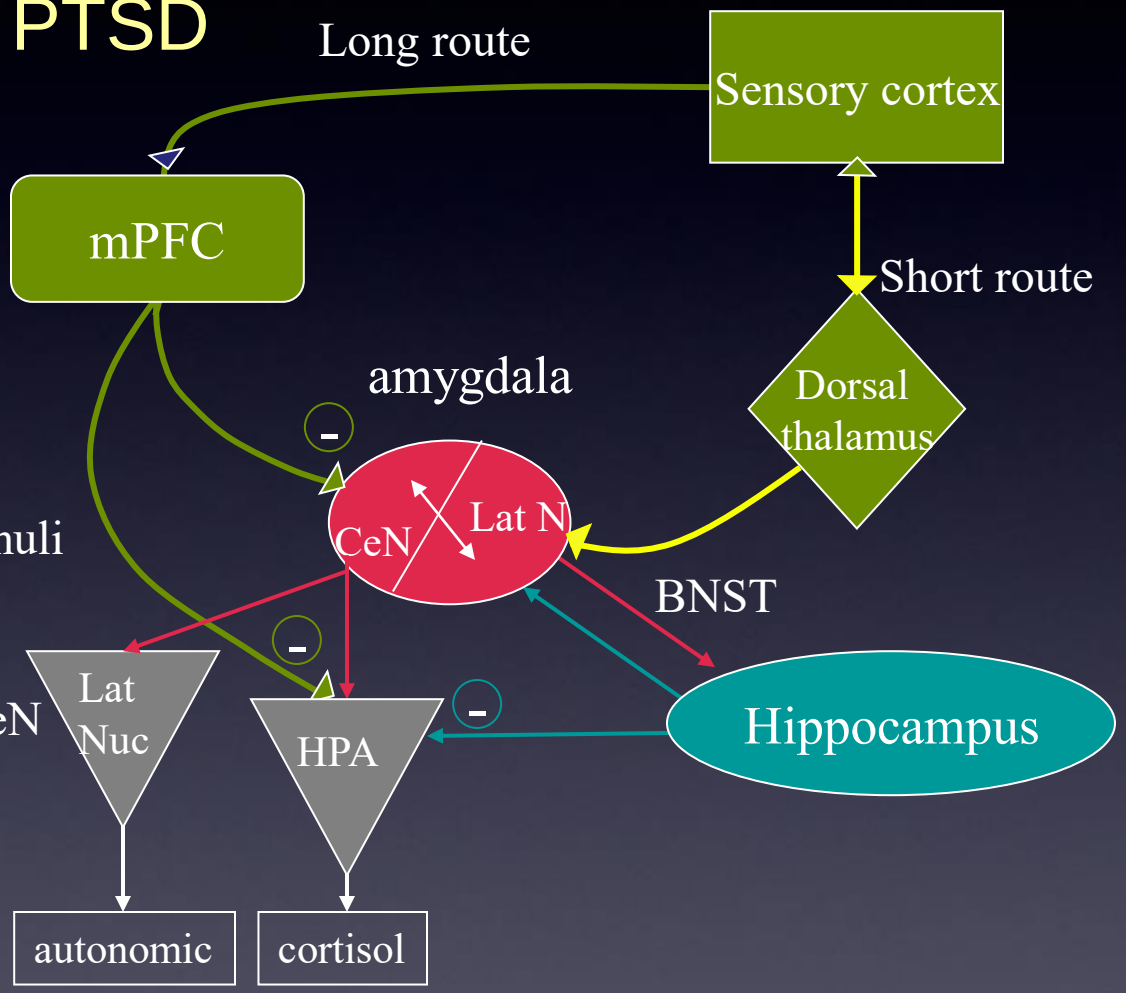
PTSD and fear circuitry

Anatomical basis of PTSD

- Fear response
  - CeN activation
    - sympathetic response
    - cortisol increases
- Behavioral sensitization
  - Lat Nc Amygdala and mPFC
    - learned response to fearful stimuli
    - avoidance behavior
- Fear extinction
  - mPFC to amygdala Lat nc → CeN
    - failure to extinguish non-adaptive fear responses



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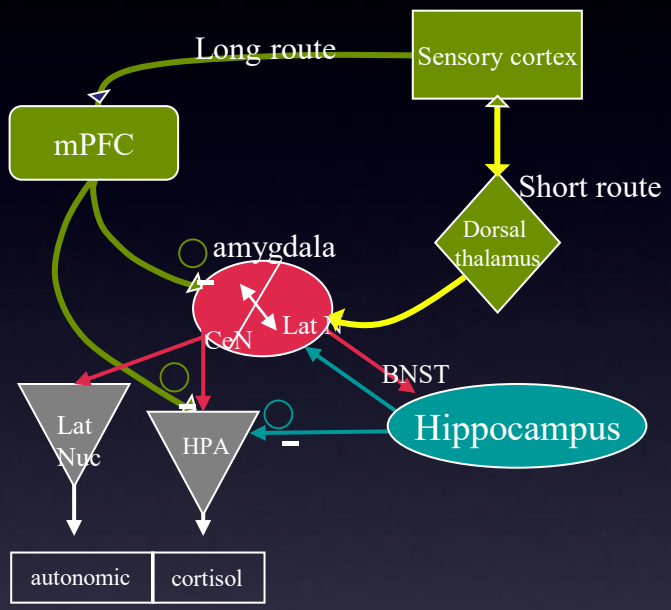
PTSD and fear circuitry

Anatomical basis of PTSD



Key points

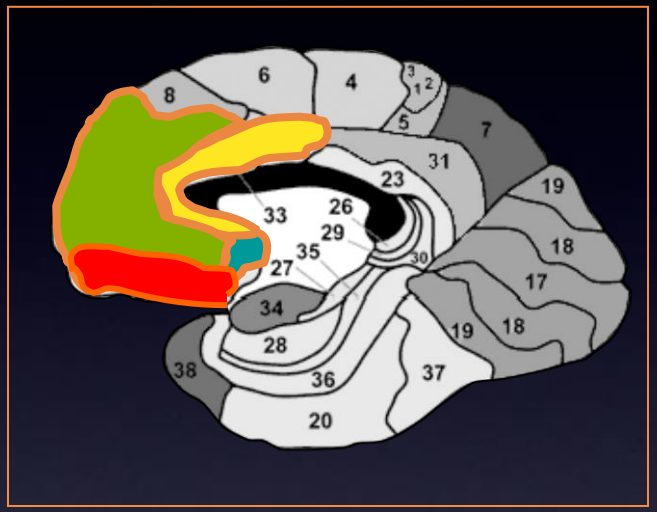
- Increased arousal, avoidance, and re-experiencing can be understood as dysregulation of the fear network
- Abnormal function in the amygdala is implicated in persisting conditioned fear responses, trauma triggers are conditioned fear responses not inhibited by the mPFC, and avoidant behavior is not extinquished without prefrontal inhibition of the fear pathway.

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 stimulus overgeneralization & 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

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

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

Abbrev medial prefrontal cortex mPFC,, anterior cingulate gyru ACCs

*

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, with receptor downregulation
- blunted ACTH response as predicted

ACTH challenge: measures adrenocortical responsiveness, expected blunted cortisol response

- increased cortisol noted in PTSD group (not as predicted)

Dexamethasone suppression test: expect increased suppression of post dex cortisol

- increased cortisol noted in PTSD group (not as predicted)

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.

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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.

PTSD references

Karl A, Schaefer M, Malta L et al. A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehavioral Rev 30(7):1004-31 2006

Bremner J. Traumatic stress: effects on the brain. Dialogues Clin Neurosci 8(4): 445-61 2006

Bremner J, Elzinga B Schmal C Vbermettern E. structural and functional plasticity of the human prain in post traumatic stress disorder. Prog Brain Res 157z:171-86 2008

Francati V, Vermetten E, Bremneer J. Functional neuroimaging studies in post traumatic stress disorder: review of current methods and findings. Depression Anxiety 24:202-18 2007

de Kloet C Vermetten E, Geuze E. et al.Assessment of HPA-axis function in posttraumatic stress disorder: Pharmacological and non-pharmacological challenge tests, a review. J Psychiatric Res 40(6); 550-56 2006

Bremner, M. Vythilingam, G. Anderson, E. Vermetten, T. McGlashan and G. Heninger *et al.*, Assessment of the hypothalamic–pituitary–adrenal axis over a 24-hour diurnal period and in response to neuroendocrine challenges disorder, Biological Psychiatry 54:710–18 2003

Bremner J, Vythilingam M ,Vermetten E et al. Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse, Psychoneuroendocrinology 28 (2003), pp. 733–750

Liberzon I, Abelson J, Flagel S, et al. Neuroendocrine and psychophysiologic responses in PTSD: a symptom provocation study, Neuropsychopharmacology 21: 40–5 1999

Elzinga B, Schmahl C,Vermetten E, R. et al. Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD, Neuropsychopharmacology 28:1656–166 2003

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

Note: the question asks what is ‘primarily’ the cause
All of the answers are contributory

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 over 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 best understood as:

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 neurocircuits.
3. Not associated with volumetric abnormalities in any cortical or limbic structures.
4. The result of clear abnormal structure and function 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

Addendum Slides:

Monoaminergic Systems and Prefrontal-Subcortical and Prefrontal-Limbic Neurocircuits Hypothalamic Pituitary Axis

Neuroendangerment and Neuroprotection in depression

Genetic Polymorphisms in Psychiatric Illness

Brief review of the molecular biology of plasticity in the brain

Brief review of the molecular biology of gene expression

Addendum Slides
Hypothalmic Pituitary Axis in Depression

HPA axis: feedback regulation of cortisol

Hypothalamic nuclei → anterior pituitary regulating ACTH release
- CRH released from paraventricular nucleus
- AVP released from magnocellular elements
- chronic stress → AVP coreleased with CRH ⇈ ACTH

ACTH → adrenal cortex regulates cortisol release

Circulating cortisol → negative feedback inhibits cortisol release in:
- Paraventricular nucleus
- Anterior pituitary
- Hippocampus
- Medial prefrontal cortex (anterior cingulate)

Other factors impacting cortisol response
- sympathetic activation,
- humoral factors derived from immune system,
- physiological variables affecting the adrenal cortex (‘exhaustion’)

HPA axis: dysregulation

Abnormal feedback at all points (hypothalamus, anterior pituitary, adrenal cortex, medial prefrontal structures)

Dysregulation of HPA is present in depression, most apparent in
- Psychotic depression HPA axis is most apparent
- Complex dysregulation of HPA
  - changes diural cycle of cortisol max (around 6am) and mimimum (8 pm)
  - may increase cortisol levers
  - CRH ,ACTH release is abnormal

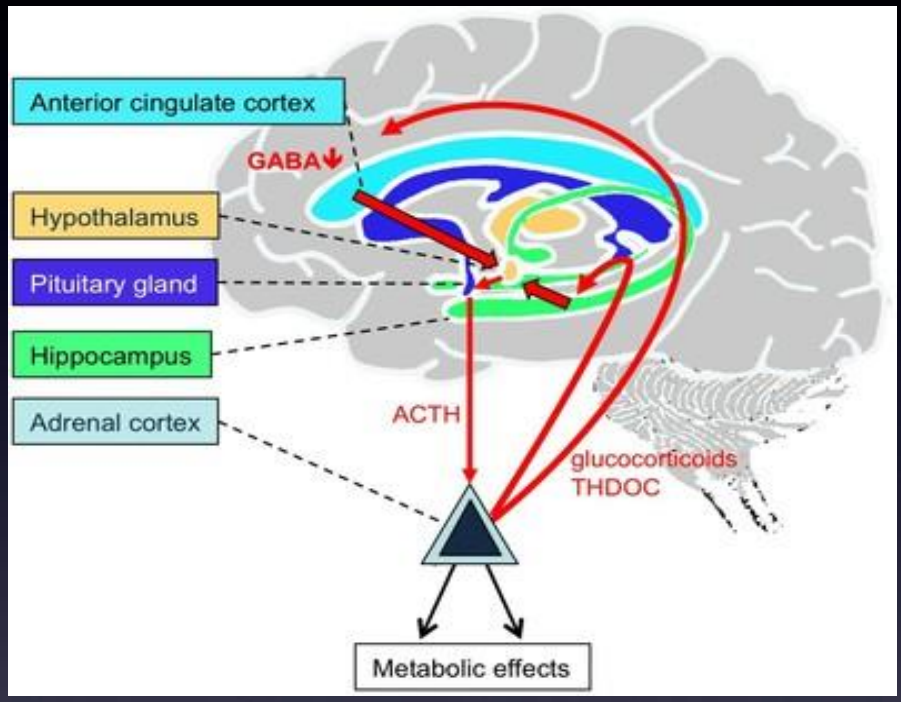
Circulating cortisol negative feedback fails to inhibit cortisol release especially in the context of a stressor

Medial prefrontal structures have abnormal metabolism in the depressed state, and these mPFC structure, as well as the hippocampus normally tightly regulate cortisol levels in blood

HPA axis: key sites of regulation in depression?

Down regulates HPA

Anterior cingulate
Cingulate area 25 (Cg25)
Medial prefrontal cortex(mPFC)
Hippocampus (HPC)

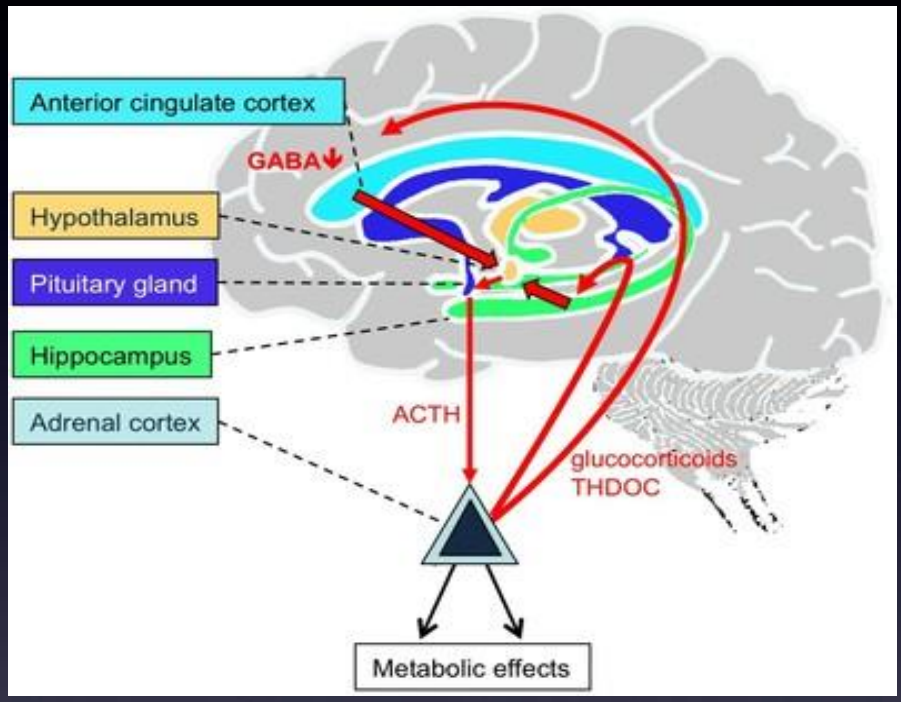


HPA axis: key sites of regulation in depression?

Target of downregulation

Paraventricular nucleus

Anterior pituitary



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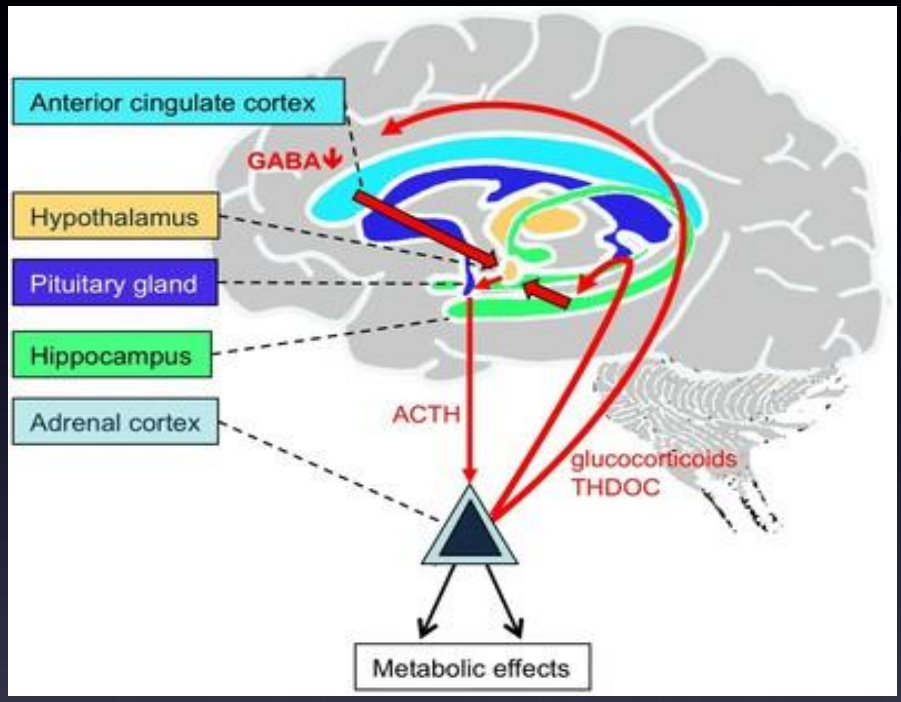


Depression

High density glucocorticoid receptors (GR) in mPFC and HPC

It is suspected that HPA dysregulation is key to neuroendangerment due to elevated levels of cortisol

This would presumably degrade negative feedback for cortisol

Structures providing negative feedback have decreased volume in depression

Addendum Slides
Neuroendangerment & Neuroprotection

Neuroendangerment & Neuroprotection

Evidence from animal and human studies suggest that apoptotic mechanisms inducing cell death may have a role in several disorders

- Major Depression
- Bipolar Disorder
- PTSD
- Schizophrenia

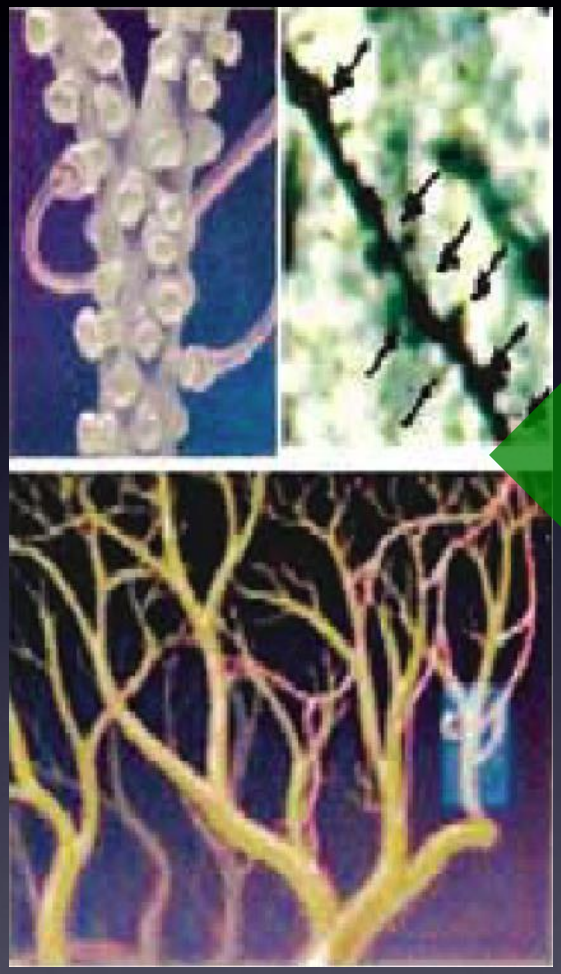
Hypothesized mechanisms

- Reduced neuronal growth factors
- Reduced BCL-2 levels or increased pro-apoptotic proteins
- Increased activity of GSK-3β

Implicated factors leading to the above

- Hypo or hyper-glutamatergic activity
- Increased cortisol
- Additive effect of insults to cell including hypoxia, hypoglycemia

Neuroendangerment in a picture

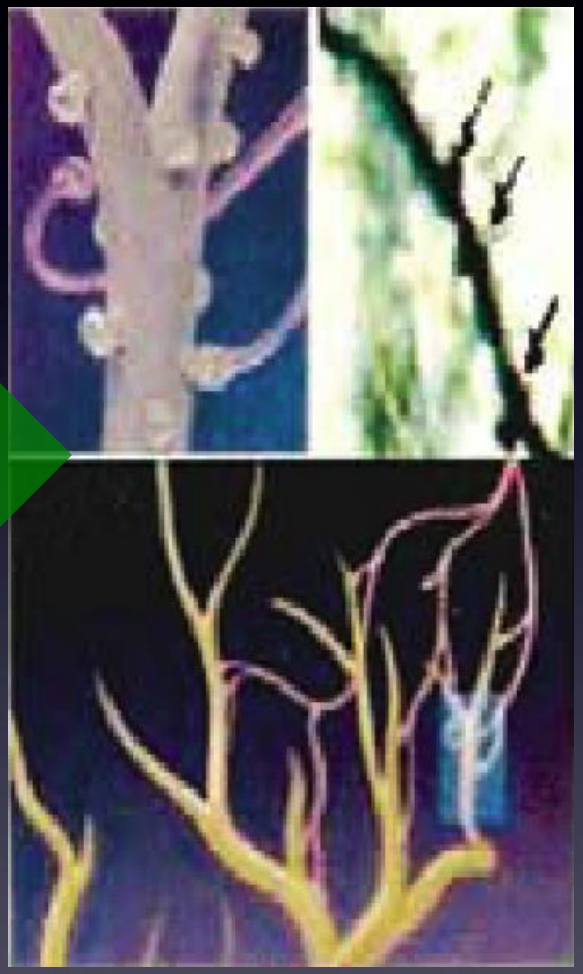


Plasticity goes both ways

Health

Illness

Effect of treatment in restoring dendrites and connectivity?



Neuroendangerment

Plasticity- not always a good thing

Psychiatric illness may cause persistent change to the brain

Neuronal insults lead to

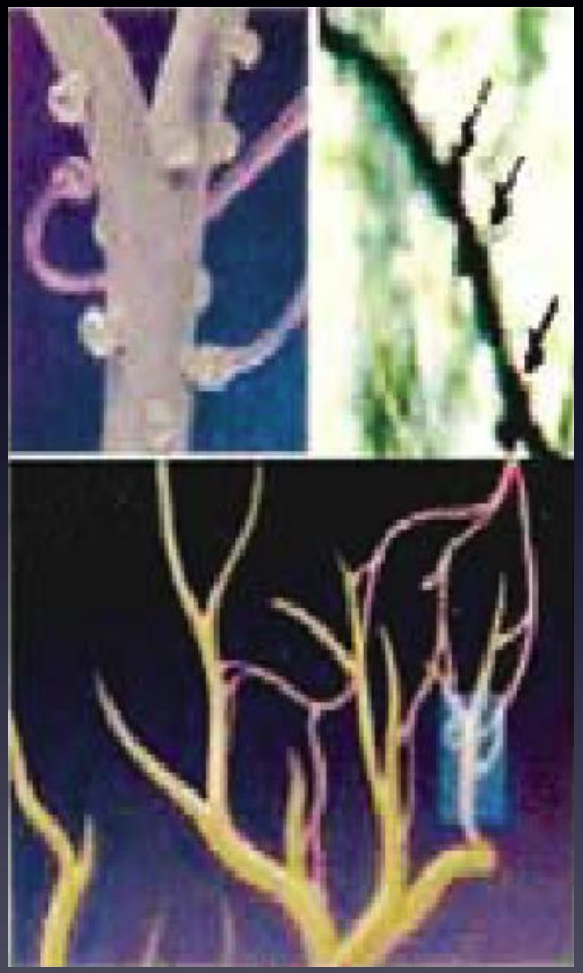
Loss of dendritic arborization, and spines

Loss of viability, and cell death?

This damage leads to decreased connectivity and results in

Dysregulated neurocircuitry

Emergence of symptoms



Dendritic spines are plastic

The synapse is at the dendritic spine

Each dendritic branch receives multiple inputs through the spines

Synaptic activity causes ultrastructural change of the spine

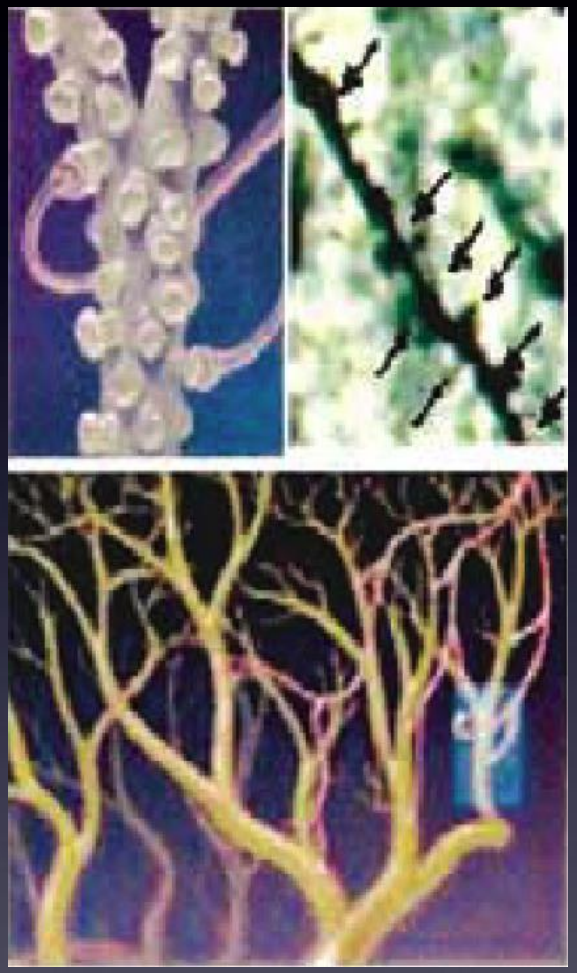
Glutamate receptors AMPA/NMDA

Brain derived neurotrophic factor (BDNF)

Ultrastructural change goes along with change in synaptic strength

Changes inter-neuronal (synaptic) connectivity and systems level connectivity

Re-establishes normal circuit behavior



Neuroprotection

Use of drug properties to promote viability and resist apoptosis

Mood stabilizers: Li, valproate, other AED?

Antidepressants, ECT, second generation antipsychotics

Drug induced epigenetic effects

Histone de-acetylase antagonists: valproate, and antidepressants

Opens 2-3% of genome resulting in increased transcription of viability promoting and antiapoptotic proteins

Direct effect on kinase cascades to re-regulate gene expression

Lithium inhibits GSK-3β

Antidepressants increase P-CREB via effect on monoamine receptors

Both increase BDNF/TrkB, and BCL-2 expression

Slowing of progression of illness in mood disorders:

Biochemical: ↑ NAA, ↑ P-CREB, ↑ BCL-2, ↓ GSK-3β,

Restore structural changes due to loss of neurons, dendrites, and glia

Addendum Slides

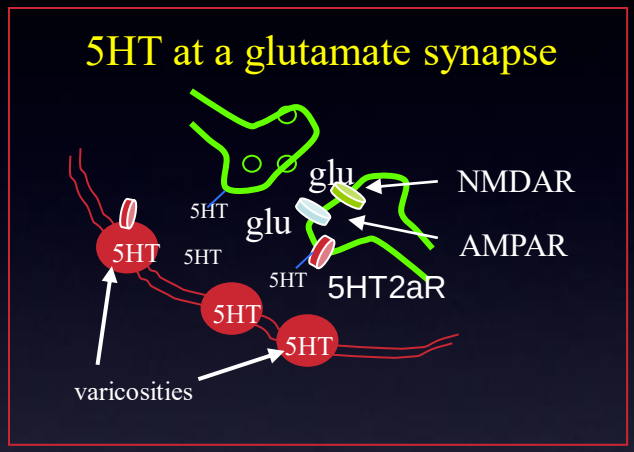
Explanation of the role of the Monoaminergic Systems in the regulation of glutamatergic and GABAergic Prefrontal-Subcortical and Prefrontal-Limbic neurocircuits

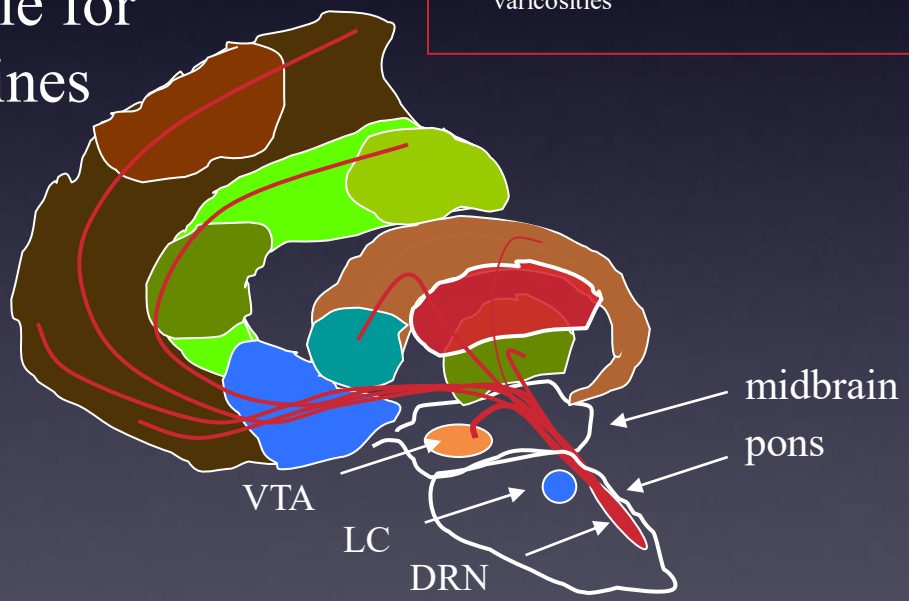
*

Cortical and limbic connections: role of the monoamines (5HT, NE, DA)

DA, NE and 5HT projections arise from brainstem nuclei

We will use the 5HT network as an example for all the biogenic amines
5HT, NE, DA,
Histamine
Acetylcholine



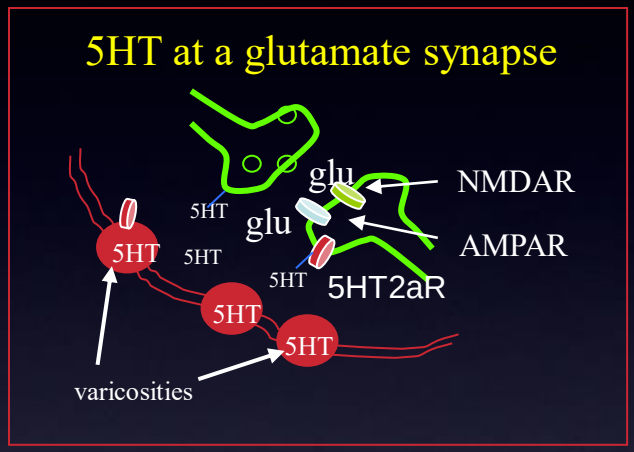


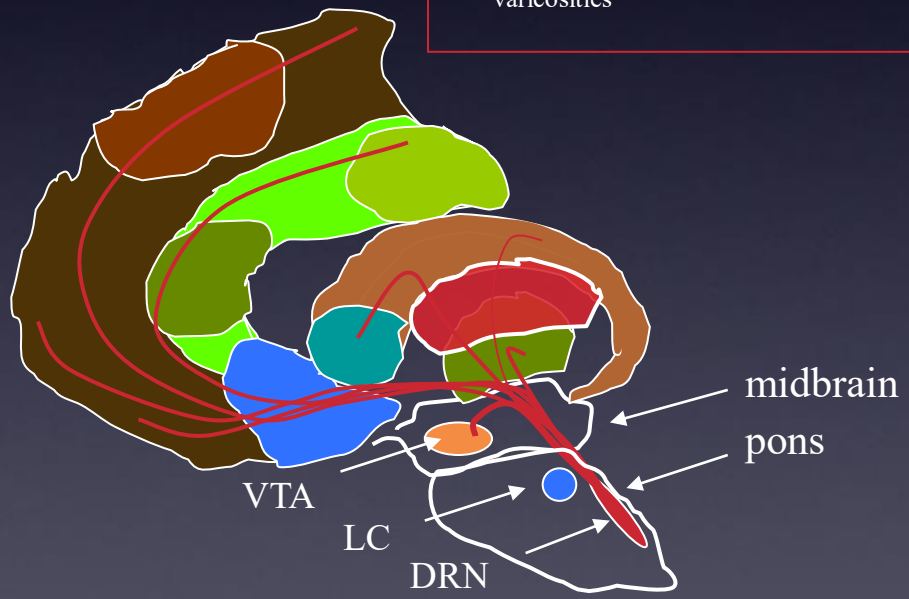
Abbrev: dorsal raphe nucleus DRN; locus ceruleus LC; ventral tegmental area VTA; dopamine DA, norepinepherine NE, serotonin 5HT, glutamate glu,

*

Cortical and limbic connections: role of the monoamines (5HT, NE, DA)

5HT modulates activity at glutamate and GABA synapses





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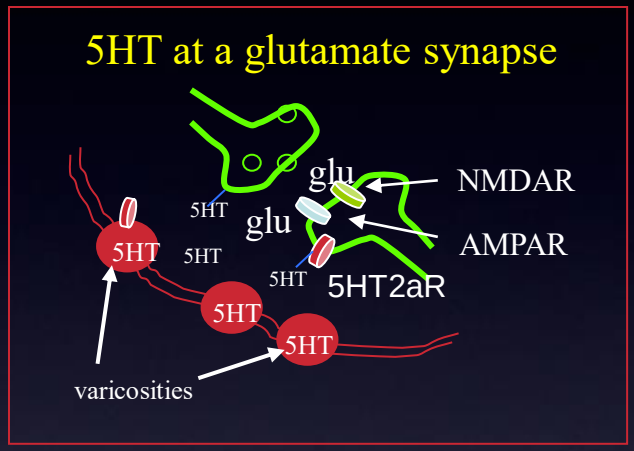
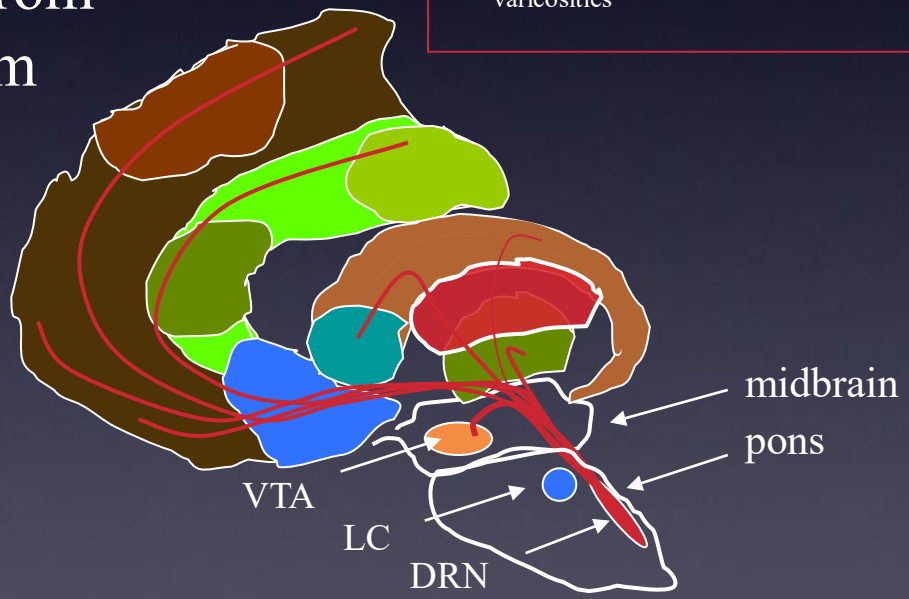
Cortical and limbic connections: role of the monoamines (5HT, NE, DA)

5HT fibers bypass these synapses and release 5HT from varicosities along the 5HT axon coming from nuclei in brainstem





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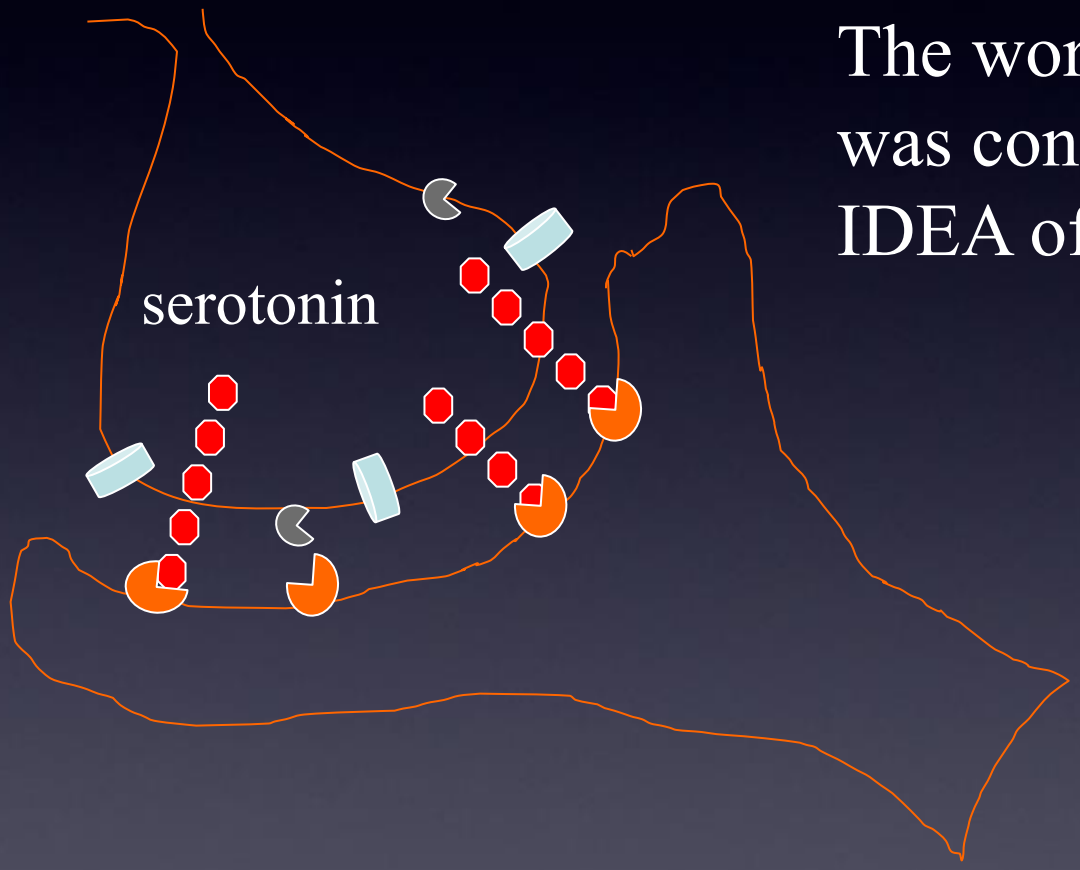
Serotonin and pathophysiology of depression



The world of psychiatry was consumed by the IDEA of serotonin

Why?

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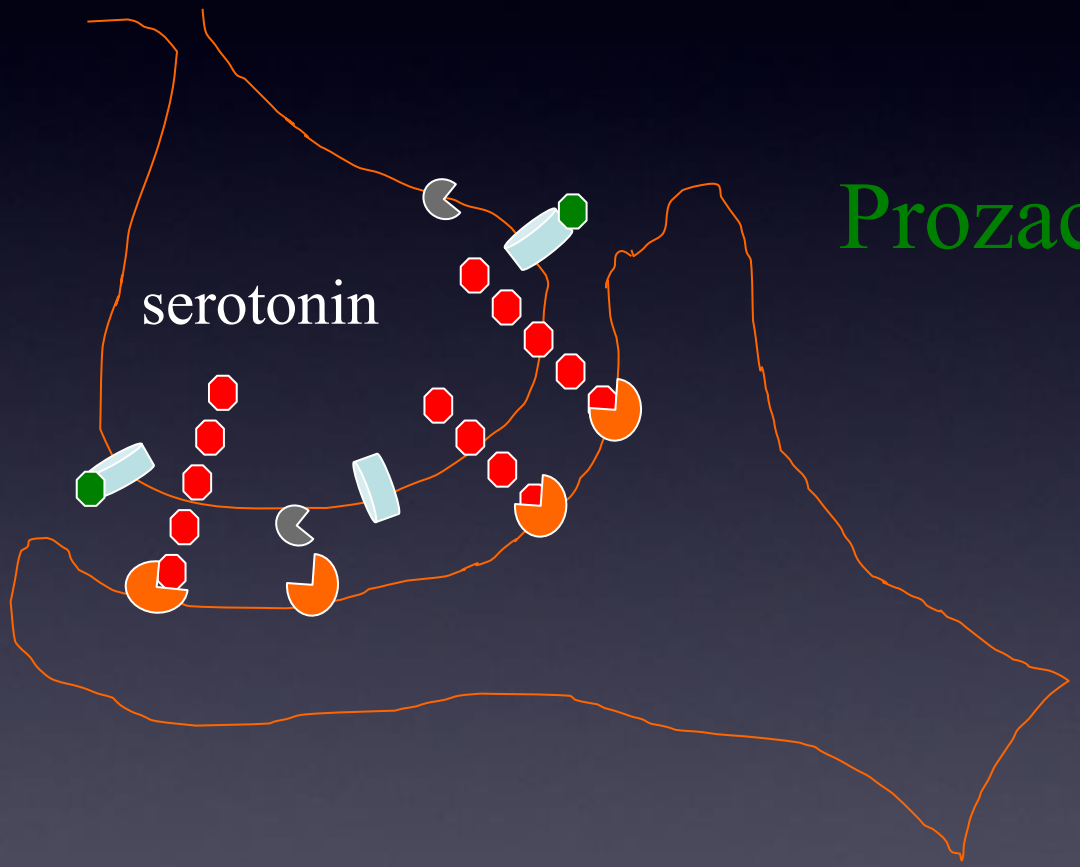
Serotonin and pathophysiology of depression



Prozac (fluoxetine)

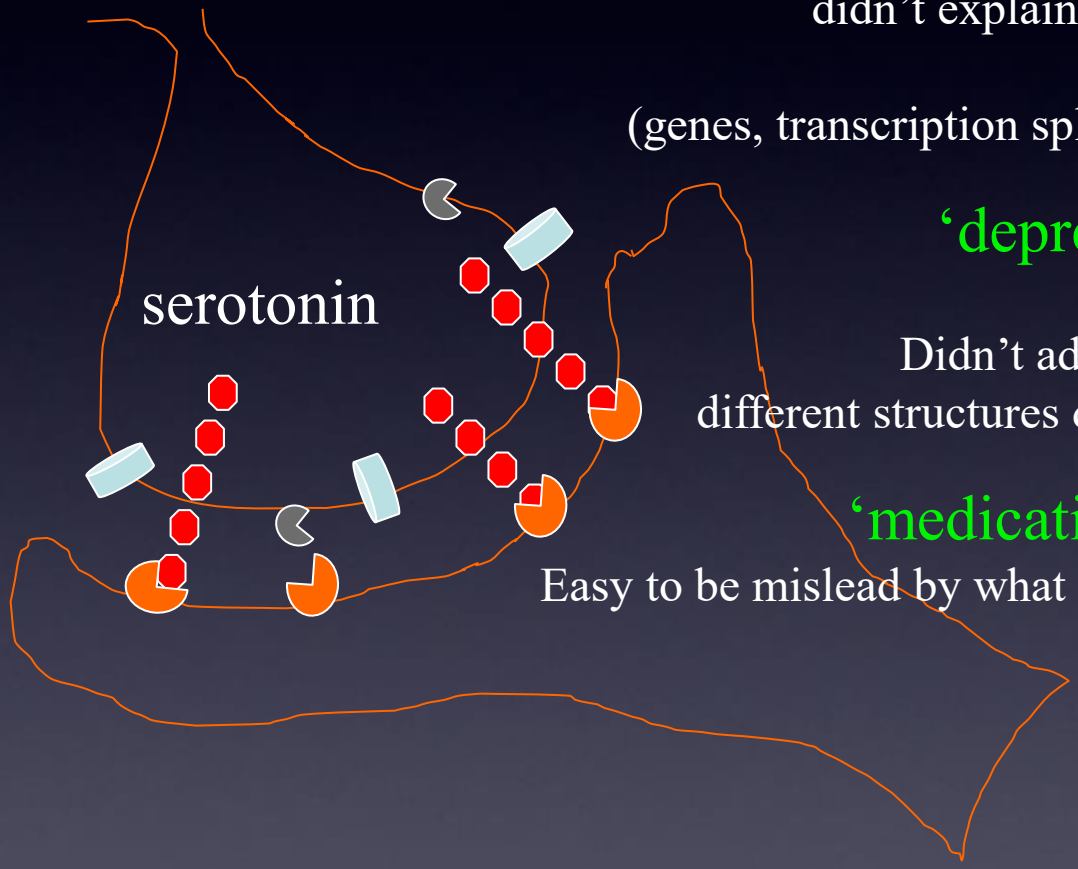
Abbrev: dorsal raphe nucleus DRN; locus ceruleus LC; ventral tegmental area VTA; dopamine DA, norepinepherine NE, serotonin 5HT, glutamate glu,

Serotonin (5HT) and pathophysiology of depression

The ‘serotonin hypothesis’ lacked robustness

‘increases 5HTergic tone’

didn’t explain an incredibly complex system:
14+ types of 5HT receptors
(genes, transcription splice variants, post translational)



‘depression is low serotonin’

Sometimes included low NE
Didn’t address locality –where is it low?
different structures do dramatically different things

‘medication increases serotonin’

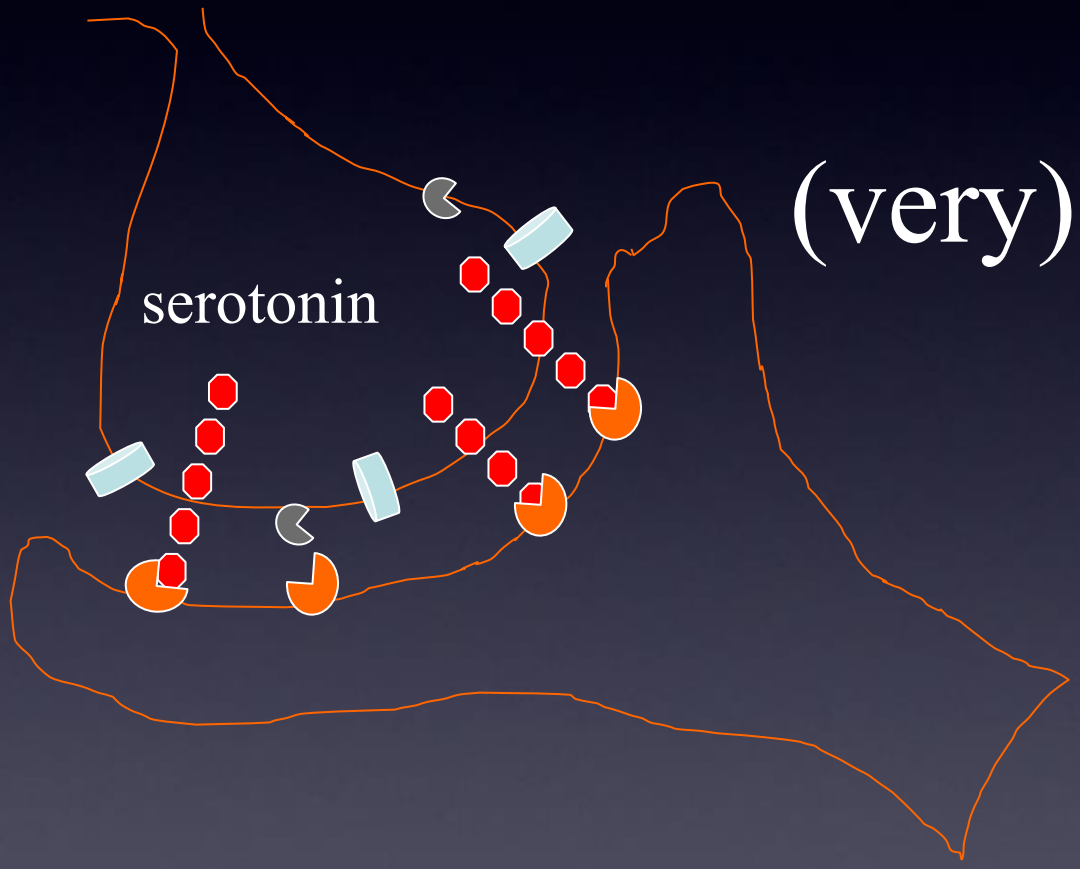
Easy to be mislead by what appears an obvious mechanism

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

Serotonin and pathophysiology of depression

And it was at its heart

(very) misleading



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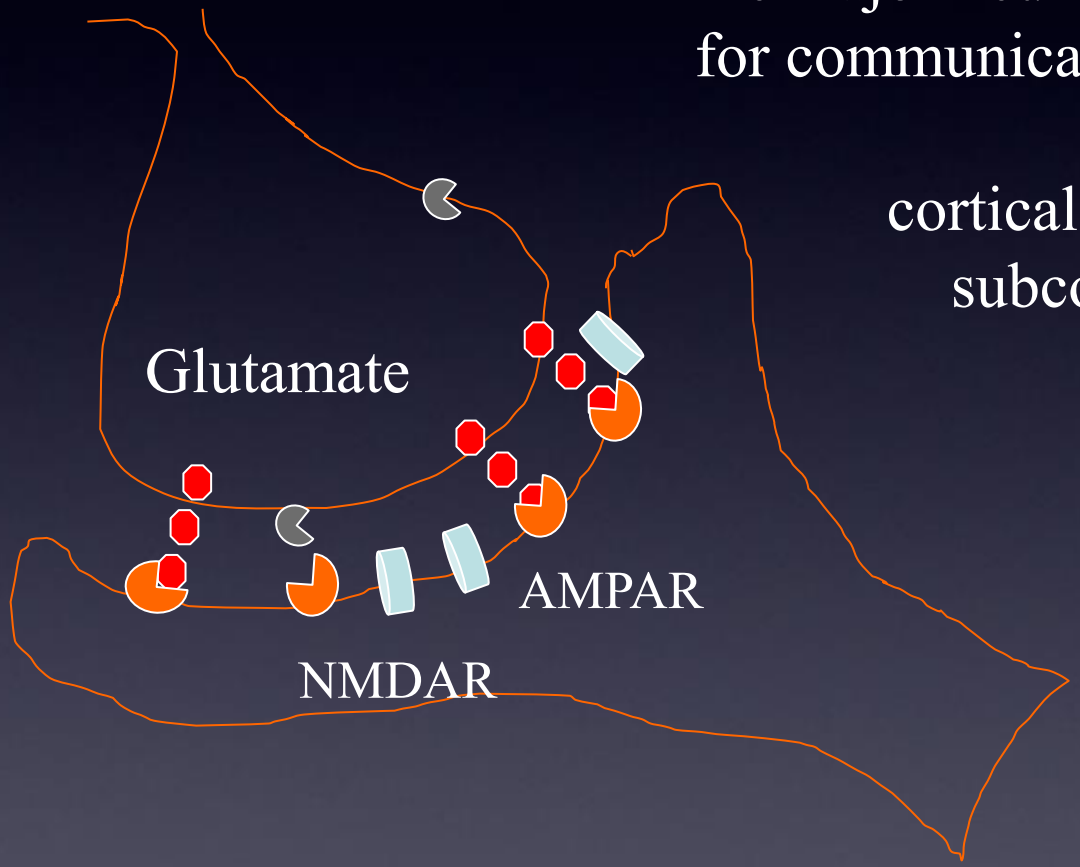
Serotonin and pathophysiology of depression

Glumate and GABA are
the major neurotransmitters
for communication in

cortical,
subcortical
and limbic circuits



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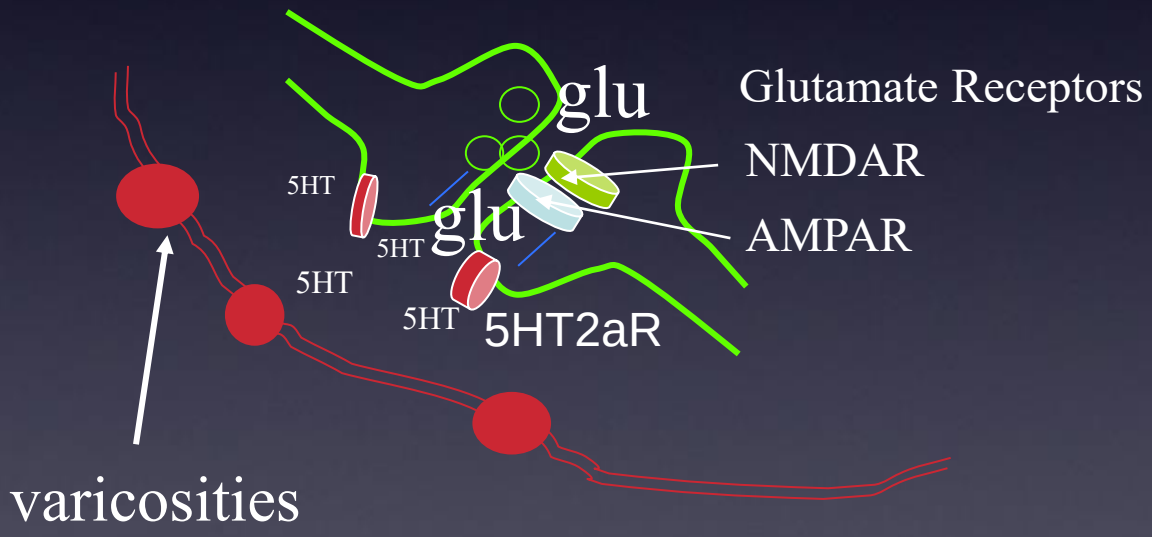
Cortical and limbic connections: role of monoamines (serotonin, norepinepherine, dopamine)

5HT AT A GLUTAMATE SYNAPSE: WHAT IT REALLY IS -- A CIRCUIT MODULATOR



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Addendum:
Brief Review of the Molecular Biology of Plasicity and the Synapse

The Glu synapse: AMPAR and NMDAR

AMPAR/NMDAR work together

First

Glu binds the AMPAR and opens the Na/Ca++ channel

This partially depolarizes the spine/dendrite

Then

Glu binds the NMDA channel

(Mg++ blocks the NMDAR at resting potential)

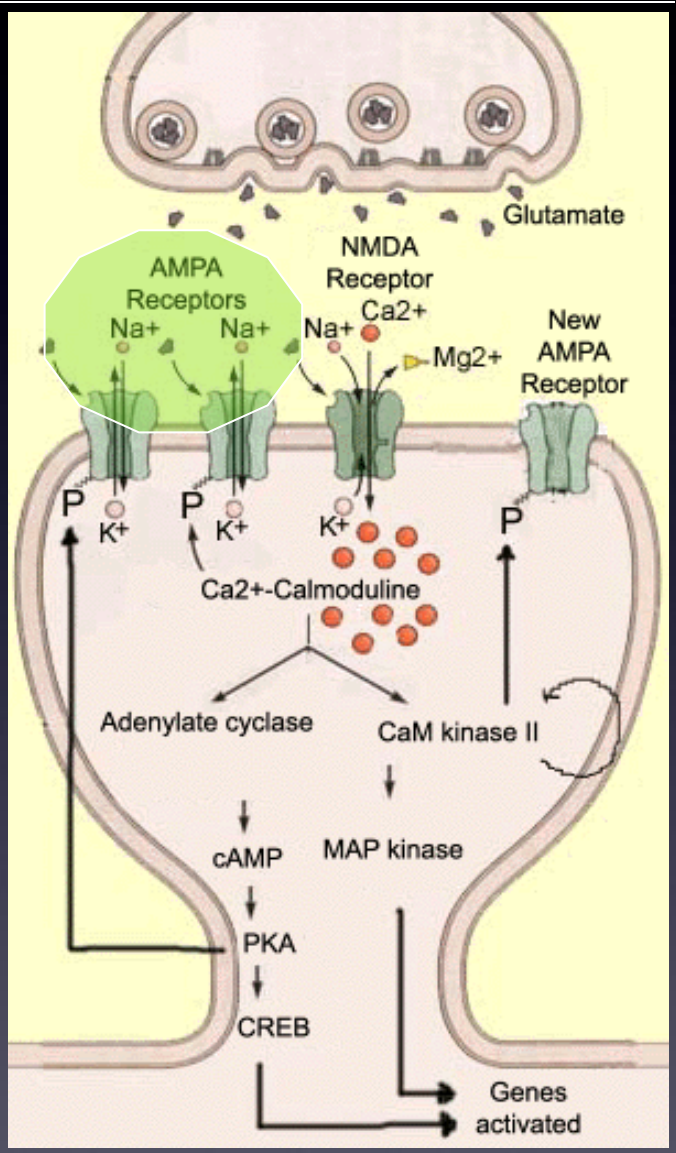
AMPA depolarizes the spine, then Mg++ leaves the NMDA channel allowing Ca++ to flow in

Glutamatergic plasticity

With activation of the AMPAR/NMDAR there is a rapid increase in AMPA channels

These rapid changes affect synaptic function*:

It is considered a basic neuronal mechanism for 'learning'



Glu = glutamate, AMPAR = AMPA receptor NMDAR NMDA receptor

* Long Term Potentialtion and Long Term Depression

The Glu synapse: AMPAR and NMDAR

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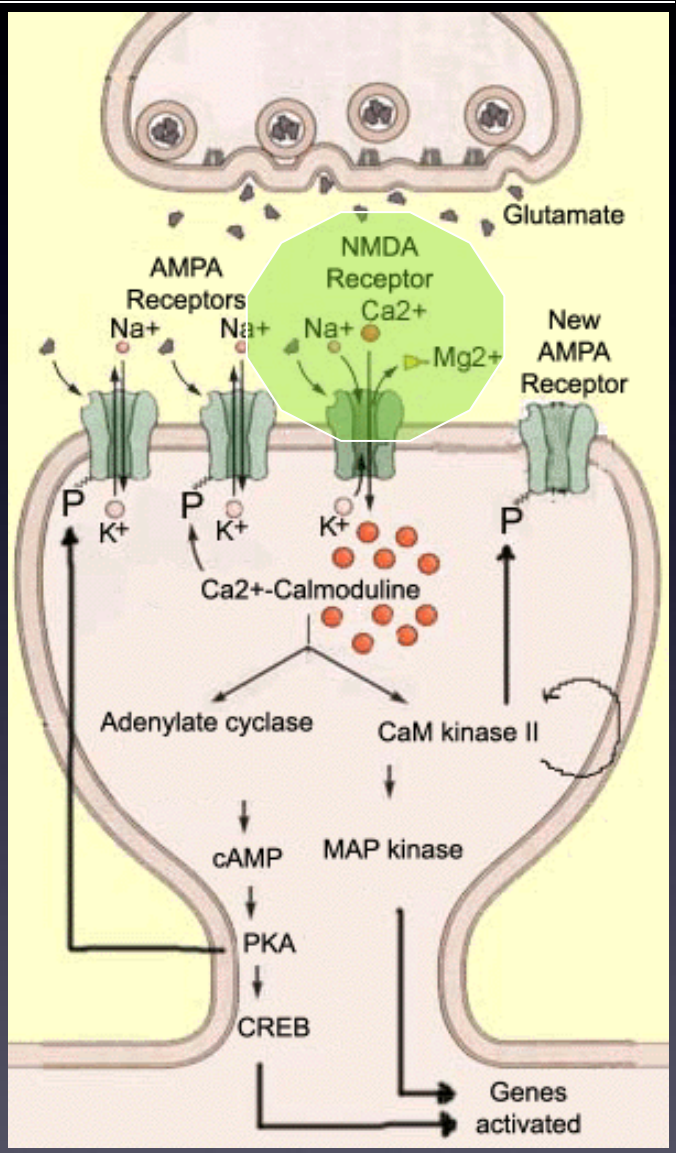

Glu = glutamate, AMPAR = AMPA receptor NMDAR NMDA receptor

* Long Term Potentialtion and Long Term Depression

The Glu synapse: AMPAR and NMDAR

AMPAR/NMDAR work together

First

Glu binds the AMPAR and opens the Na/Ca++ channel

This partially depolarizes the spine/dendrite

Then

Glu binds the NMDA channel

(Mg++ blocks the NMDAR at resting potential)

AMPA depolarizes the spine, then Mg++ leaves the NMDA channel allowing Ca++ to flow in

Glutamatergic plasticity

With activation of the AMPAR/NMDAR there is a rapid increase in AMPA channels

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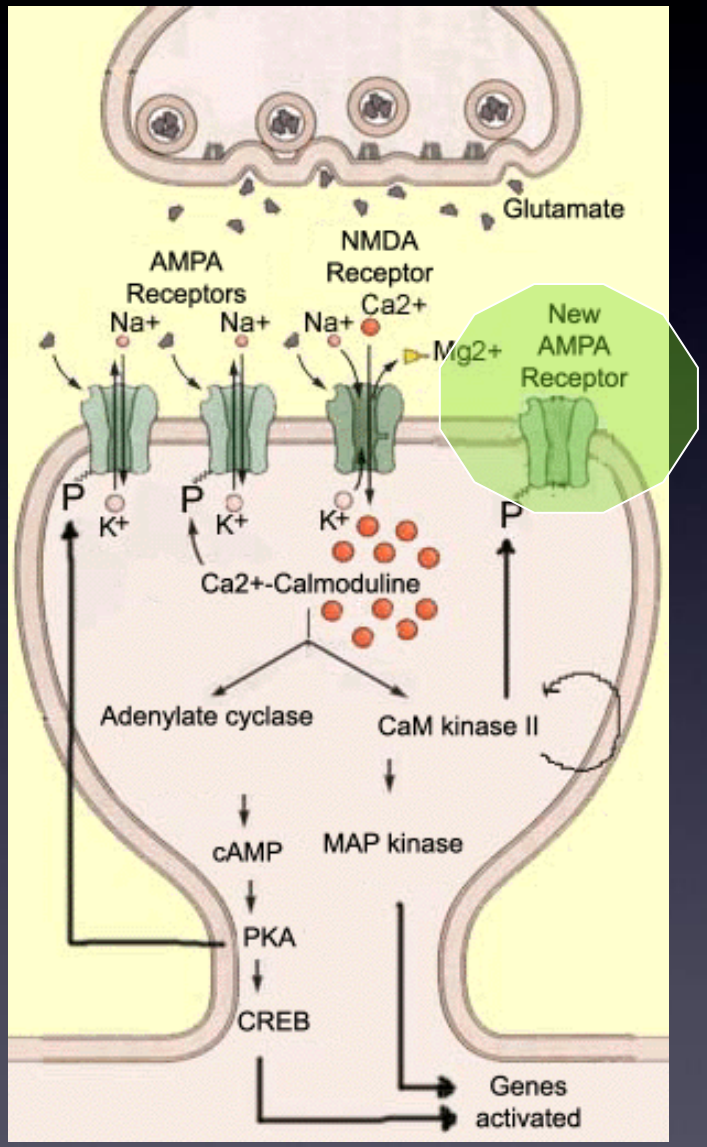

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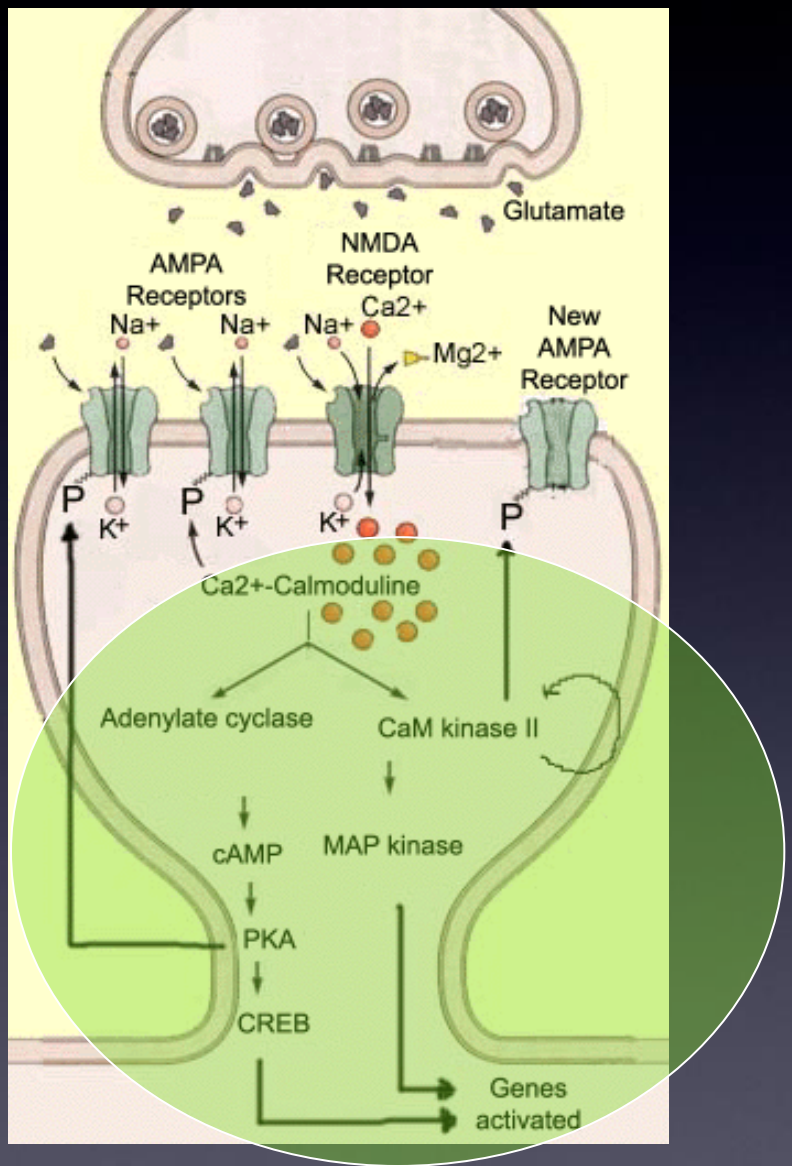


There are multiple glutamate receptor types

<table>
<tr><th colspan="3">Ionotropic
ion channel</th><th>Metabotropic
G protein linked</th></tr>
<tr><td>AMPAR 1-4</td><td>NMDAR 1, 2 _{A-D},3</td><td>KainateR 1, 2, 5-7</td><td rowspan="3">Group I
mGluR1, mGlu5</td></tr>
<tr><td>Na/Ca++</td><td>Ca++</td><td></td></tr>
<tr><td></td><td>Glycine co-agonist</td><td></td></tr>
<tr><td rowspan="2"></td><td rowspan="2">Antagonists:
PCP, Ketamine
(drugs of abuse)
Memantine
(treatment of
Alzheimer Dementia)
Acamprosate
(treatment of
alcohol dependence)</td><td rowspan="2"></td><td>Group II
mGluR2, mGlu3</td></tr>
<tr><td>Group III
mGluR4, 6 - 8</td></tr>
</table>

Monoamine receptors help regulate glutamatergic synaptic activity via 2nd messenger cascades

The monoamines have receptors linked to proteins which activate 2nd messenger cascades and cause plastic change

G protein	Gs ↑ cAMP	**Gi/Go** ↓ cAMP	GqG11 ↑ DAG & IP3
2nd messenger	**Adenyl cyclase**	**Adenyl cyclase**	**Phopholipase C**
Noradrenergic receptor types	**βAR 1, 2, 3**	αAR2 a, b, c	**αAR** 1 a, b, c
dopaminergic receptor types	**D1, D5**	**D2, D3, D4**	
Serotonergic receptor types	**5HT 4, 6, 7**	**5HT1 a**	**5HT2 a, c**

Glu Regulates of plasticity at the synapse

Regulation of spine morphology

The basis of synaptic plasticity

Dendritic spines can duplicate or vanish

Long Term Potentiation

results from short burst of firing at the synapse

It increases synaptic strength

by duplicating the synapse which is

A form of persisting

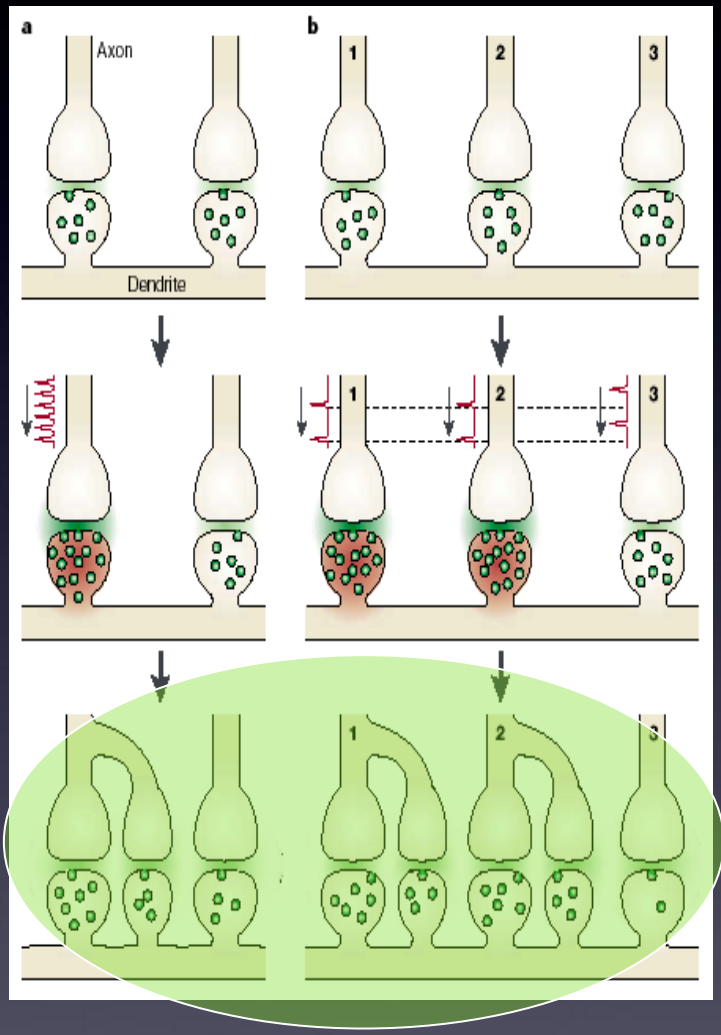
AMPA and NMDA GluR dependent plasticity

Activity dependent plasticity of synaptic connections

Increased by timed firing of synapses

This is the trophic effect of synaptic firing

Increases the number of dendritic spines



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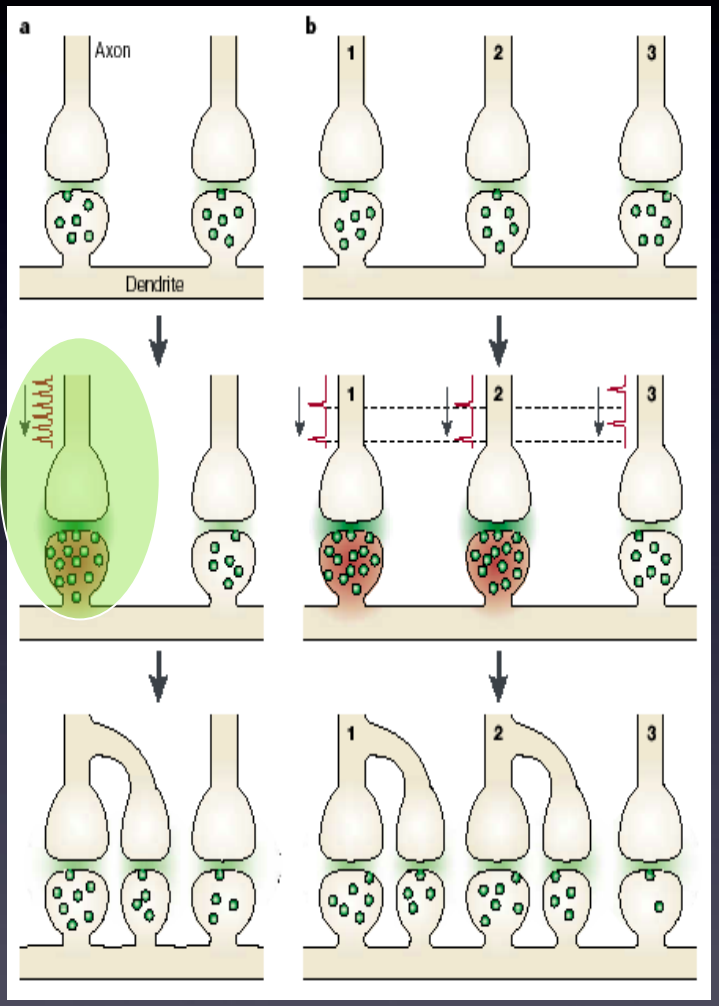

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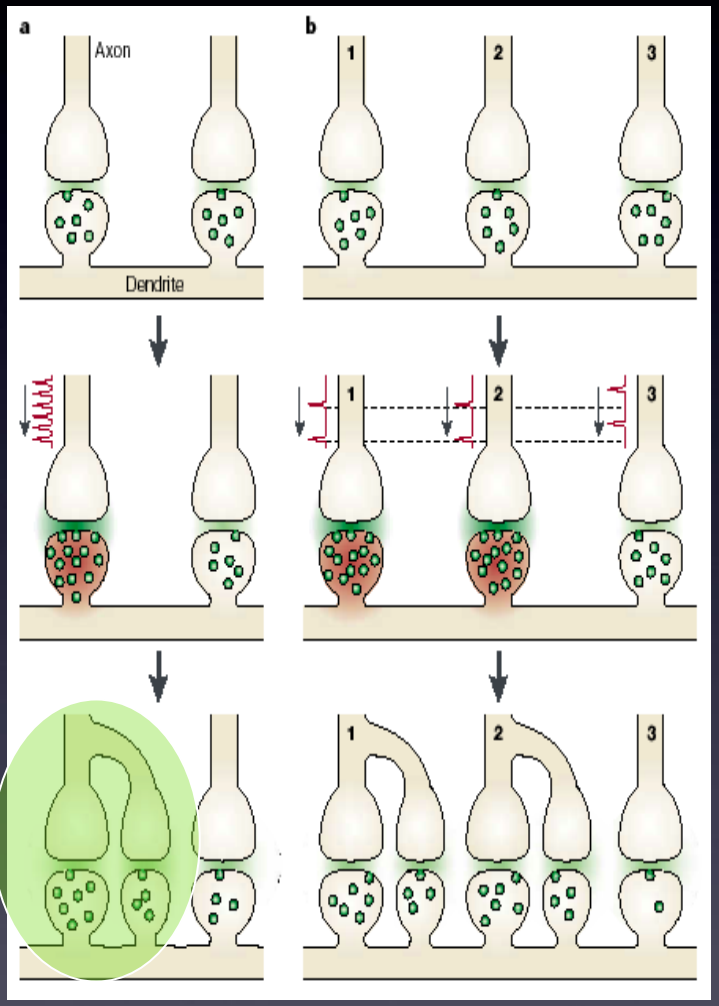

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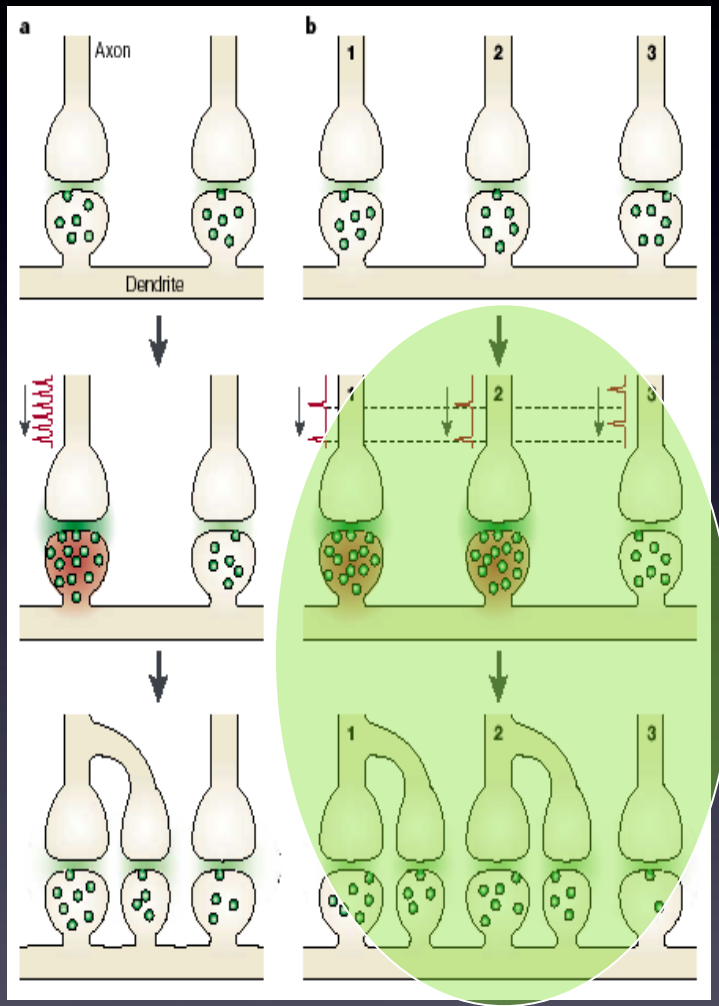

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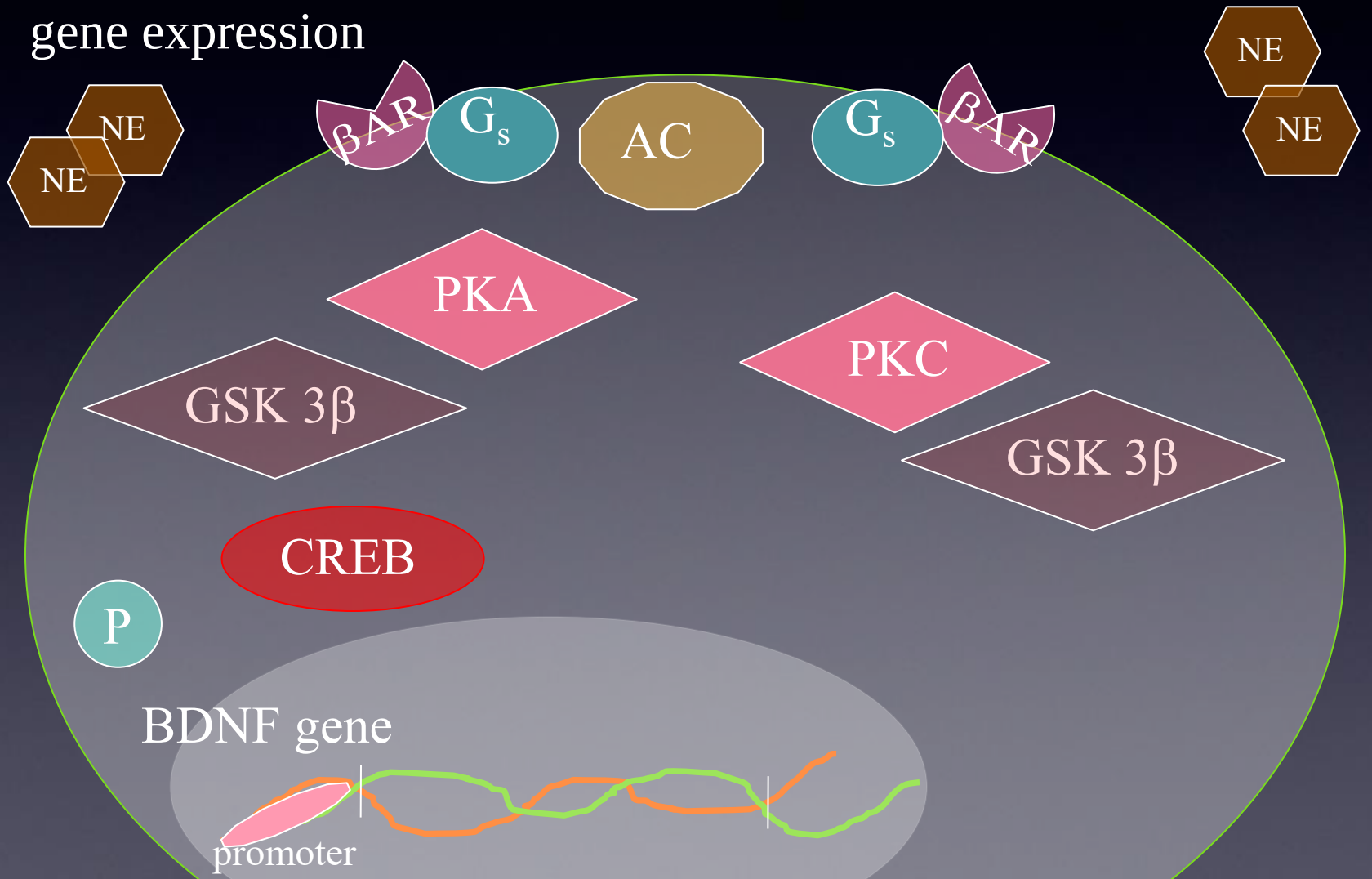
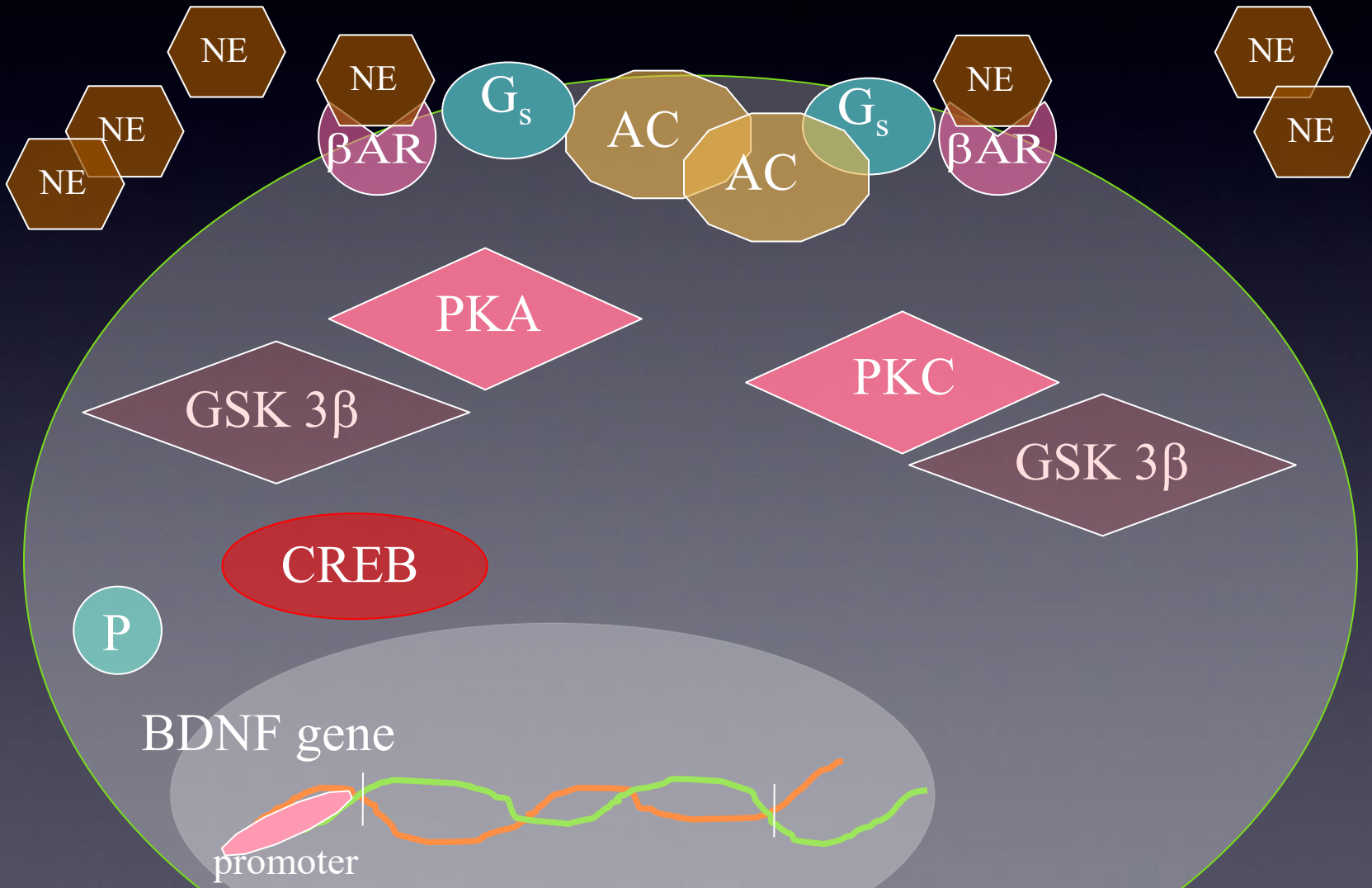
Molecular biology at the NE synapse

How NE binds its receptor and changes gene expression



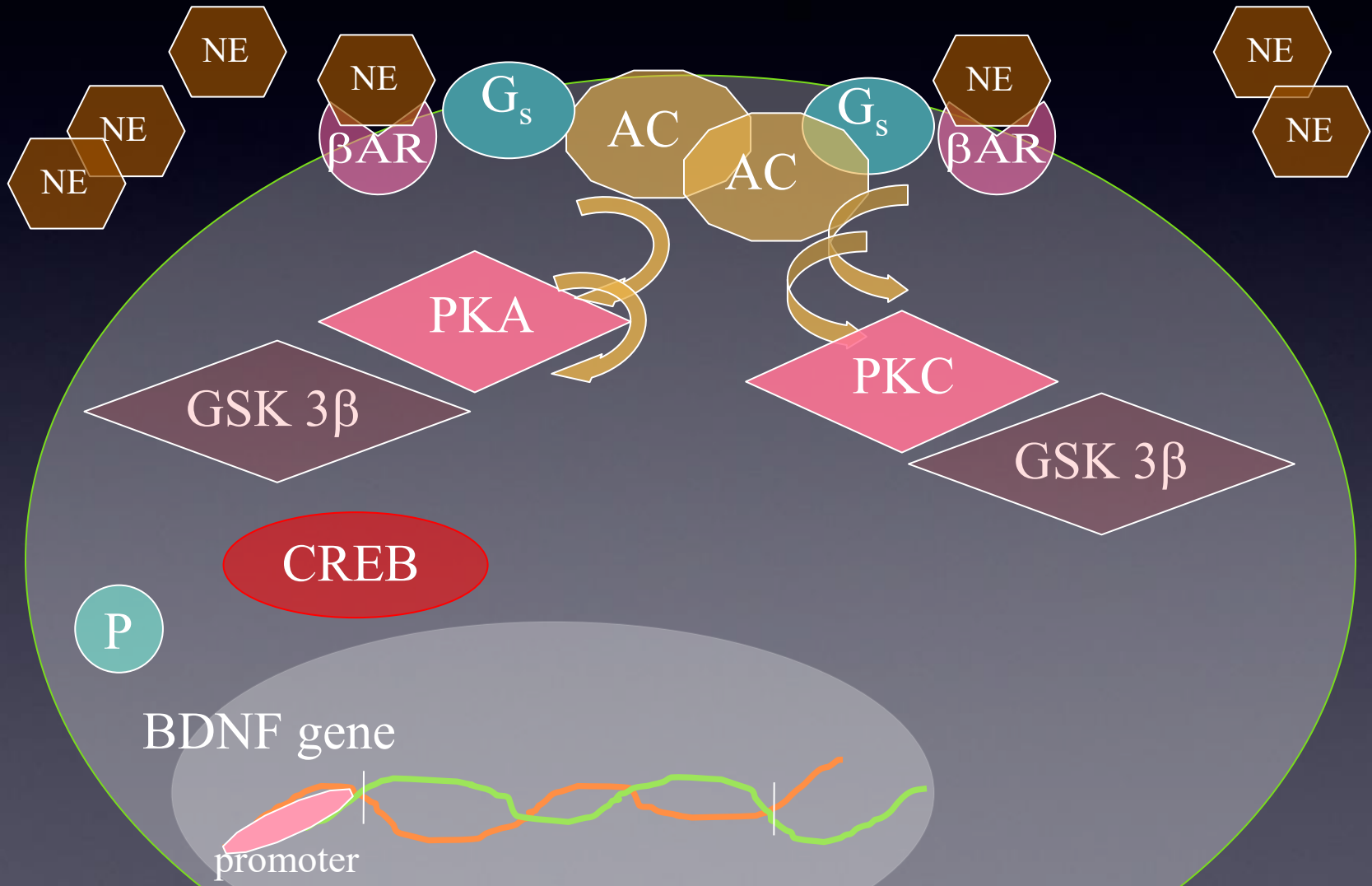
Molecular biology at the monoaminergic synapse: Noradrenergic neuron

Bound receptor Gs activates Adenyl Cyclase



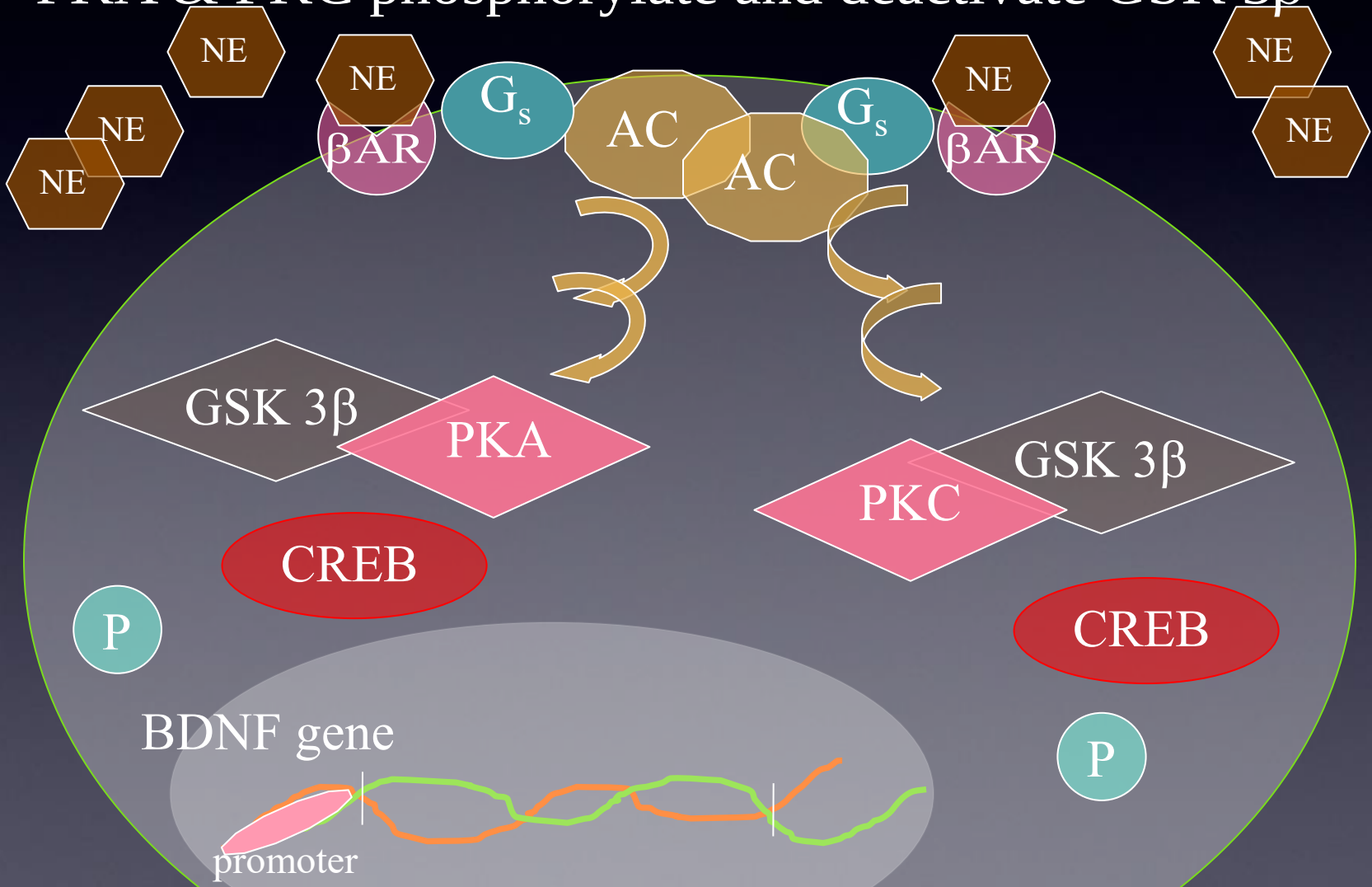
Molecular biology at the NE synapse

PKA & PKC are activated



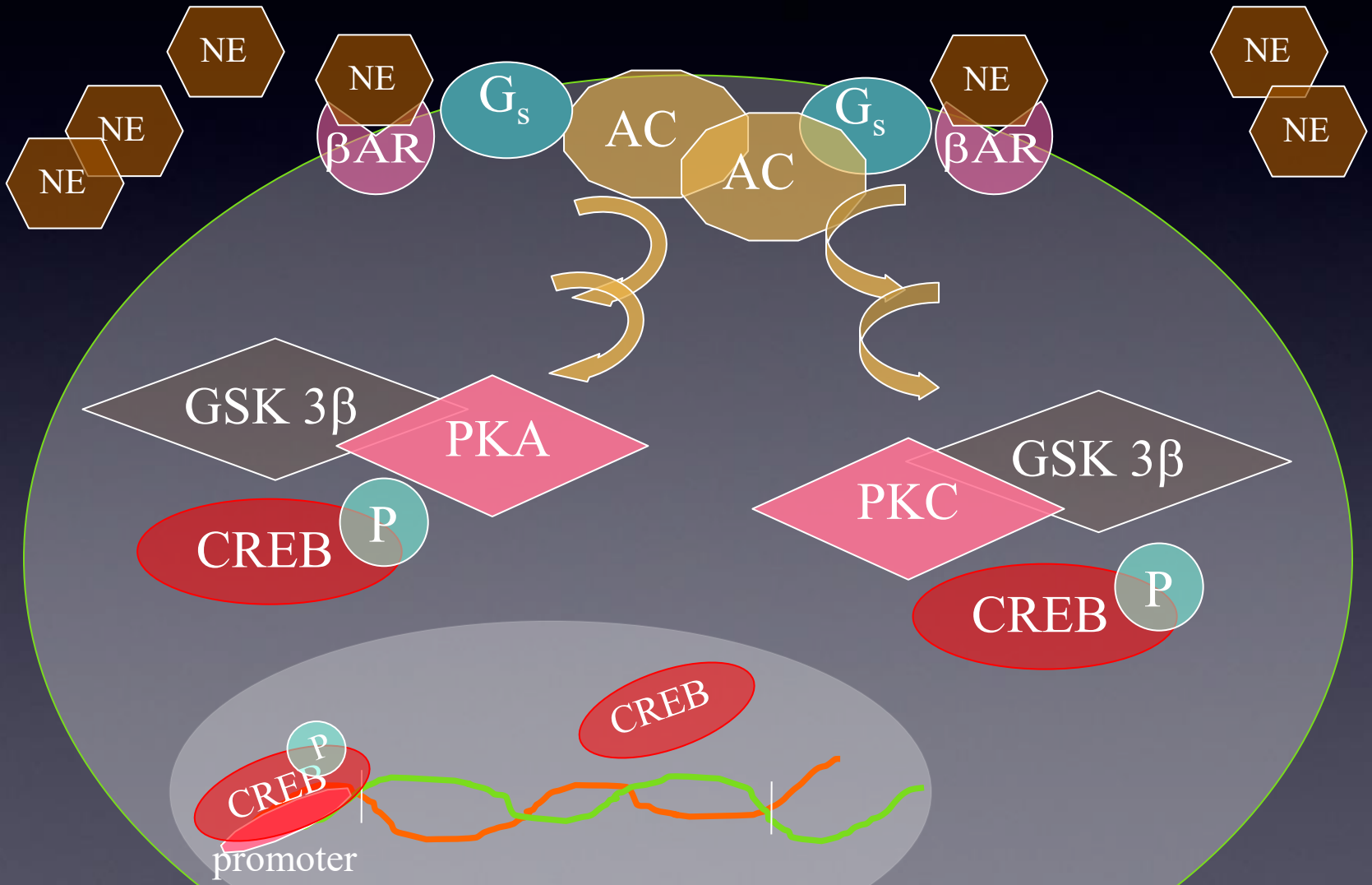
Molecular biology at the NE synapse

PKA & PKC phosphorylate and deactivate GSK 3β



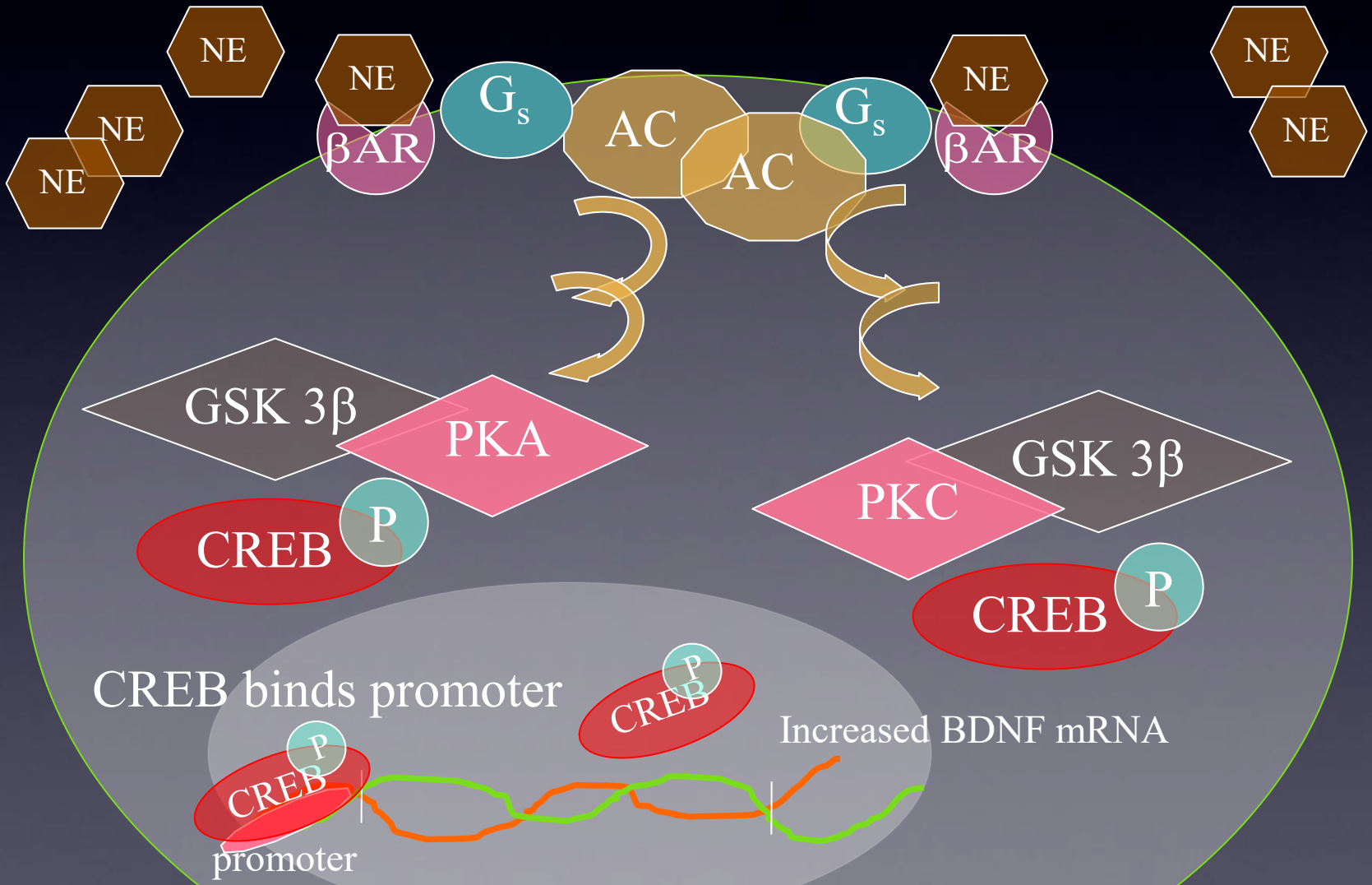
Molecular biology at the NE synapse

CREB phosporylated: can now enter nucleus



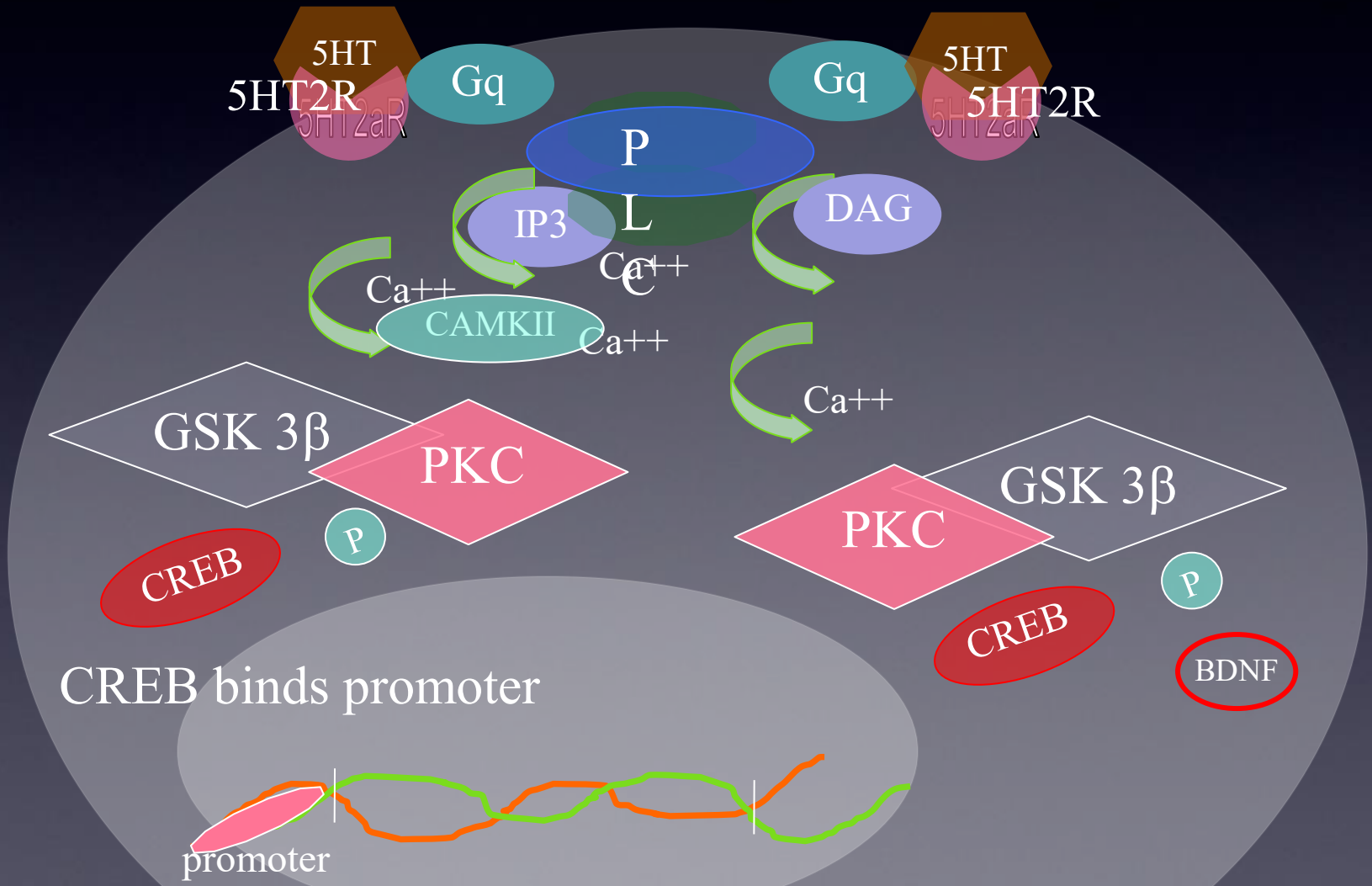
Molecular biology at the NE synapse

Phosphorylated CREB binds upstream promoter



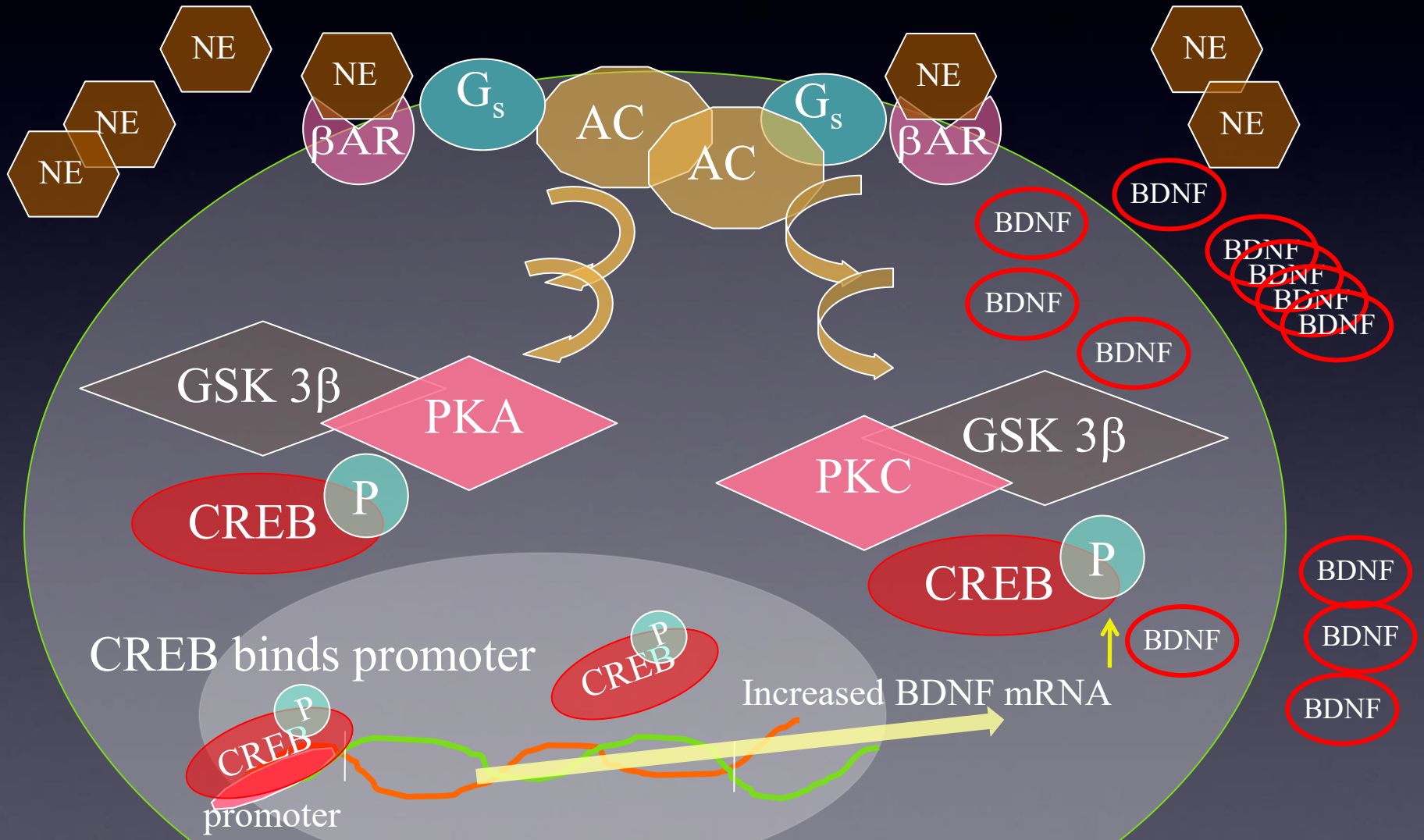
Molecular biology at the 5HT synapse

Phospoinositol pathway: 2nd messengers DAG &IP3



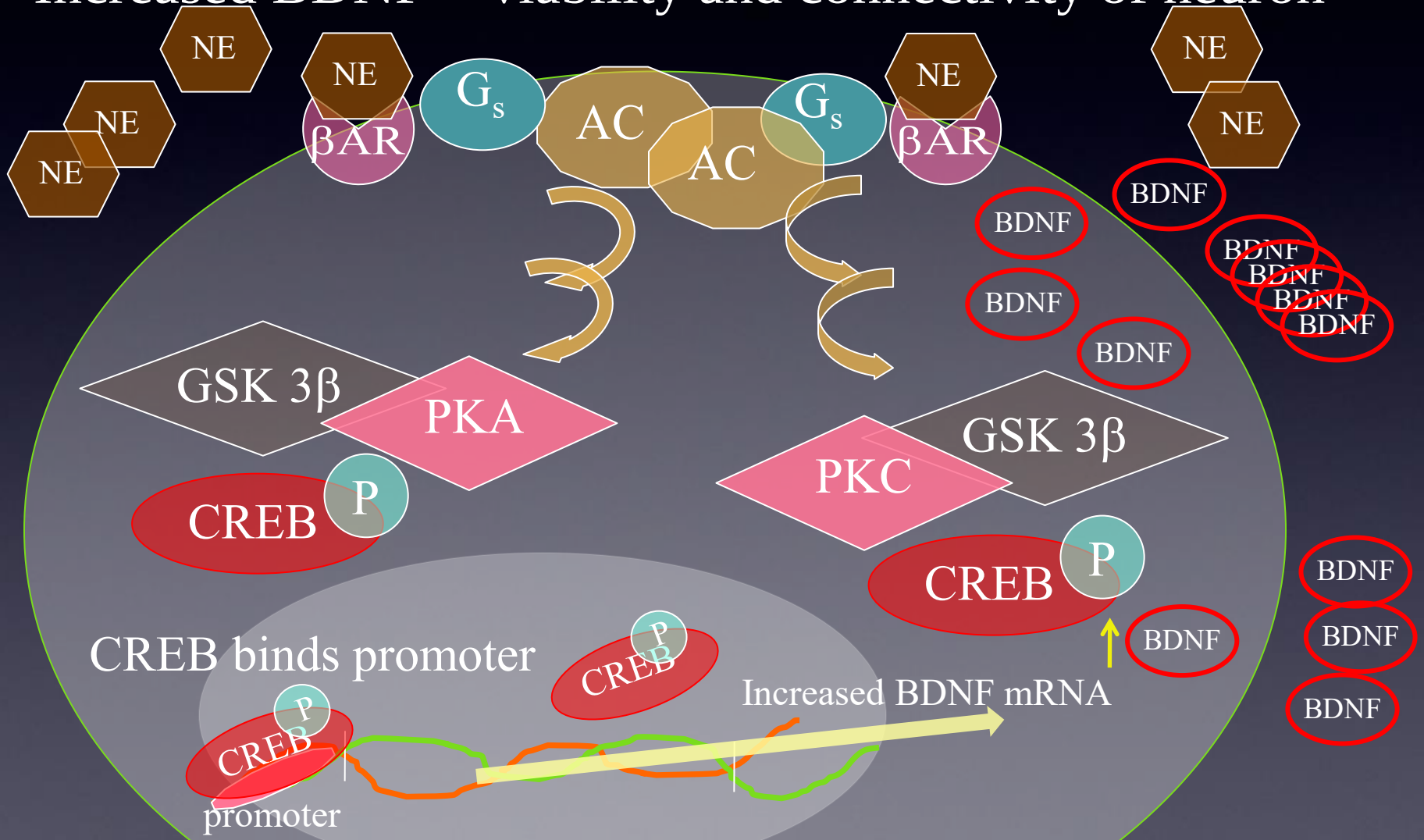
Molecular biology at the NE synapse

Upregulation of BDNF gene expression



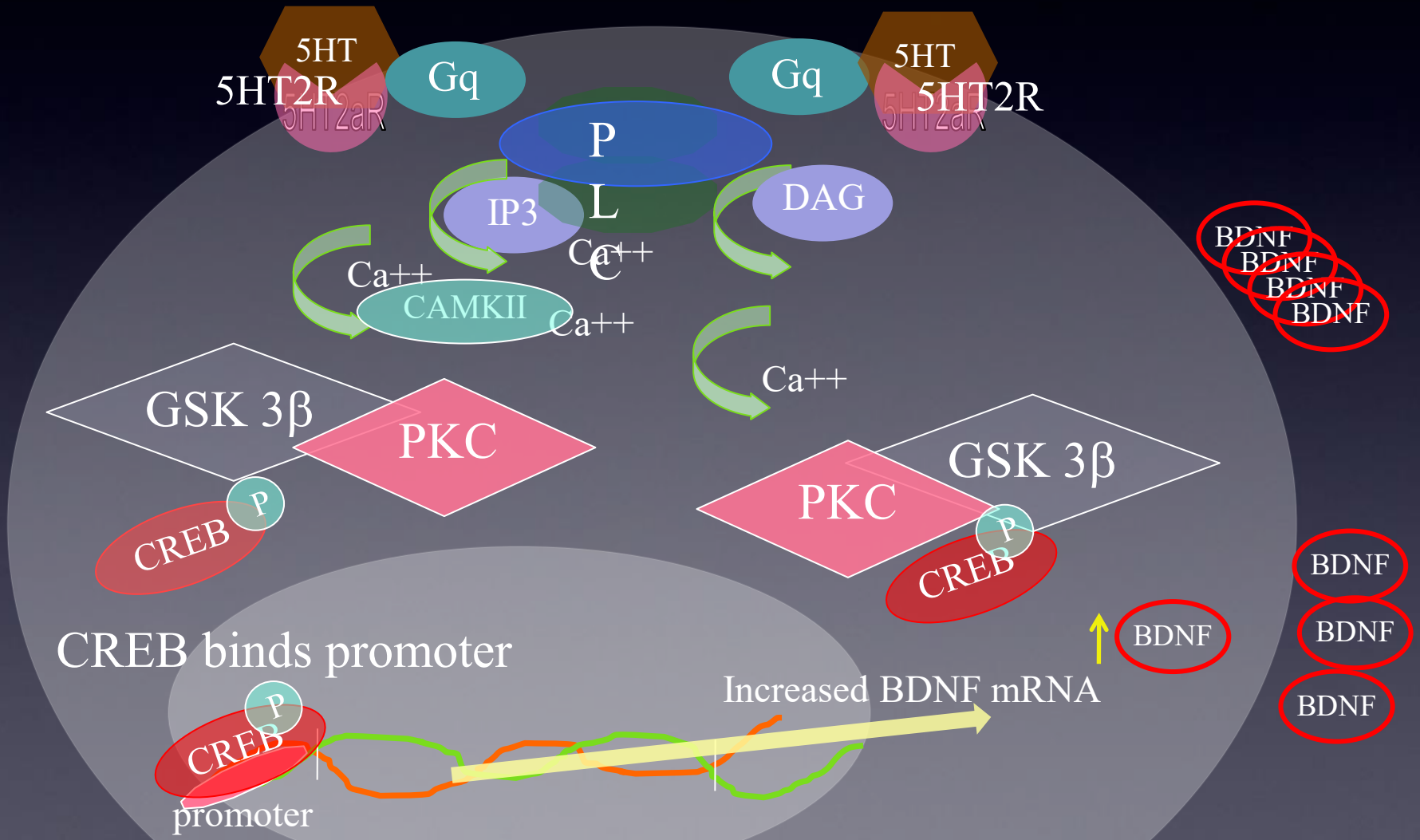
Molecular biology at the NE synapse

Increased BDNF = viability and connectivity of neuron



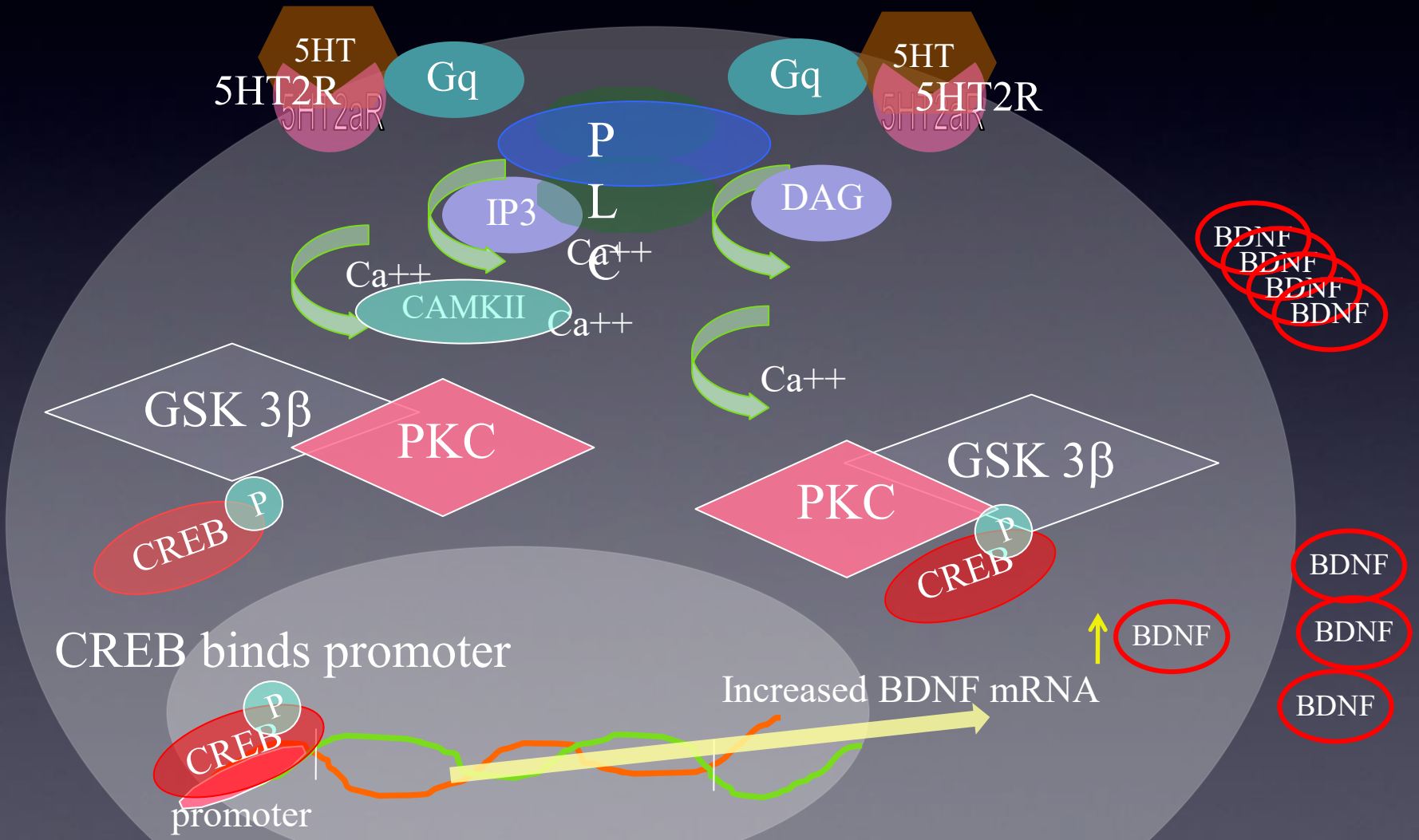
Molecular biology at the 5HT synapse

5HT2 receptor linked to Gq-PLC:



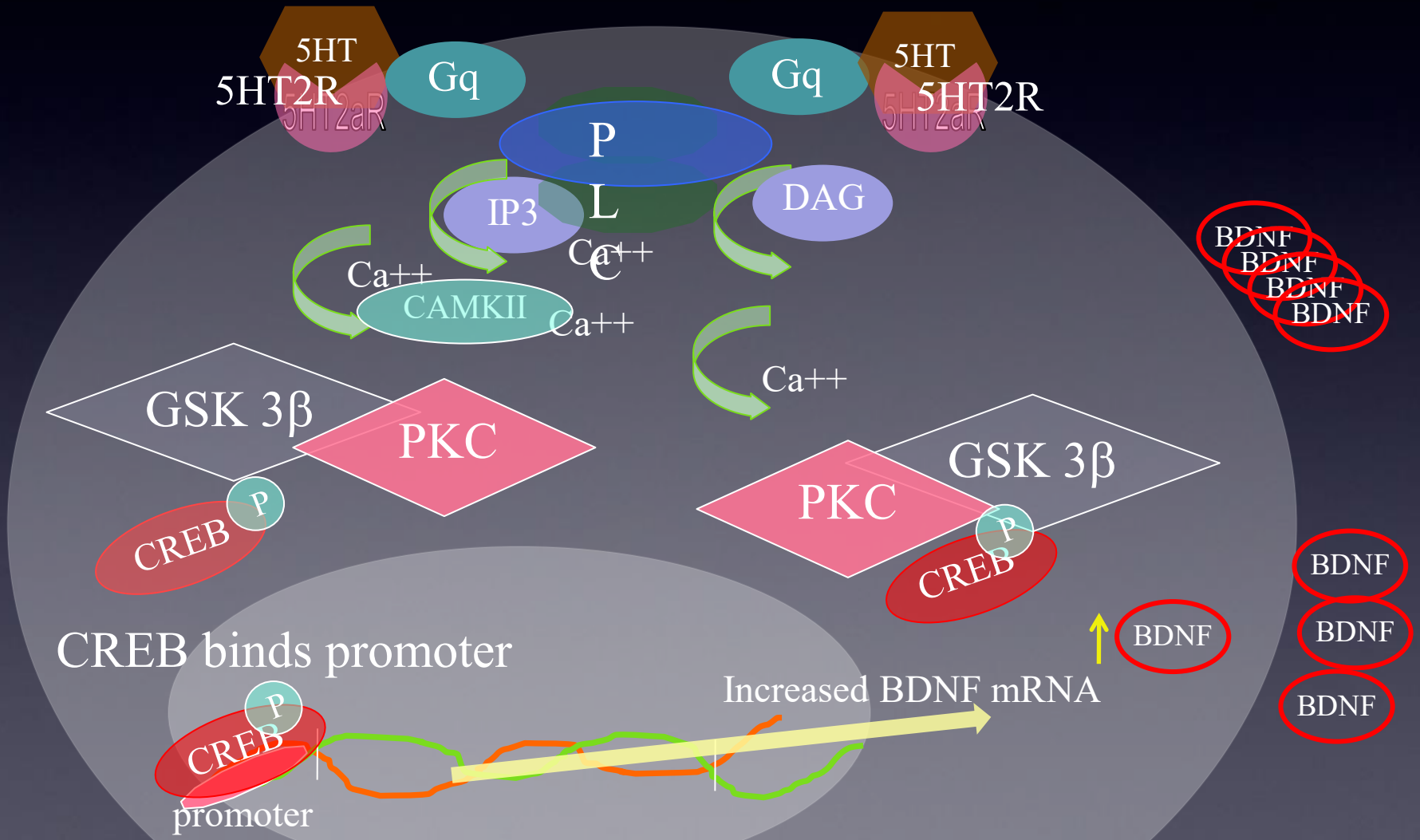
Molecular biology at the 5HT synapse

Common pathway: phosphorylated CREB



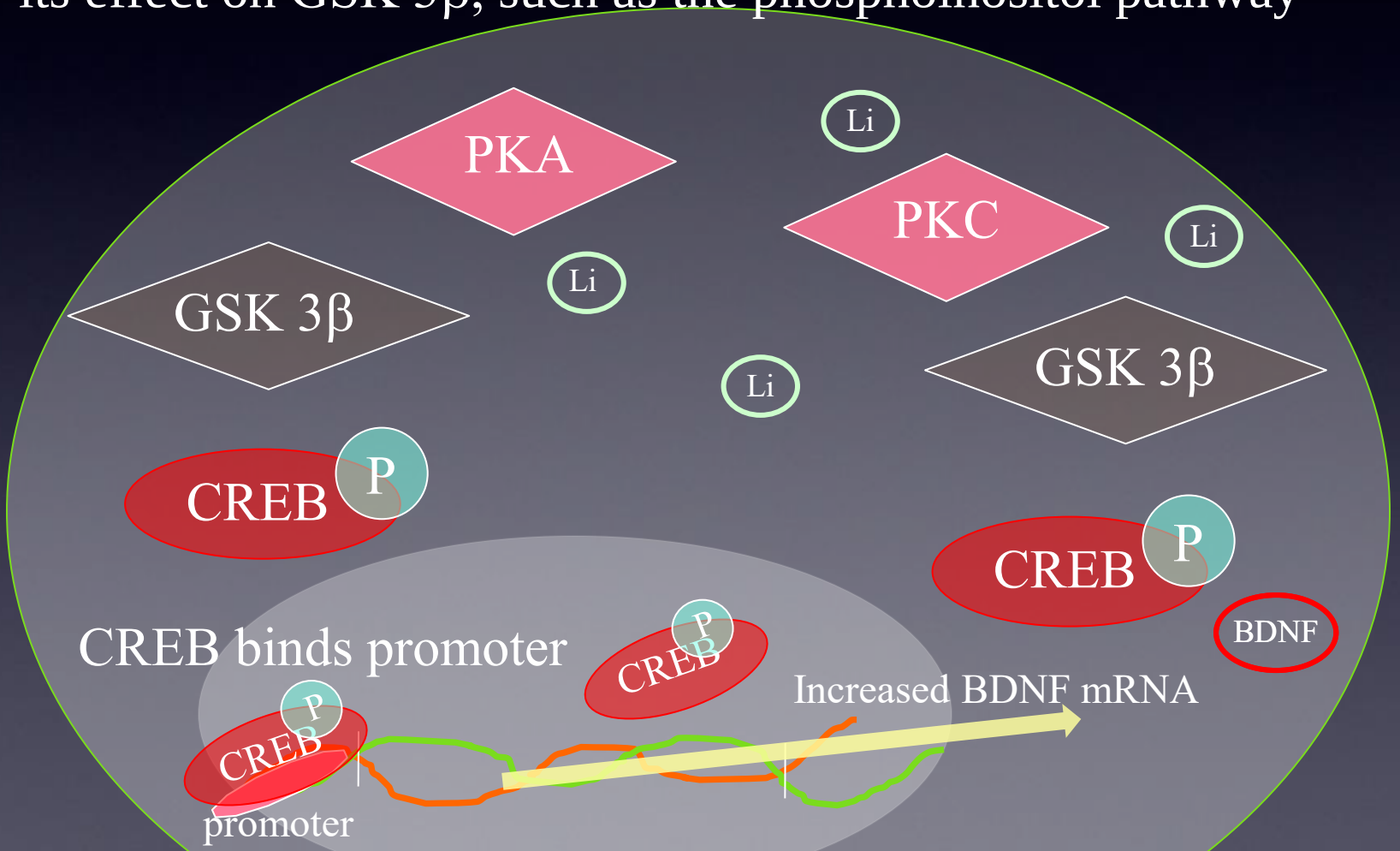
Molecular biology at the 5HT synapse

Increased BDNF expression



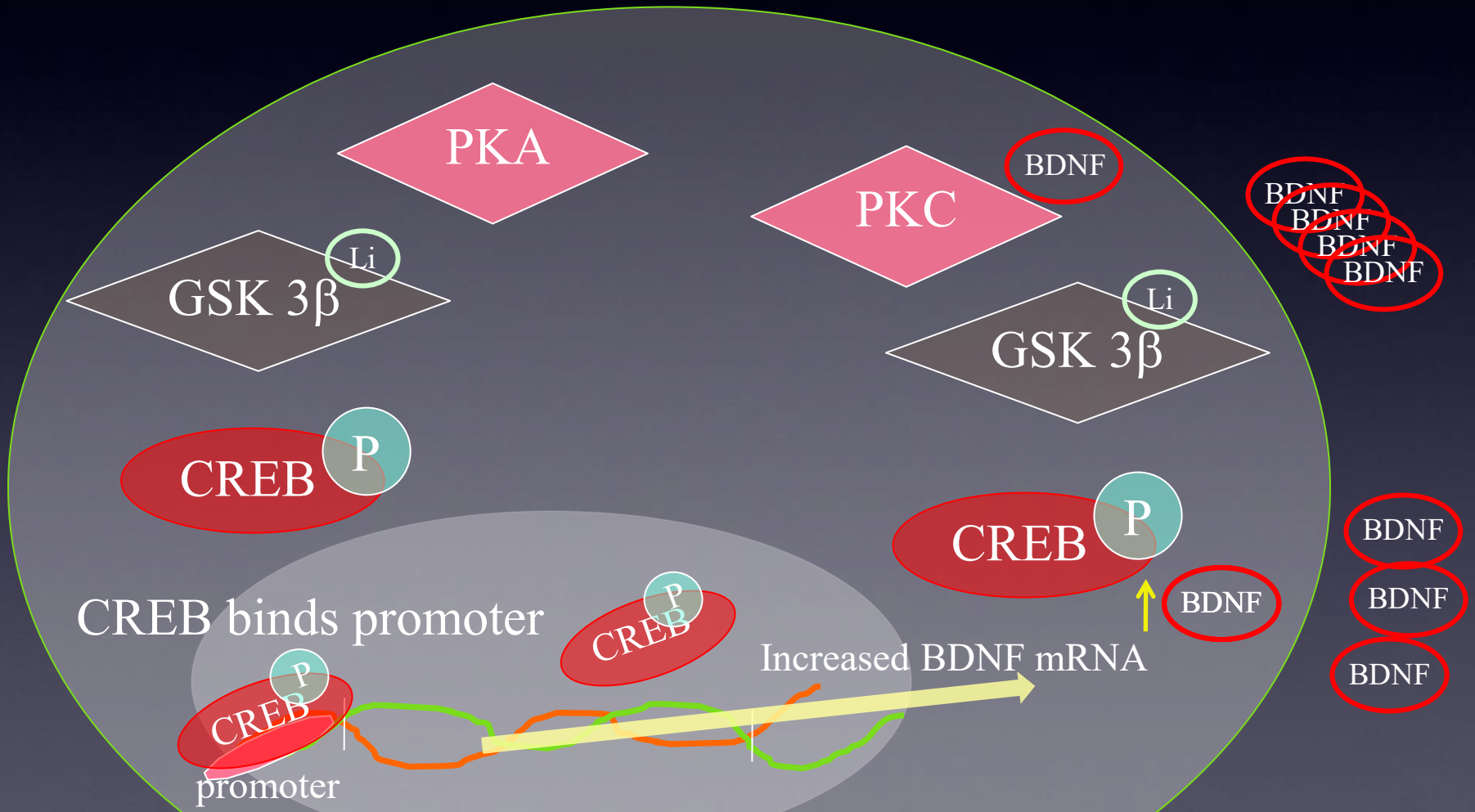
Lithium mechanism of action: inhibition of GSK 3β

There are many postulated mechanisms for Li in addition to its effect on GSK 3β, such as the phosphoinositol pathway

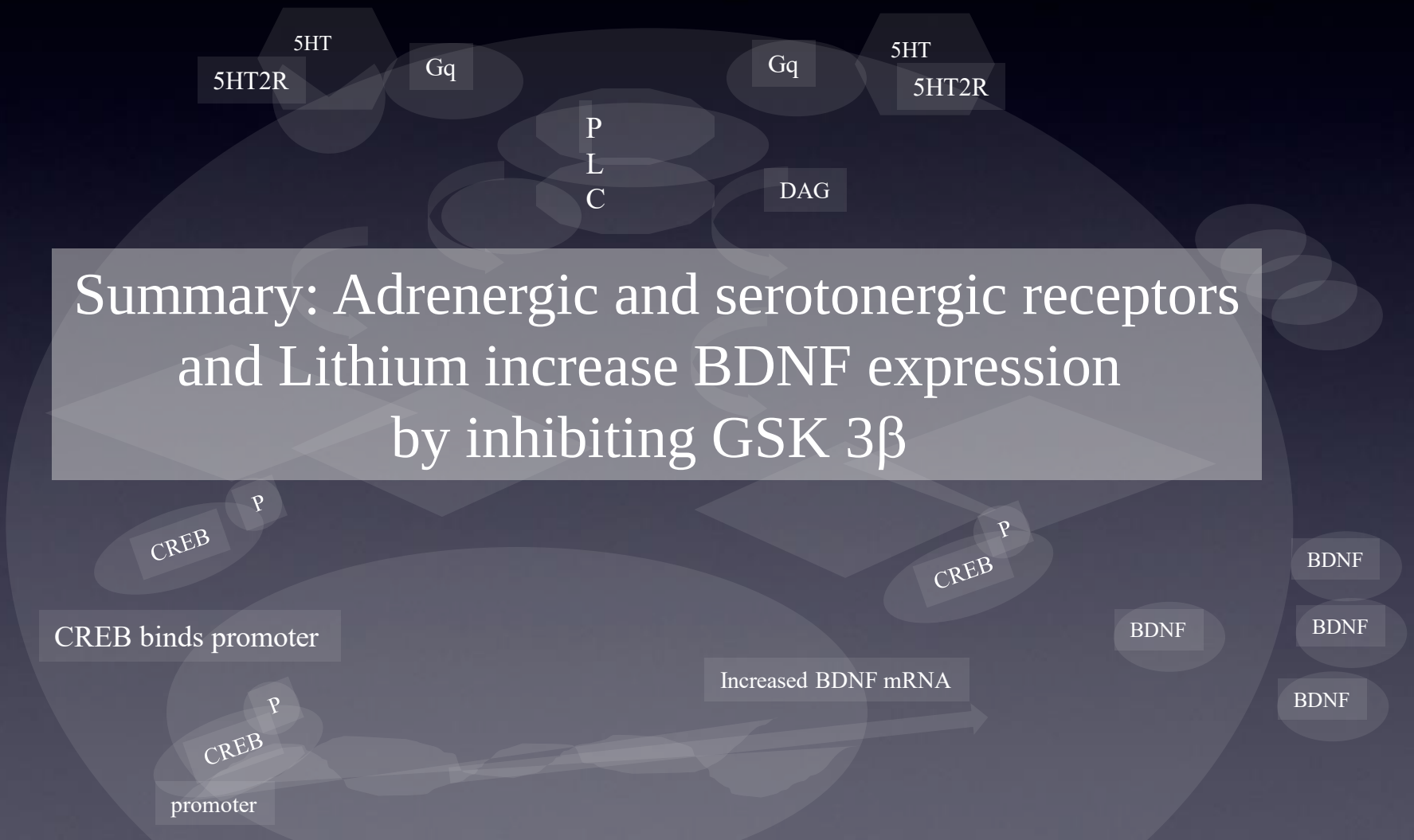


Molecular biology at the NE synapse

By inhibiting GSK 3β, Lithium *disinhibits* gene expression of BDNF



Molecular biology of the synapse and BDNF



Addendum:
Breif review of Genetic Polymorphisms and Psychiatric Illness

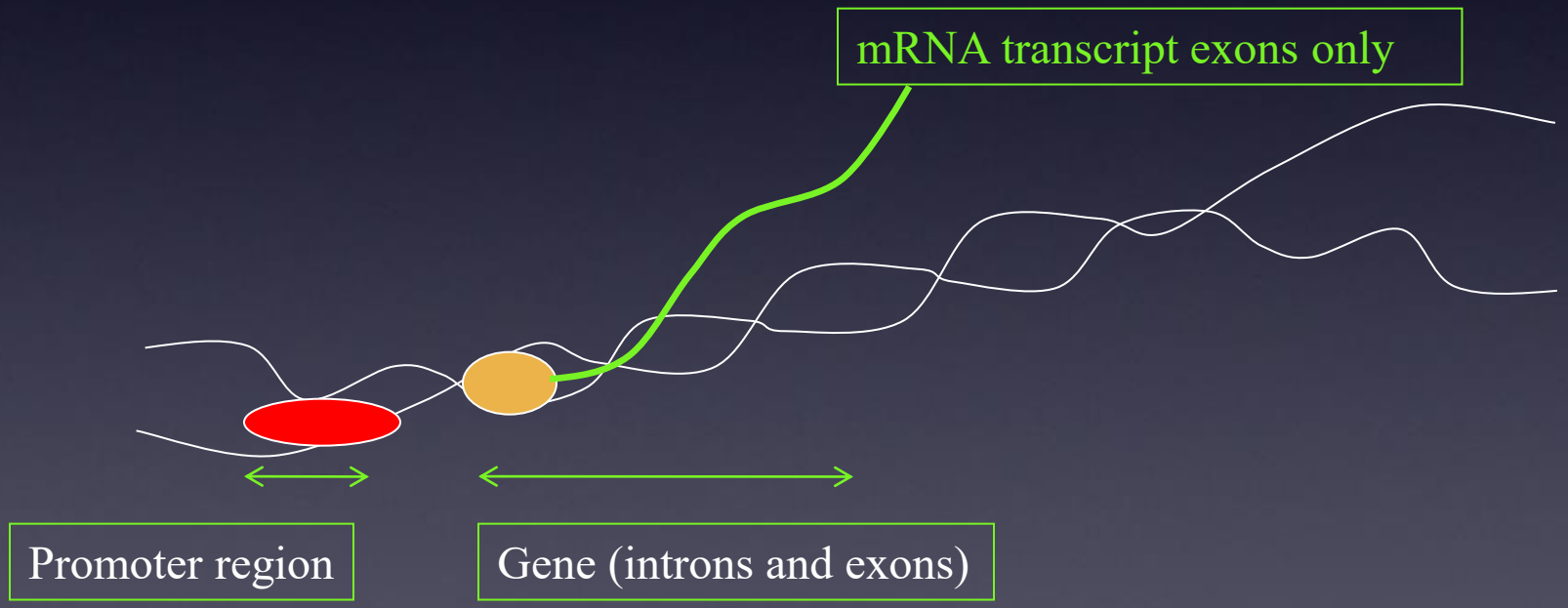
Gene expression

Genetic polymorphisms may occur in the:

promoter area – influences gene expression

gene introns – consequence not always predictable

gene exons – become the mRNA then protein



Regulation of gene expression

Upstream ‘promoter’ areas regulate gene transcription

Regulatory proteins go to the nucleus and bind the promoter region located ‘upstream’ (in front of) the gene

Examples of proteins that control gene expression

CREB (Cyclic AMP Response Element Binding protein)
Has to be phosphorylated to go into the nucleus where it binds the promoter area near the gene it regulates

AP-1 (Protein Kinase A Protein 1)
important in many messenger cascades
Regulates transcription of genes important in control of cell cycle proteins

Local dendritic control of tranlation

mRNA is transported from the nucleus to dendrites and translated by ribosomes locally

Local translation is regulated by phosphorylation of enzymes in 2^{nd} and 3^{rd} messenger cascades

Dendritic synaptic activity regulates translation

Final common pathway proteins such as CREB are regulated through phosphorylation.

$CREB^{P}$ → nucleus and regulates gene expression

Promoter genetic polymorphisms

Upstream promoter areas regulate transcription

Polymorphisms in the promoter alter its ability to regulate gene expression

Example of promoter polymorphism in psychiatry: 5HTTPRL (5HT transporter promoter region)

Exon polymorphism: BDNF

BDNF is a neurotrophin. It stimulates neuronal growth and supports its healthy functioning

BDNF promoter region has a val-met substitution at position 66

BDNF is a pro-molecule, meaning it requires enzymatic cleavage to remove the ‘pro’ part, to leave the active protein

This change in gene sequence and the translated protein, makes it hard to cleave off the pro-molecule. The pro-molecule binds poorly to its receptor

Exon polymorphism: BDNF

The met/met and met/val genotypes have decreased normal BDNF and more pro-BDNF in the brain

BDNF binds the TrkB receptor. The difficulty cleaving the Pro-BDNF leaves lots of the pro-BDNF molecule which binds poorly to TrkB

This causes a reduction in the neurotrophic effect of BDNF

In non-psychiatric subjects: met/met genotype correlates with poor performance on California Verbal Learning Test CVLT) and with smaller hippocampal volume, critical for memory formation

Exon polymorphism: BDNF

BDNF is decreased in rat models of depression, and recovers to normal levels when the rat is given an antidepressant.

Low BDNF in the context of depression (like stress) is thought to put neurons at risk for poor function and apoptosis (programmed cell death)

Hence this genetic polymorphism in BDNF has been hypothesized to be a risk factor for depression/anxiety

It does correlate with scoring high on a ‘neuroticism’ scale which has been shown in multiple studies to be associated with a vulnerability to depression

All antidepressants increase BDNF in animal models

Example of exon polymorphism: COMT

Background:
DA (via D1R) is thought to improve prefrontal processing

COMT metabolizes dopamine and norepinepherine at the synapse

Changes in COMT activity will alter DA levels at the synapse

Higher DA levels at the synapse improve prefrontal efficiency

Example of exon polymorphism: COMT

COMT polymorphism at position 158: val to met

Val haplotype has increased enzymatic activity

- clears DA from the synapse more rapidly
- results in lower DA levels at synapse

Met haplotype has less enzymatic activity

- DA more slowly cleared from synapse
- DA levels at the synapse are higher

Clinical impact:

- Val-Val genotype is associated with greater prefrontal cortical volume reduction in schizophrenia

Genetic polymorphisms in depression

5HTTLPR - the serotonin reuptake channel gene

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

- 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, major depressive episode, and suicidality

- hippocampus
  - l/l genotype associated with smaller hippocampus in MDD

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..

Example of epigenetic regulation

Epigenetic

Histones provide structure to the chromatin

When acetylated histone is present, the chromatin is opened by the bulky acetyl group

Open chromatin can allow genes to be transcribed to mRNA

Closed chromatin results in diminished gene expression

Mechanism for long term control of gene expression

Example of epigenetic regulation

Epigenetic
HDAC 5 is the molecular target of antidepressants

Antidepressants and valproate are both HDAC antagonists
Opens 3-4% of the genome.

Chromatin opened by valproate and antidepressants have genes for Neurotrophins and anti-apoptotic proteins

Key Points: Genetic polymorphisms

Can control gene expression

Can modify proteins that affect post-translational modification

Can affect the activity of enzymes and other proteins, some of which may significantly modulate cascade messenger systems, or affect synaptic plasticity (eg cytoskeleton)

Some of these will likely be found to play an important role in vulnerability to psychiatric illness, illness course, and changes in brain structure or plasticity

Not clear they will affect somatic treatment approaches

Addendum:
Brief review of the molecular biology of gene expression

Gene expression: from gene to protein

The connection between genes and proteins

The synthesis and processing of RNA

The synthesis of protein

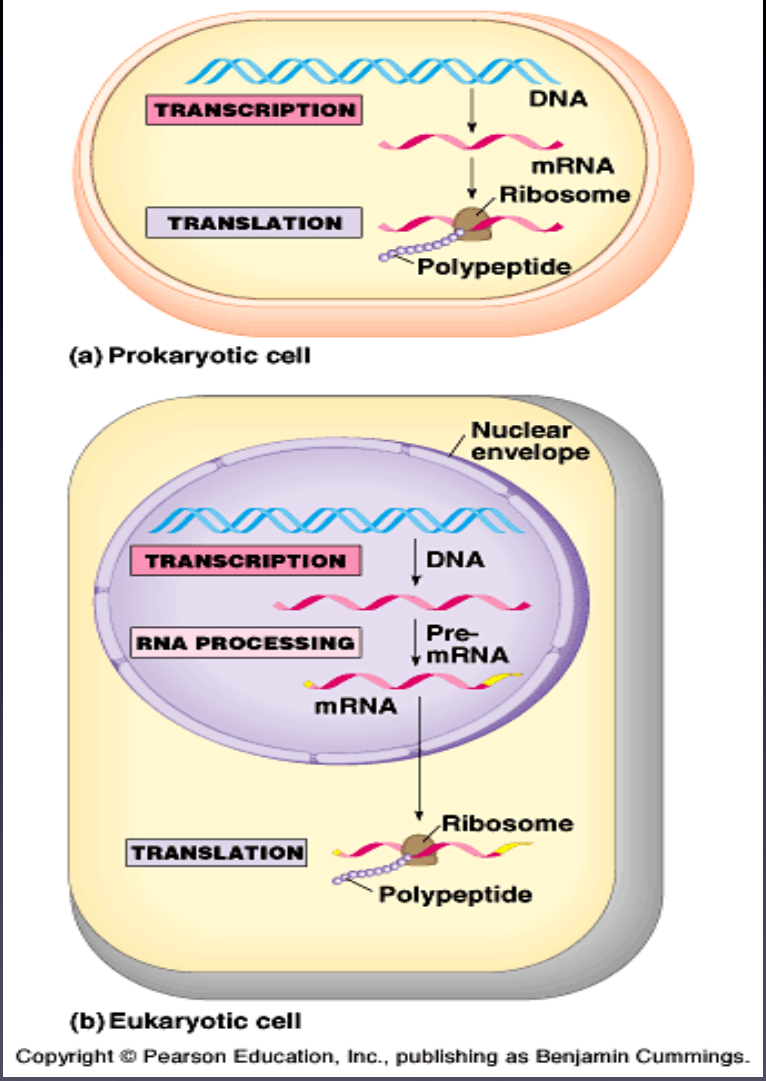
Genetic code

DNA: Synthesizes

RNA: Transcription

RNA: Synthesizes

Protein: Translation

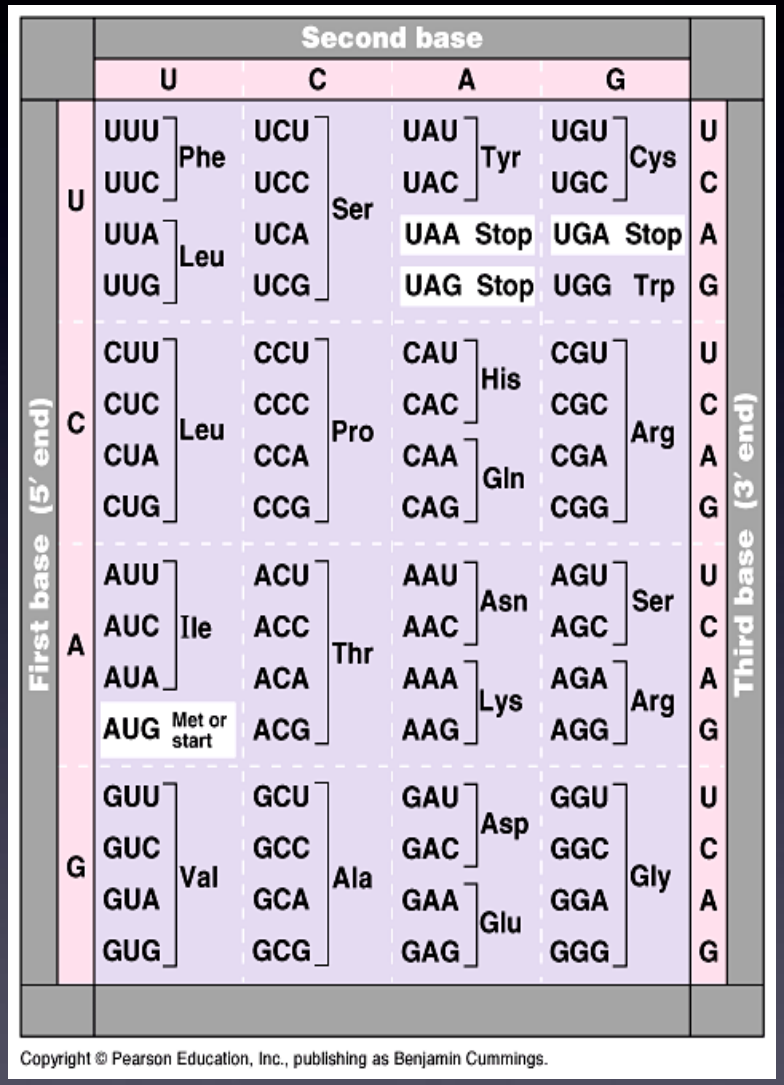


Genetic code

Codon:
Triplet sequence of nucleotides

Smallest unit of uniform length to allow translation of all 20 amino acids

triplet in mRNA
spliceosome brings the ends of the intron together



Synthesis and processing of RNA

Three types of RNA: mRNA, tRNA, and rRNA
eukaryotes have three polymerases

RNA polymerase II responsible for mRNA synthesis

Transcription subdivided into three stages: Initiation, elongation, and termination

RNA must be processed before it can function

Transcription of mRNA

Initiation: RNA polymerase binds to promoter region,TATA box plays critical role during initiation

Elongation: RNA polymerase unwinds DNA and adds nucleotides, 10 bases long, grows 5' to 3' direction.

Termination: terminator sequence (AAUAAA) stops transcription

DNA re-anneals: reforms double helix, RNA “peals” off template DNA (gene)

Function of the 5’ cap and poly (A) tail

Protect mRNA from hydrolytic degradation in cytosol

Identifies and brings mRNA to small ribosomal subunit
Inhibits degradation of mRNA in the cytosol

Facilitates mRNA export from the nucleus

Separated from the stop codon by a *trailer sequence*

RNA splicing

Introns: noncoding sequences that are removed

Exons: coding sequences that are *spliced* together

Small nuclear ribonucleoproteins (snRNPs): identify and help bring about the splicing process

Spliceosome: catalyzes splicing reactions

RNA splicing: introns left behind

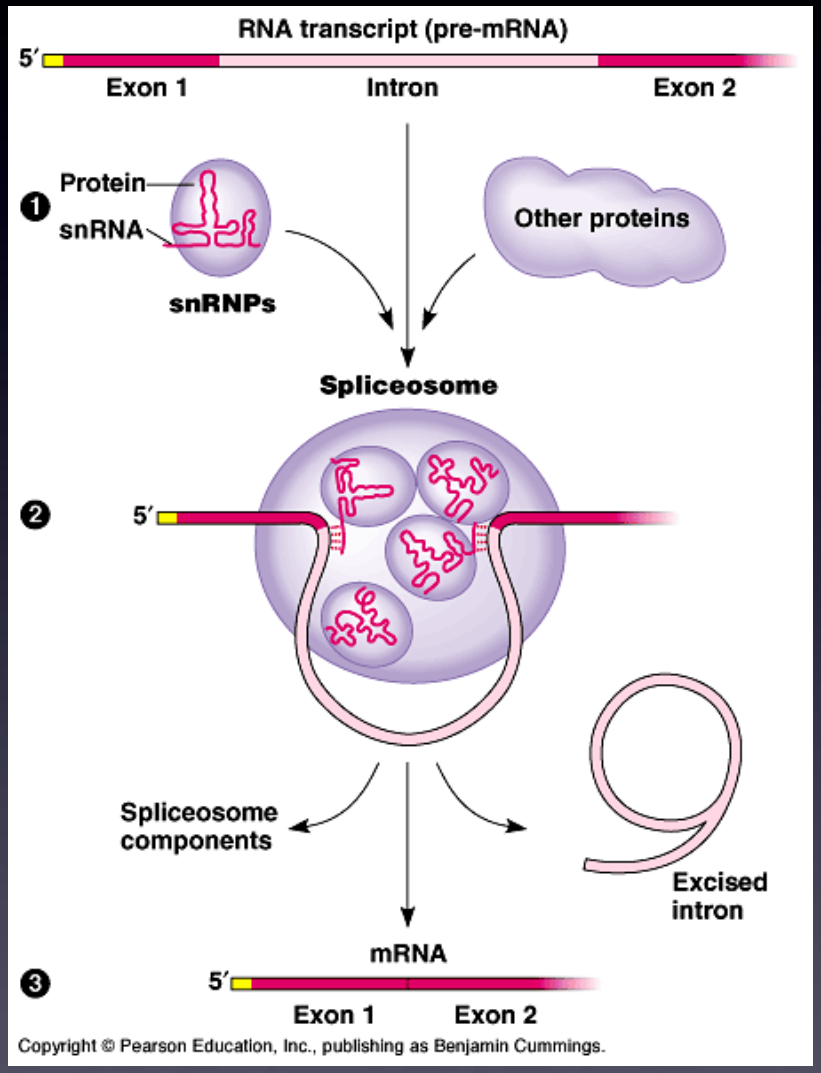
Complex of mRNA +

protein +

snRNA

Spliceosome brings the ends of the intron together

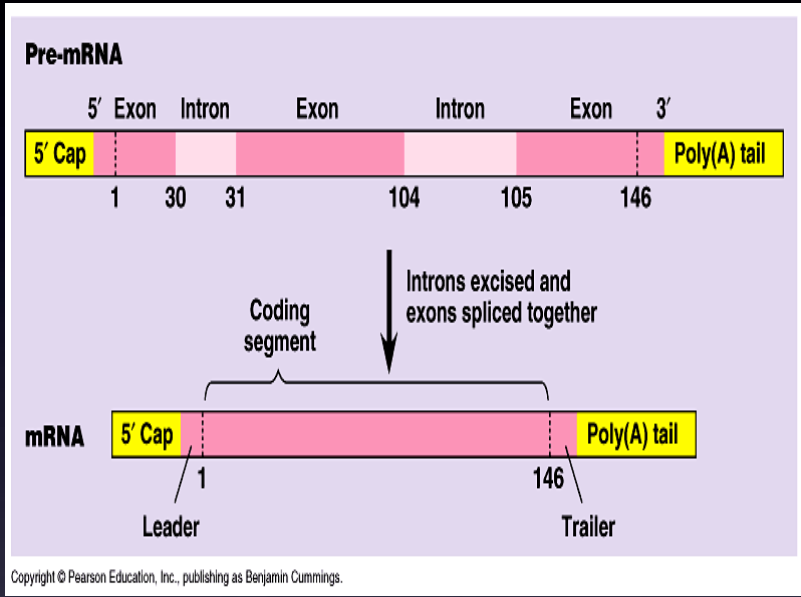
Results in final spliced version of mRNA which will be translated



Role of introns in the gene sequence

May have sequences that can control gene activity

May allow a single gene to synthesize several different Proteins

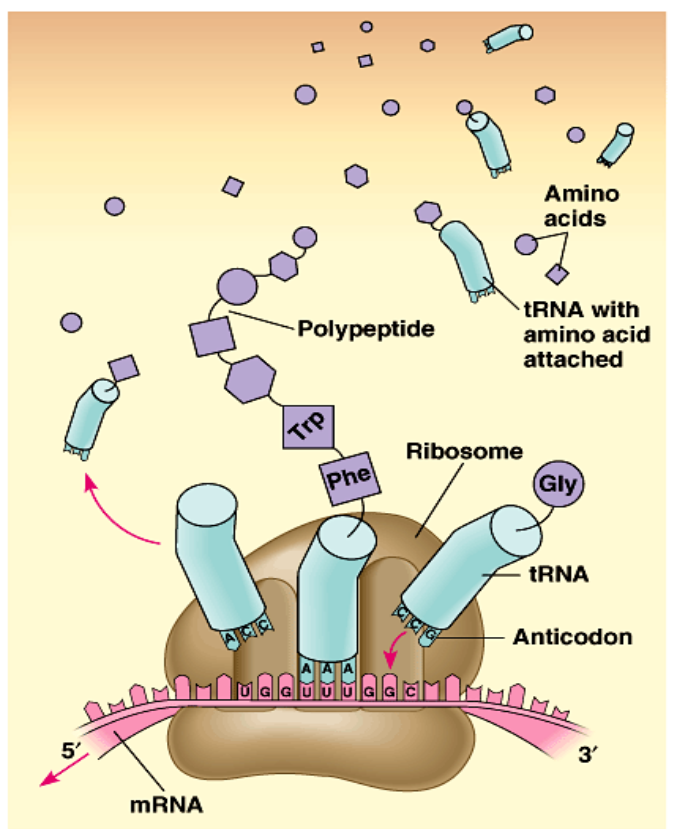


Translation: the synthesis of proteins

tRNA +

Ribosomes +

Aminoacyl-tRNA synthases



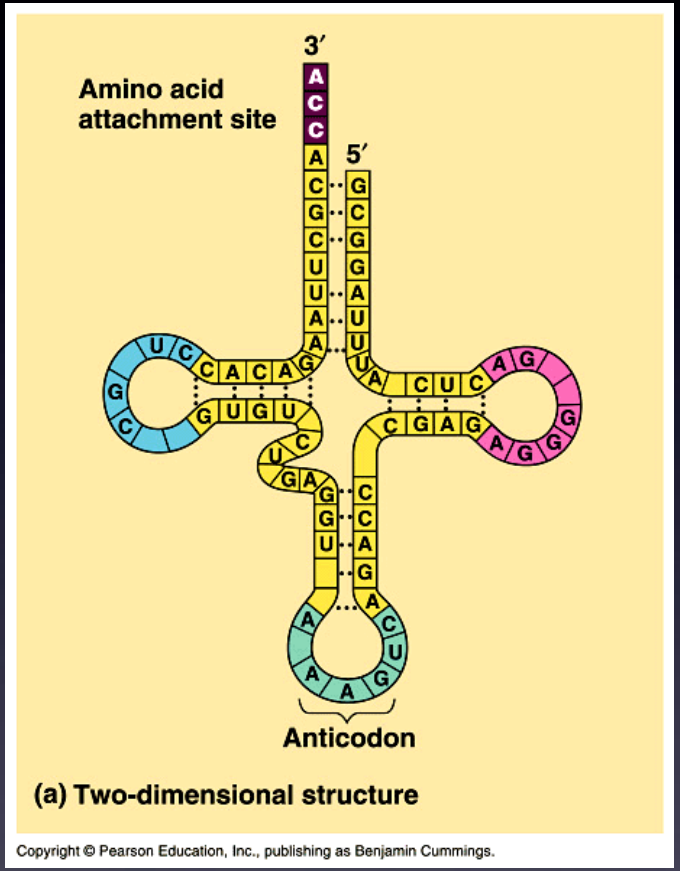
tRNA: structure and function

Interpreter between base sequence of mRNA and amino acid sequence of protein with 3 nucleotide sequence

45 different types

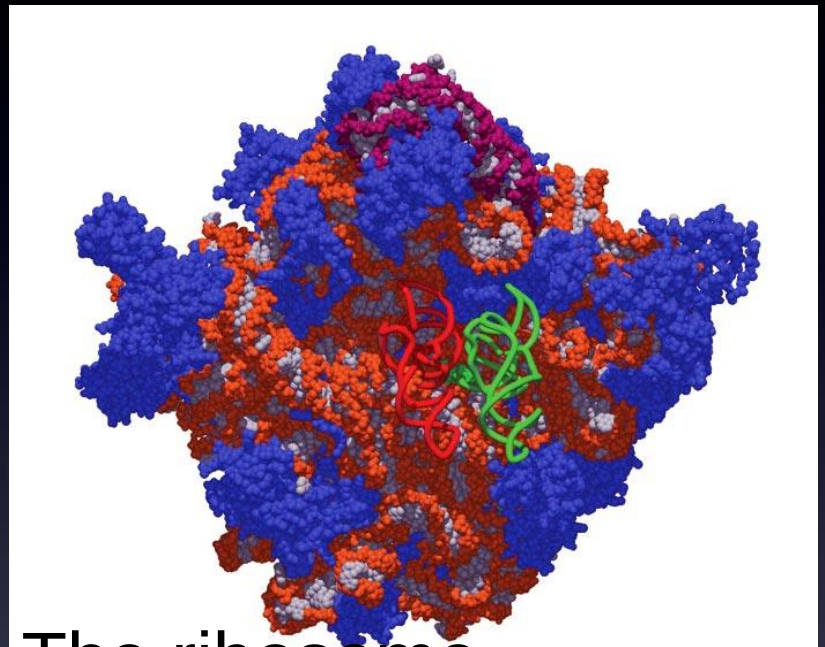
About 80 nucleotides long

The anticodon base pairs with codon of mRNA



Ribosomes: the site of translation

Coordinates pairing of tRNA with mRNA



The ribosome

Two subunits

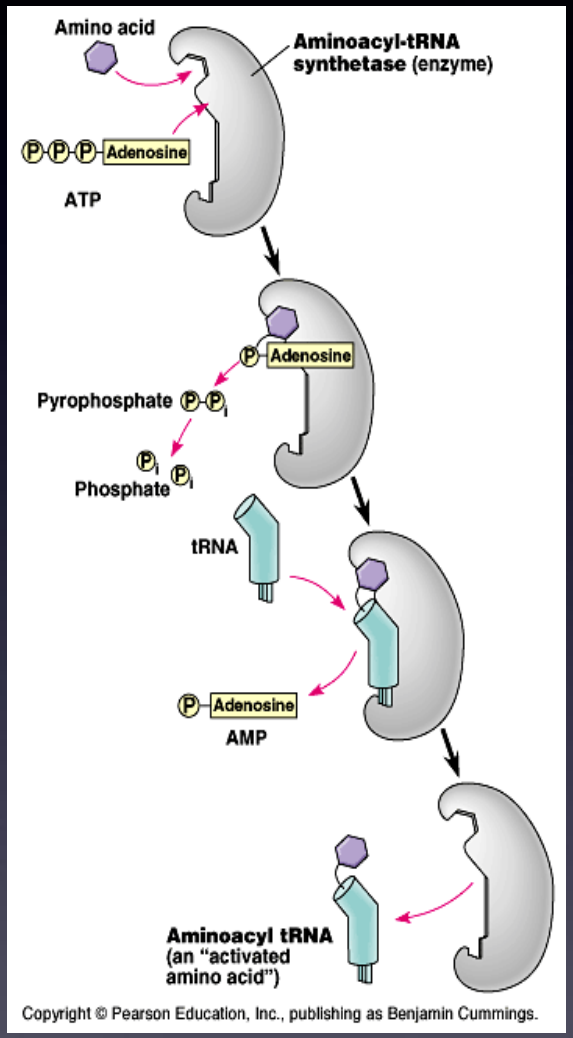
Constructed in the nucleus

Three binding sites: P site, A site and E site

tRNA – amino acid go to the ribosome

Activation and attachment

20 types of mRNA + amino acid complexes



Two steps:

Activation of amino acid with AMP

attachment of the amino acid to tRNA

Steps in the translation of protein

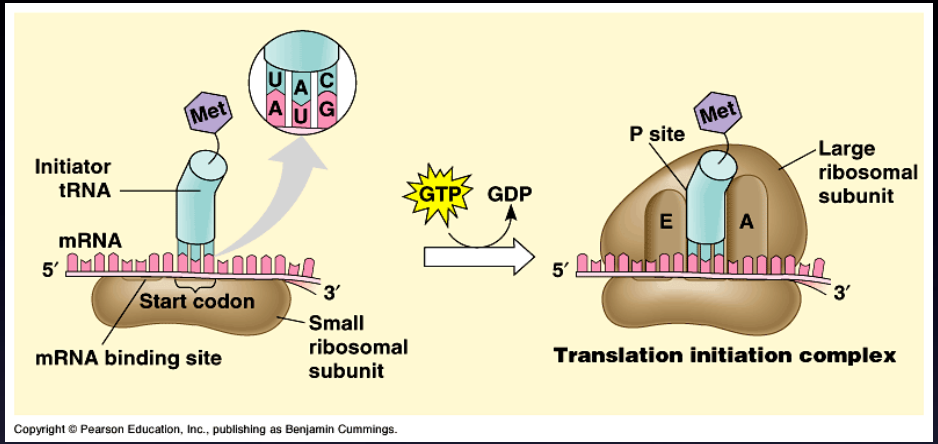
Initiation:
brings the ribosome together with the mRNA, and tRNA to prepare for translation

Elongation:
three-step cycle that adds amino acids one by one to the initial amino acid

Termination:
release of the polypeptide chain from the complex.

Initiation of translation

The start of translation



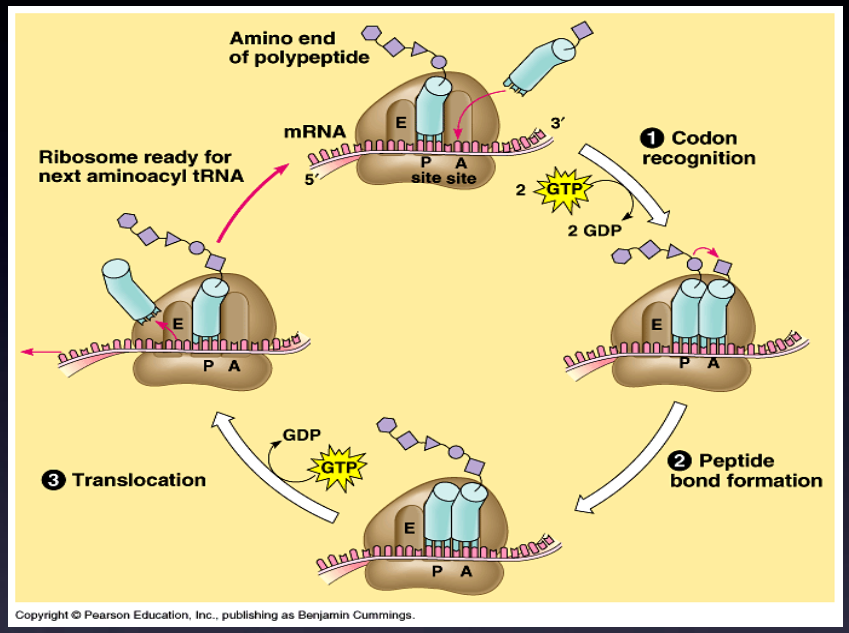
5' cap attaches to small ribosome subunit

tRNA carrying methionine attaches to mRNA codon

Large ribosomal subunit attaches

Elongation

The mRNA is synthesized



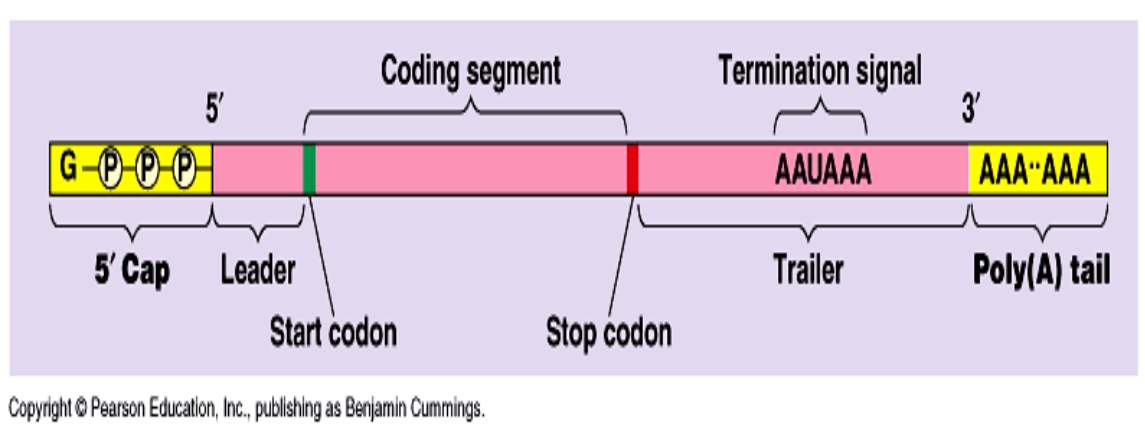
Peptide bond forms between adjacent amino acids

Translocation: amino acid in the A site is moved to the P site

mRNA moves through the ribosome 5'→3' direction

mRNA: structure to function

mRNA: how it plays its role in protein synthesis



mRNA: additional modification in post- transcriptional modification

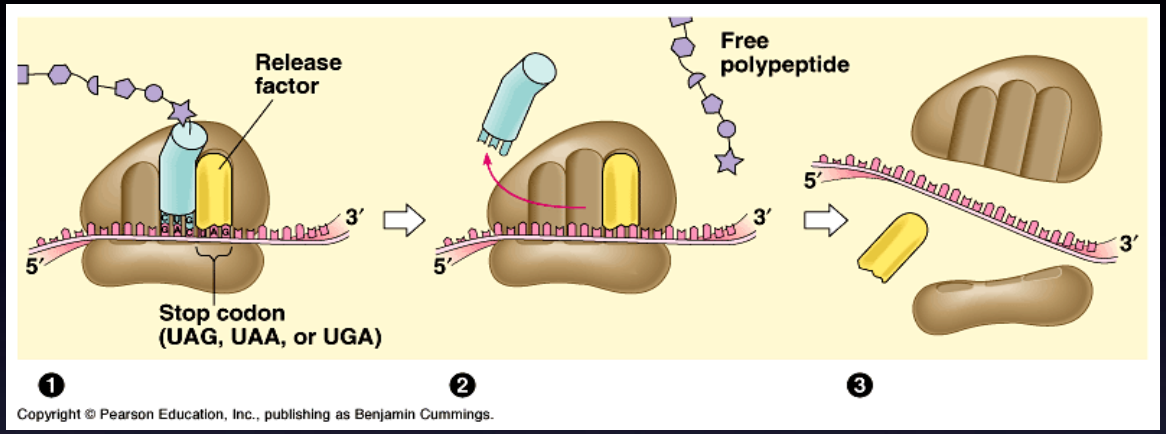
Capping: modified GTP added to 5' end of mRNA

Poly (A) tail: 20-200 adenine nucleotides added to 3' end of mRNA

Poly (A) tail will help terminate protein synthesis

Termination

The protein is synthesized



Termination sequence is encountered

Release factor binds to sequence

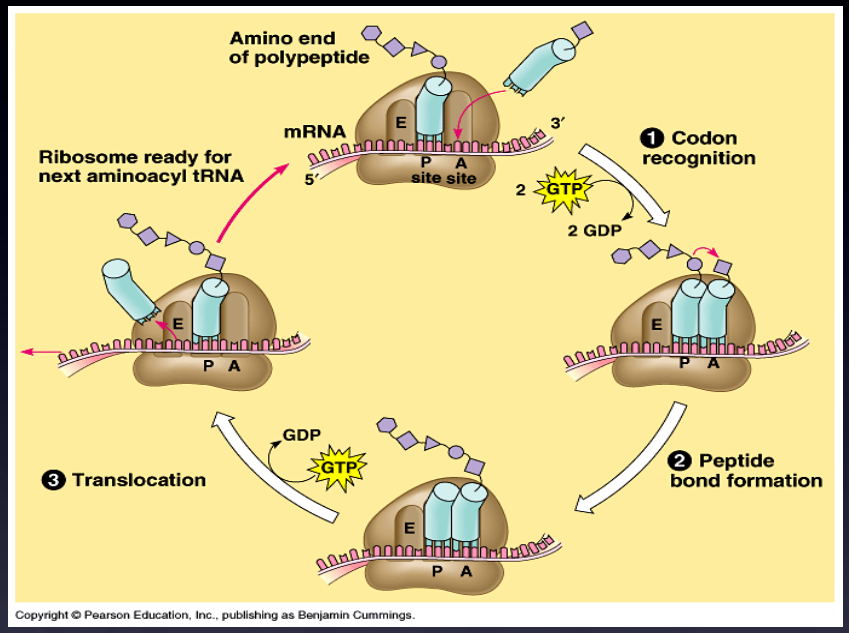
Release factor separates polypeptide from the tRNA

Finished translated protein leaves ribosome

May go on for post-translational modification

Elongation

The mRNA is synthesized



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Transcription of nRNA

One look at the control of
Gene expression by promoters
RNA polymerase and mRNA
synthesis