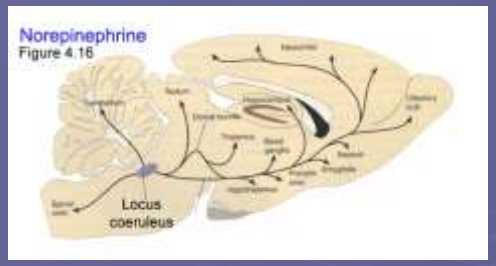
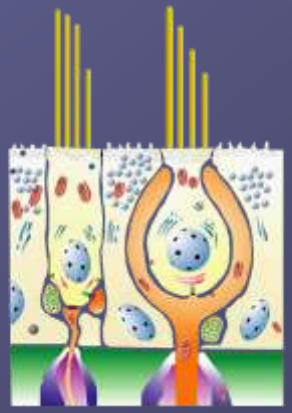
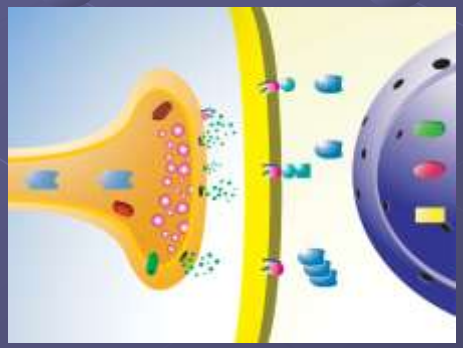




An Introduction to Basic Science Underlying Psychopharmacology

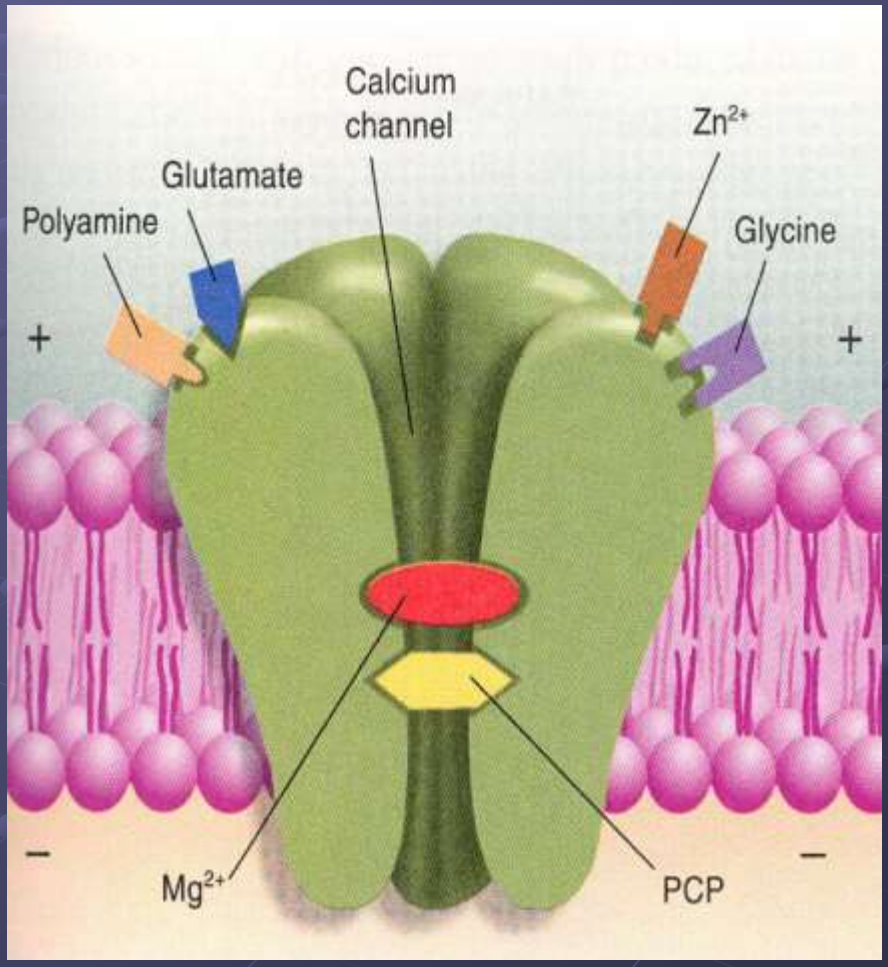
Mani Pavuluri, MD, PhD



- Neurotransmitters
- Neuropeptides
- Neurotransmitters, Receptors, and Localization
  - Dopamine
  - Norepinephrine
  - Serotonin
  - Acetylcholine
- Discussion

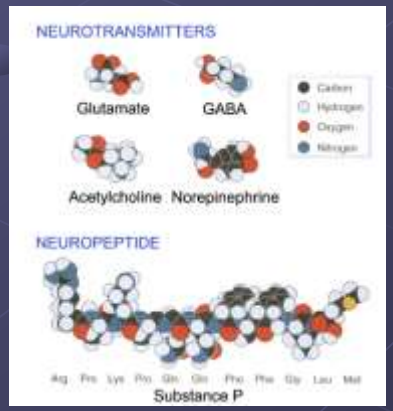
Neurotransmitters

- Definition
  - Endogenously synthesized chemical used to relay, amplify, or modulate signals between presynaptic and postsynaptic neurons.



Classification

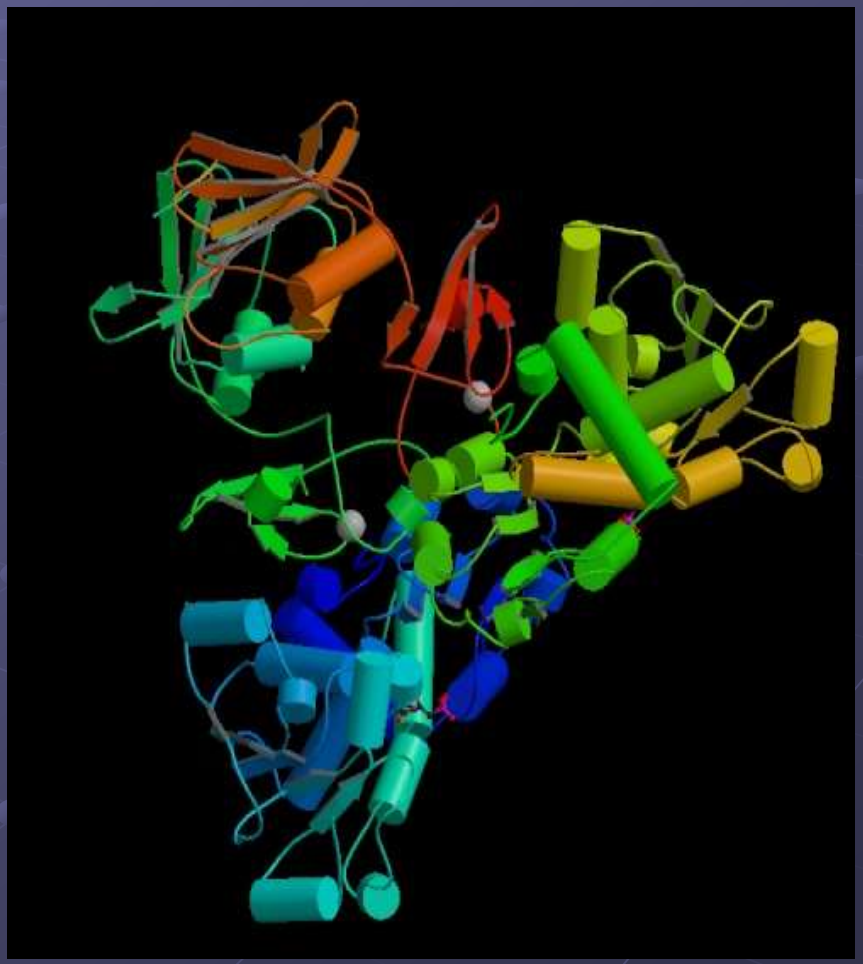
- Broadly classified into:
  - True neurotransmitters
    - About 10 types
  - Neuroactive peptides
    - About 50 types
    - Packaged in soma
- May be either:
  - Inotropic
    - Ion-channel gated
    - Fast effects
  - Metabotropic
    - G-protein gated
    - Slow
    - Long-lasting effects



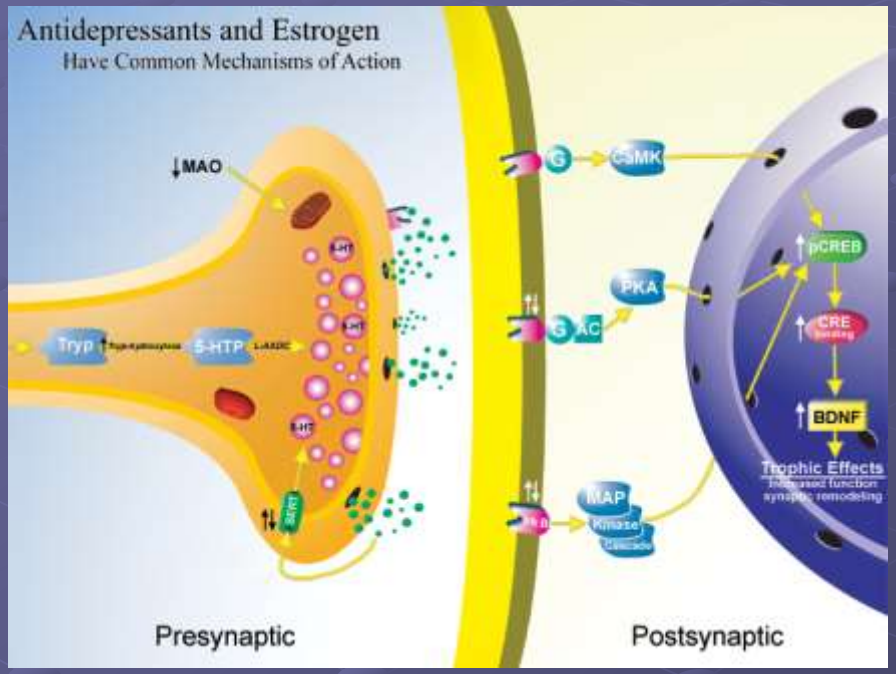
Neurotransmitters

Neurotransmitters Derived From Amino Acids:

- Aspartate
- Glutamate
- GABA
- Glycine



Neurotransmitters Derived From Monoamines



- Tyrosine → Dopamine → Norepinephrine → Epinephrine
- Tryptophan → Serotonin
- Histidine → Histamine

Neuropeptides

Major Neuropeptides

Pituitary Peptides

- Corticotropin
- Growth hormone
- Lipotropin
- α-Melanocyte stimulating hormone
- Oxytocin
- Prolactin
- Vasopressin

Gut Peptides

- Cholecystokinin
- Gastrin
- Motilin
- Pancreatic polypeptide
- Secretin
- Substance P
- Vasoactive intestinal polypeptide

Miscellaneous Peptides

- Angiotensin
- Bombesin
- Bradykinin
- Carnosine
- Glucagon
- Insulin
- Neuropeptide Y
- Neurotensin
- Proctolin

Hypothalamic Peptides

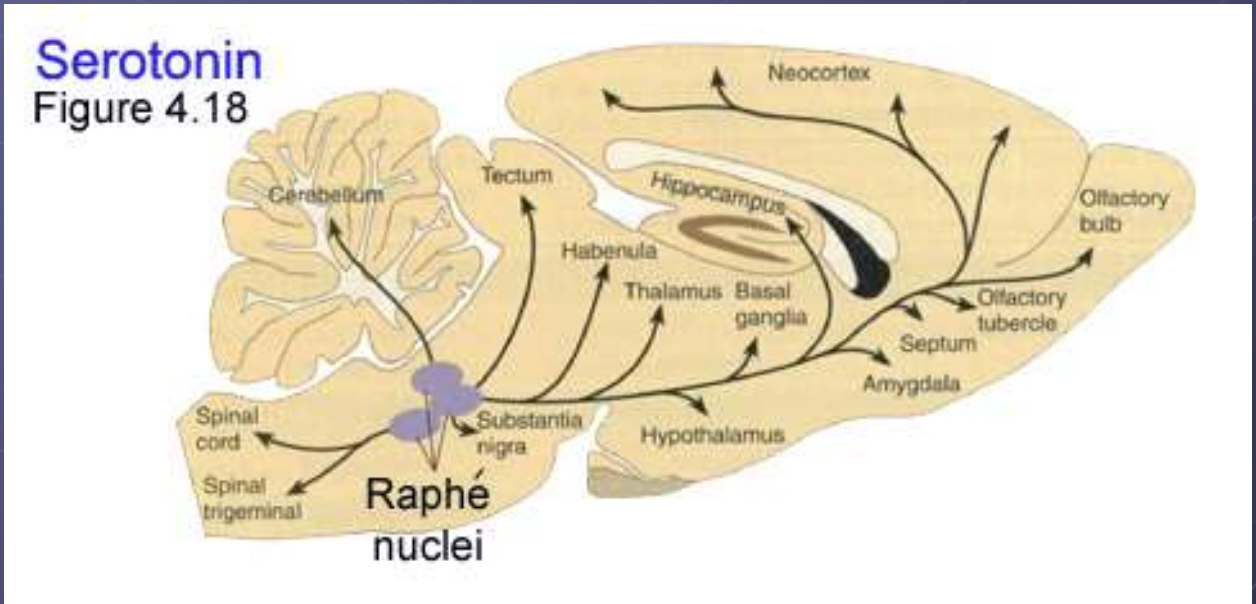
- Luteinizing hormone-releasing hormone
- Somatostatin
- Thyrotropin-releasing hormone

Endorphins

- Dynorphin
- β-Endorphin
- Met Enkephalin
- Leu Enkephalin

Localization

- Neurotransmitters may be found throughout the CNS, such as glutamate, glycine, and GABA, or in particular pathways.



Selected Neurotransmitters

Dopamine

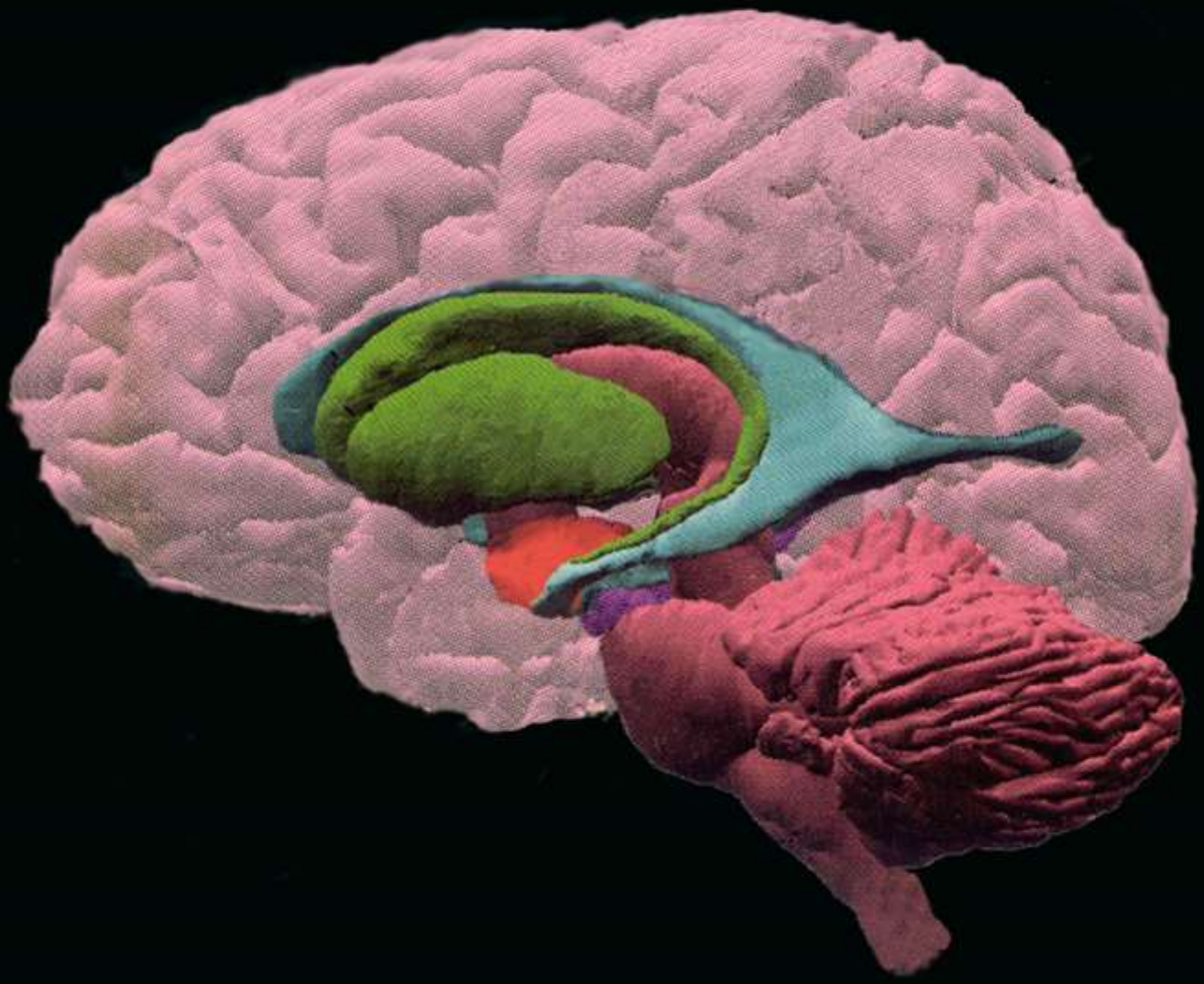
- Catecholamine derived from tyrosine
- Formed by decarboxylation of DOPA by aromatic L-amino-acid decarboxylase
- Cornerstone of multiple diverse pathways in the brain
  - Movement as part of the basal ganglia motor loop (Parkinson disease if deficient in the nigrostriatal pathway)
  - Flow of information in frontal lobe (decreased memory, attention, problem-solving, and cognition if deficient in mesocortical pathway)

Dopamine

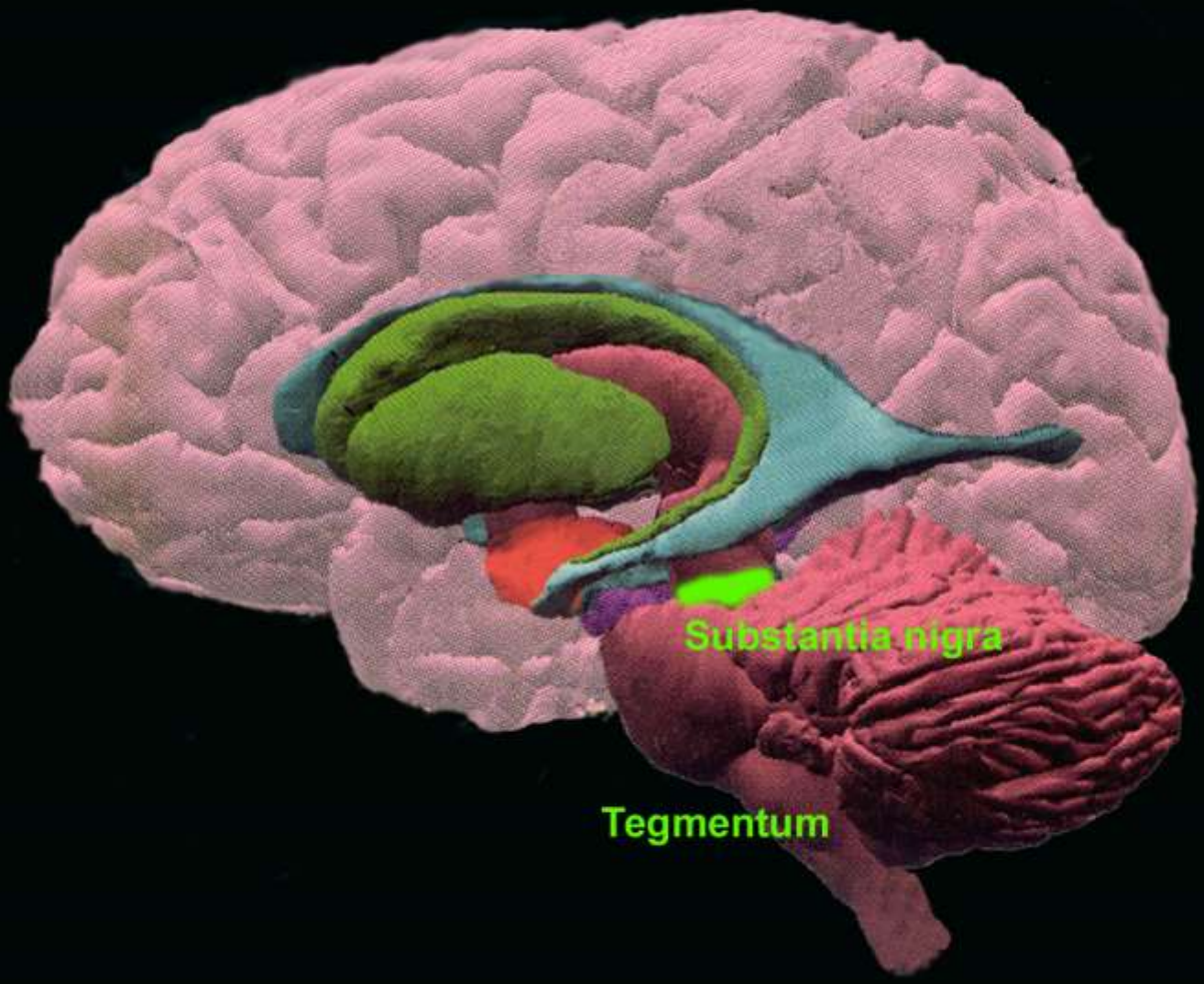
- Pathways (cont.)
  - Pleasure and reinforcement pathways in nucleus accumbens and striatum (MOA of cocaine).
  - Psychosis and schizophrenia may occur when disrupted in mesolimbic pathway, especially through D2-receptor-mediated effects
  - Tuberoinfundibular pathway with dopamine acting as prolactin-inhibiting factor
  - Schizophrenia: Overstimulation of D2 receptors in mesolimbic and mesocortical systems ("dopamine excess" theory). These two pathways play a role in motivation by attaching cognition of incentive significance to stimuli.

Dopamine

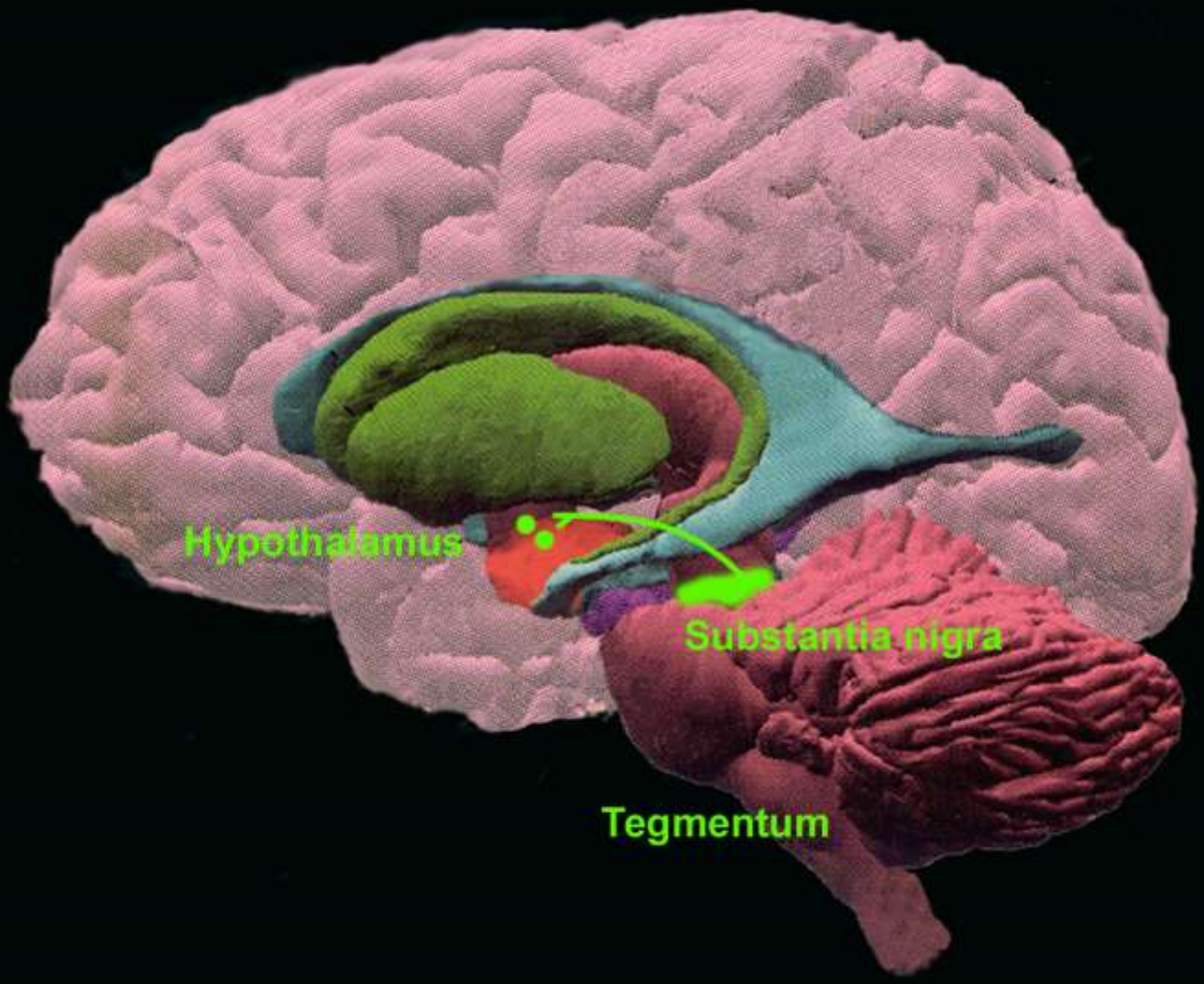
Dopamine



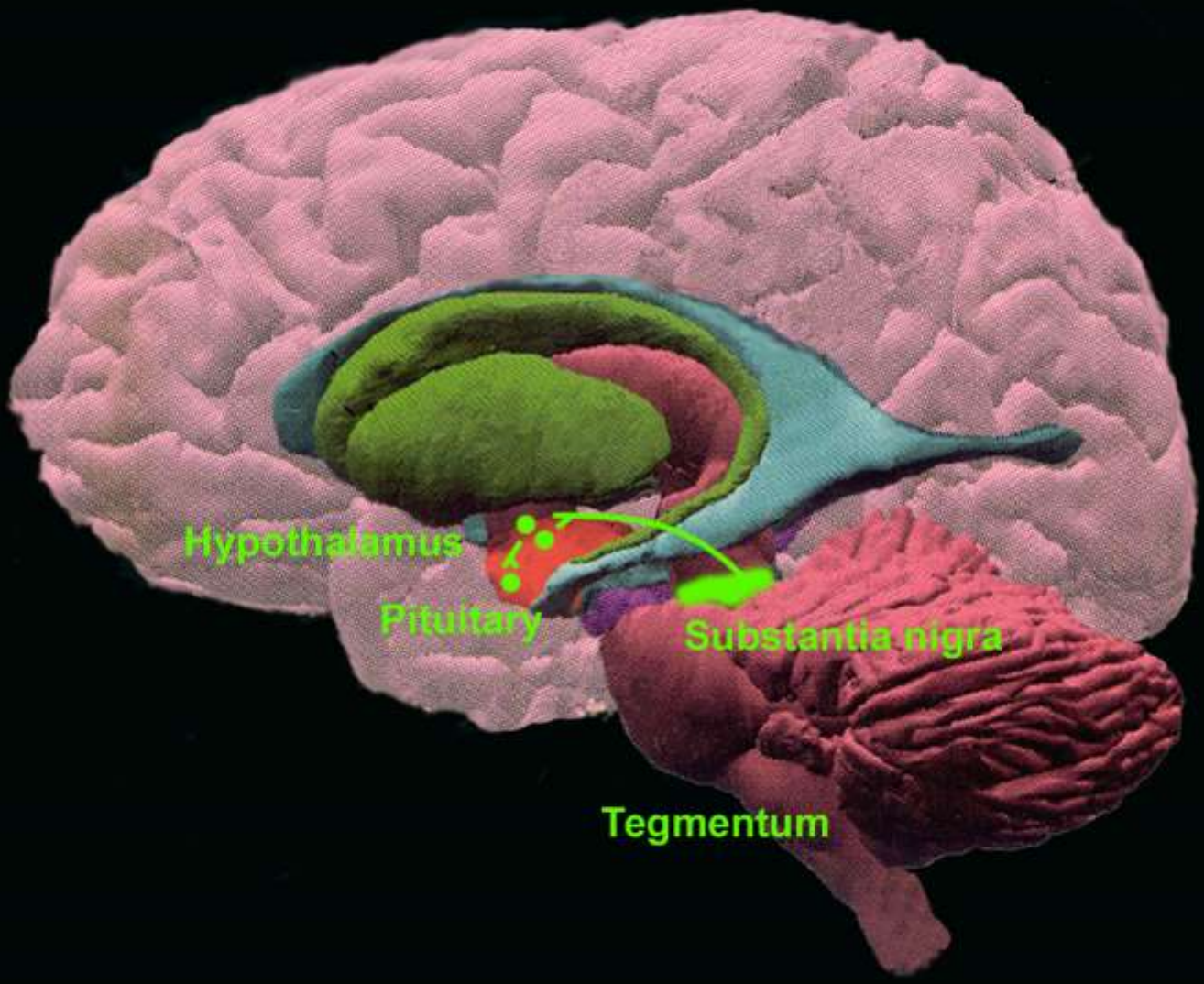
Dopamine



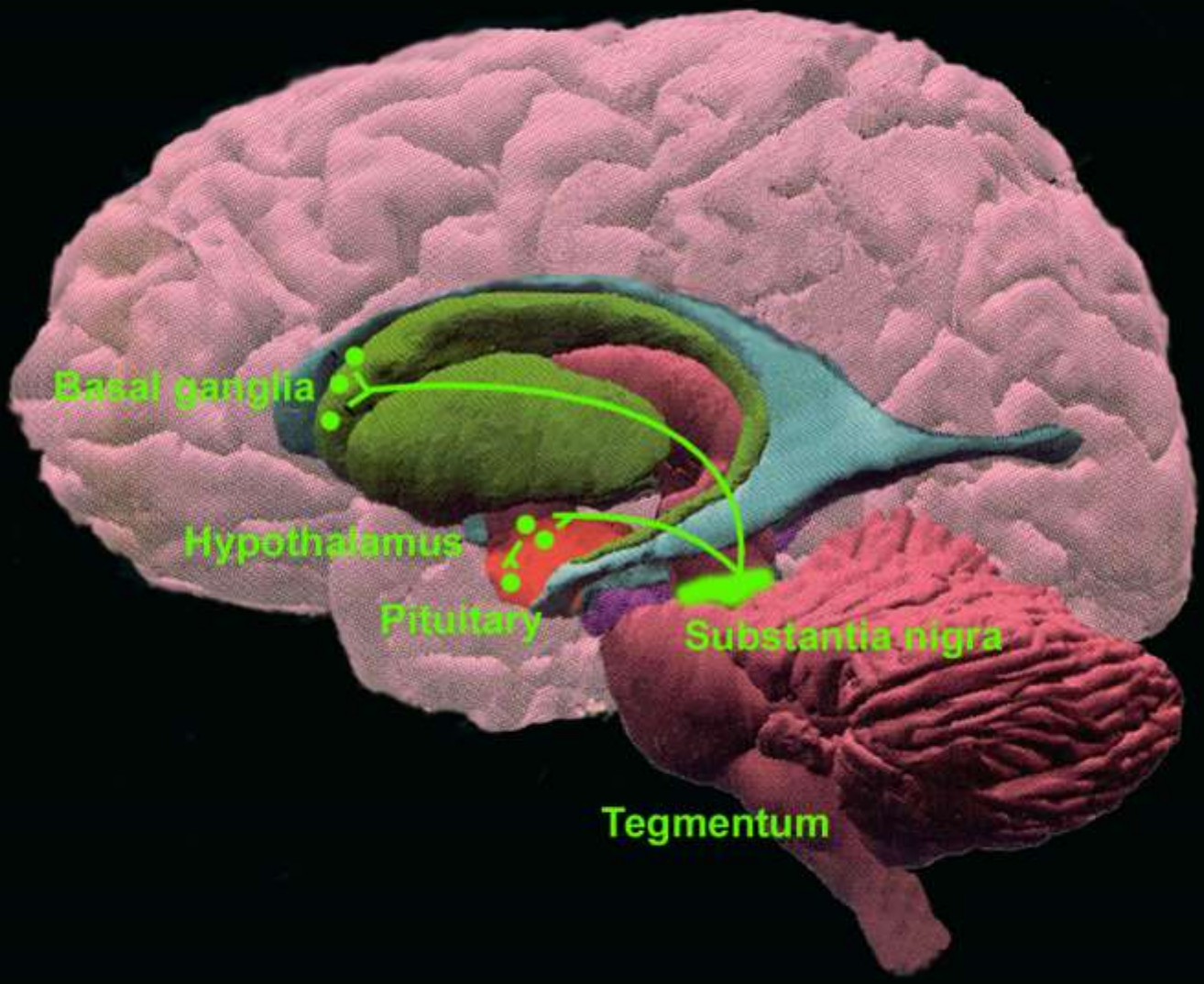
Dopamine



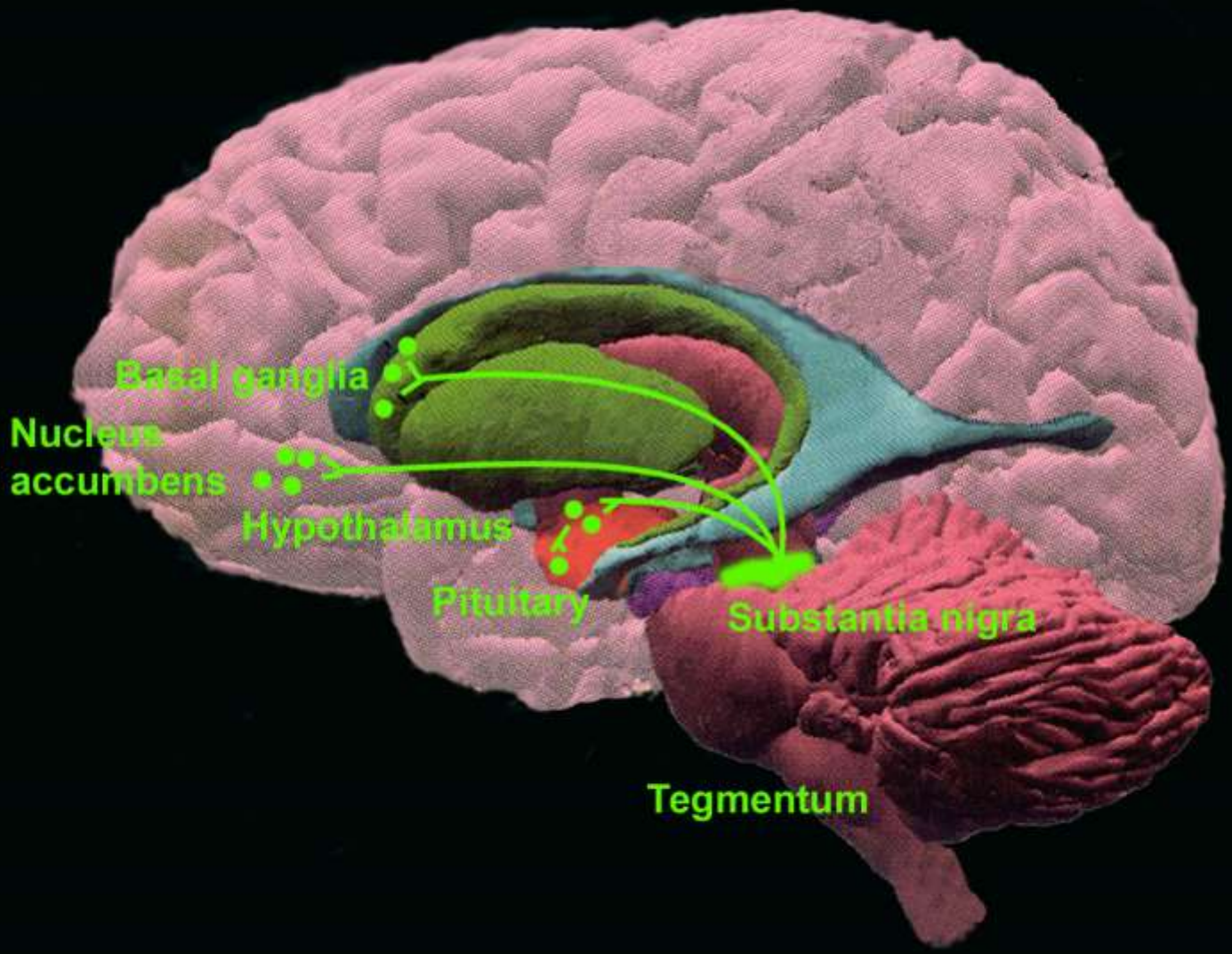
Dopamine



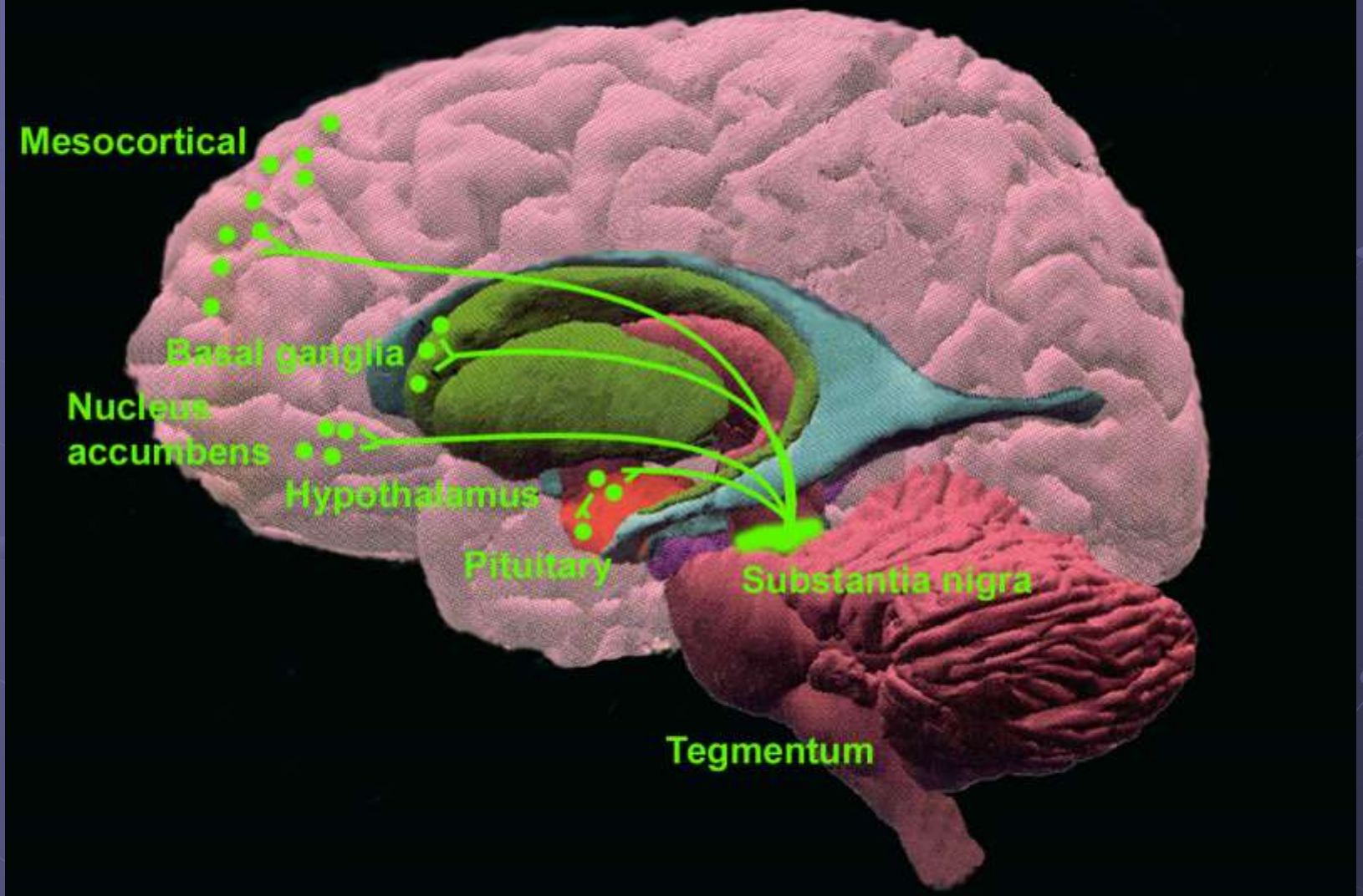
Dopamine


Basal ganglia
Hypothalamus
Pituitary
Substantia nigra
Tegmentum

Dopamine


Basal ganglia
Nucleus accumbens
Hypothalamus
Pituitary
Substantia nigra
Tegmentum

Dopamine

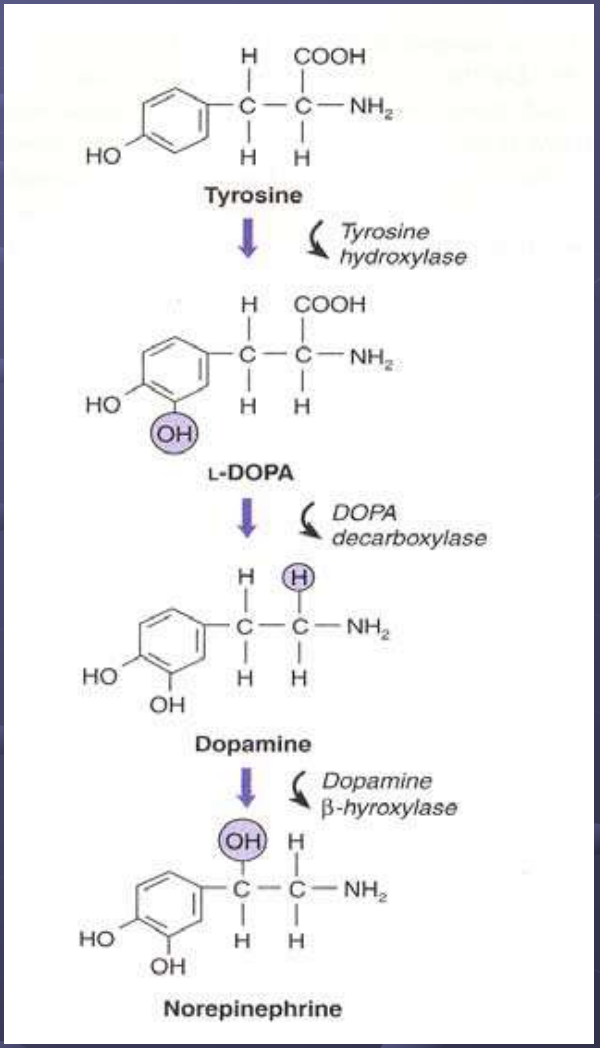

Mesocortical
Basal ganglia
Nucleus accumbens
Hypothalamus
Pituitary
Substantia nigra
Tegmentum

Dopamine Receptors

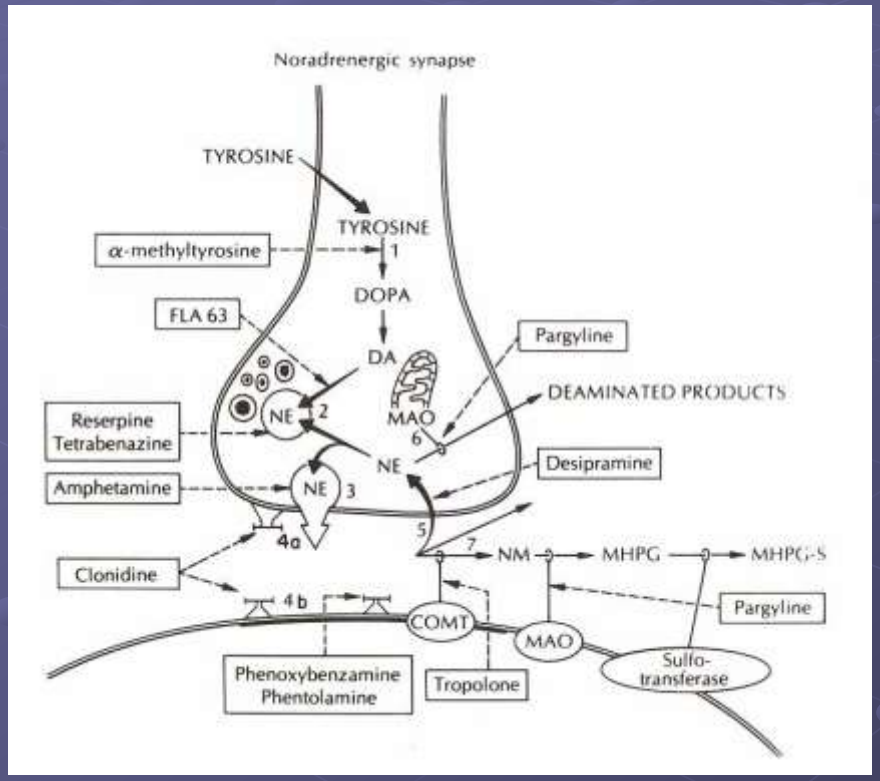
- Receptors
  - D1, D5 – Located in brain, smooth muscle – Stimulatory role, role in schizophrenia
  - D2, D3, D4 – Located in brain, cardiovascular system, presynaptic nerve terminals – Inhibitory role, role in schizophrenia

Norepinephrine

- Formed from B-oxidation of dopamine, and may be methylated to form epinephrine



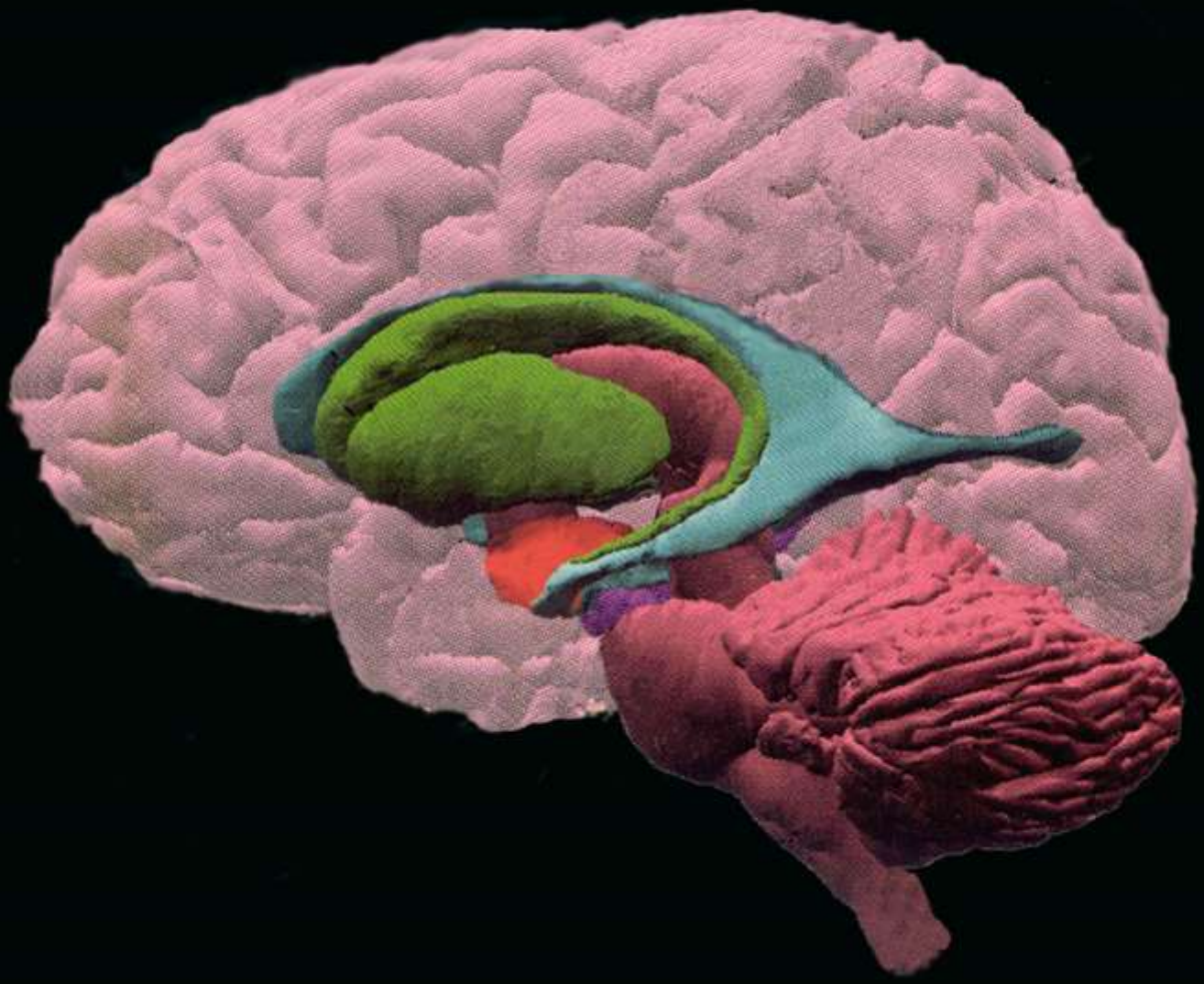
Norepinephrine



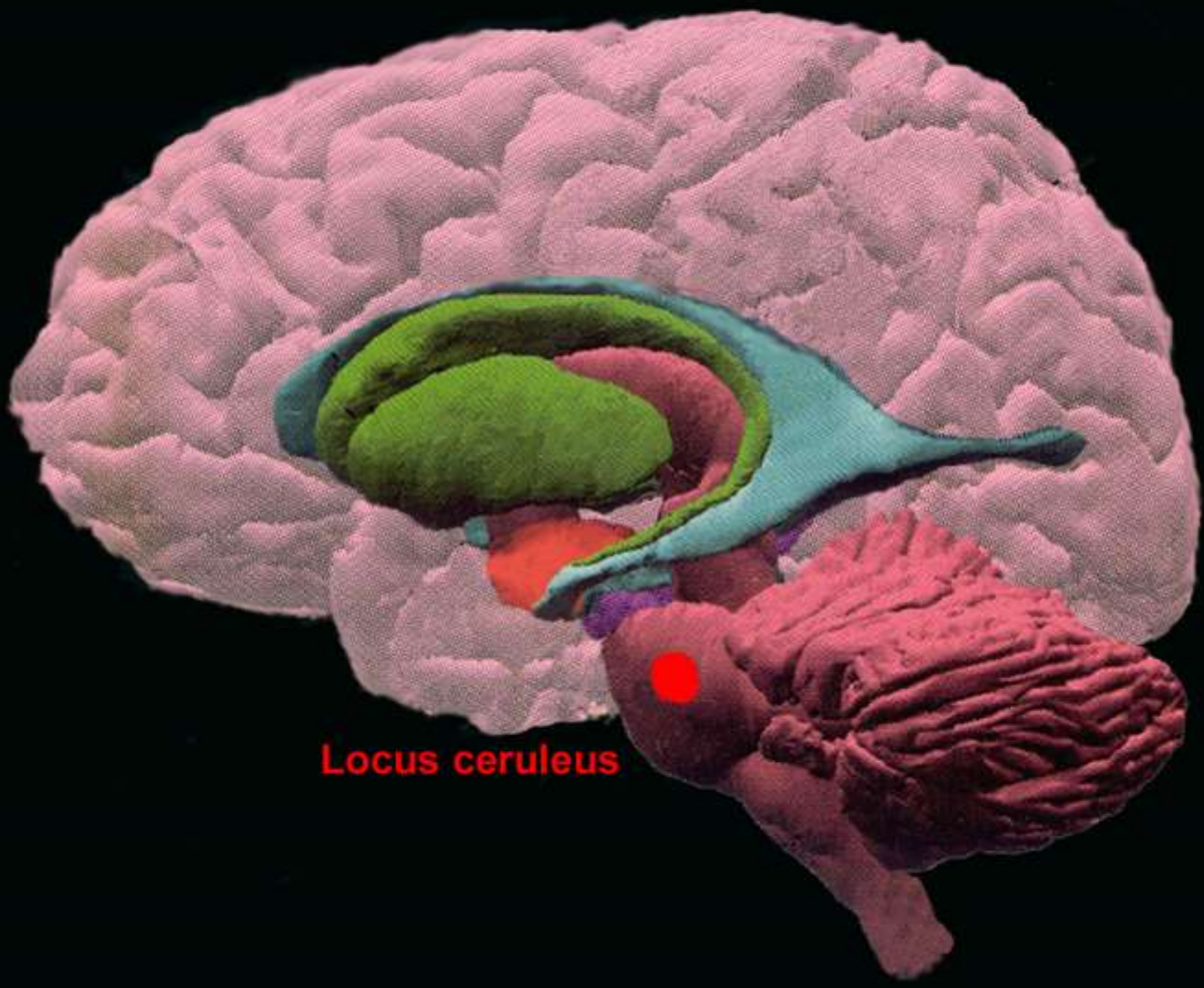
- Stress hormone that affects attention pathways and impulsivity
- Also plays a role in the fight or flight response and has a positive drive on the sympathetic nervous system

Norepinephrine

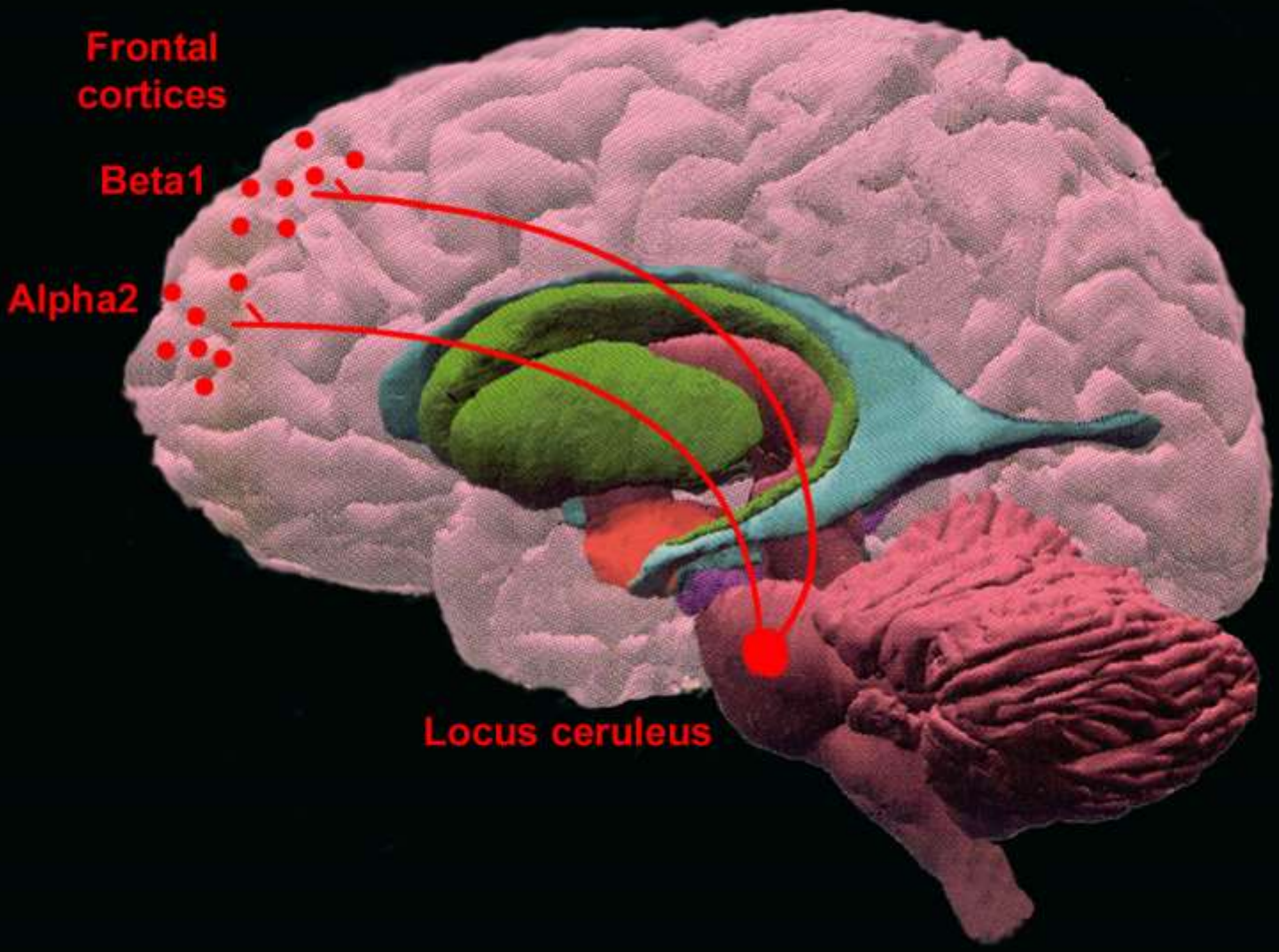
Norepinephrine



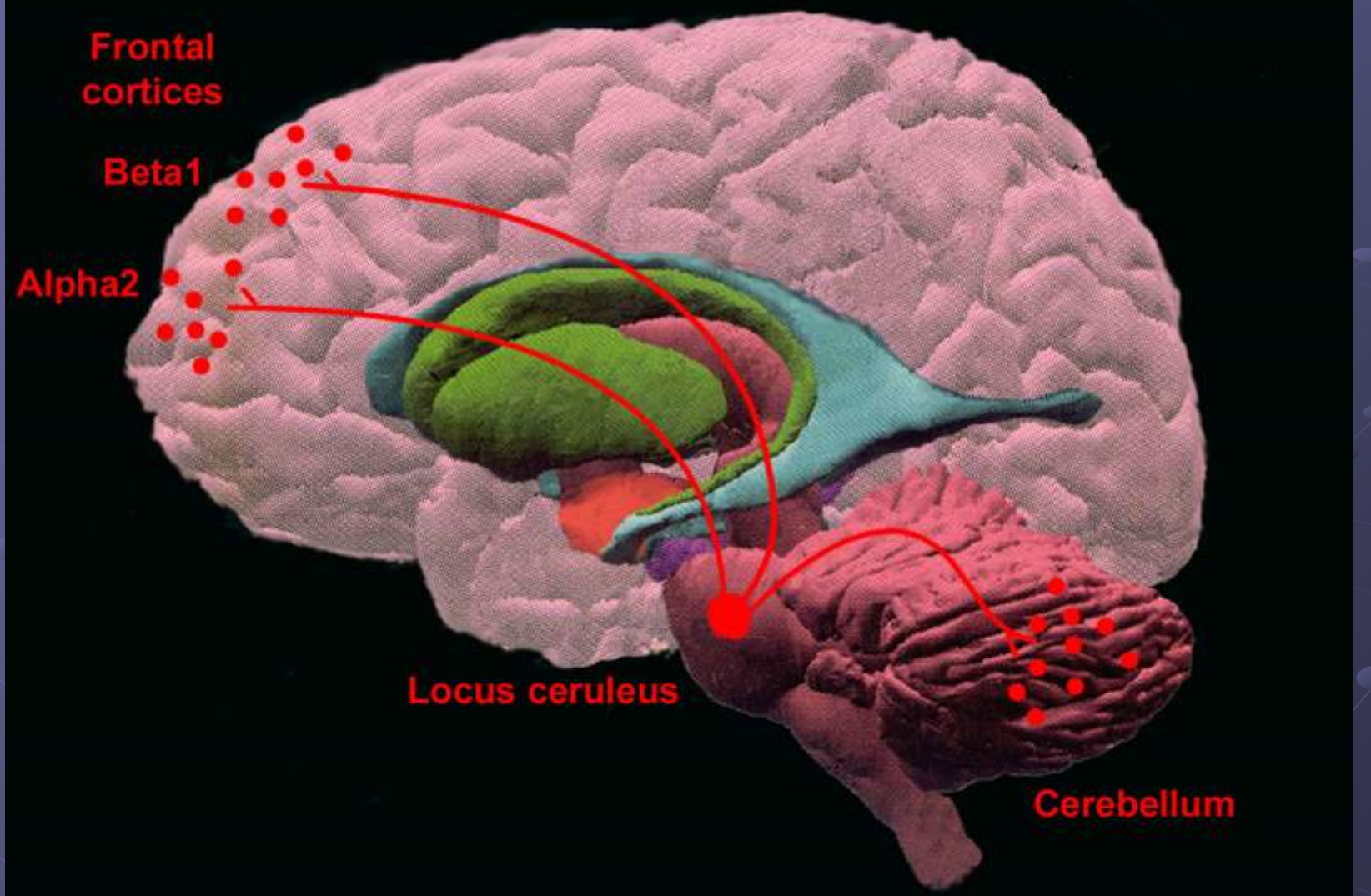
Norepinephrine



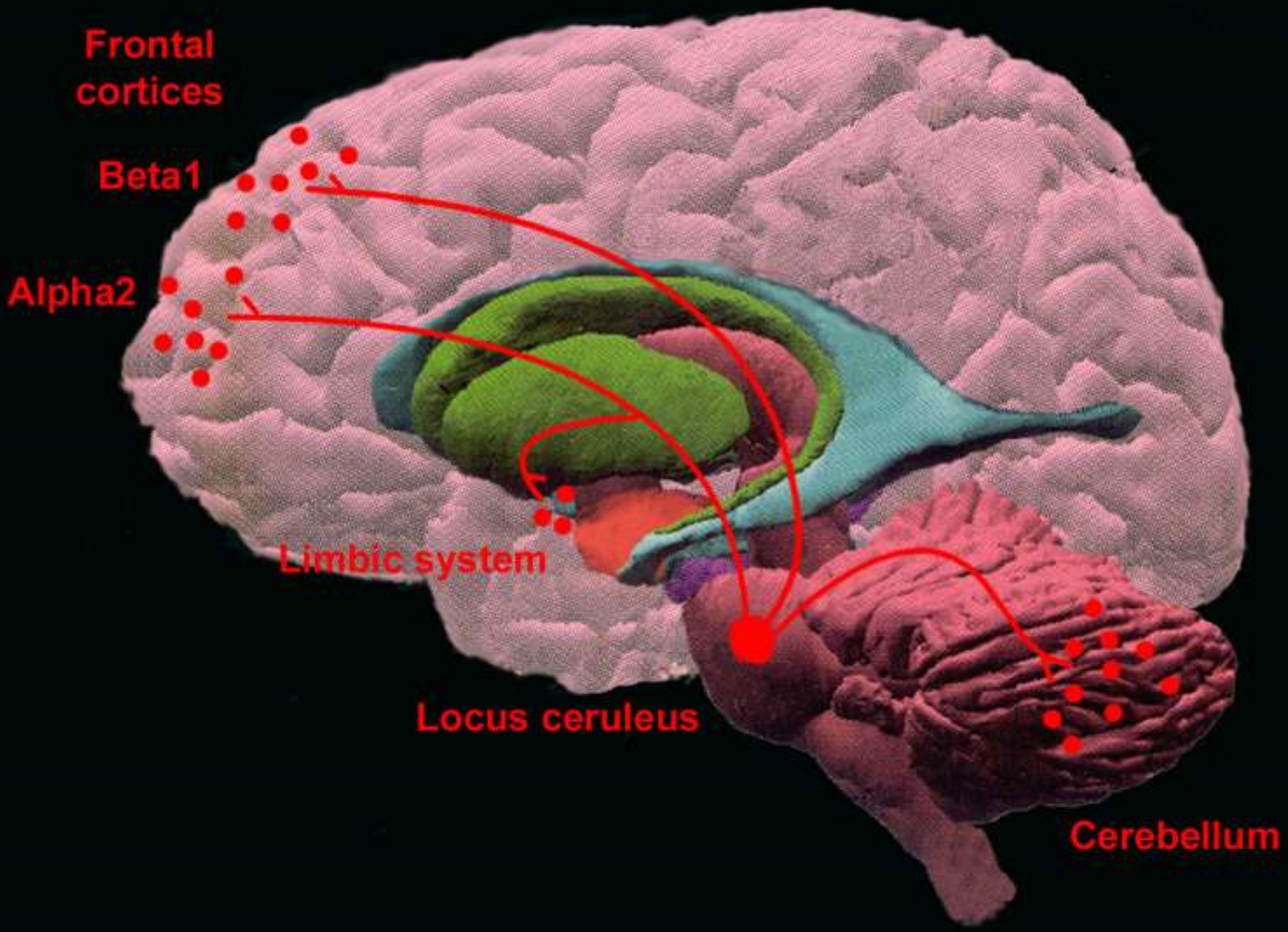
Norepinephrine



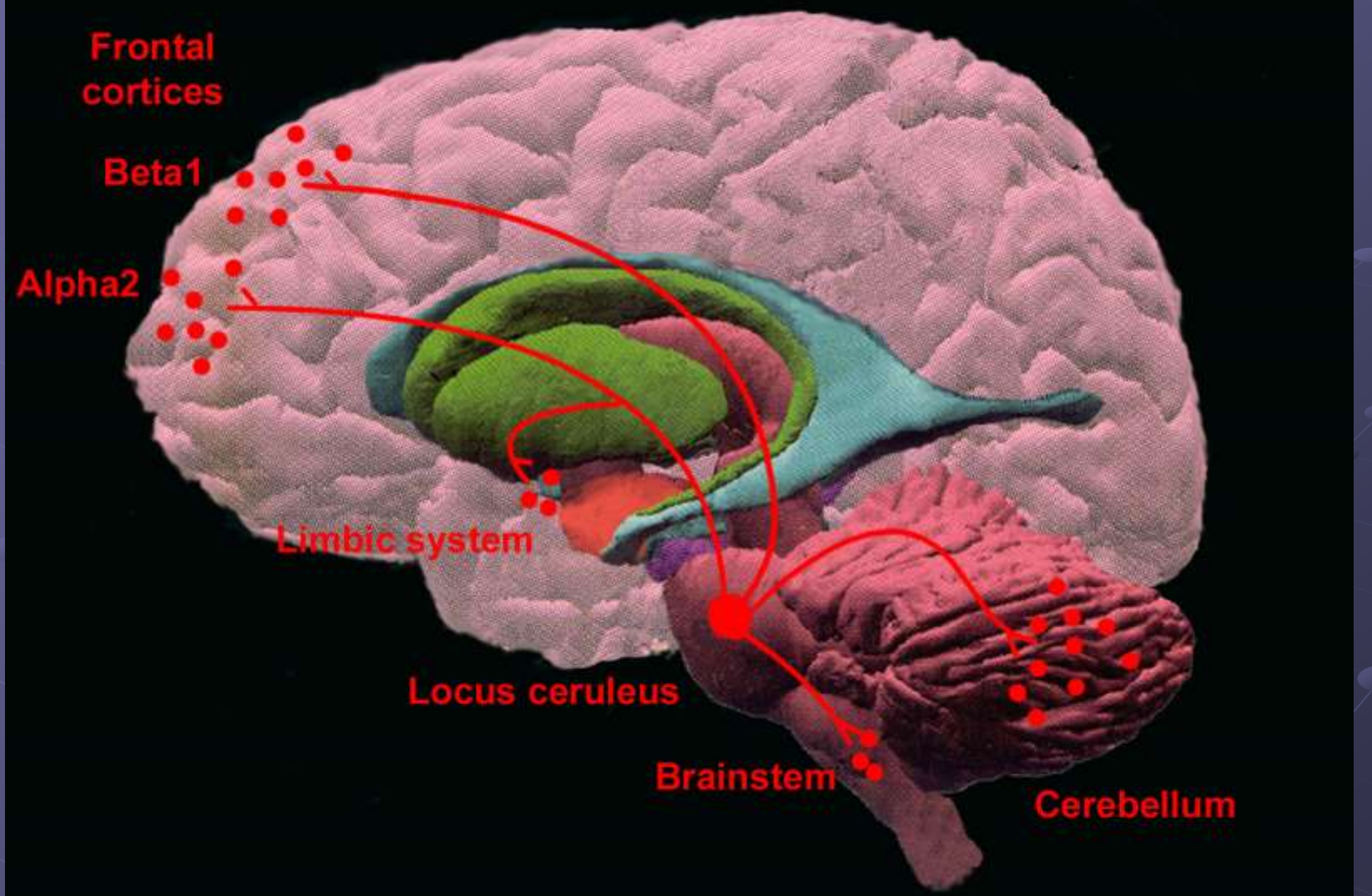
Norepinephrine



Norepinephrine

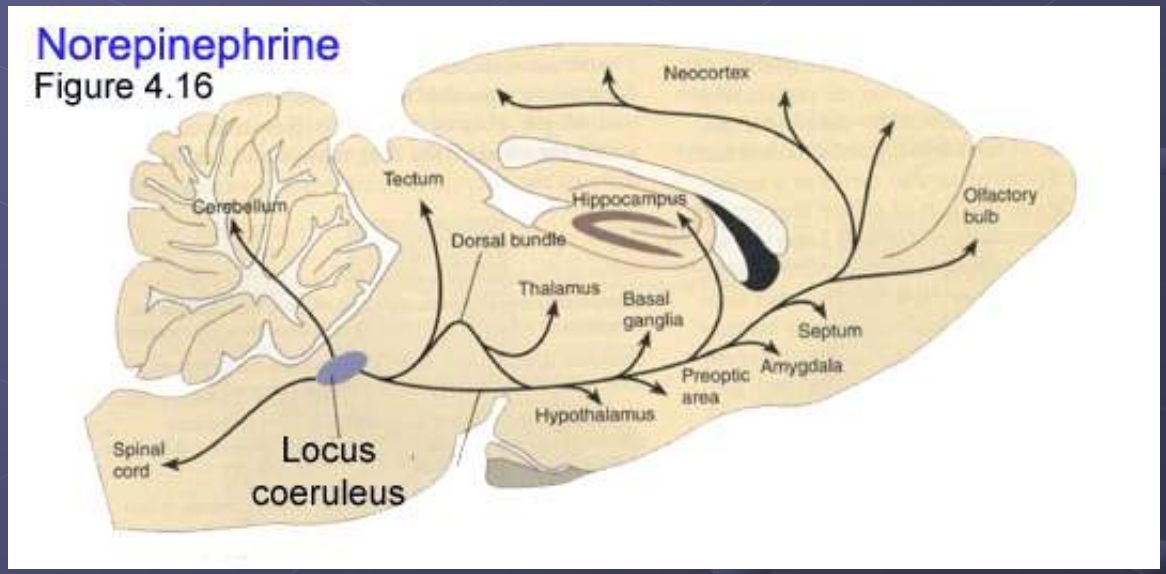


Norepinephrine



Norepinephrine

- CNS activity predominantly due to action of locus ceruleus, which has projections to the cerebral cortex, limbic system, and spinal cord.
- Also found in lateral tegmental area, which projects to hypothalamus.



Norepinephrine

- Role in depression, and appears tightly linked to levels of serotonin and dopamine
- Explains why SNRI's have a positive effect on depression, along with TCAs that also affect norepinephrine levels
- Dysregulation of norepinephrine in locus ceruleus also tied to panic disorder, anxiety disorder, depression, and REM sleep disturbances

Norepinephrine Receptors

- Receptors
  - Alpha 1 – Brain, heart, smooth muscle – Vasoconstriction, smooth muscle control
  - Alpha2 - Brain, pancreas, smooth muscle - Vasoconstriction, presynaptic effect in GI (relaxant)
  - Beta1 - Heart, brain - Heart rate (increase)
  - Beta2 - Lungs, brain, skeletal muscle - Bronchial relaxation, vasodilatation
  - Beta3 - Postsynaptic effector cells - Stimulation of effector cells