# Pay Attention: ADHD Through the Lifespan

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## Week 5: Neurochemistry of ADHD

# Homework Review

# Neurotransmitter systems

Derived from Monoamines

- Serotonin (5-HT)
- Norepinephrine (NE)
- Dopamine (DA)
- Acetylcholine (Ach)
- Histamine

Derived from Amino Acids

- Glutamate
- γ amino butyric acid (GABA)
- Aspartate
- Glycine

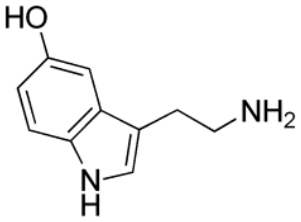
# Human Brain

- Contains over 100 billion neurons,
  - Manifold neurotransmitter systems & subsystems.
- The earth contains over 6 billion people.
- Glutamate system > 20 billion neurons.
- GABA system > 8 billion cortical neurons.
- 30,000 to 50,000 norepinephrine neurons.
- 250,000 serotonin neurons.
- 250,000 dopamine neurons.

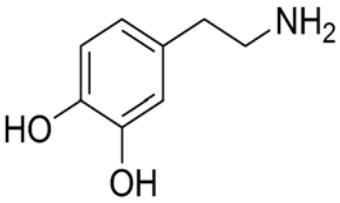
# Human Brain

- Billion-cell systems DO something
  - Glutamate.
  - GABA.
- Thousand-cell systems FINE TUNE the billion cell systems.
  - Serotonin.
  - Catecholamines (norepinephrine, dopamine)
  - Histamine

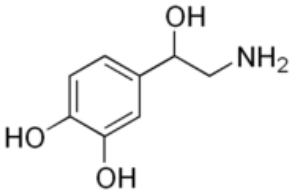
## Chemical Structure of Serotonin, Norepinephrine and Dopamine




Serotonin

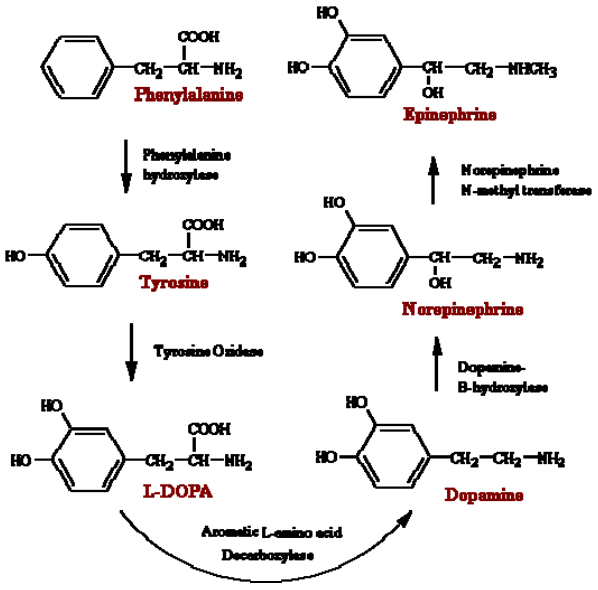



Norepinephrine

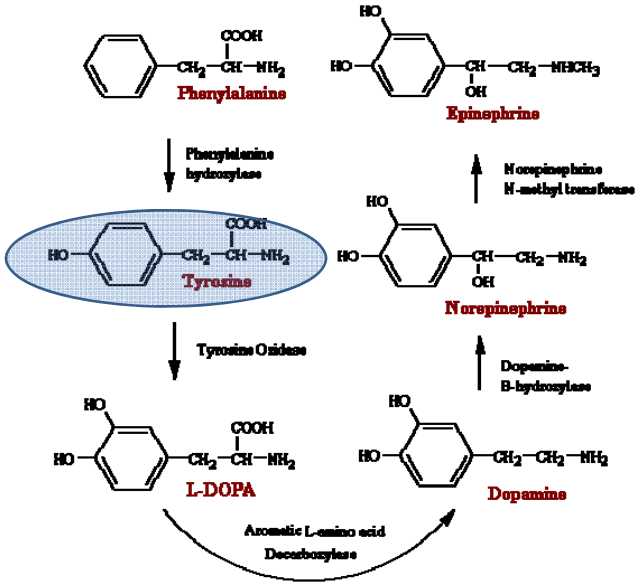



Dopamine

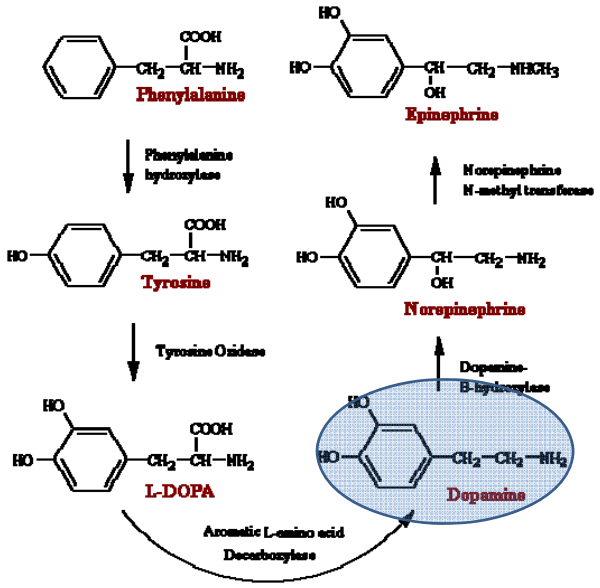
## Catecholamine Synthesis



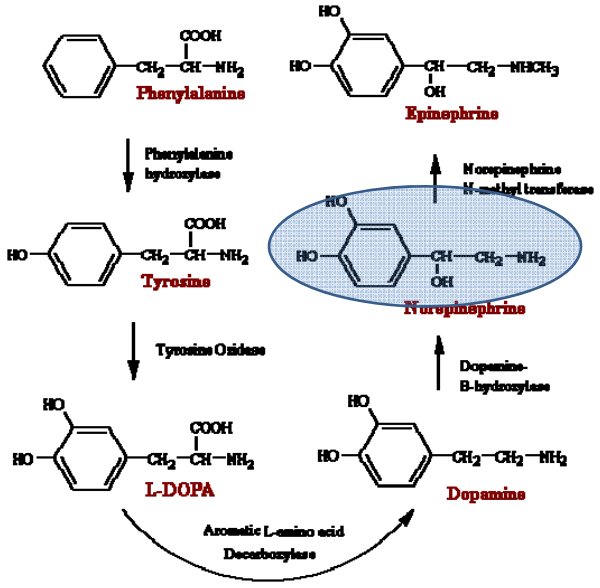
# Catecholamine Synthesis



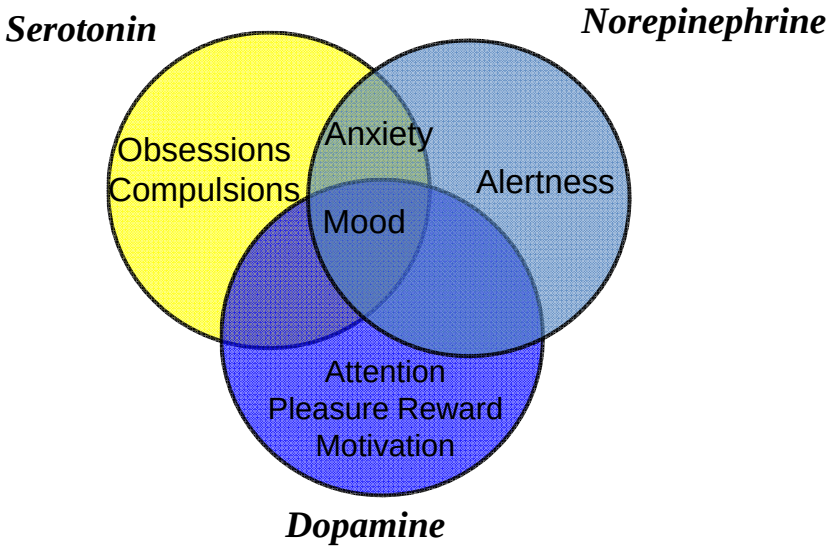

# Catecholamine Synthesis



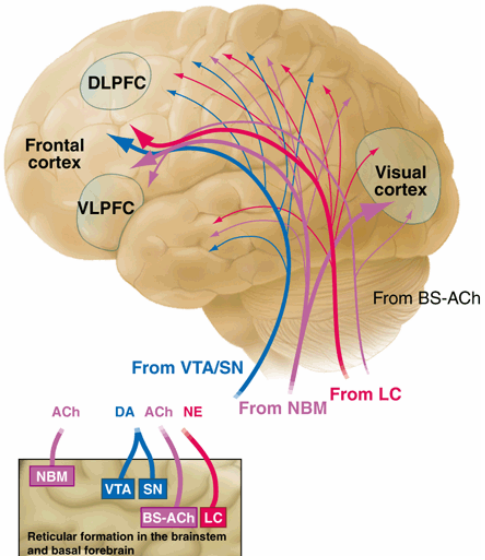
# Catecholamine Synthesis




# Functionality of Monoamines



# Catecholamines and Brain Activity

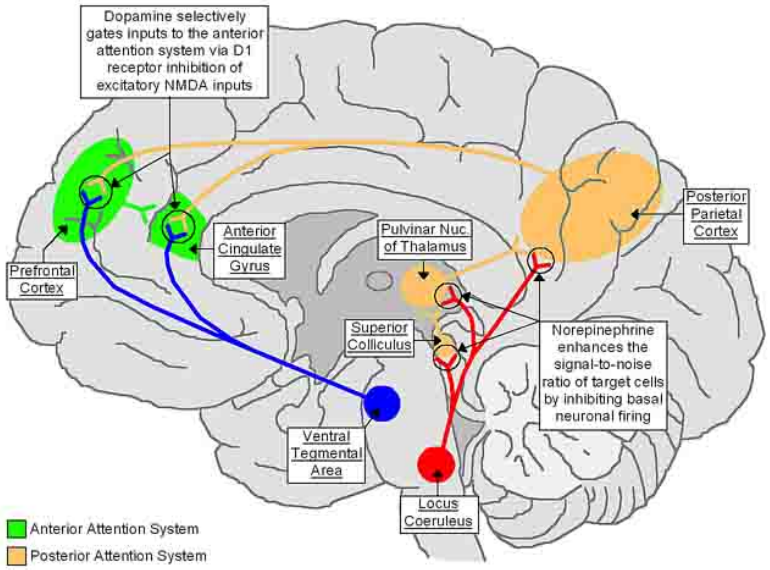



DLPFC, dorsolateral prefrontal cortex; VLPFC, left ventrolateral prefrontal cortex; BS-ACh, pedunculopontine/laterodorsal tegmental nuclei; VTA/SN, ventral tegmental area-substantia nigra; NBM, nucleus basalis magnocellularis; LC, locus coeruleus; DA, dopamine; A acetylcholine; NE, norepinephrine ; NBM, nucleus basalis magnocellularis; VTA, ventral tegmental area; SN, substantia nigra.

# Neurochemical Deficits in ADHD

- Dopamine dysregulation
- Norepinephrine dysregulation
- Evidence from
  - Drug responding:
    - Stimulants increase dopamine outside nerves
    - Methylphenidate works by slowing re-uptake
    - Amphetamines work by increasing production/release
    - Atomoxetine decreases norepinephrine reuptake
  - Molecular genetics: genes to date are dopamine and norepinephrine regulators
  - Distribution of neurotransmitters in identified brain regions associated with ADHD

# Dual Systems of Attention




# Mid-Lecture Questions

## Dopamine (DA) is a key neurotransmitter in the biology of a wide array of brain processes

- Control of movement
- Reward
- Motivation
- Attention
- Experience of Pain or Pleasure
- Emotions

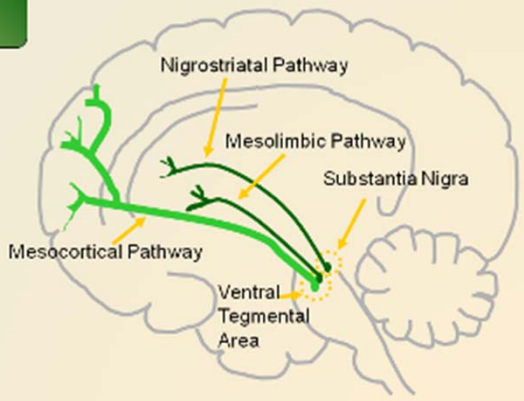
## DA modulates cortical and basal ganglia neural circuits

- Dorsolateral Prefrontal Cortex (DLPFC)
- Orbital Frontal Cortex
- Anterior Cingulate Cortex
- Insular Cortex
- Limbic System
- Nucleus Accumbens

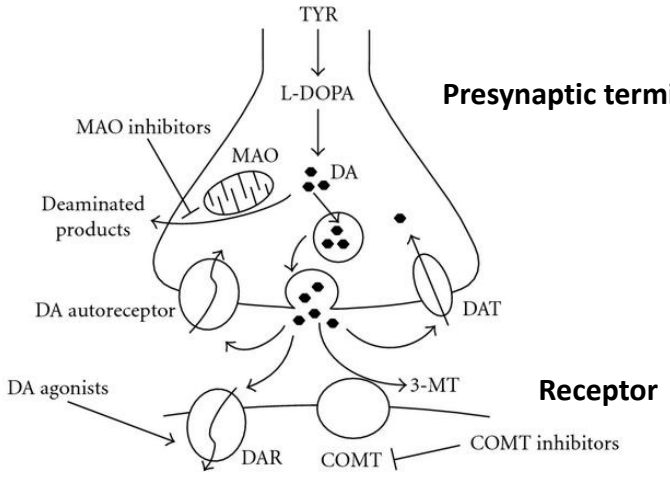
## Dopamine Neurotransmission Relative to ADHD

**Dopamine**

- Enhances signal
- Improves attention
  - Focus
  - On-task behavior
  - On-task cognition




## Dopamine Neurotransmission




**Presynaptic terminal**

**Receptor**

# Dopamine clearance from the synaptic cleft is regulated by:

- Dopamine Transporter Protein (DAT1)
  - Responsible for rapid uptake of DA from synaptic cleft
- Monoamine Oxidase A (MAO-A)
  - Catabolism of DA
- Catechol-O-Methyl-Transferase (COMT)
  - Catabolism of DA

*Note: genetic studies of ADHD have focused on candidate genes coding for elements of DA metabolism

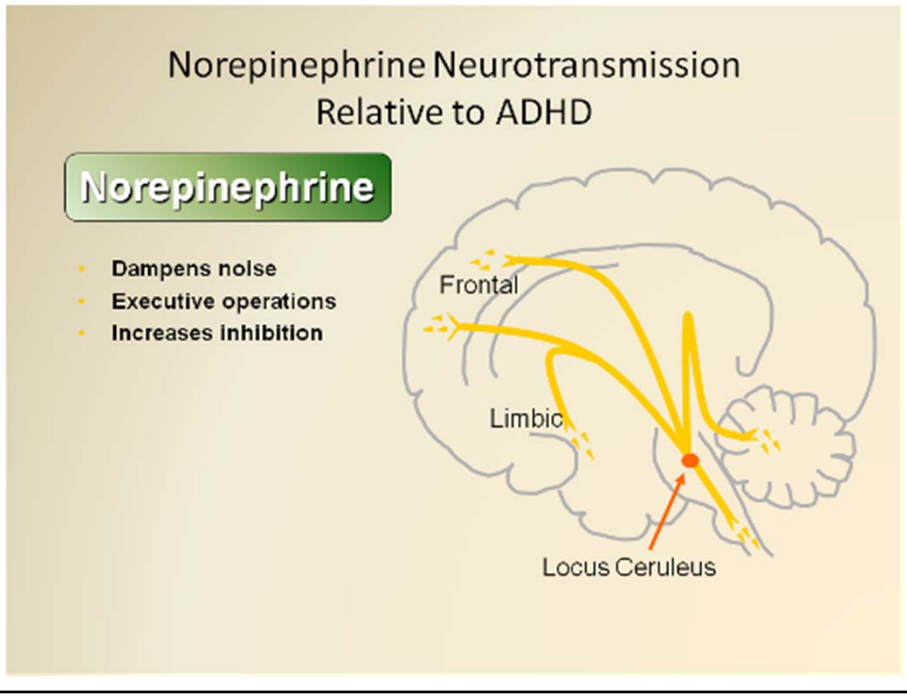
# Mechanism of Action MPH: Insights from PET Imaging Studies

(Volkow et al. *J Att Dis.* 2002;(suppl)1)

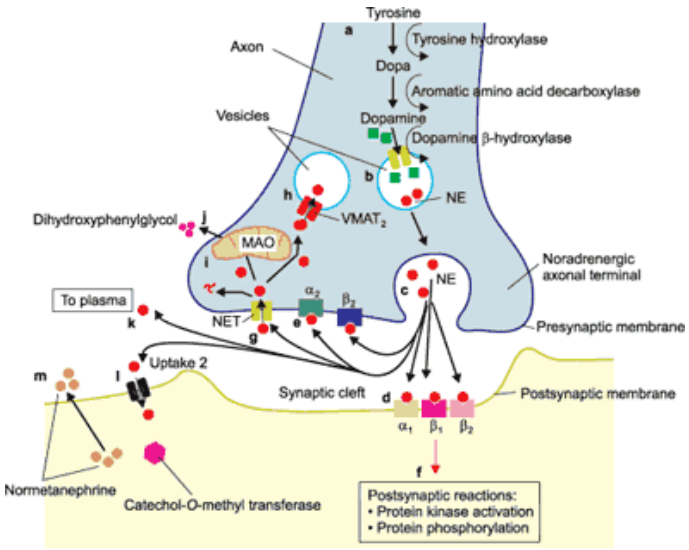
- Therapeutic doses of MPH significantly enhance extracellular dopamine (DA) in the basal ganglia
  - (a) MPH's therapeutic effects are in part due to amplification of DA signals
  - (b) Variability in responses is in part due to differences in DA tone between subjects
  - (c) MPH's effects are *context dependent*
- Because DA enhances task-specific neuronal signaling and decreases noise, MPH-induced increases in DA could improve attention and decrease distractibility
- Since DA modulates motivation, the increases in DA would also enhance the *saliency* of the task facilitating the "interest it elicits" and thus improving performance

# Norepinephrine

- Acts on Post-synaptic Alpha-2 Receptors
- Three Subtypes of Alpha-2 Receptors: A, B and C
- Most Alpha-2 Receptors post-synaptic to NE cells
  - e.g., dendritic spines of PFC Pyramidal Cells
- The A Subtype most important for NE action in PFC
- Alpha-2A receptor stimulation strengthens PFC network connections



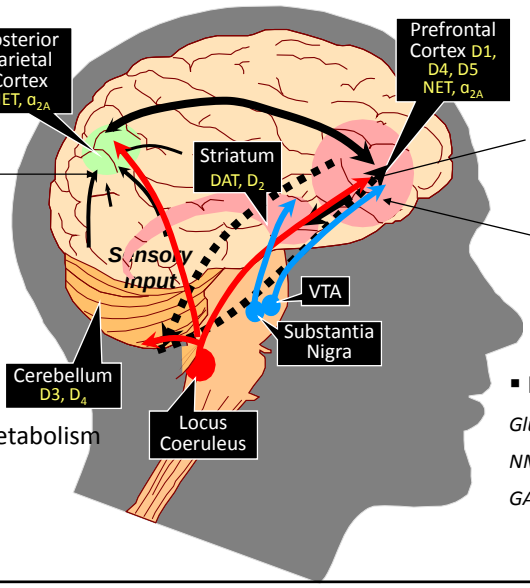
# Norepinephrine Neurotransmission




# Mid-Lecture Questions

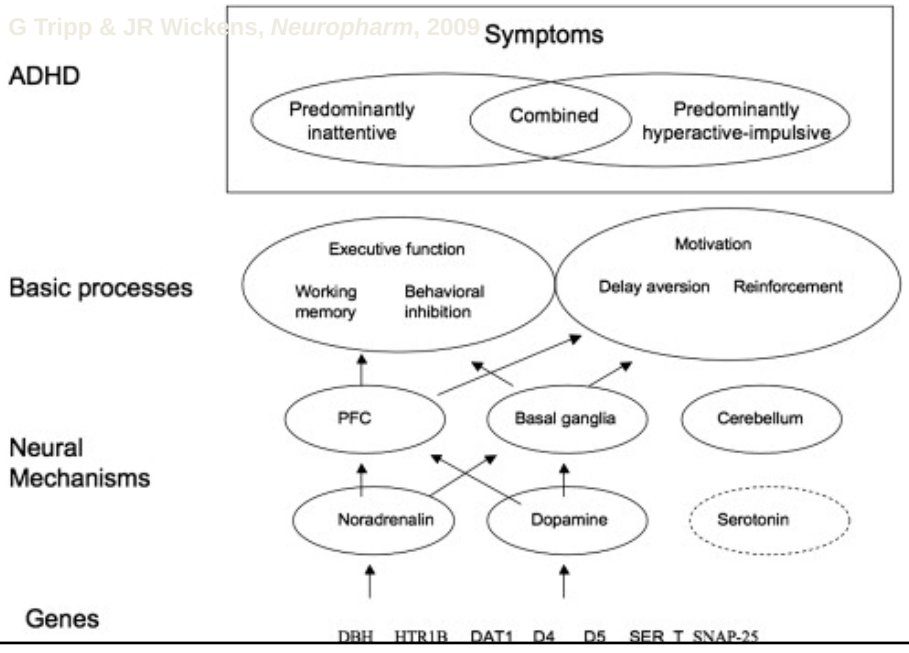
# Neurobiological Basis of ADHD

(with permission of Jeffrey Newcorn, MD)

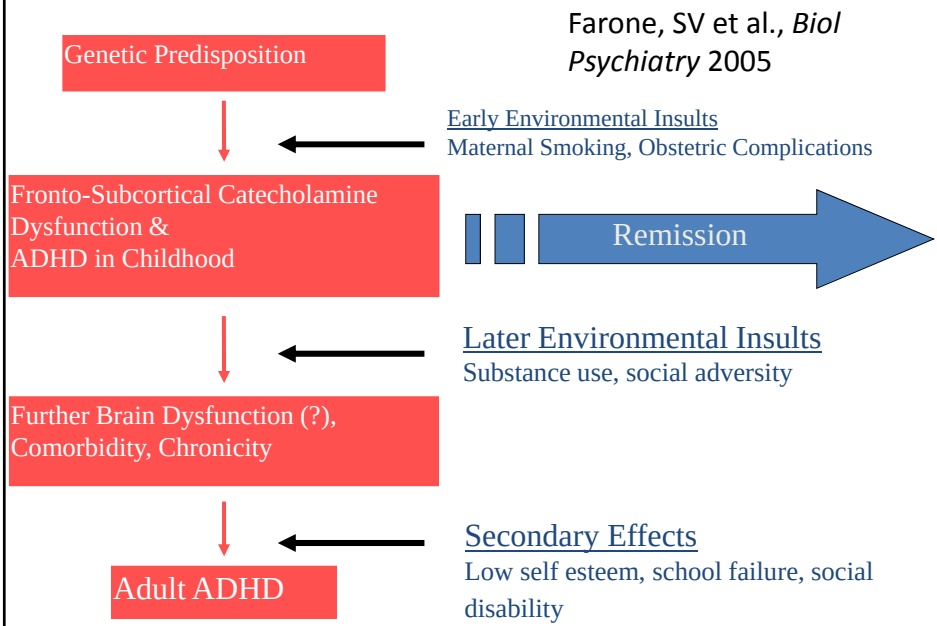



- Modulators
  - *Nicotinic/ Cholinergic*
  - *5-HT$_{1A, 1B}$*
  - *$H_3$*
- Synthesis/ metabolism
  - *DBH*
  - *COMT*
  - *MAO (A)*
- Interface with:
  - *Glutamate*
  - *NMDA/ AMPA*
  - *GABA*

# Summary: Neurobiology of ADHD



## Developmental Pathophysiology of ADHD




## Quiz Questions