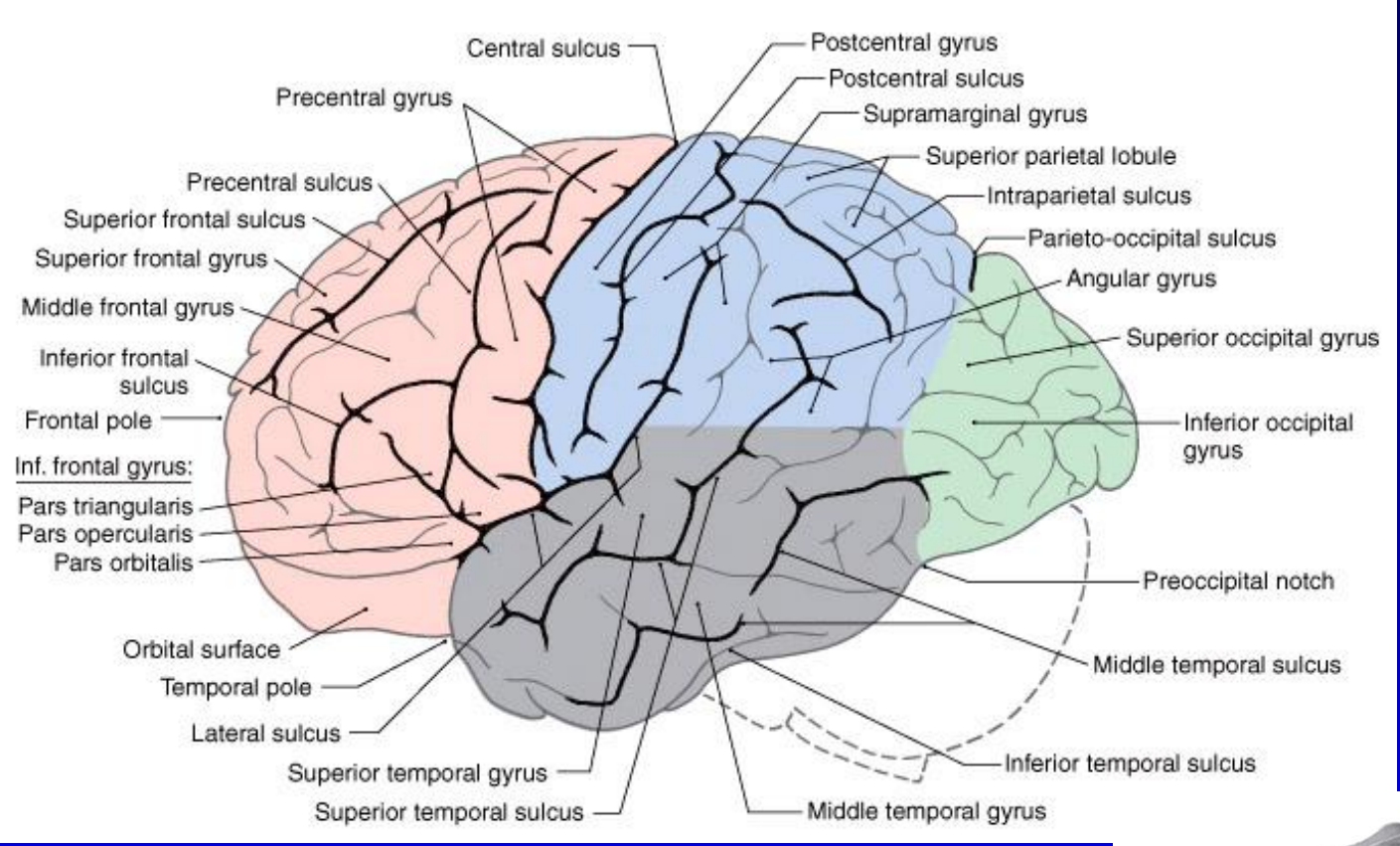
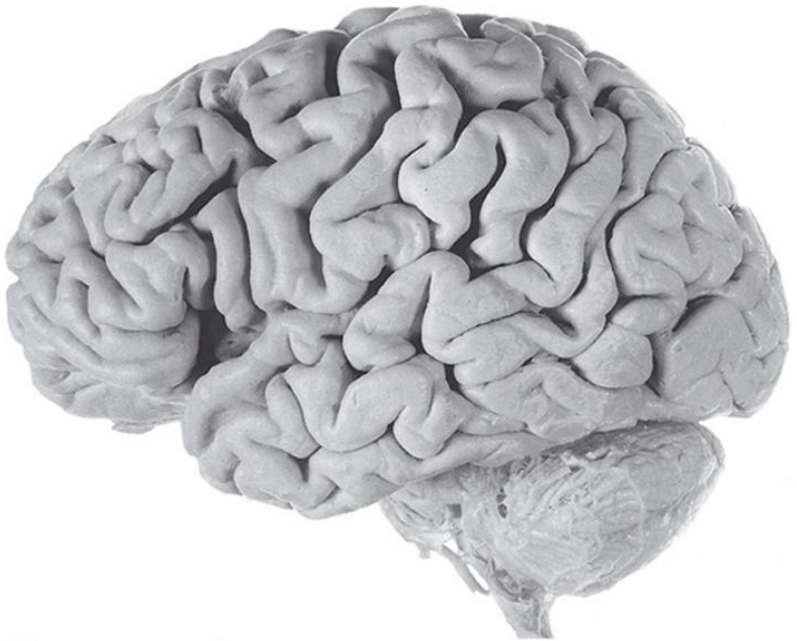
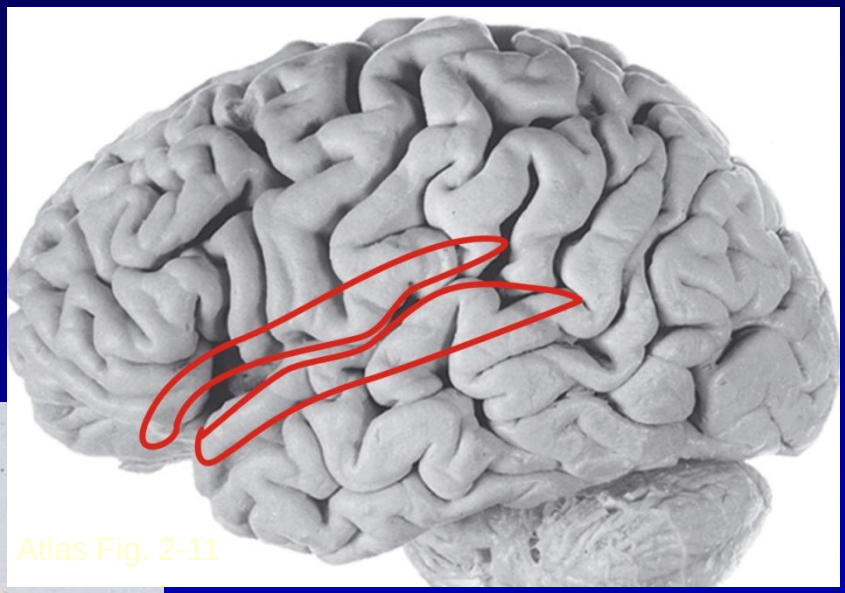
The Cerebral Cortex
and
Higher Intellectual Functions

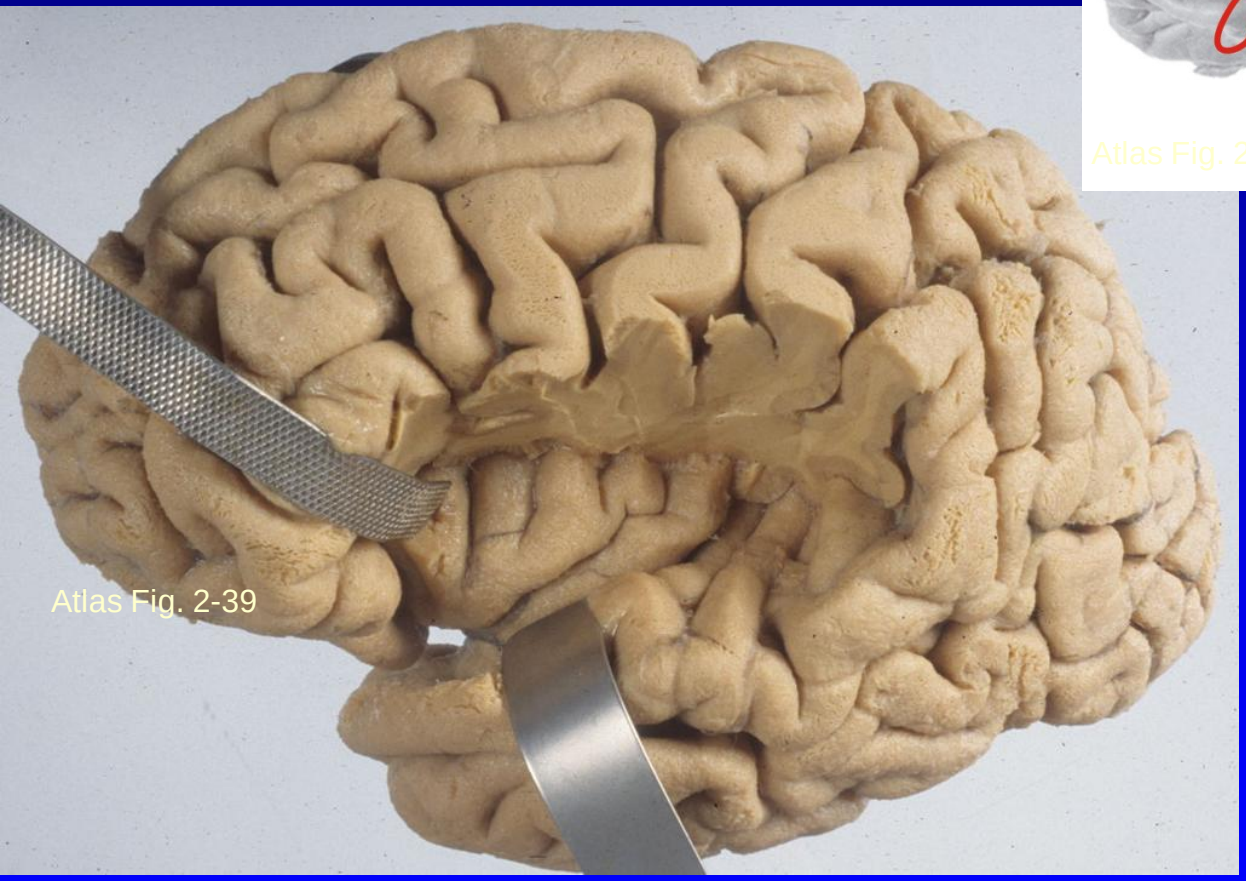


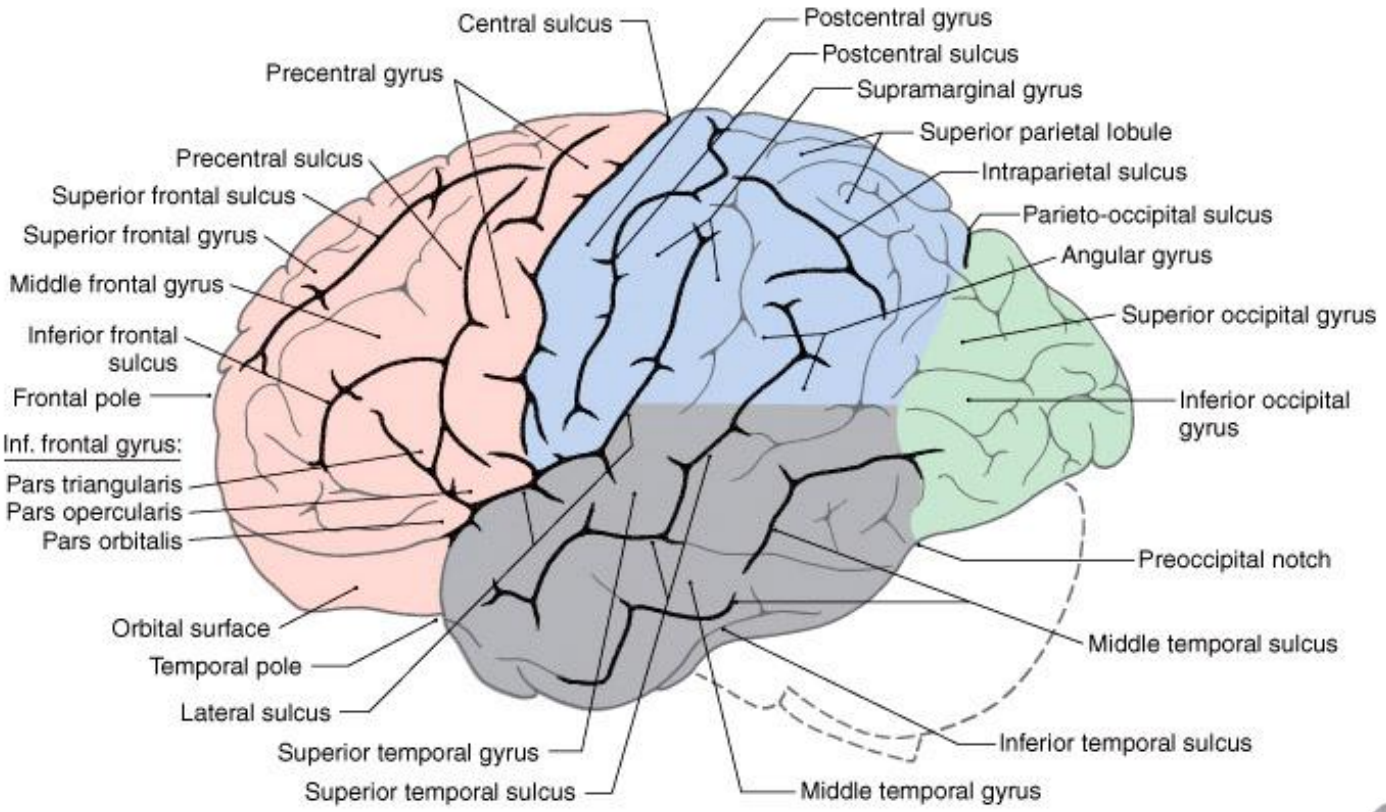
Lobes in a lateral view of left hemisphere



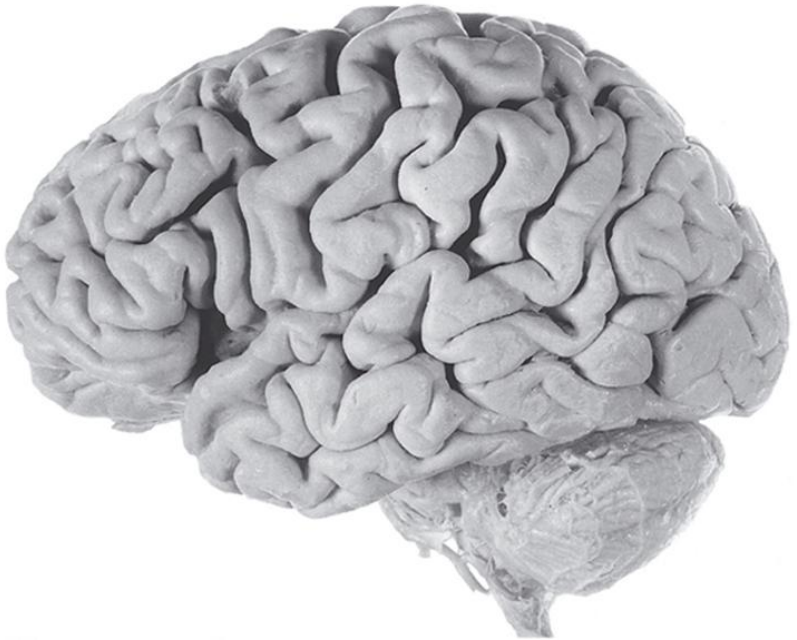
The Insula
The Hidden Lobe



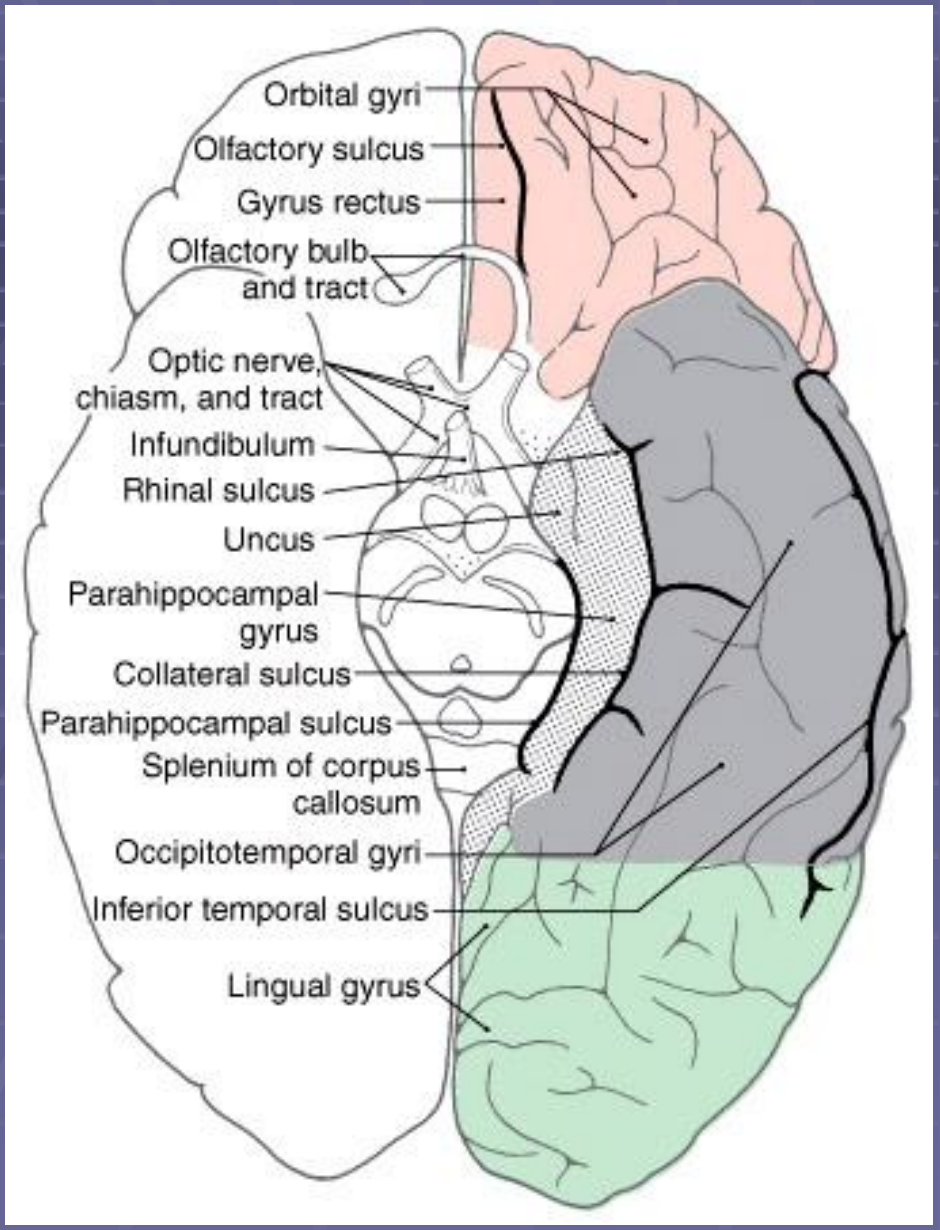


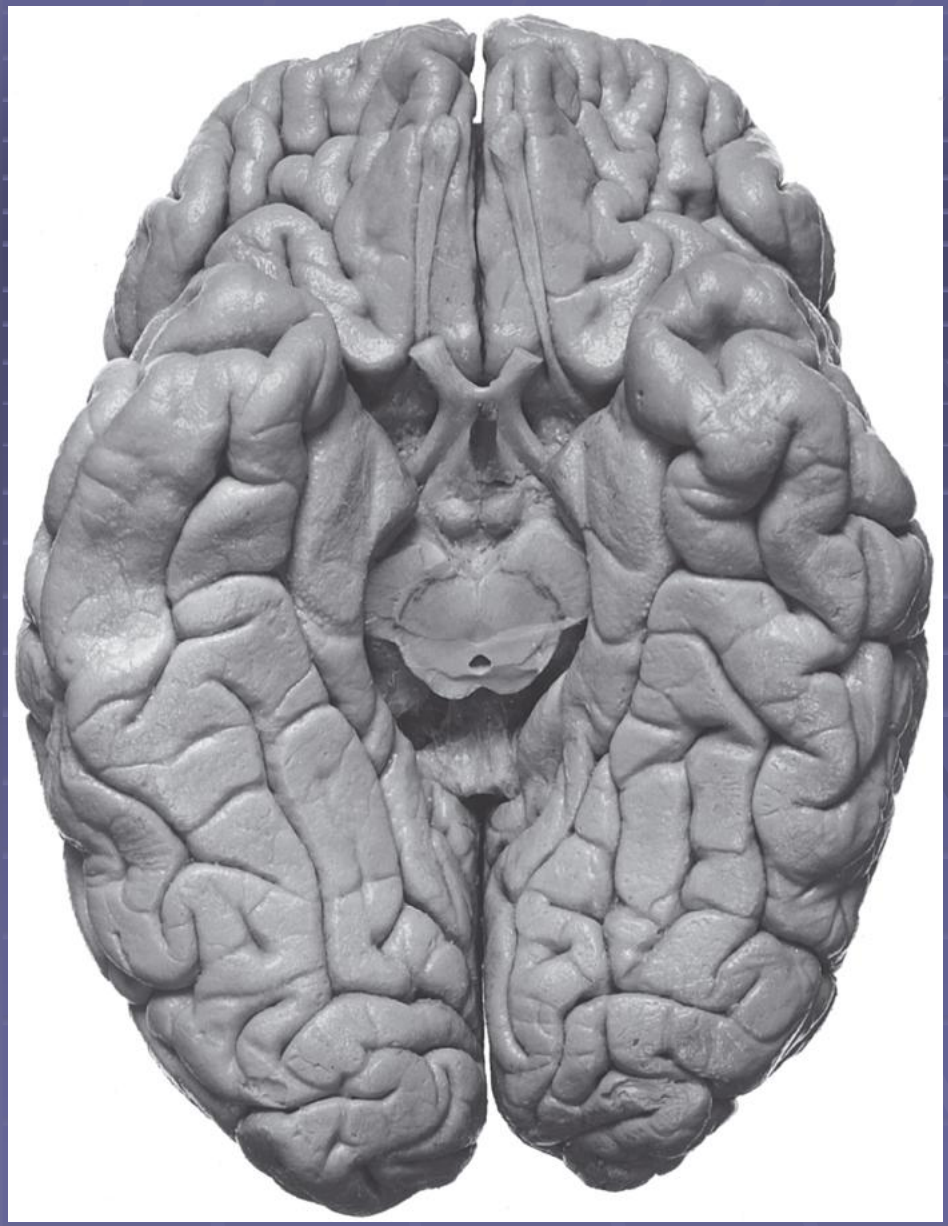


Lobes in a lateral view of left hemisphere



Lobes in a anterior (ventral) view

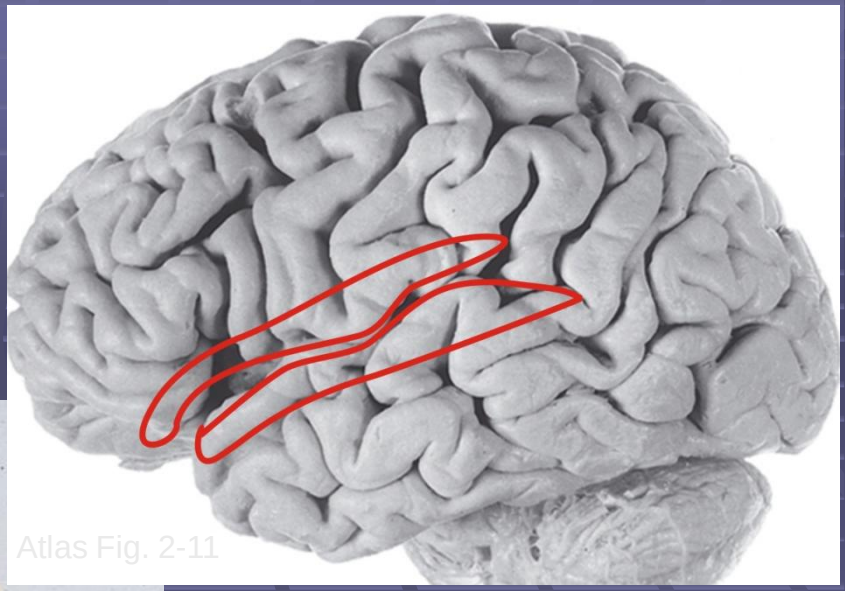


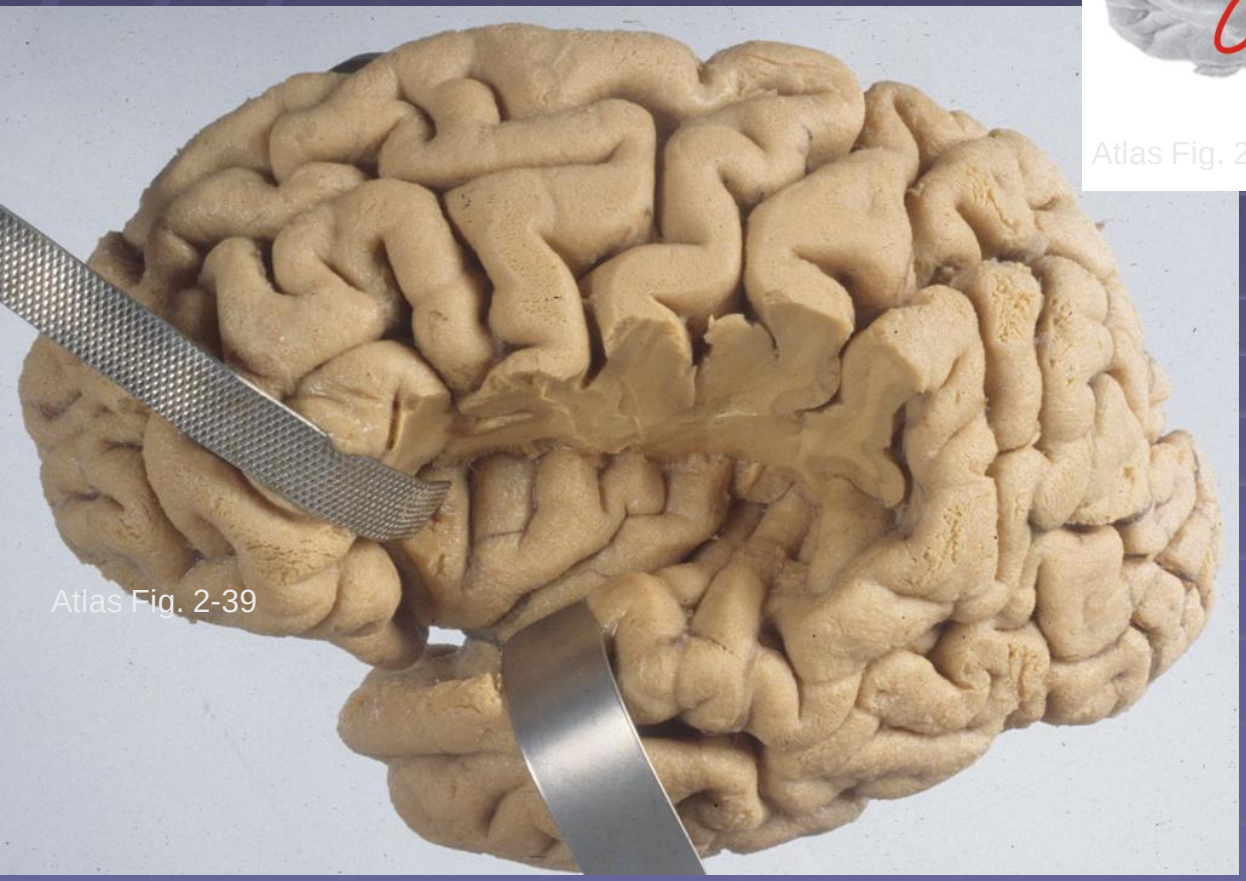


Text, Fig. 16-6

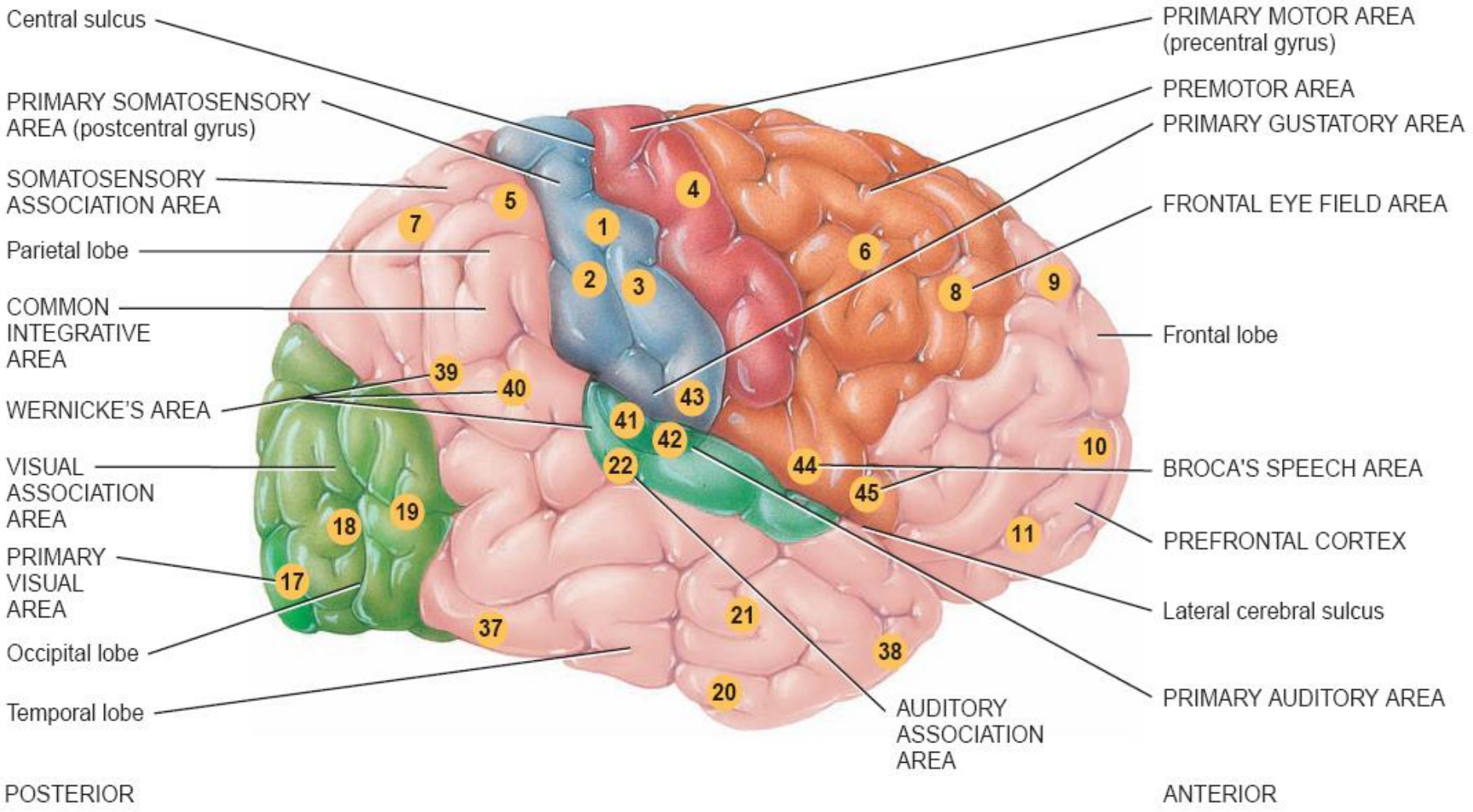
Atlas, Fig. 2-14

The Insula
The Hidden Lobe

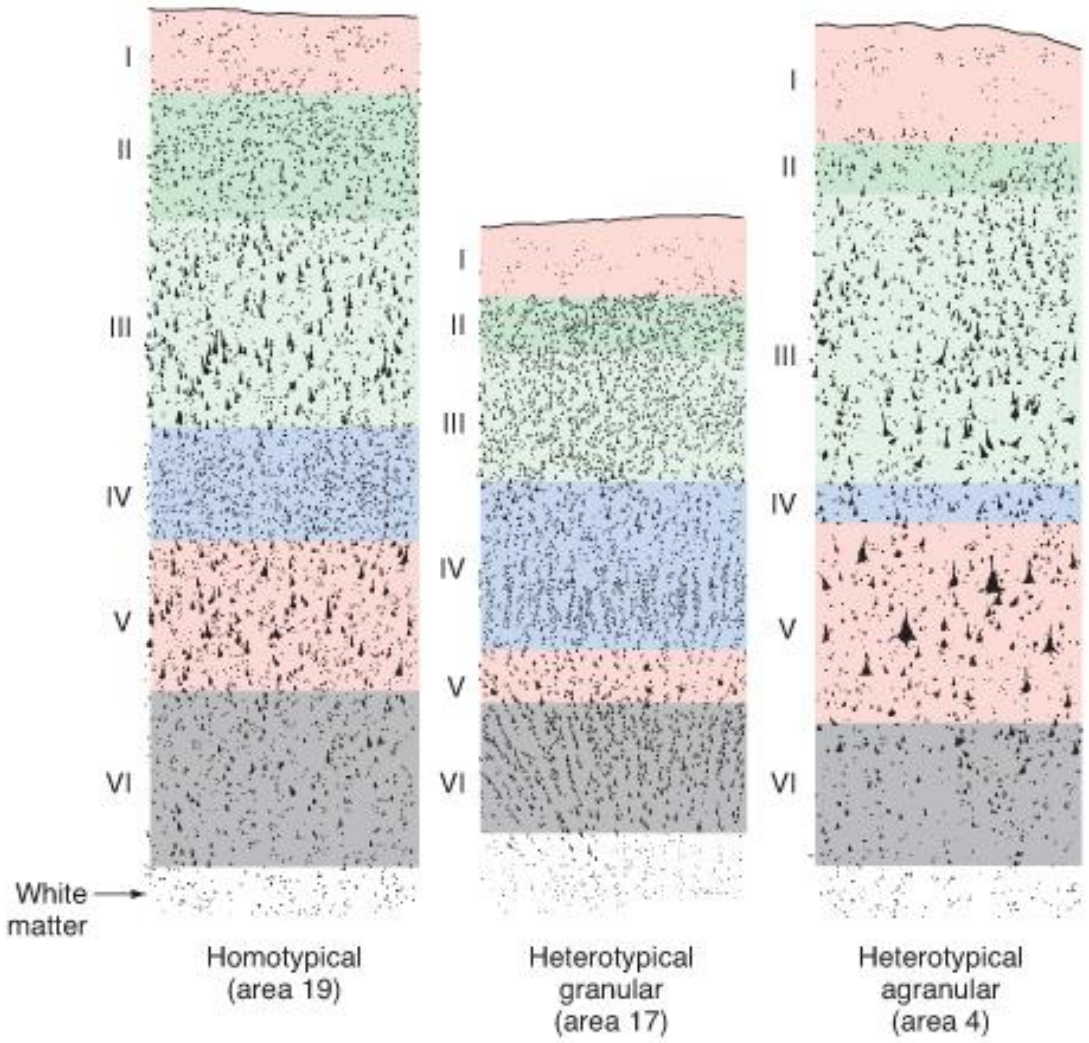


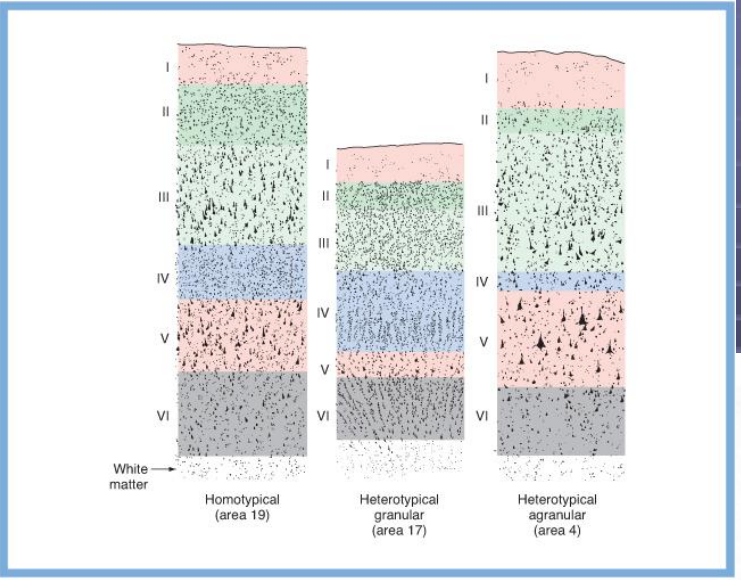


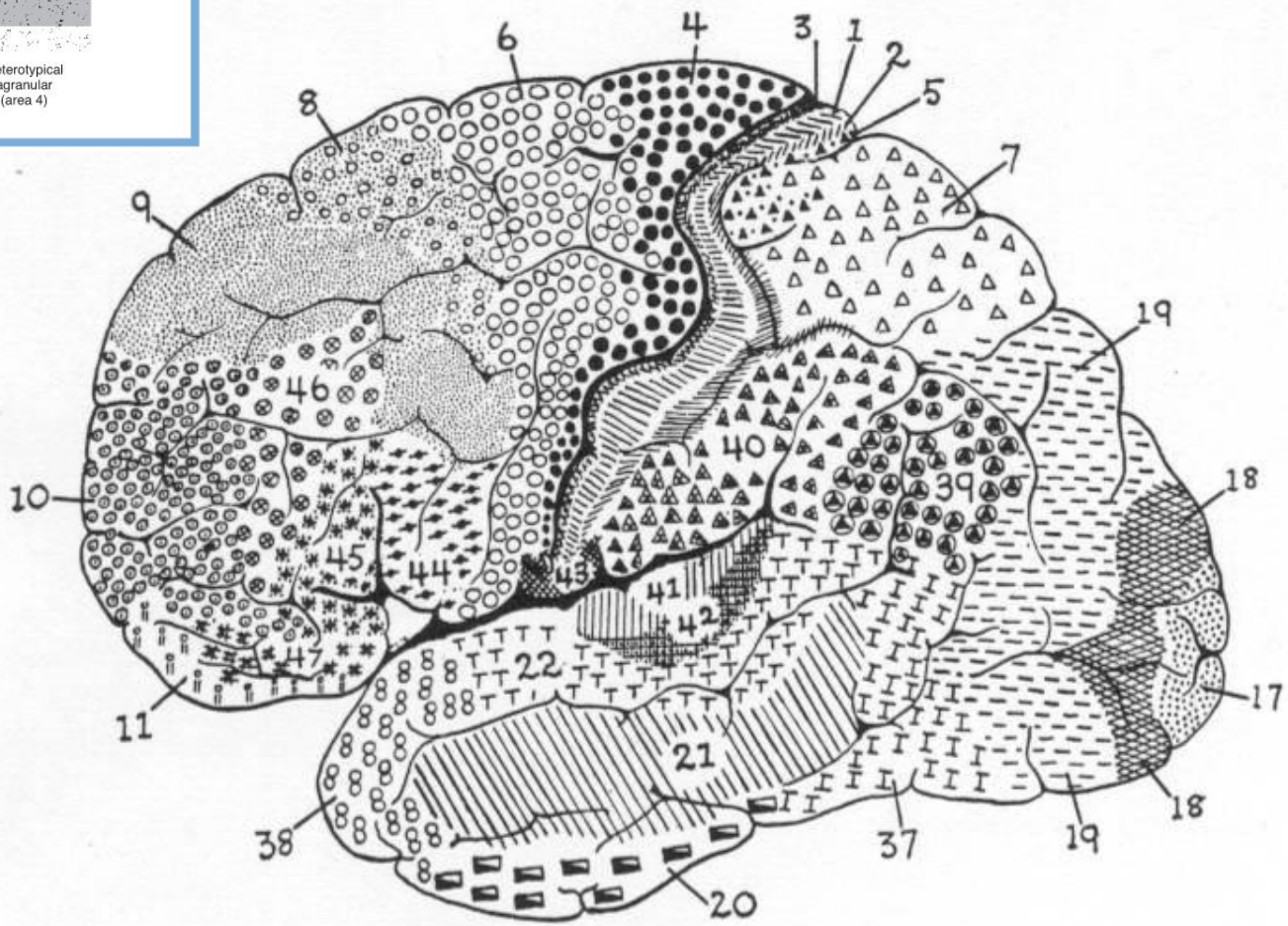
Primary, Secondary and Association

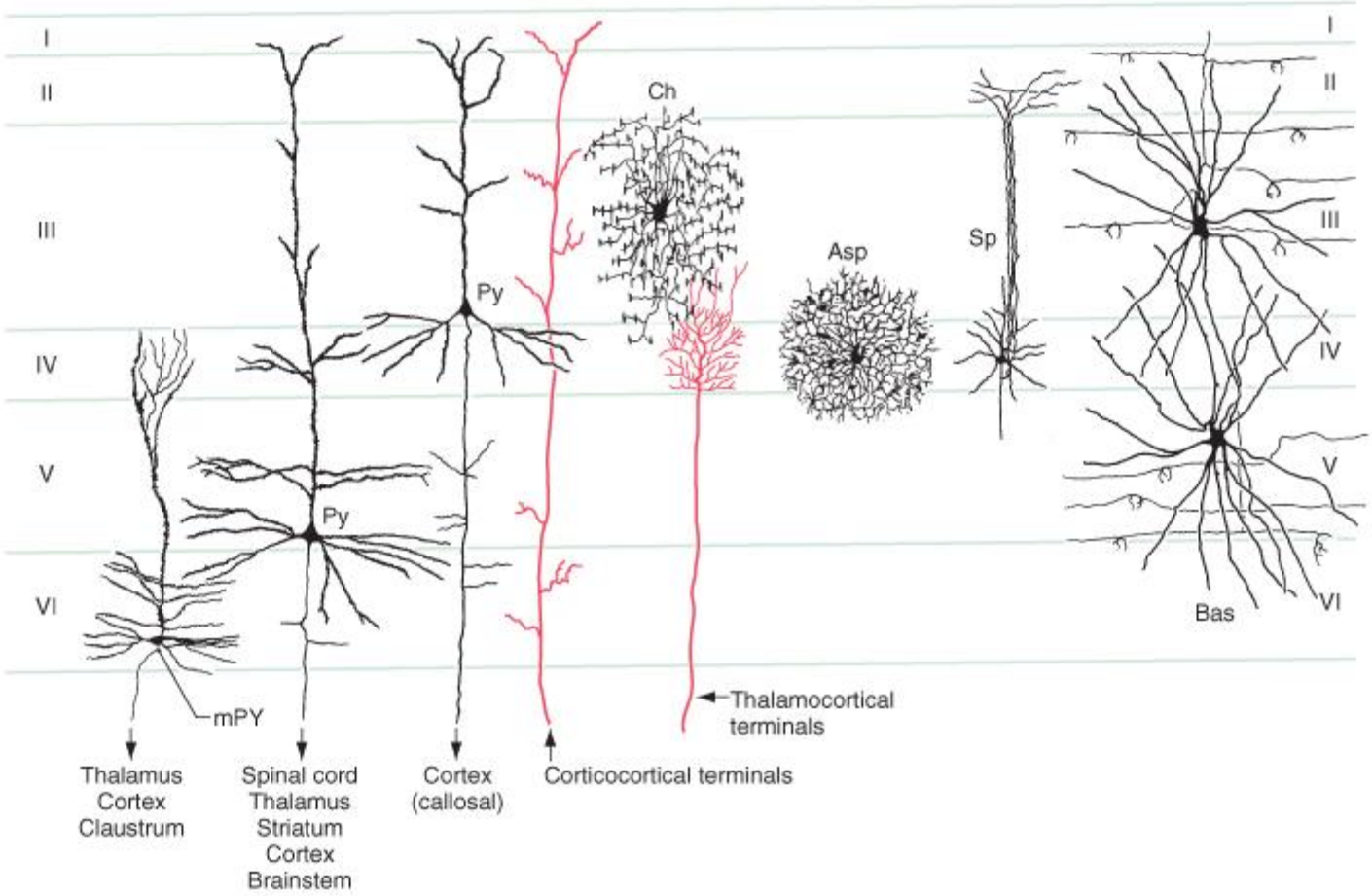


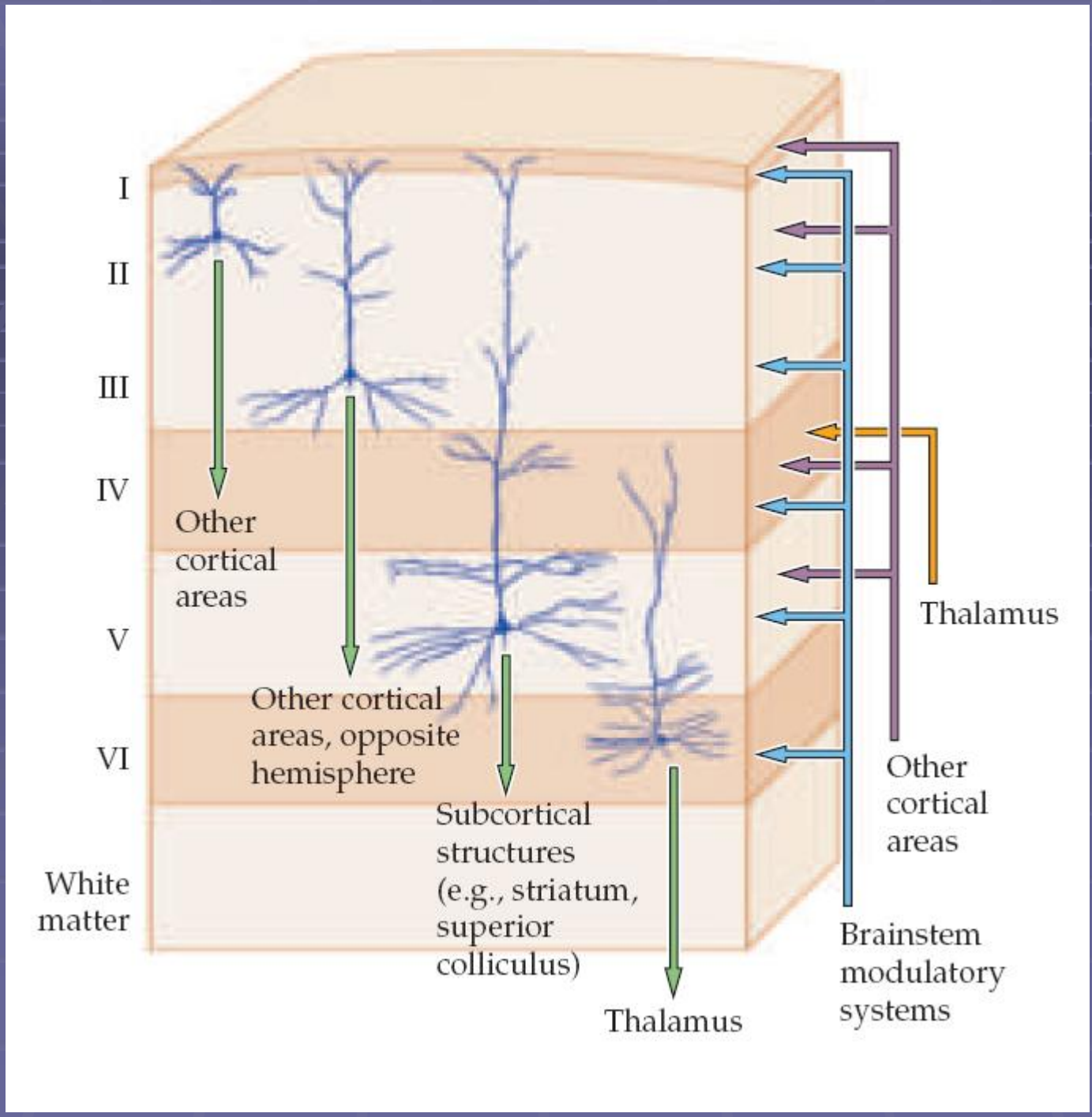
Lateral view of right cerebral hemisphere

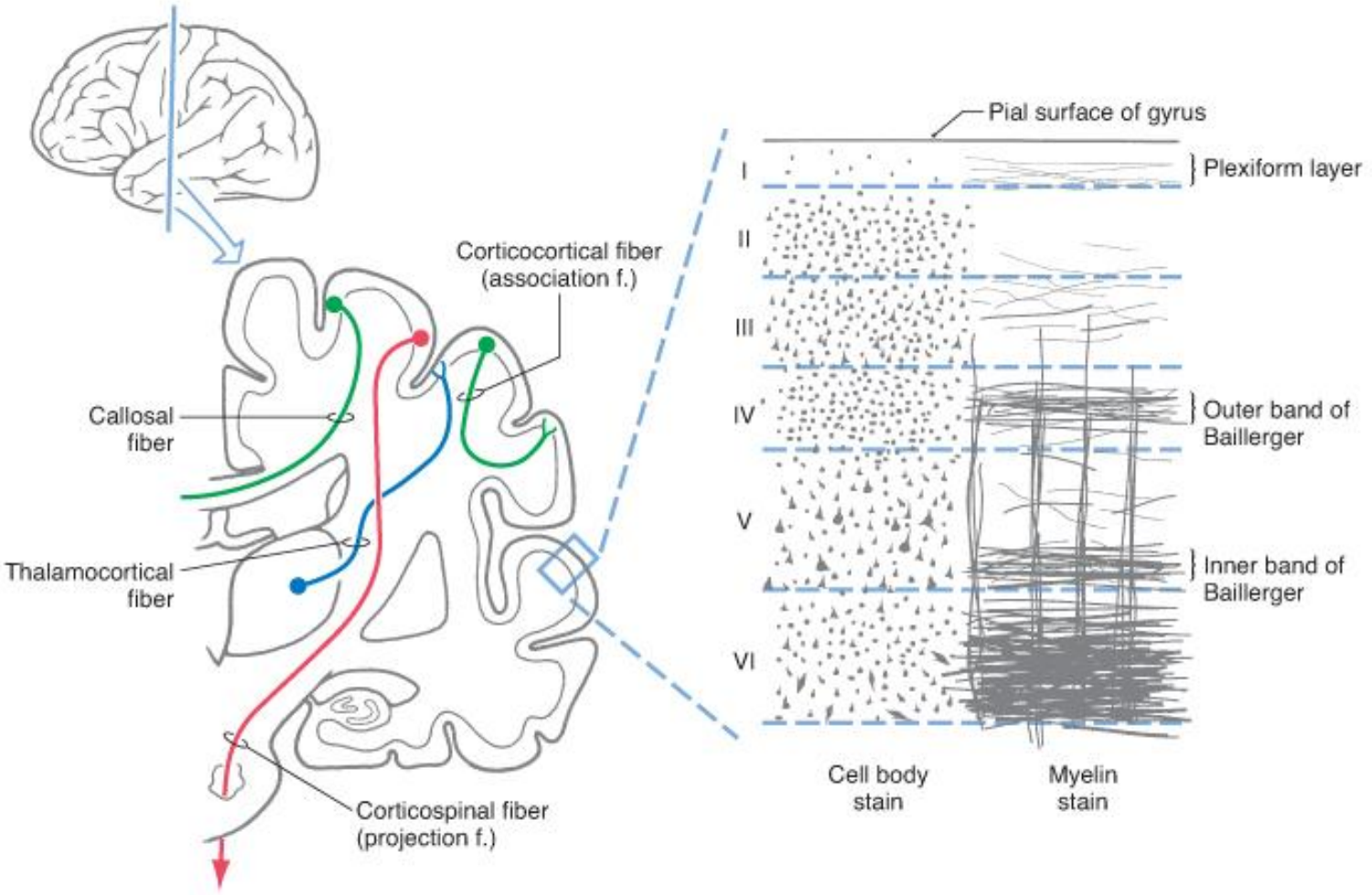

I
II
III
IV
V
VI
White matter
Homotypical (area 19)
I
II
III
IV
V
VI
Heterotypical granular (area 17)
I
II
III
IV
V
VI
Heterotypical agranular (area 4)


I
II
III
IV
V
VI
White matter
Homotypical (area 19)
Heterotypical granular (area 17)
Heterotypical agranular (area 4)


1
2
3
4
5
6
7
8
9
10
11
17
18
19
20
21
22
37
38
39
40
41
42
43
44
45
46
47


I
II
III
IV
V
VI
Ch
Py
Py
Asp
Sp
I
II
III
IV
V
VI
Bas
mPY
Thalamocortical terminals
Thalamus
Cortex
Claustrum
Spinal cord
Thalamus
Striatum
Cortex
Brainstem
Cortex
(callosal)
Corticocortical terminals


I
II
III
IV
V
VI
White matter
Other cortical areas
Other cortical areas, opposite hemisphere
Subcortical structures (e.g., striatum, superior colliculus)
Thalamus
Thalamus
Other cortical areas
Brainstem modulatory systems


Corticocortical fiber
(association f.)
Callosal
fiber
Thalamocortical
fiber
Corticospinal fiber
(projection f.)
Pial surface of gyrus
I
II
III
IV
V
VI
Plexiform layer
Outer band of
Baillerger
Inner band of
Baillerger
Cell body
stain
Myelin
stain

Communication Between Neurons

- **Synapse: A specialized site of contact, and transmission of information between a neuron and an effector cell**

Anterior Motor Neuron

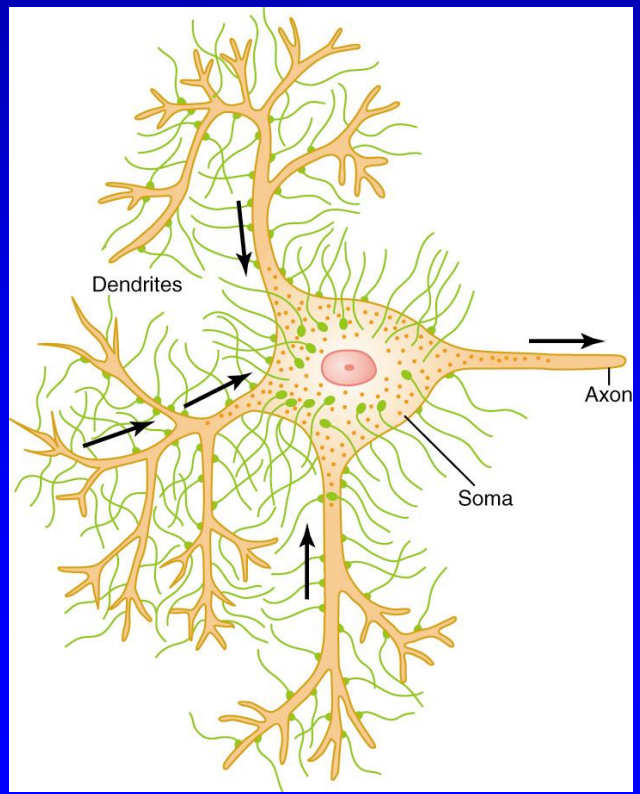
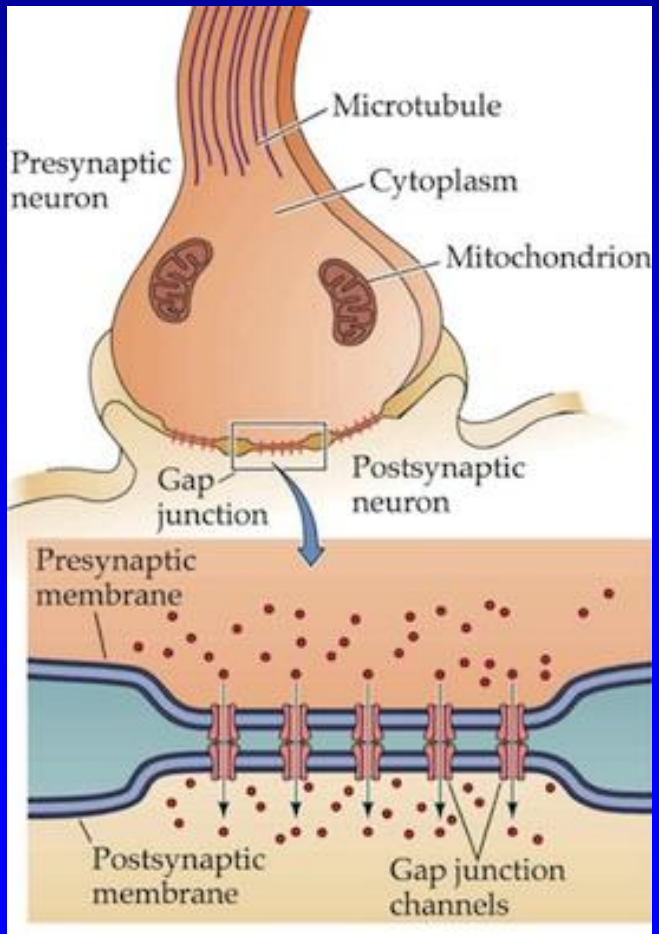


Figure 45-5

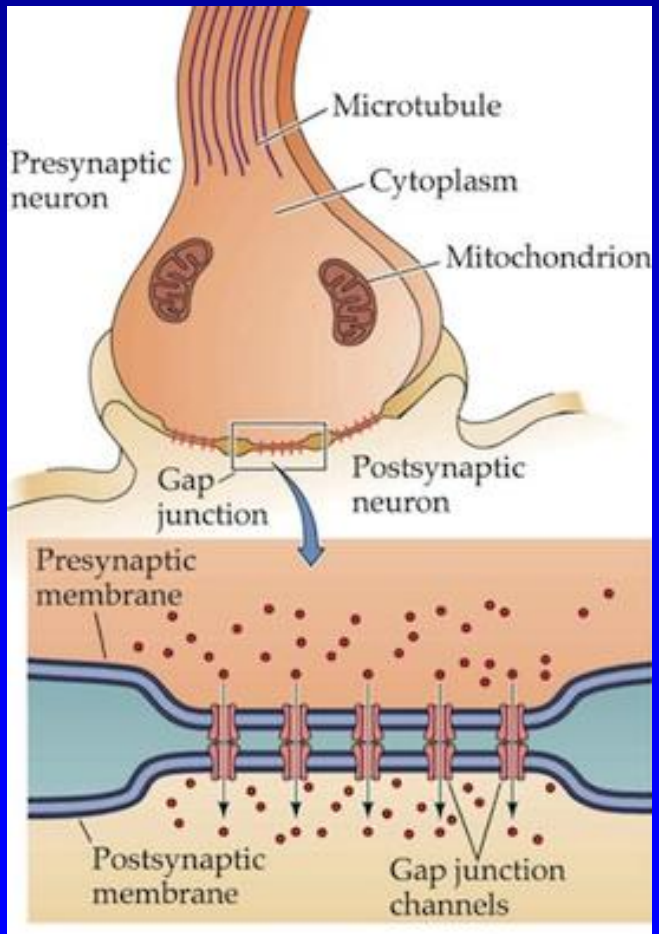
Communication Between Neurons

- Electrical synapse

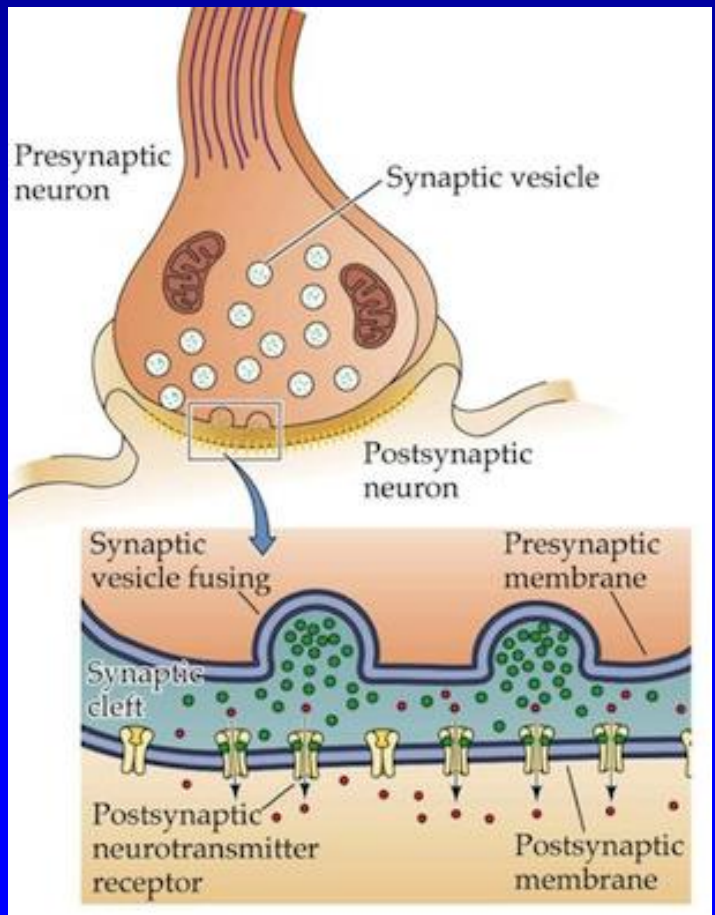


Communication Between Neurons

- Electrical synapse

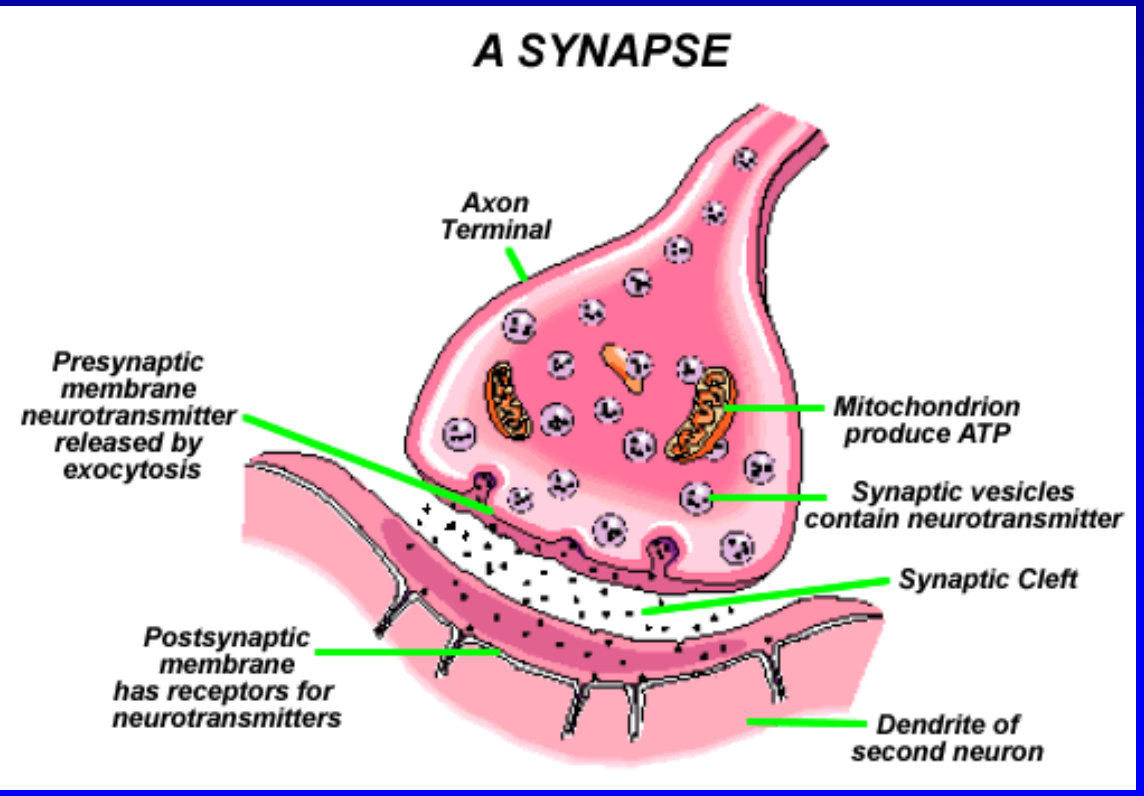


Chemical synapse



Communication Between Neurons

- Chemical synapse



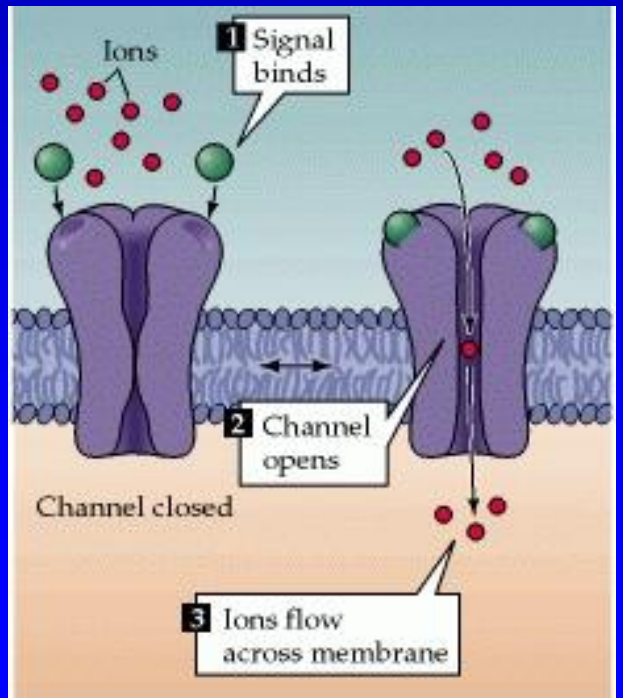
Neurotransmitter: is a messenger of neurologic information from one cell to another.

Action of Neurotransmitter on Postsynaptic Neuron

- postsynaptic membrane contains receptor proteins for the transmitter released from the presynaptic terminal.
- The effect of neurotransmitter on the post synaptic neuron depend on the type of the receptor

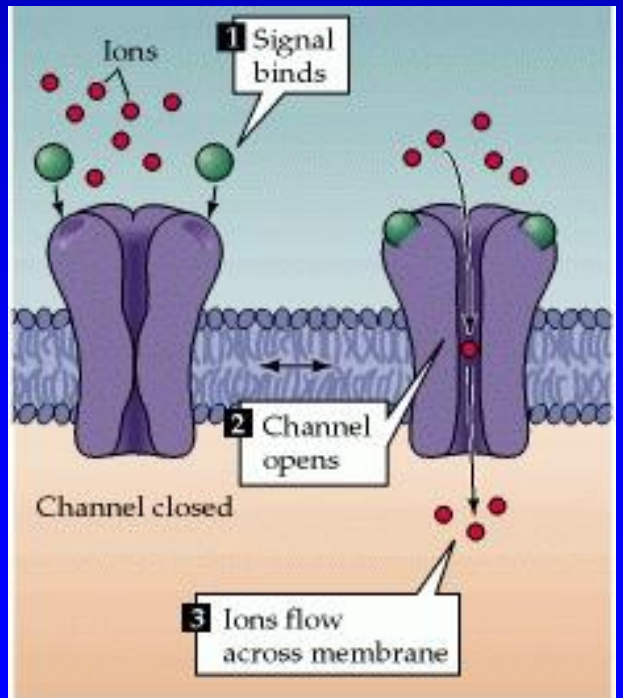
Action of Neurotransmitter on Postsynaptic Neuron

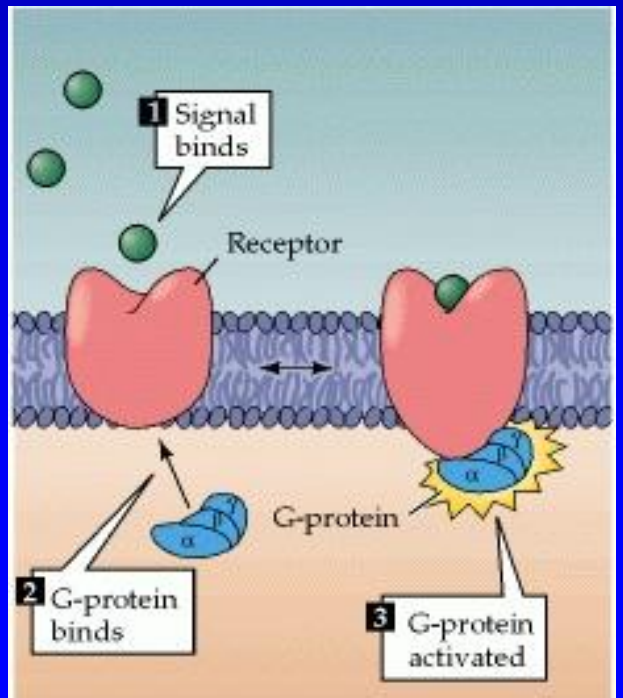
- Two types of receptors
  - Ion channels receptors



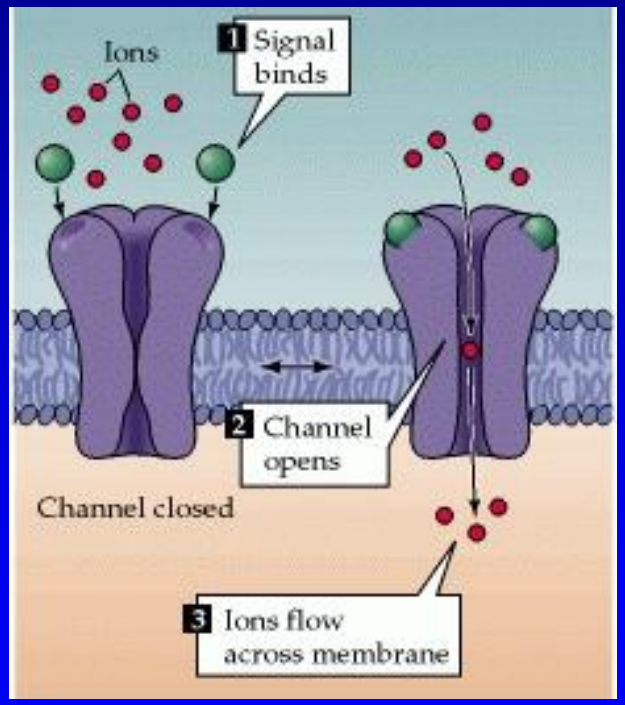
Action of Neurotransmitter on Postsynaptic Neuron

- Two types of receptors
  - Ion channels receptors **Ionotropic**
  - Second messenger receptors **Metatropic**





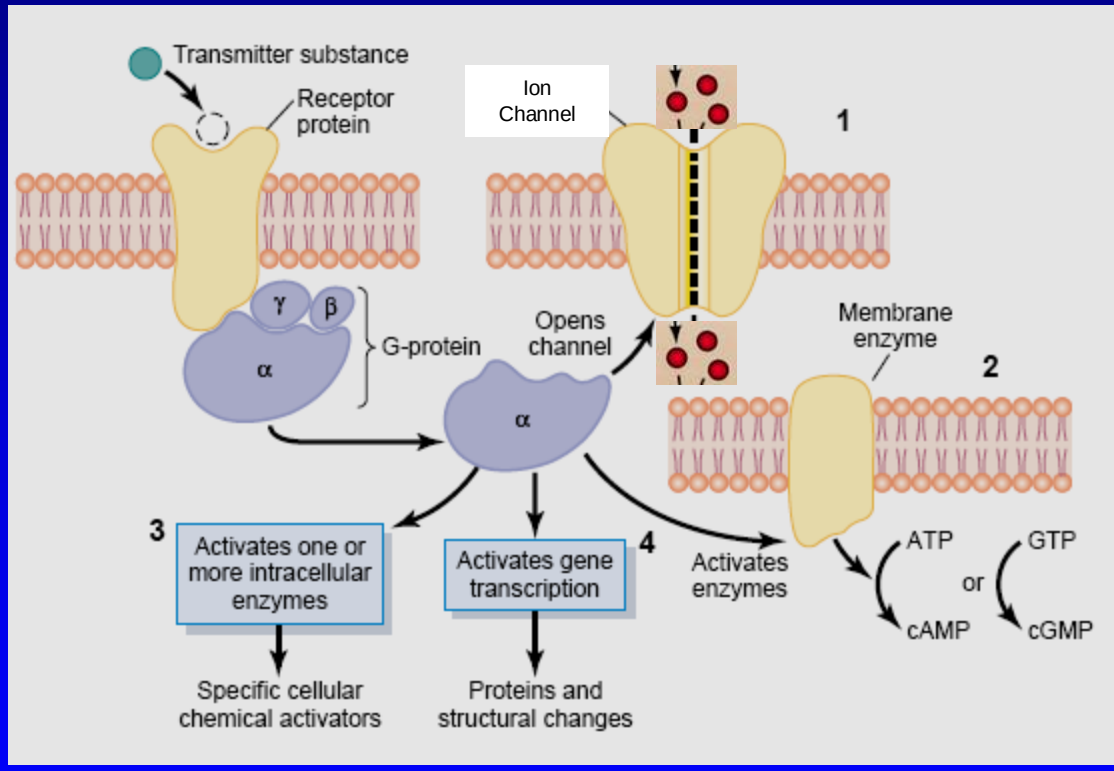
Ion Channels receptors



- transmitters that open sodium channels excite the postsynaptic neuron.
- transmitters that open chloride channels inhibit the postsynaptic neuron.
- transmitters that open potassium channels inhibit the postsynaptic neuron.

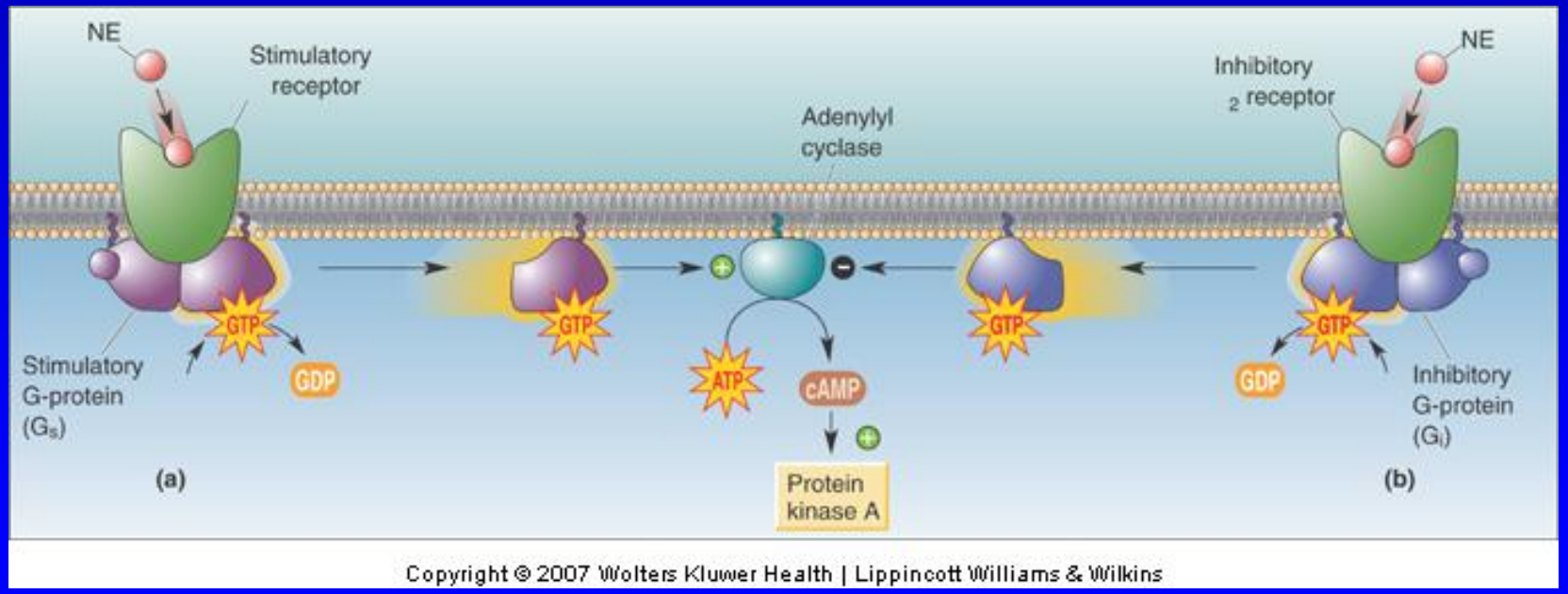
Seconded messenger receptors (as example G-protein)

1. *Opening specific ion channels*
2. *Activation of cAMP or cGMP*
3. *Activation of one or more intracellular enzymes*
4. *Activation of gene transcription.*



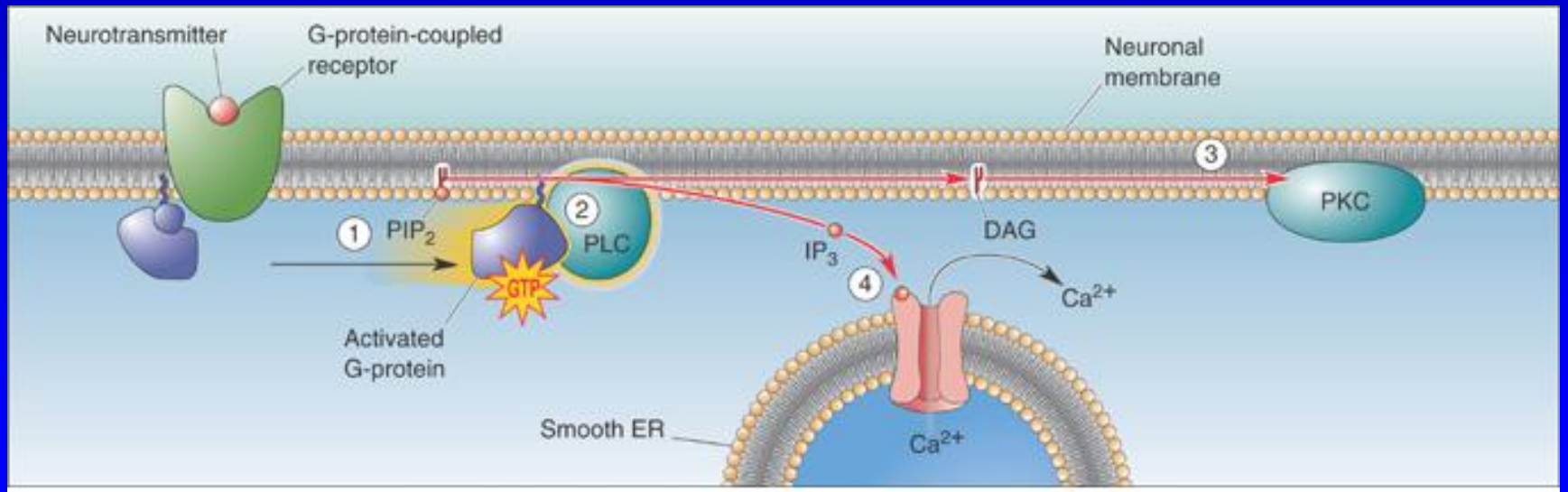
G-Protein-Coupled Receptors and Effectors

- GPCR Effector Systems (Cont'd)
  - Push-pull method (e.g., different G proteins for stimulating or inhibiting adenylyl cyclase)



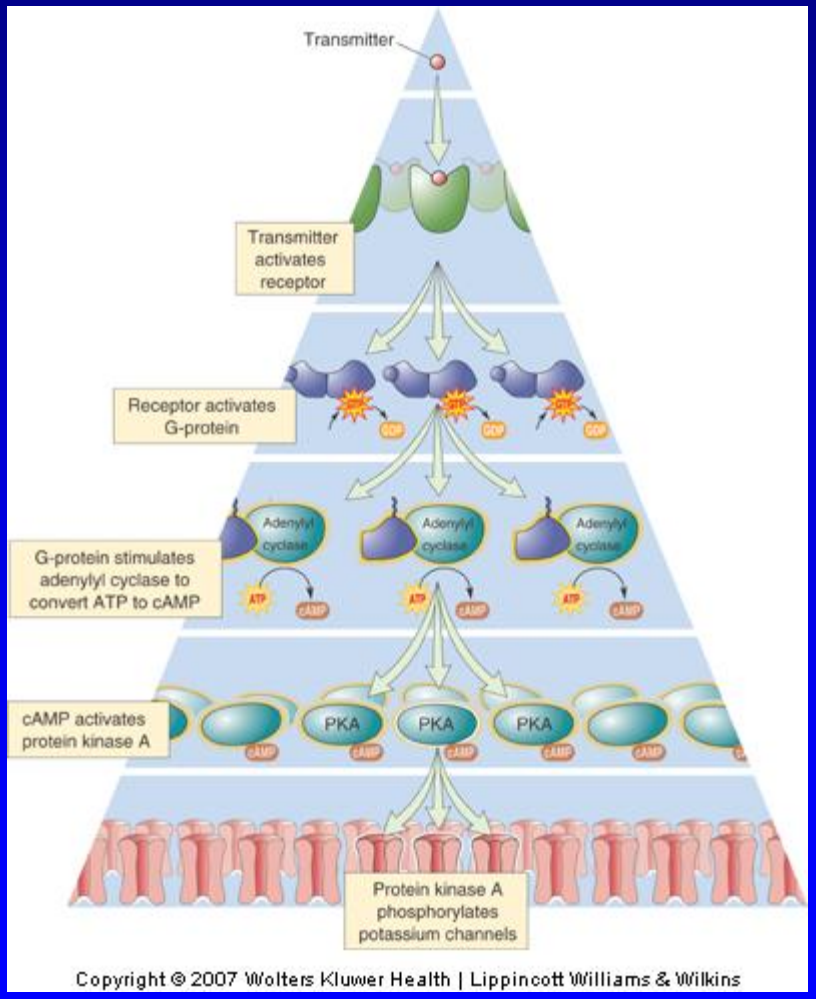
G-Protein-Coupled Receptors and Effectors

- GPCR Effector Systems (Cont'd)
  - Some cascades split
    - G-protein activates PLC→ generates DAG and IP3→ activate different effectors



G-Protein-Coupled Receptors and Effectors

- GPCR Effector Systems (Cont'd)
  - Signal amplification



Drugs and the Synapse
1) at the receptor

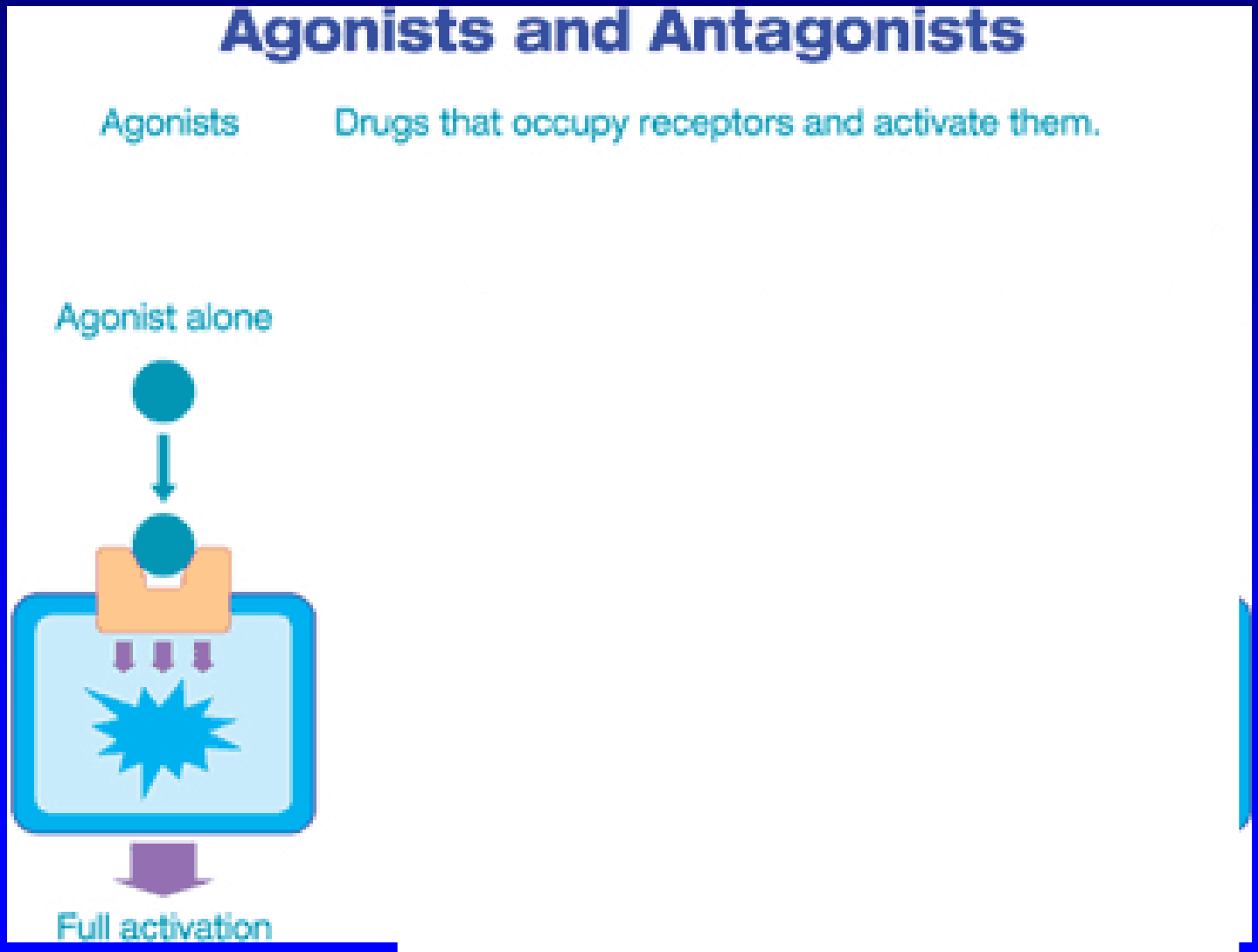
- The study of the influence of various kinds of drugs has provided us with knowledge about many aspects of neural communication at the synaptic level.
- Drugs either facilitate or inhibit activity at the synapse.
  - Antagonistic drugs block the effects of neurotransmitters (e.g., novacaine, caffeine).
  - Agonist drugs mimic or increase the effects of neurotransmitters (e.g., receptors in the brain respond to heroin, LSD and cocaine)
  - Allosteric modulation

Drugs and the Synapse

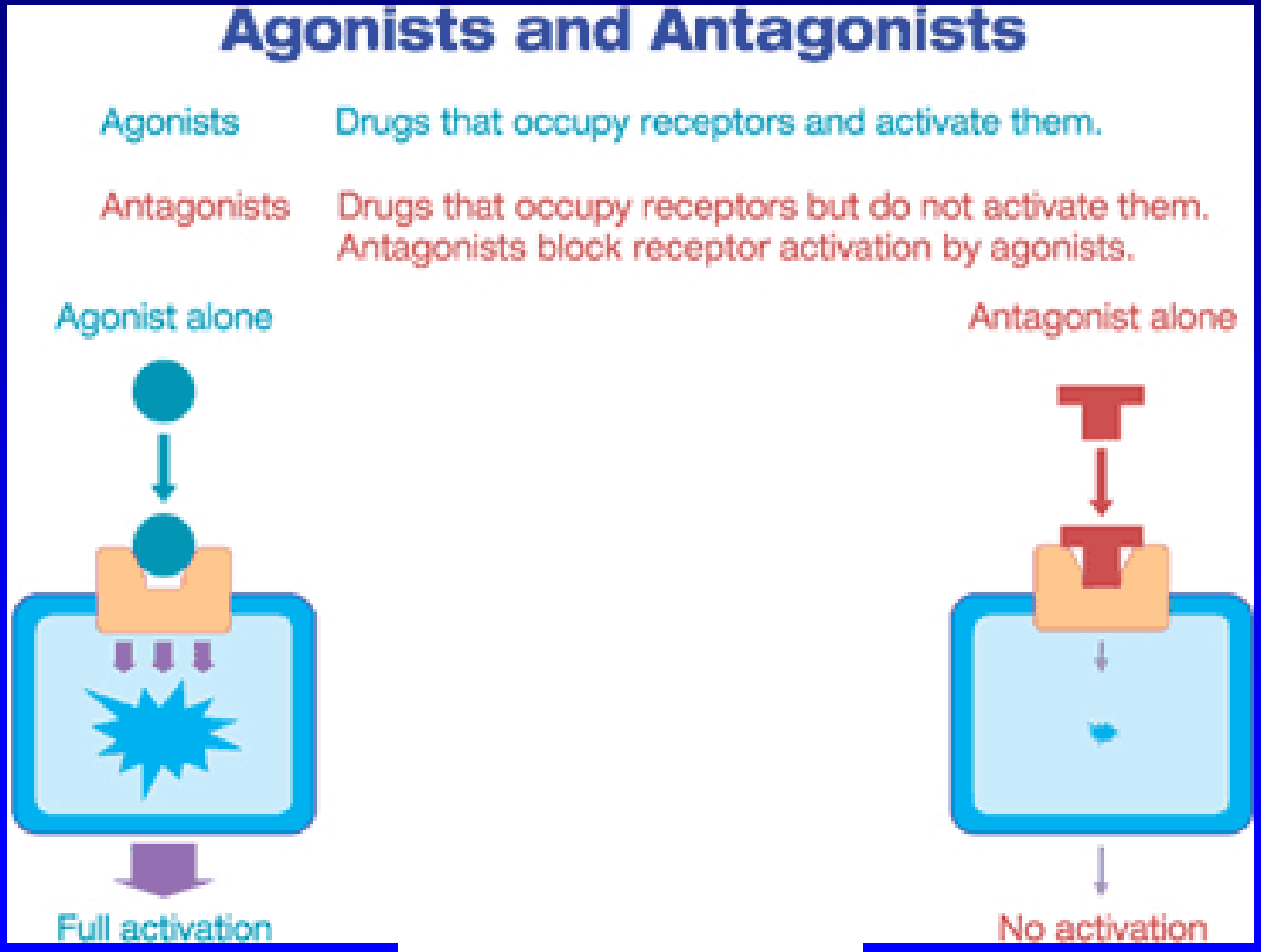
- A drug has an affinity for a particular type of receptor if it binds to that receptor.
  - Can vary from strong to weak.
- The efficacy of the drug is its tendency to activate the receptor .
- Drugs can have a high affinity but low efficacy.

Agonists and Antagonists

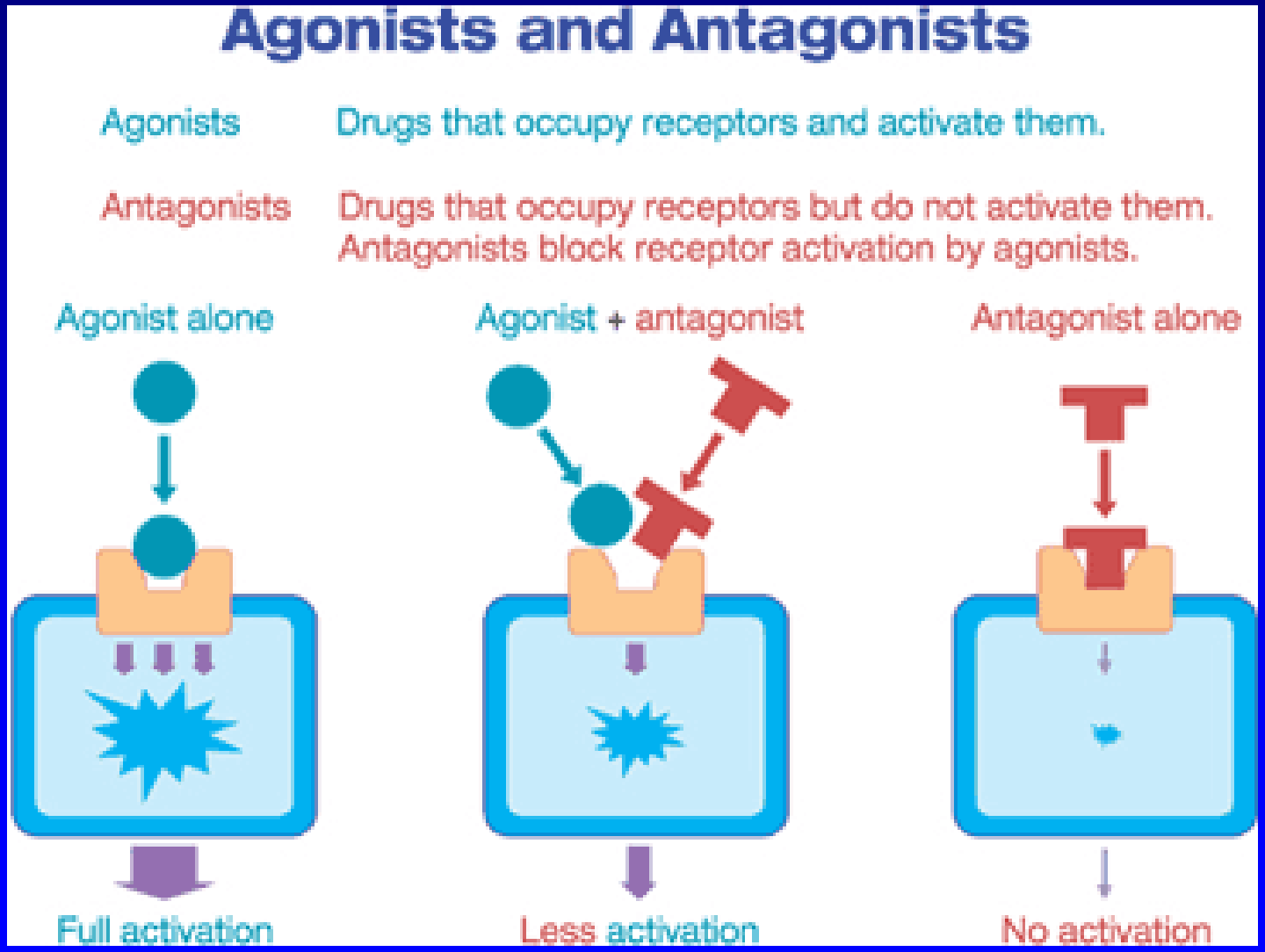
Agonists and Antagonists



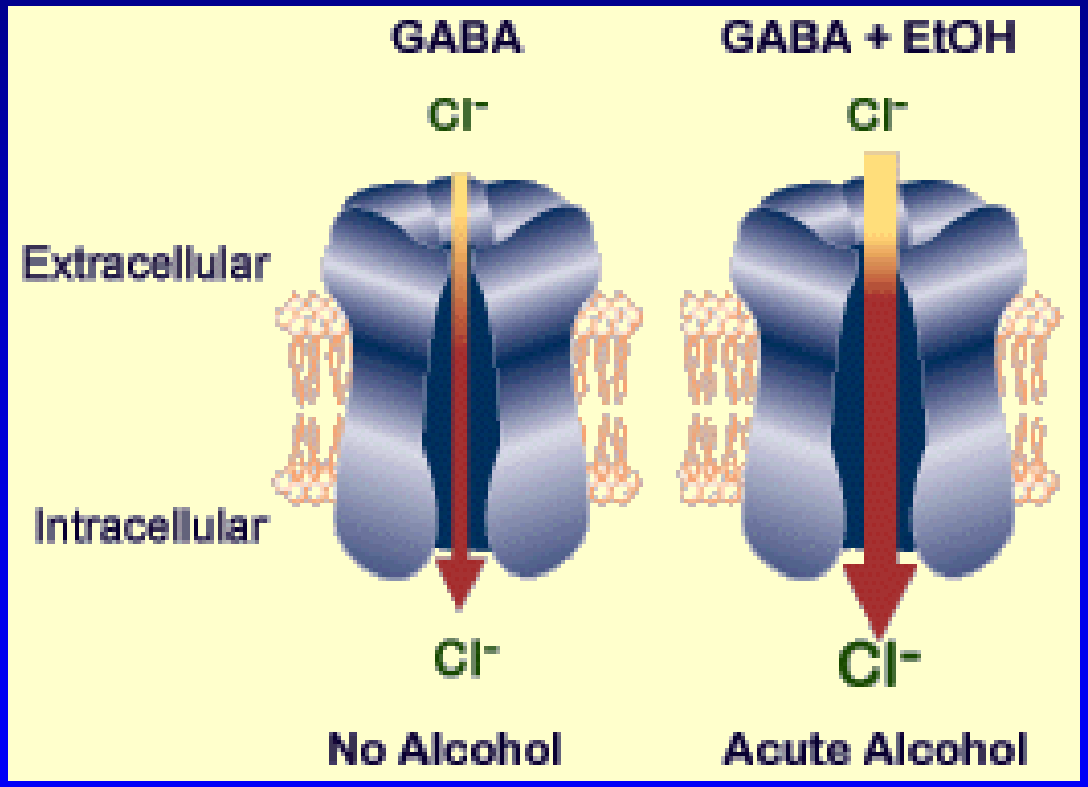
Agonists and Antagonists



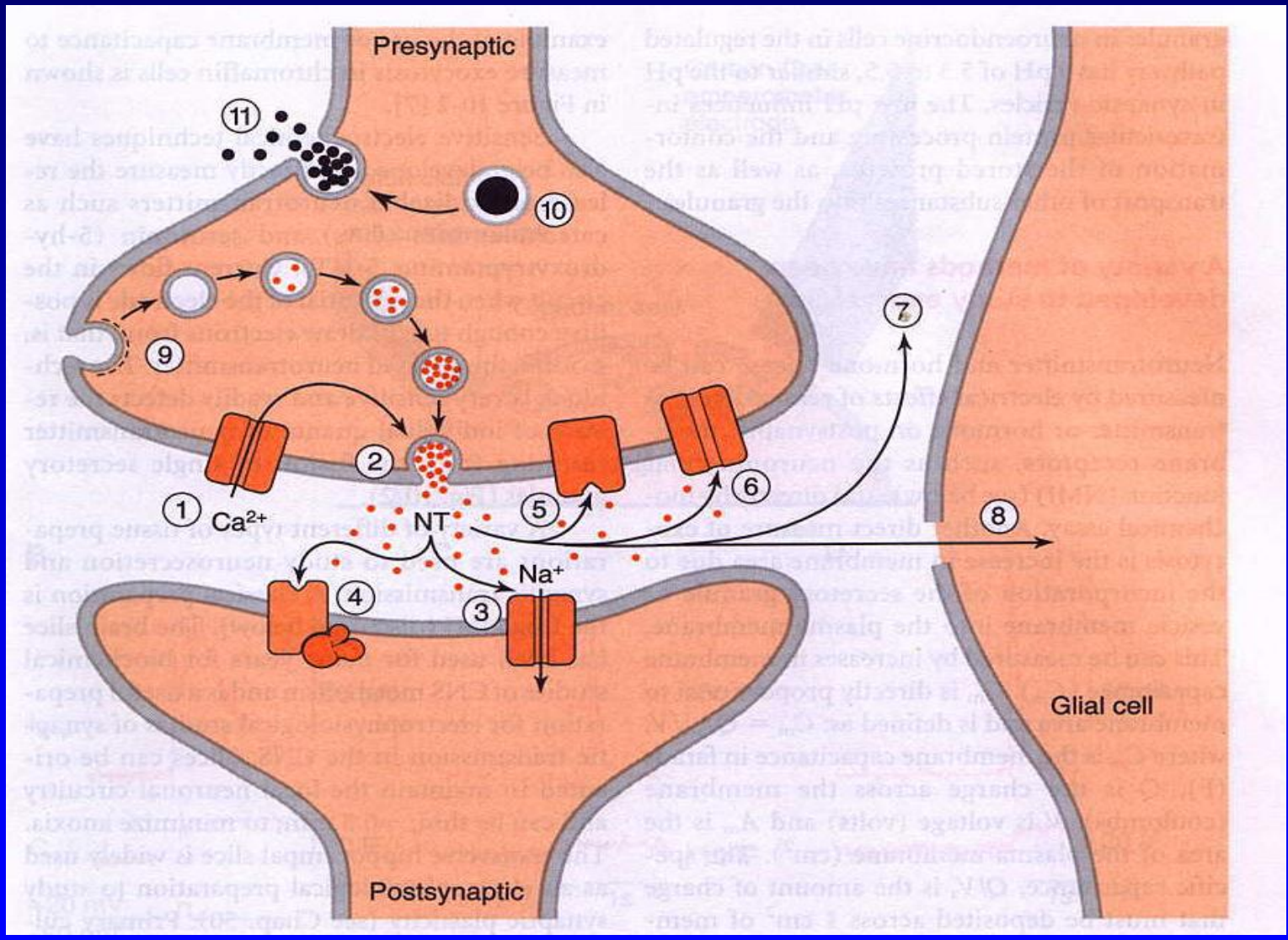
Agonists and Antagonists



Allosteric modulation



Synaptic Transmission



Drugs and the Synapse
2) alter various stages of synaptic processing.

- Drugs work by doing one or more of the following to neurotransmitters:
  1. Increasing the synthesis.
  2. Causing vesicles to leak.
  3. Increasing release.
  4. Decreasing reuptake.
  5. Blocking the breakdown into inactive chemical.
  6. Directly stimulating or blocking postsynaptic receptors.

Neurotransmitters

- Synthesis : esp. rate-limiting enzyme and/or substrate
- Clearance and inactivation
- Location and pathway
- Dysfunction and CNS pathology

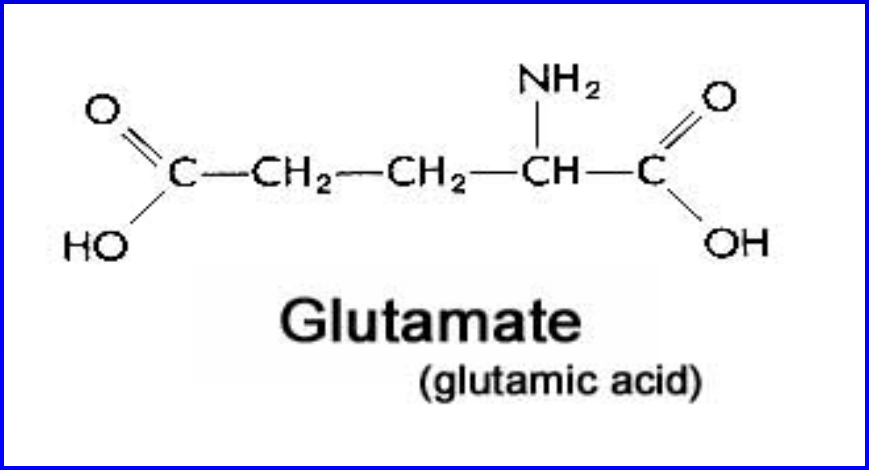
Neurotransmitters

- More than 50 chemical substances does function as synaptic transmitters.
  - small molecules which act as rapidly acting transmitters.
    - acetylcholine, norepinephrine, dopamine, serotonin, GABA, glycine, glutamate, NO.
  - neuropeptides.
    - endorphins, enkephalins, VIP, ect.
    - hypothalamic releasing hormones.
      - TRH, LHRH, ect.
    - pituitary peptides.
      - ACTH, prolactin, vasopressin, ect.

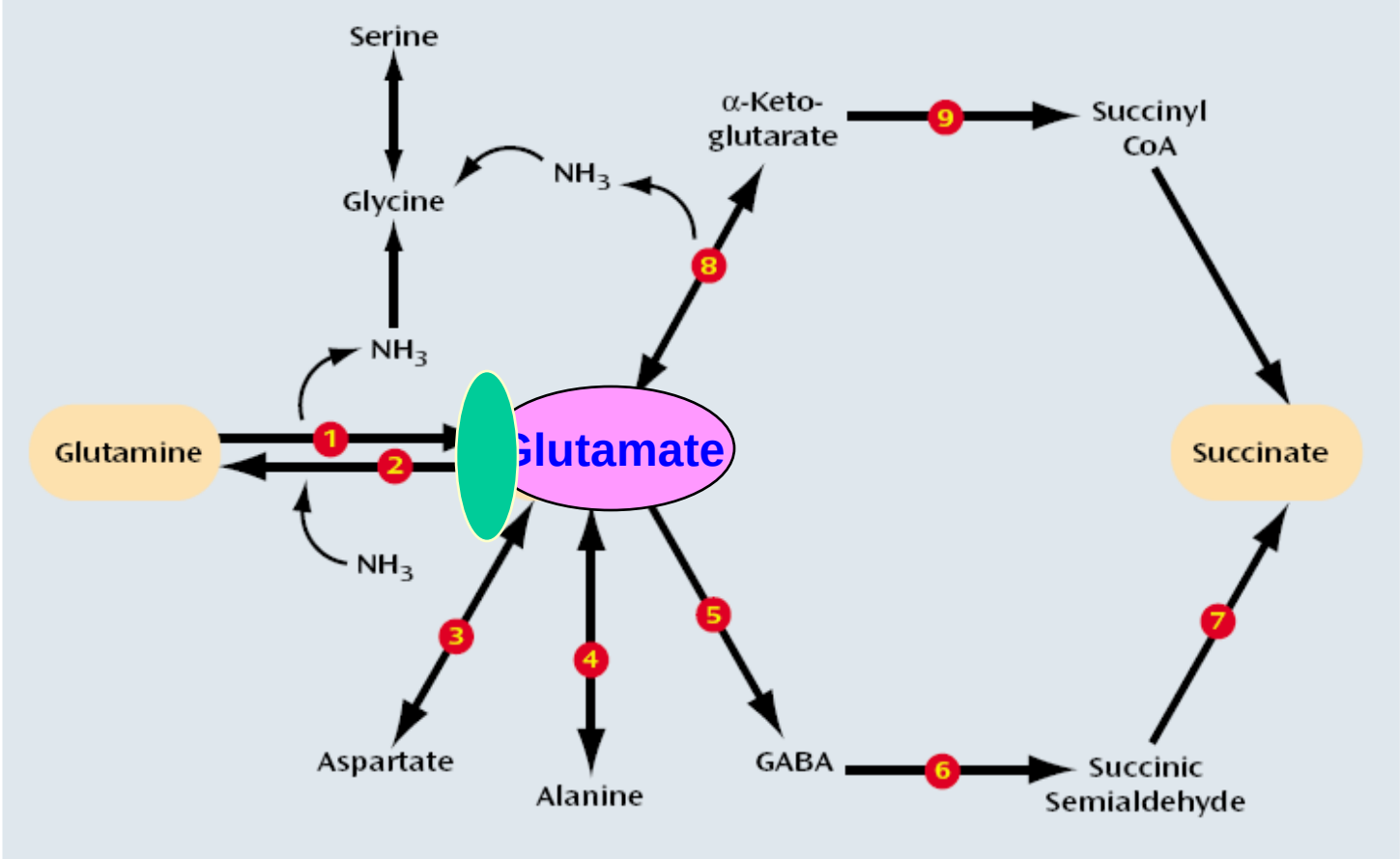
Fast Neurotransmitteres

Glutamate (L-glutamic acid)

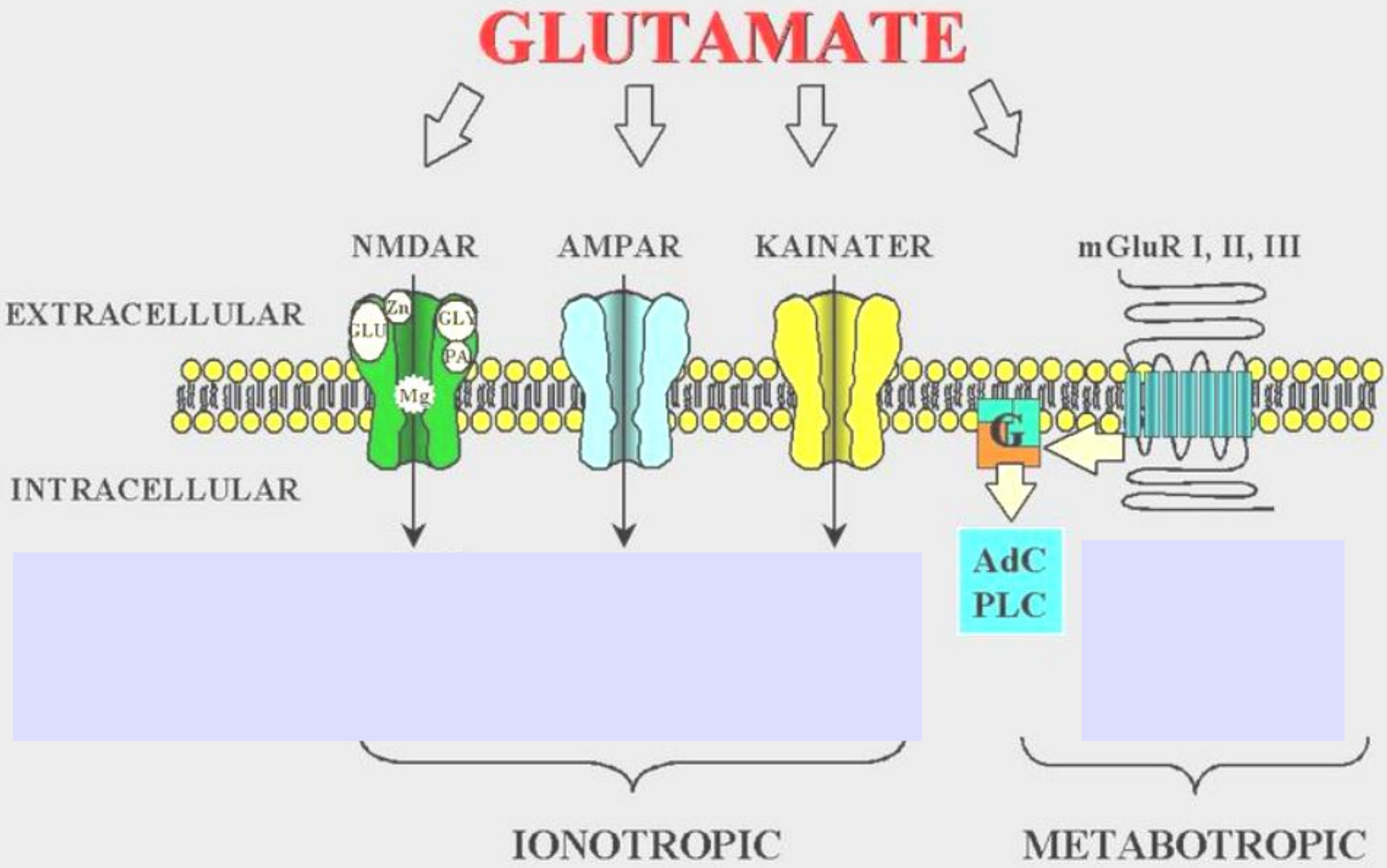
- Main excitatory neurotransmitter in the mammalian CNS
- 95% of excitatory synapses in the brain are glutamatergic
- Precursor for the GABA (major inhibitory neurotransmitter)



Enzymatic Pathways Involved in the Metabolism of Glutamate

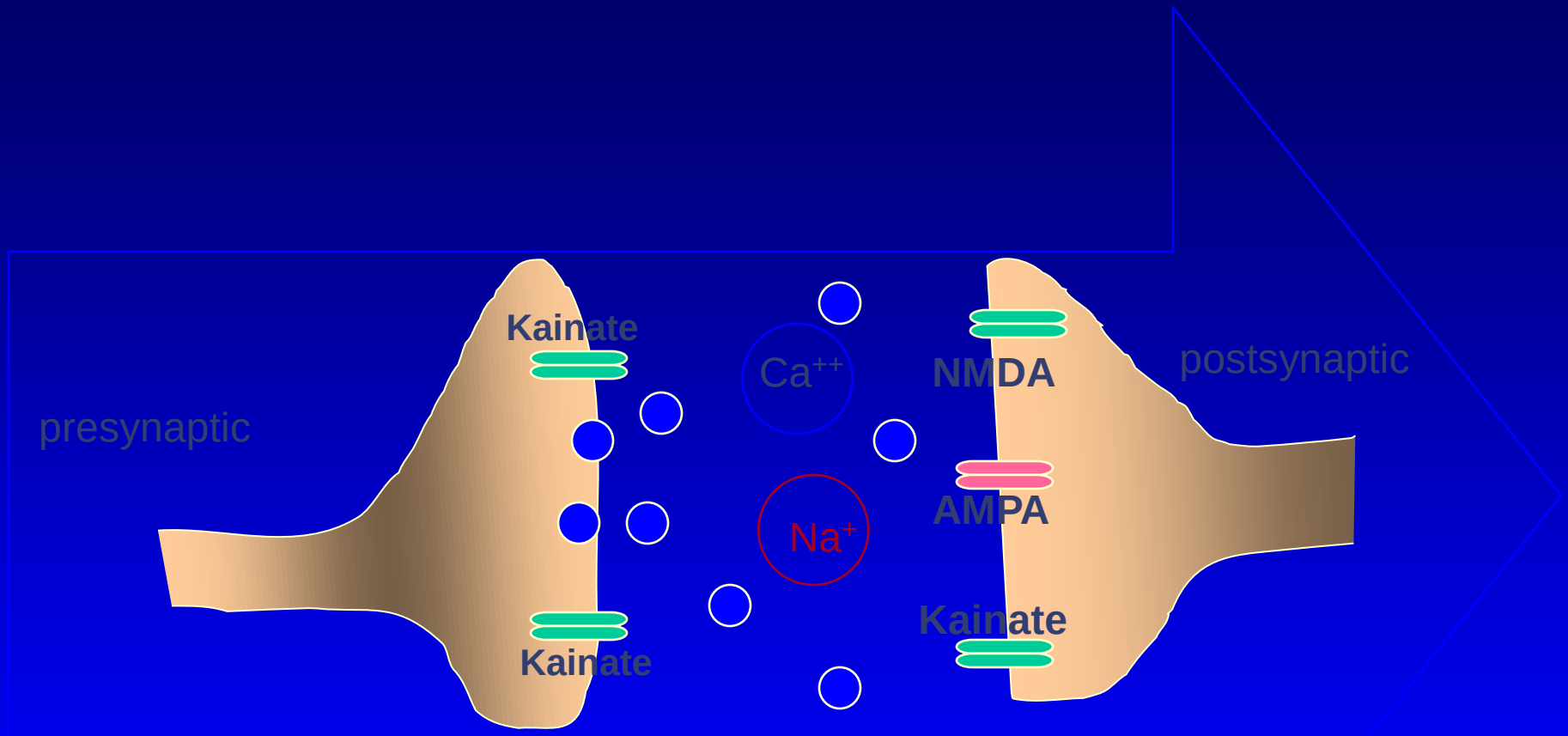


Enzymes are indicated as follows: 1) phosphate-activated glutaminase, 2) glutamine synthetase, 3) aspartate aminotransferase, 4) alanine aminotransferase, 5) glutamic acid decarboxylase, 6) GABA transaminase, 7) succinic semialdehyde dehydrogenase, 8) glutamate dehydrogenase, 9) α-ketoglutarate dehydrogenase.



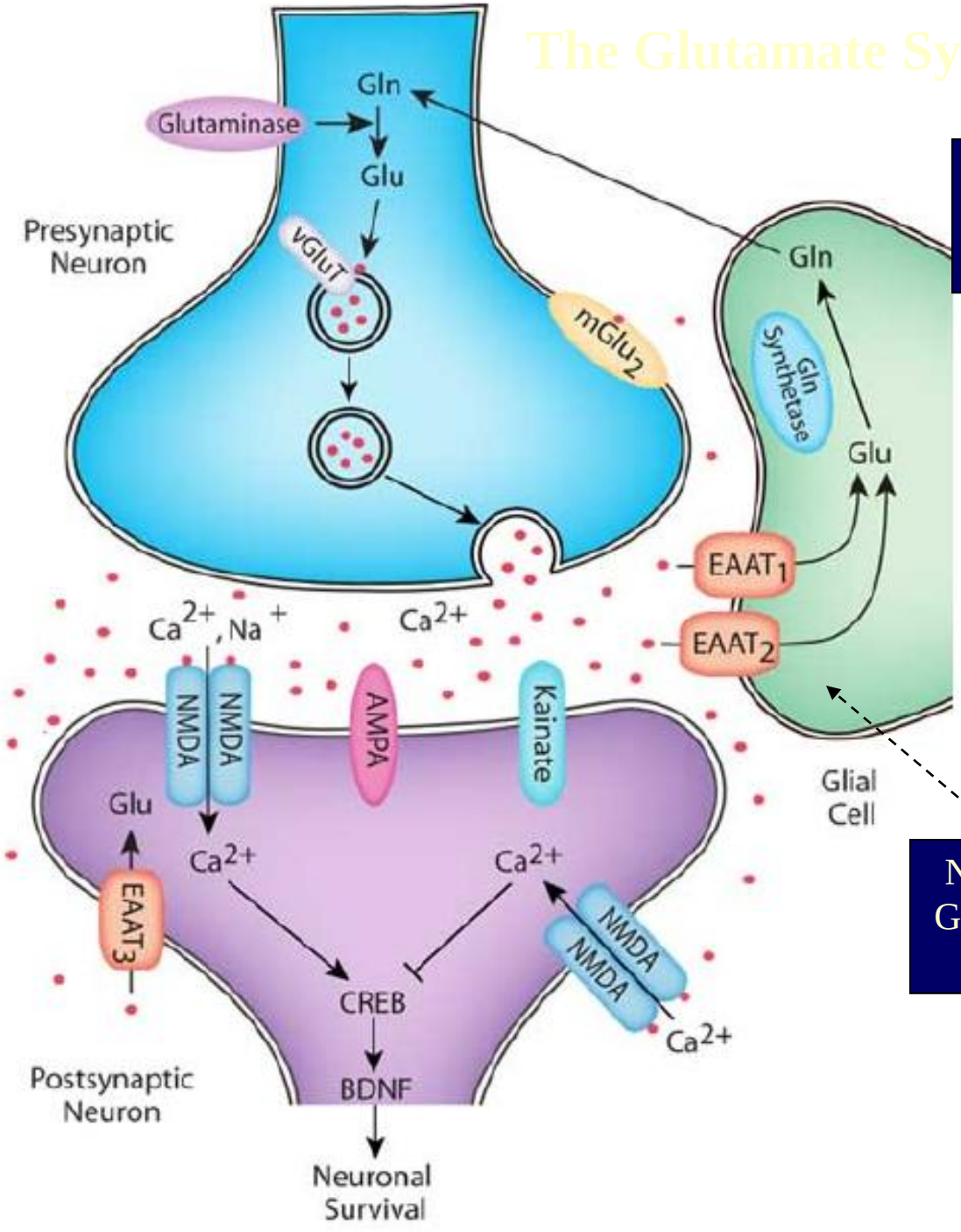
Fast synaptic transmission

Slow synaptic transmission



95% of excitatory synapses in the brain are glutamatergic

The Glutamate Synapse



Interconversion of glutamate to glutamine

Note – significant Glu uptake (mainly astrocytes)

Glutamate and CNS disorders

1) Stroke

Ischemia →

Glutamate and CNS disorders

1) Stroke

Ischemia → no ATP →

Glutamate and CNS disorders

1) Stroke

Ischemia → no ATP → increase Glutamate

→

Glutamate and CNS disorders

1) Stroke

Ischemia → no ATP → increase Glutamate

→ Over activation NMDA R & AMPA R →

Glutamate and CNS disorders

1) Stroke

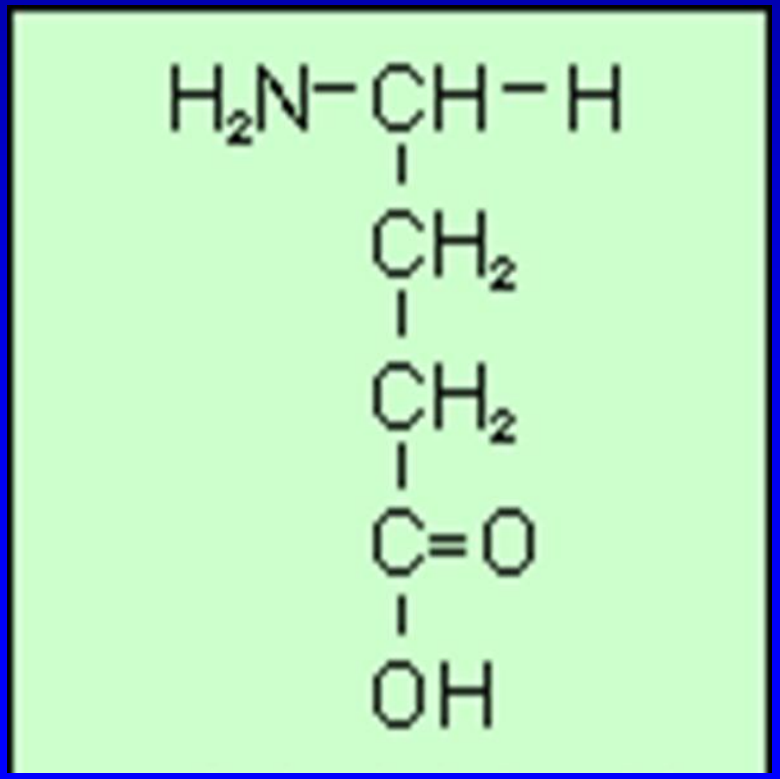
Ischemia → no ATP → increase Glutamate

→ Over activation NMDA R & AMPA R → increase Ca+ → cell death

2) dysfunction of glutamatergic transmission may also involve in schizophrenia-like symptoms, cognitive dysfunction, Depression and memory impairment

GABA

- Main inhibitory neurotransmitter in the mammalian CNS



GABA

- Main inhibitory neurotransmitter in the mammalian CNS

Ionotropic

$GABA_A$

Heterooligomeric protein complex that consists of several binding sites coupled to an integral **Cl^- channel**

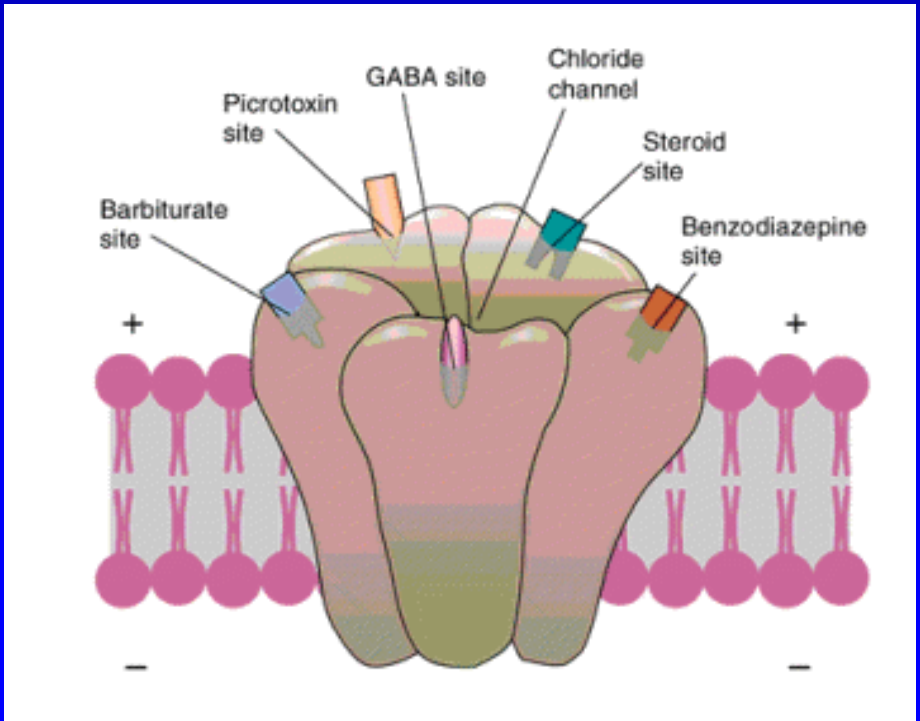
Metabotropic

$GABA_B$

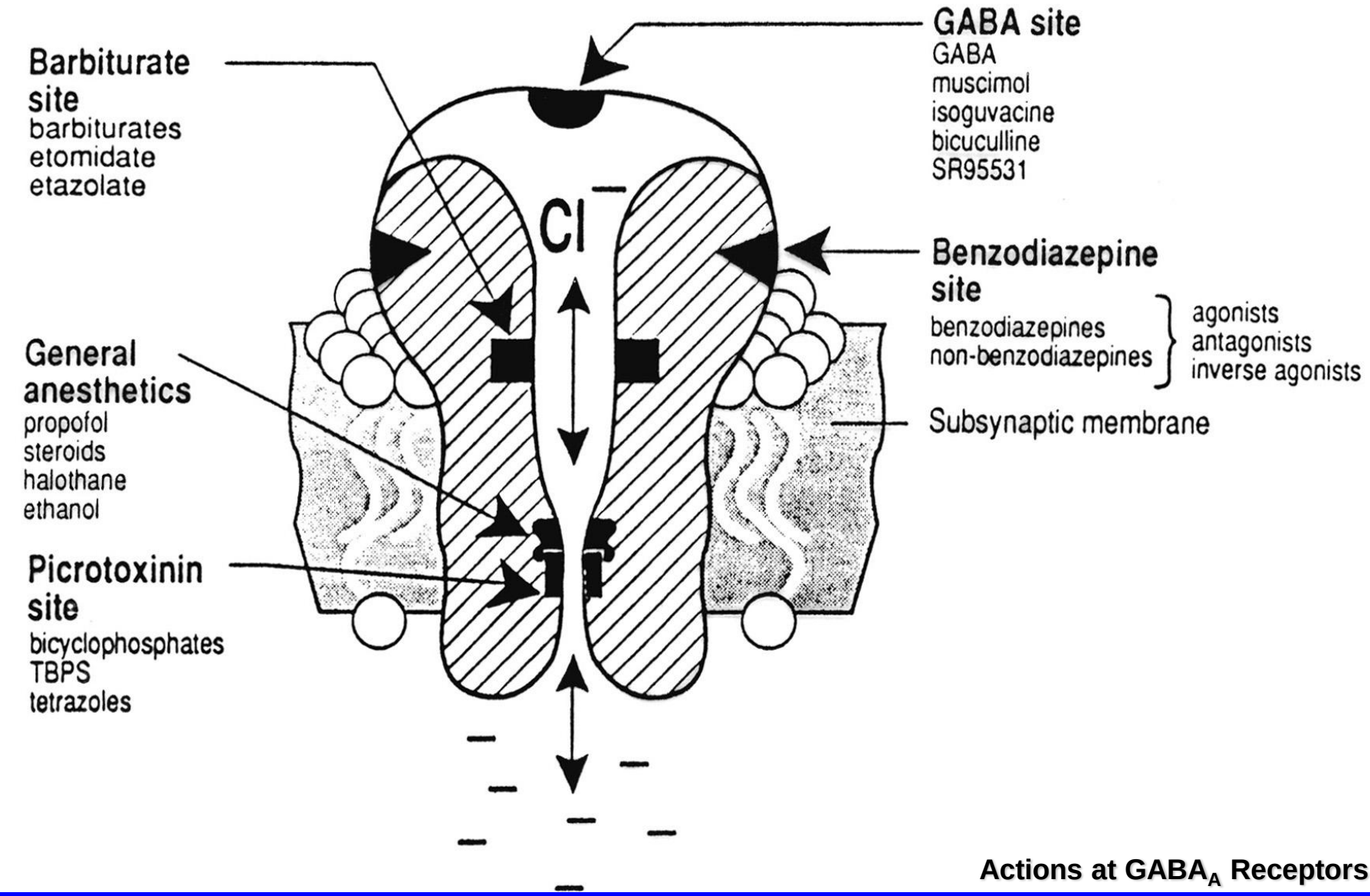
G - protein coupled receptor, seven transmembrane domain protein

GABA-A- ionotropic receptor

- An integral chloride channel activated by competitive agonists: GABA and muscimol
- Blocked by convulsant bicuculine (competitive antagonist) and picrotoxin (noncompetitive antagonist)
- Allosterically modulated by benzodiazepines and barbiturates, which potentiate the effect of GABA

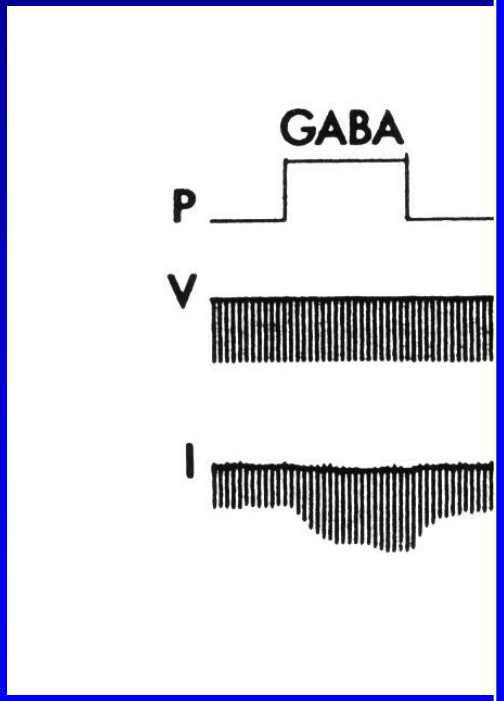


$GABA_A$ receptor

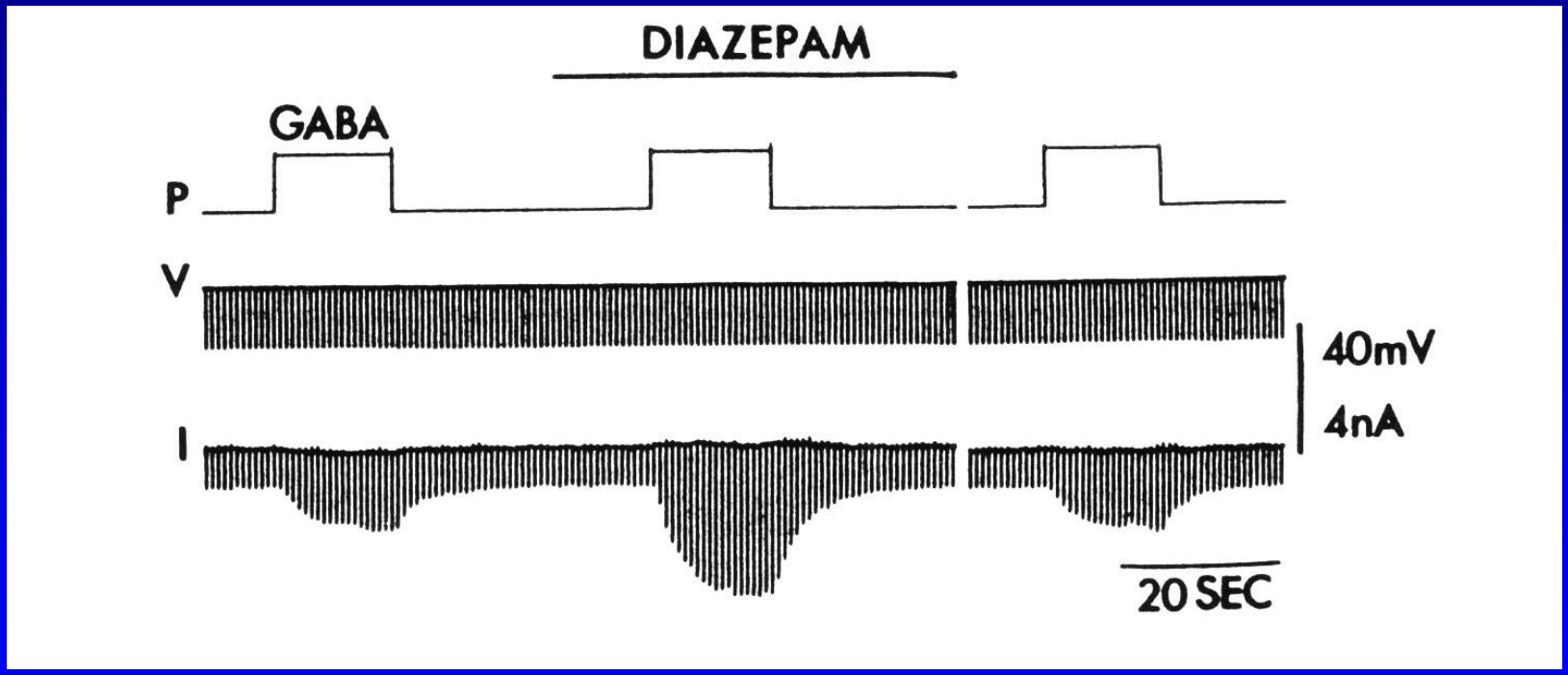


Actions at $GABA_A$ Receptors

Benzodiazepines potentiate GABA-induced responses

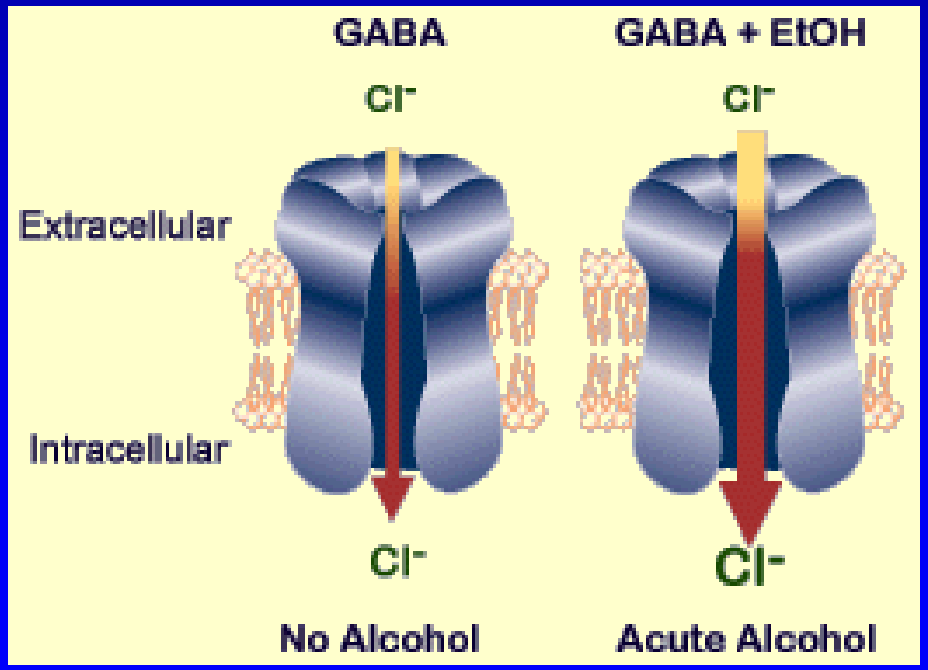


Benzodiazepines potentiate GABA-induced responses



$GABA_A$ and ethanol

- Ethanol facilitates GABA ability to activate the receptor and prolongs the time that the Cl^- channel remains open



GABA

Synthesis

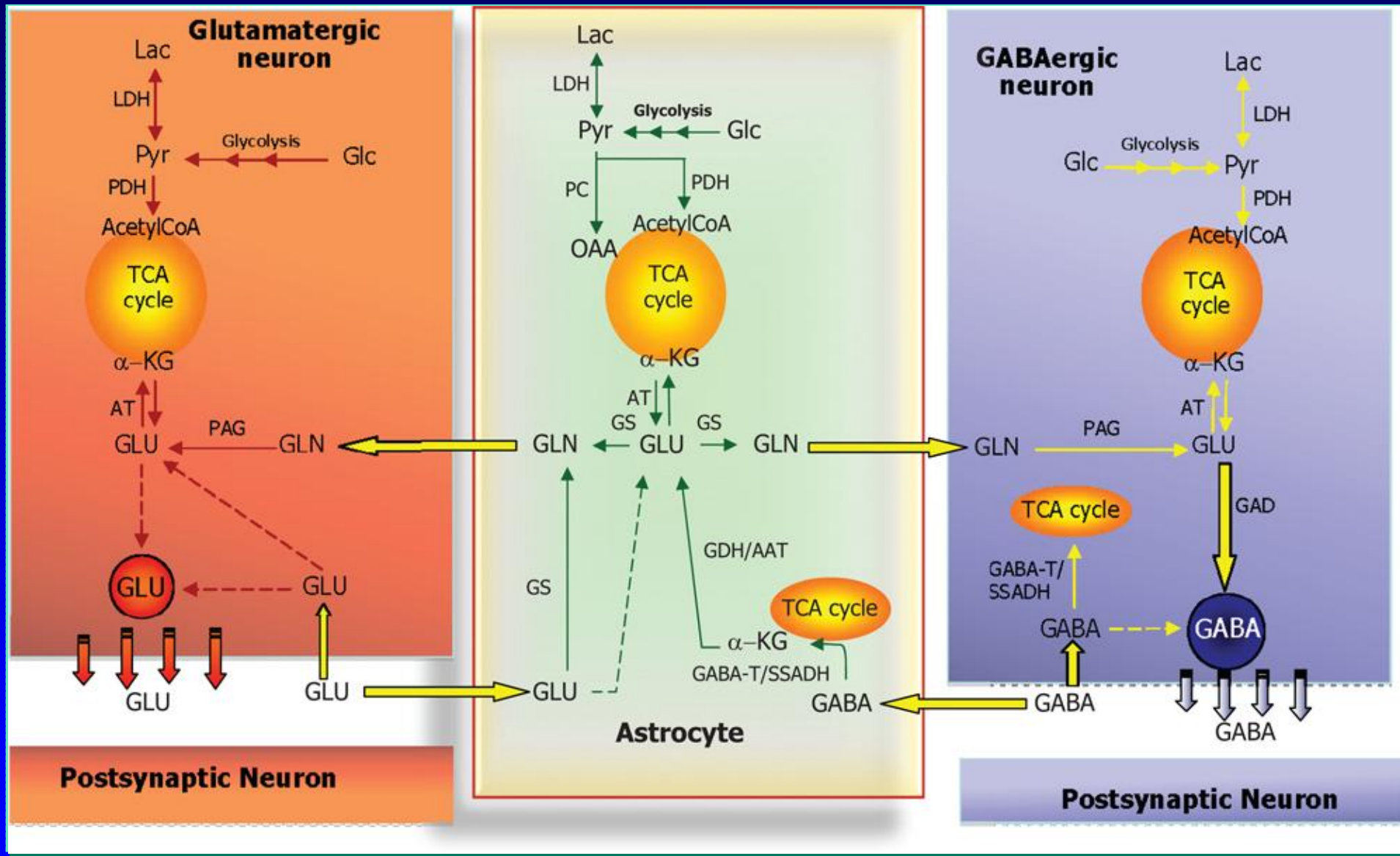
GABA is formed by the α-decarboxylation of glutamate in the reaction catalyzed by GAD (glutamic acid decarboxylase)

GABA

Degradation

GABA —***GABA-T***→ succinic semialdehyde

GABA is catabolized into the succinic semialdehade
in the reaction catalyzed by **GABA-T** (***GABA-Transaminase***)


Glutamatergic neuron
Lac
LDH
Pyr
Glycolysis
Glc
PDH
AcetylCoA
TCA cycle
α–KG
AT
GLU
PAG
GLN
GLU
GLU
GLU
Postsynaptic Neuron
Lac
LDH
Pyr
Glycolysis
Glc
PC
PDH
AcetylCoA
OAA
TCA cycle
α–KG
AT
GS
GS
GLN
GLU
GLN
GS
GDH/AAT
TCA cycle
α–KG
GABA-T/SSADH
GLU
GABA
Astrocyte
GABAergic neuron
Lac
LDH
Glc
Glycolysis
Pyr
PDH
AcetylCoA
TCA cycle
α–KG
AT
GLN
PAG
GLU
GAD
TCA cycle
GABA-T/ SSADH
GABA
GABA
GABA
GABA
Postsynaptic Neuron

EEG and Seizures

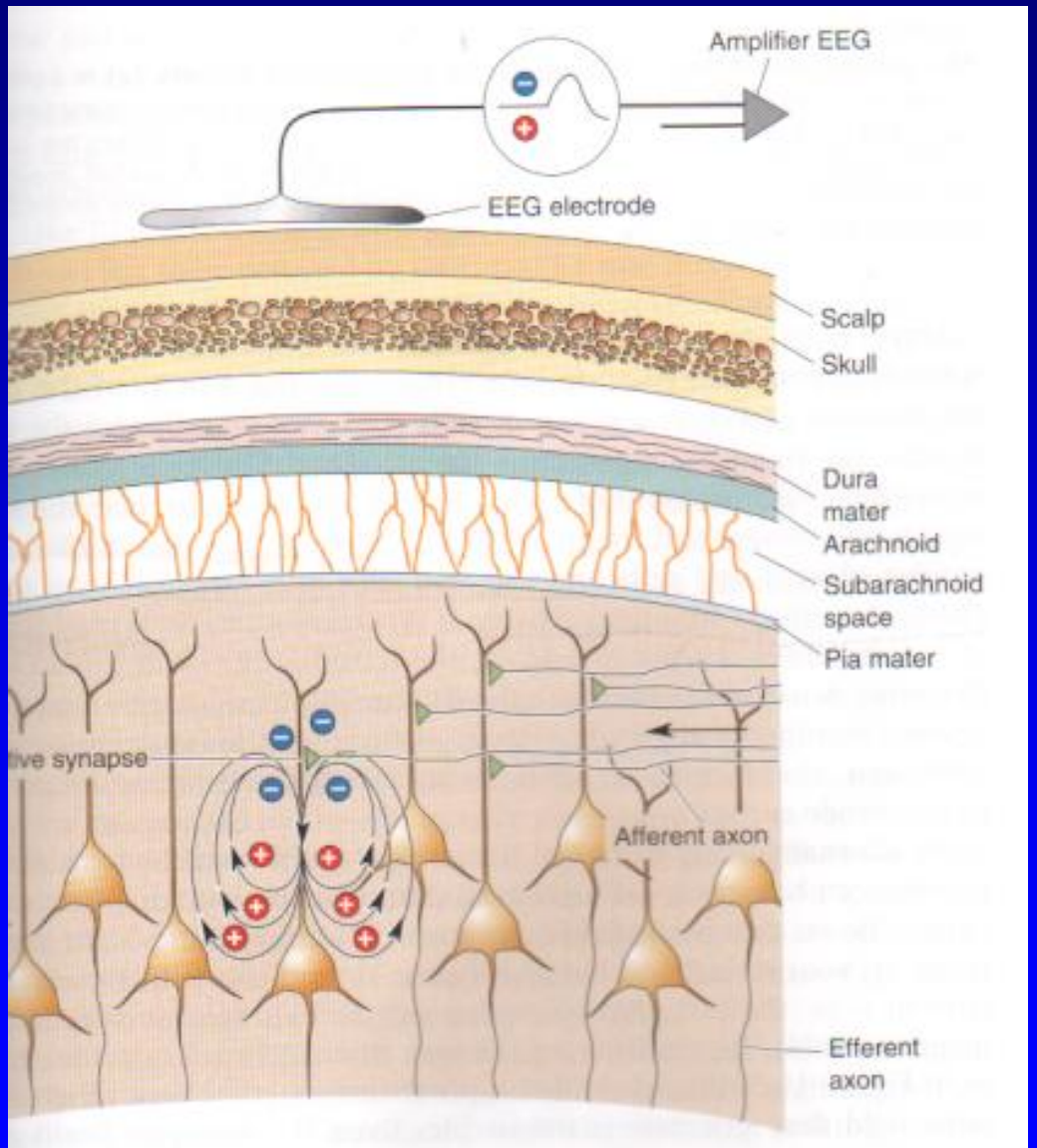
Electroencephalography (EEG)

- Electro: relating to electricity.
- Encephalo: relating to the brain.
- Graphy: writing or representation produced in a specified manner.

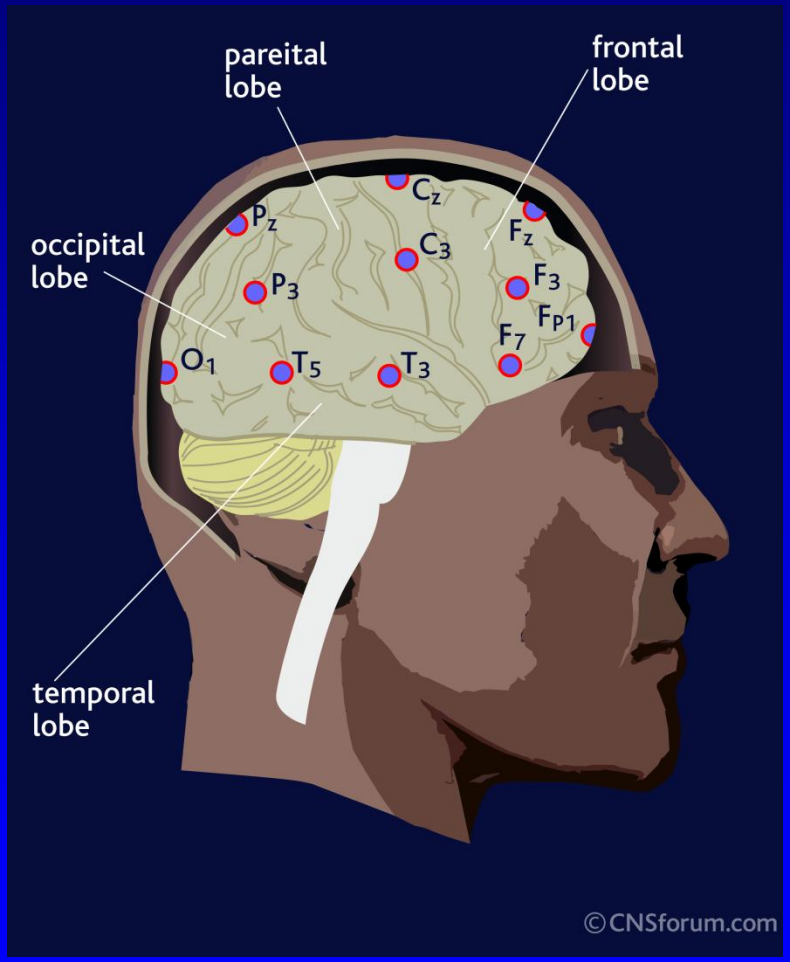
- Therefore, EEG produces a graphed representation of the electrical activity occurring in a person's brain.

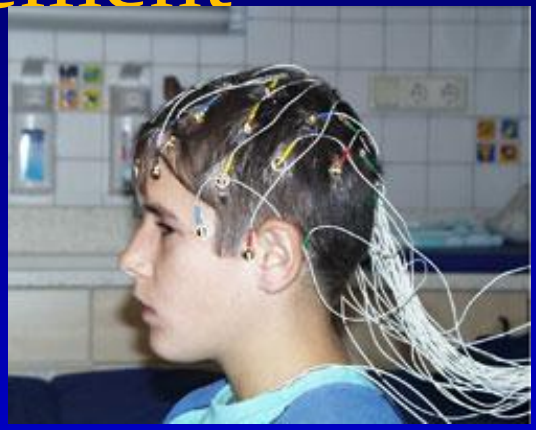
Origin of EEG waves

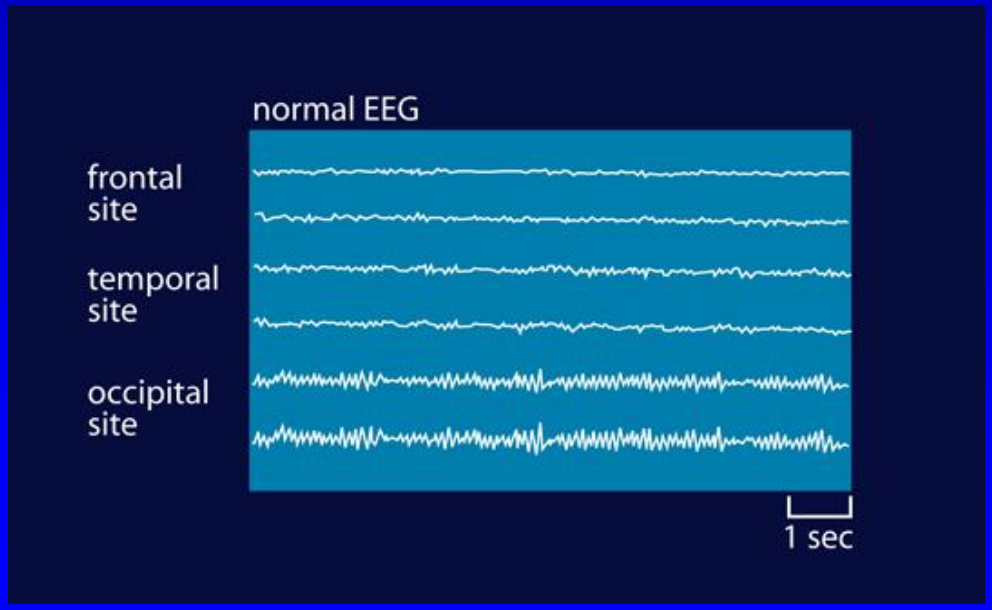
EEG is the record of electrical activity of brain(superficial layer i.e. the dendrites of pyramidal cells) by placing the electrodes on the scalp.



EEG Electrode Placement

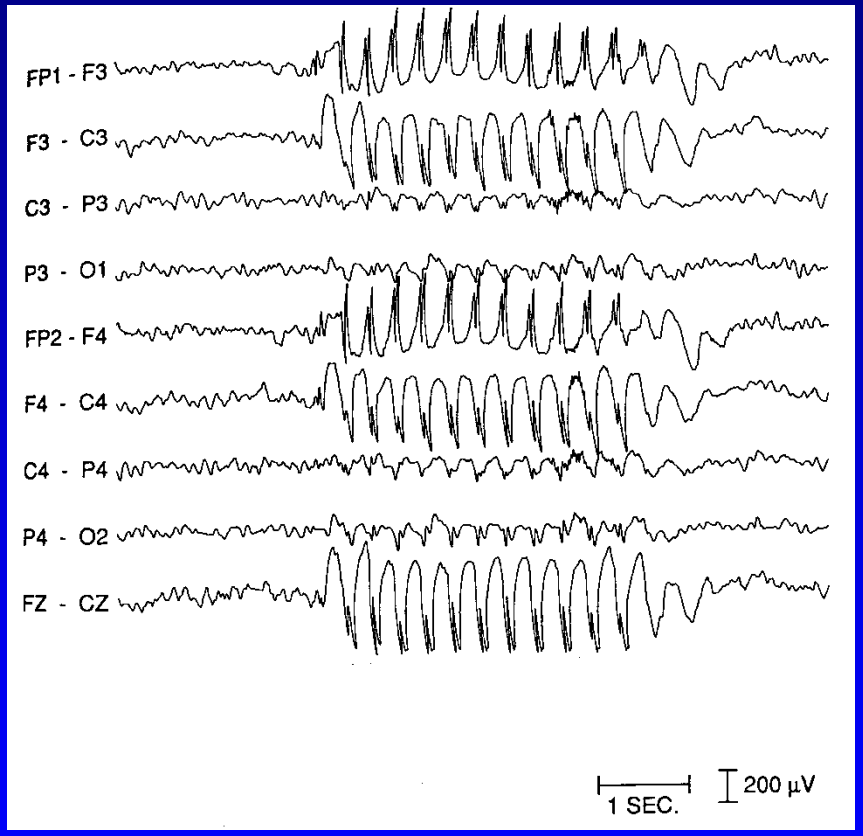






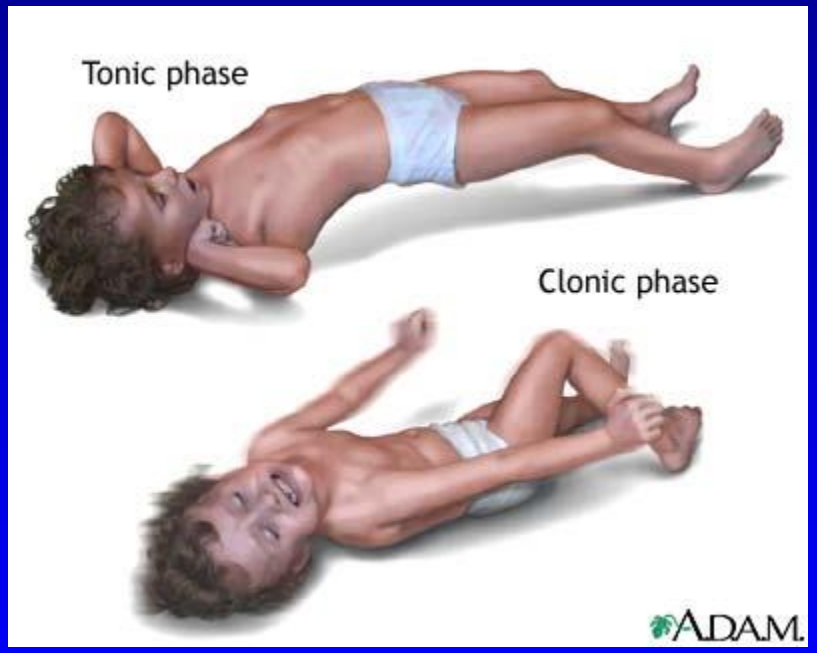
Seizure

- Abnormal electrical discharge.
- Initially synchronous
- May have no motor component



Convulsion

- Indicative of seizure activity
- Motoric output of synchronous neuronal firing.



Primary (Idiopathic) Seizure Disorders

- No identifiable cause
- Not the result of overt disease or injury
- In short, a guess.

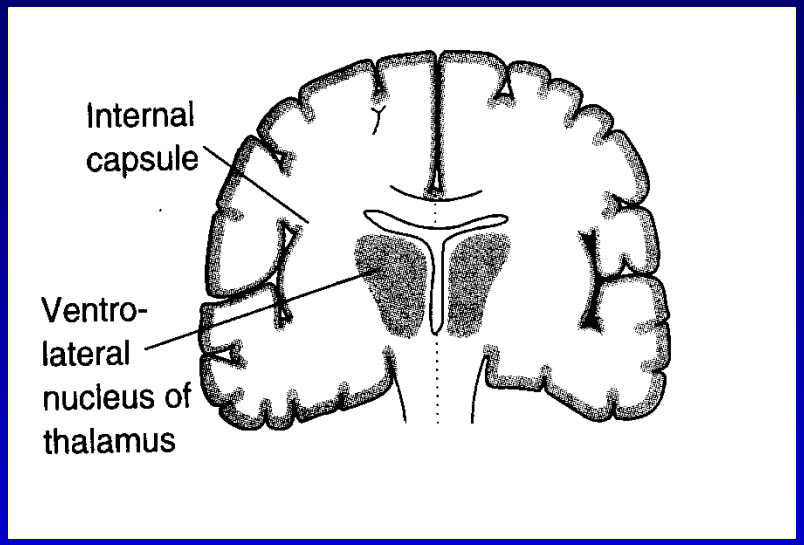
Secondary (Symptomatic) Seizure Disorders

- Associated with or secondary to disease or injury
- e.g. trauma, neoplasm, or infection.

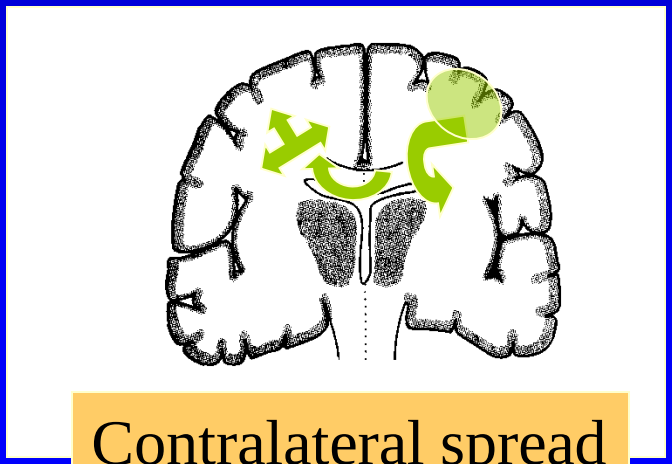
Epilepsy

- Seizures and/or convulsions can be acute and isolated…
- …they can be associated with a treatable organic disorder…
- When seizures/convulsions are chronic and of undefined origin…
- …the condition is described as epilepsy.

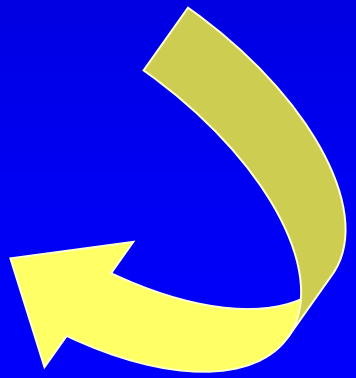
Scheme of Seizure Spread



Simple (Focal) Partial Seizures



Contralateral spread

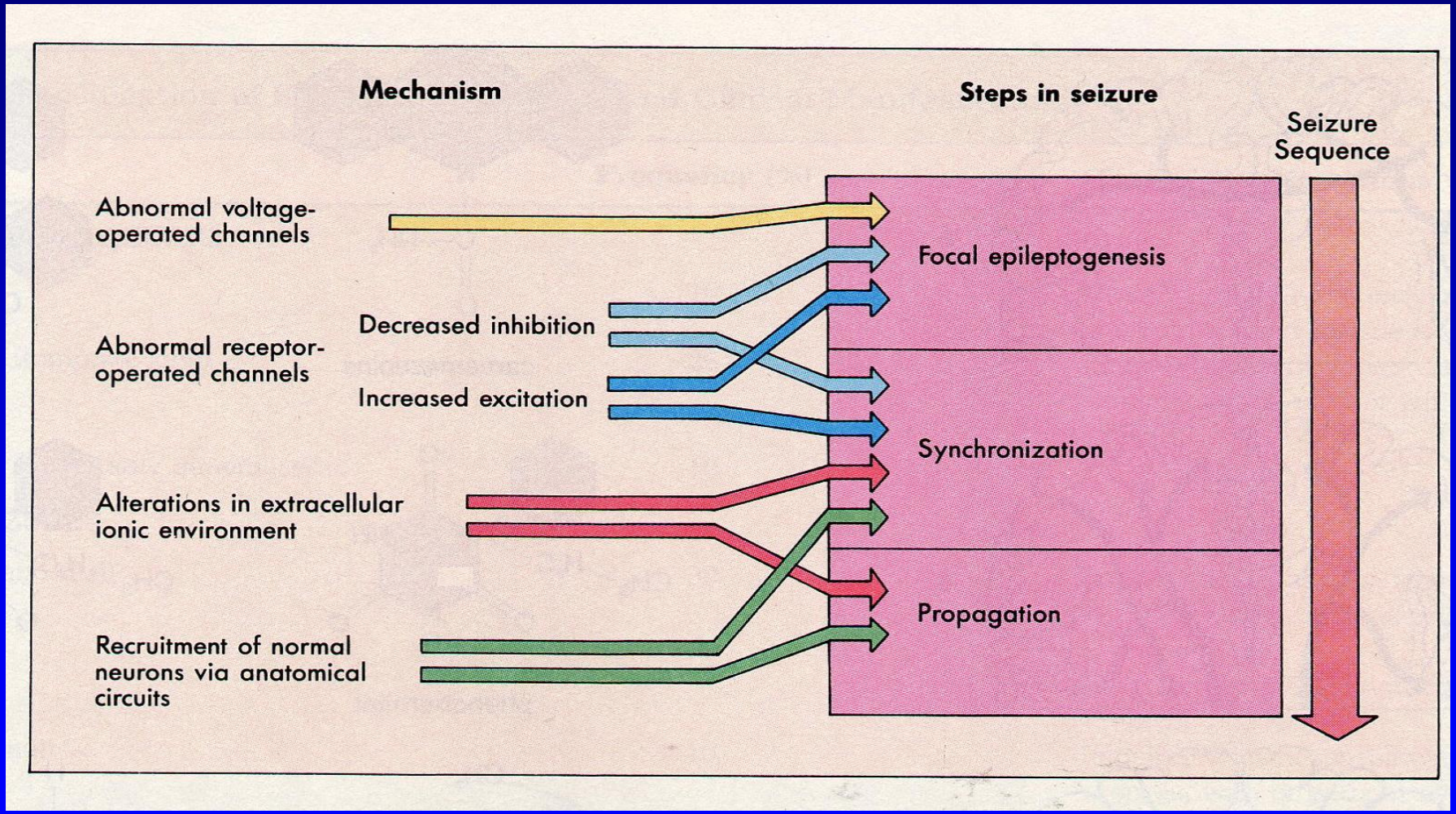


From M.I. Davila-Garcia, Howard Univ., 2003

Seizure Pathophysiology

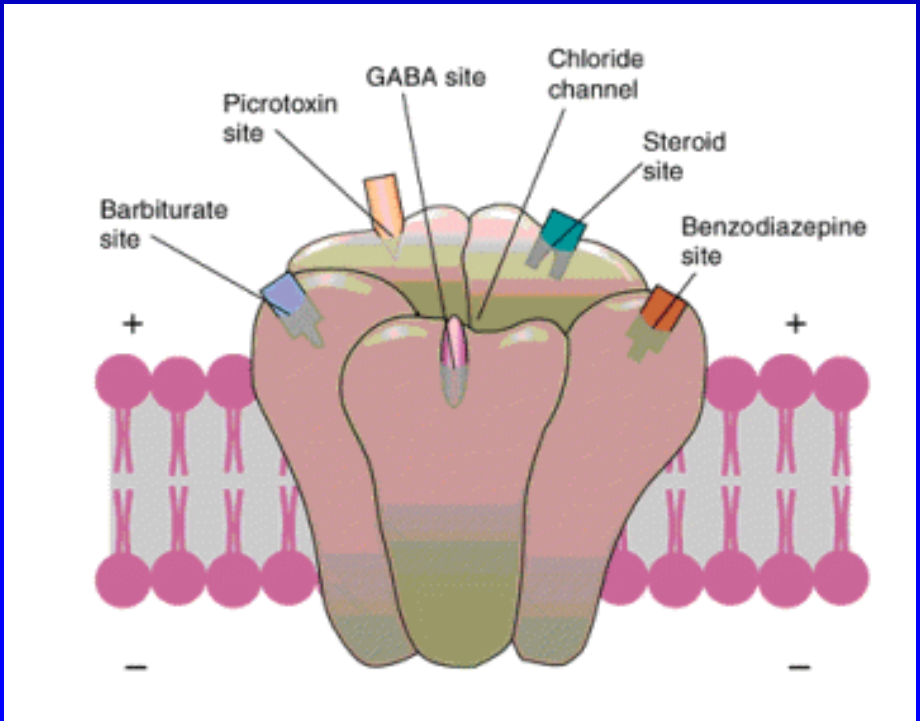
- Altered ionic conductance (increased excitability) of neuron.
- Reduced inhibitory neuronal (primarily GABAergic) control.
- Increased excitatory neuronal (primarily glutamatergic) control.
- Probable mechanisms tend to overlap.

Cellular and Synaptic Mechanisms of Epileptic Seizures

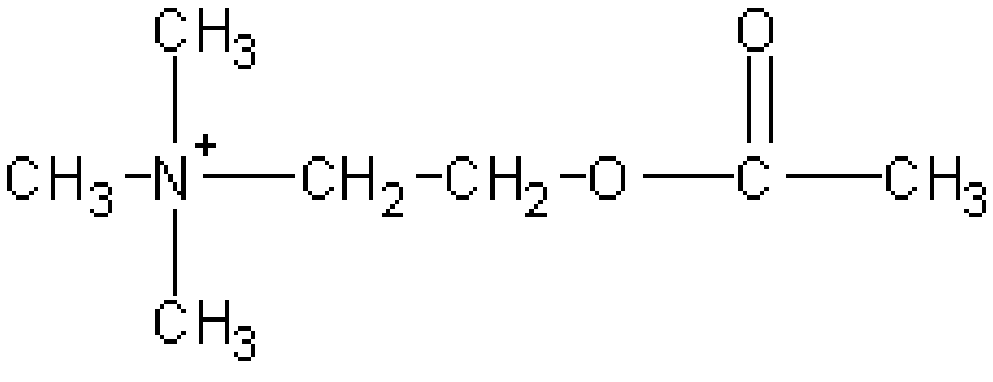


GABA-A- ionotropic receptor

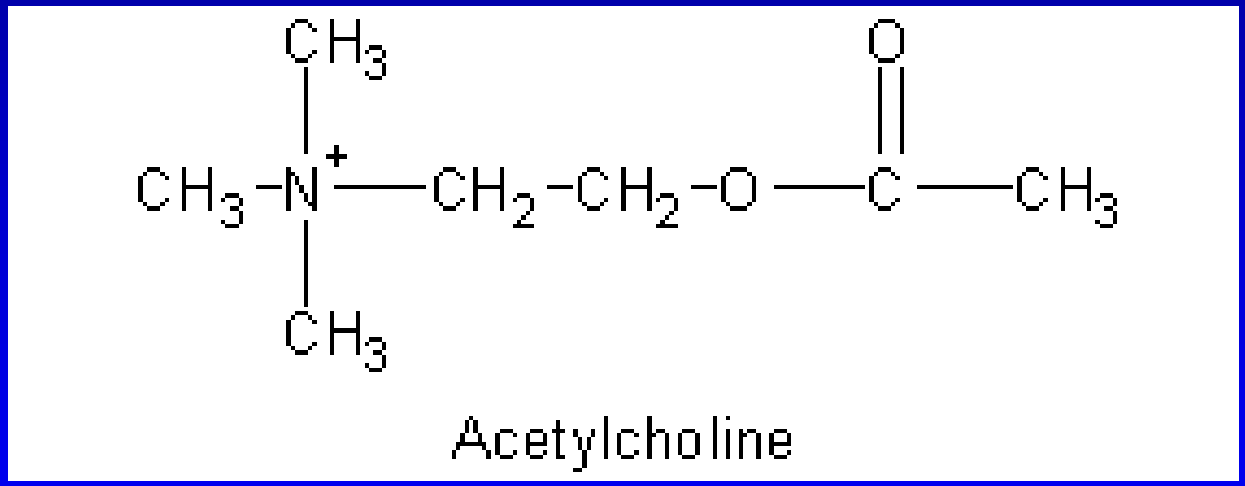
- An integral chloride channel activated by competitive agonists: GABA and muscimol
- Blocked by convulsant bicuculine (competitive antagonist) and picrotoxin (noncompetitive antagonist)
- Allosterically modulated by benzodiazepines and barbiturates, which potentiate the effect of GABA



Acetylcholine

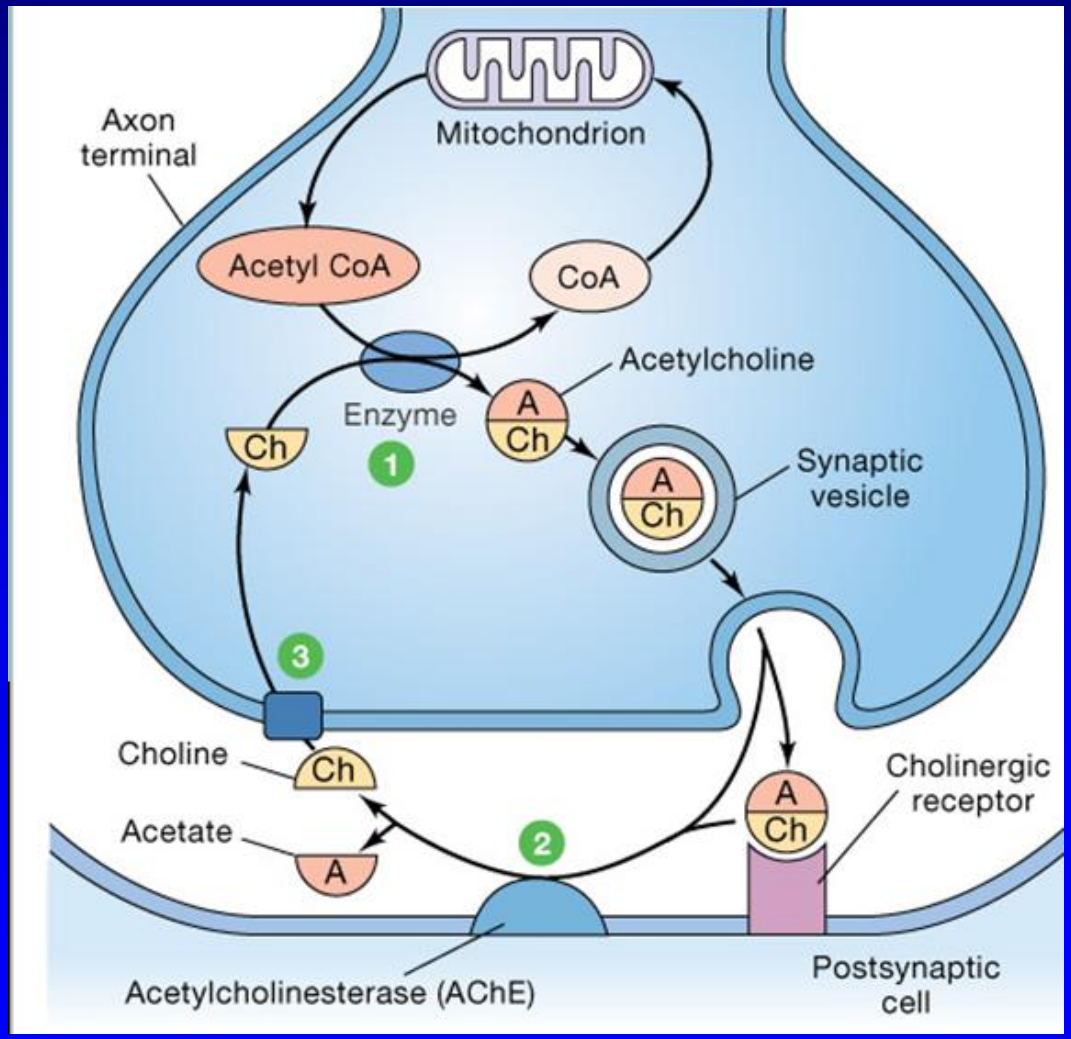


Acetylcholine

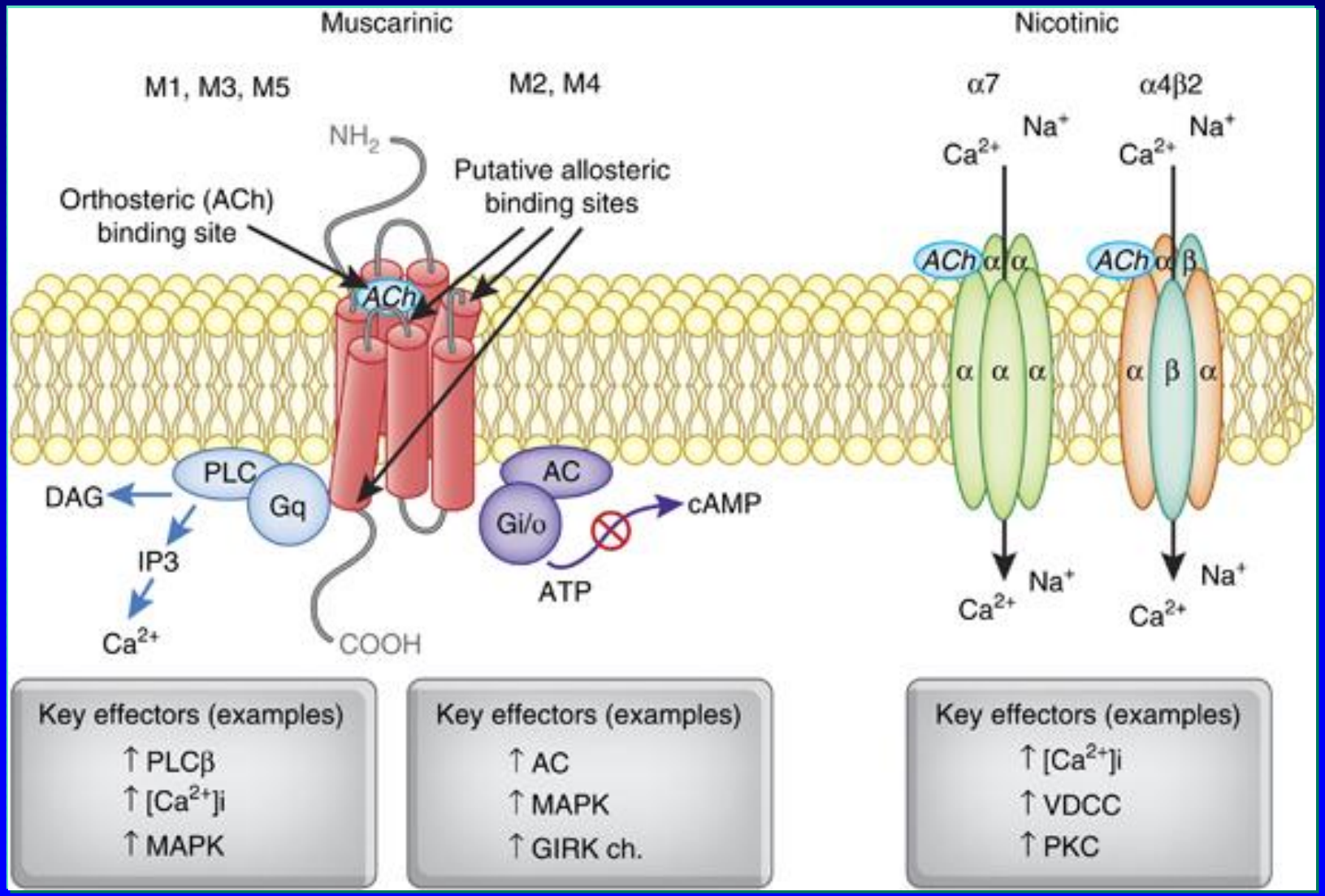


Choline + Acetyl CoA $\xrightarrow{\text{ChAT}}$ Acetyl choline + CoA

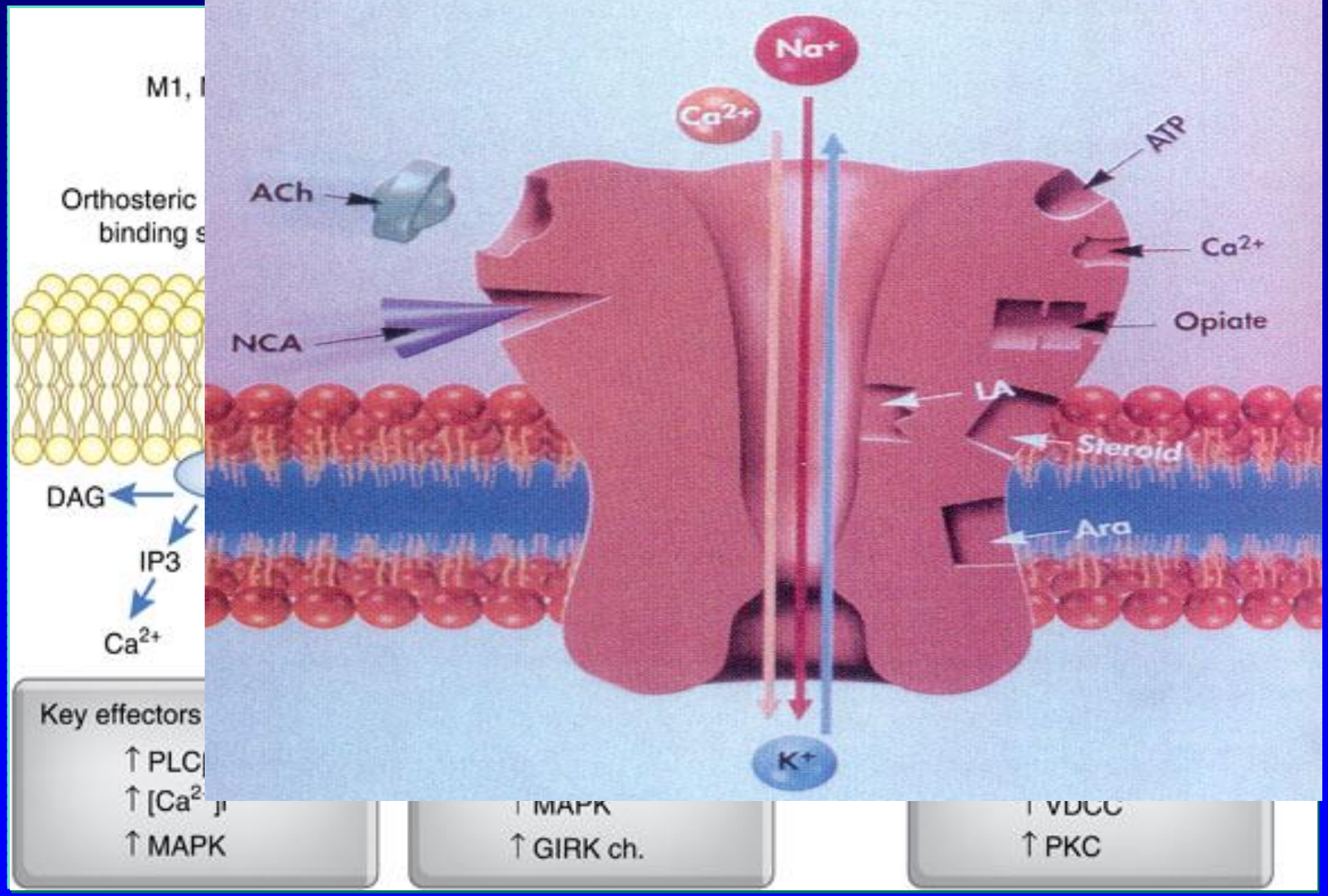
Acetylcholine synapse



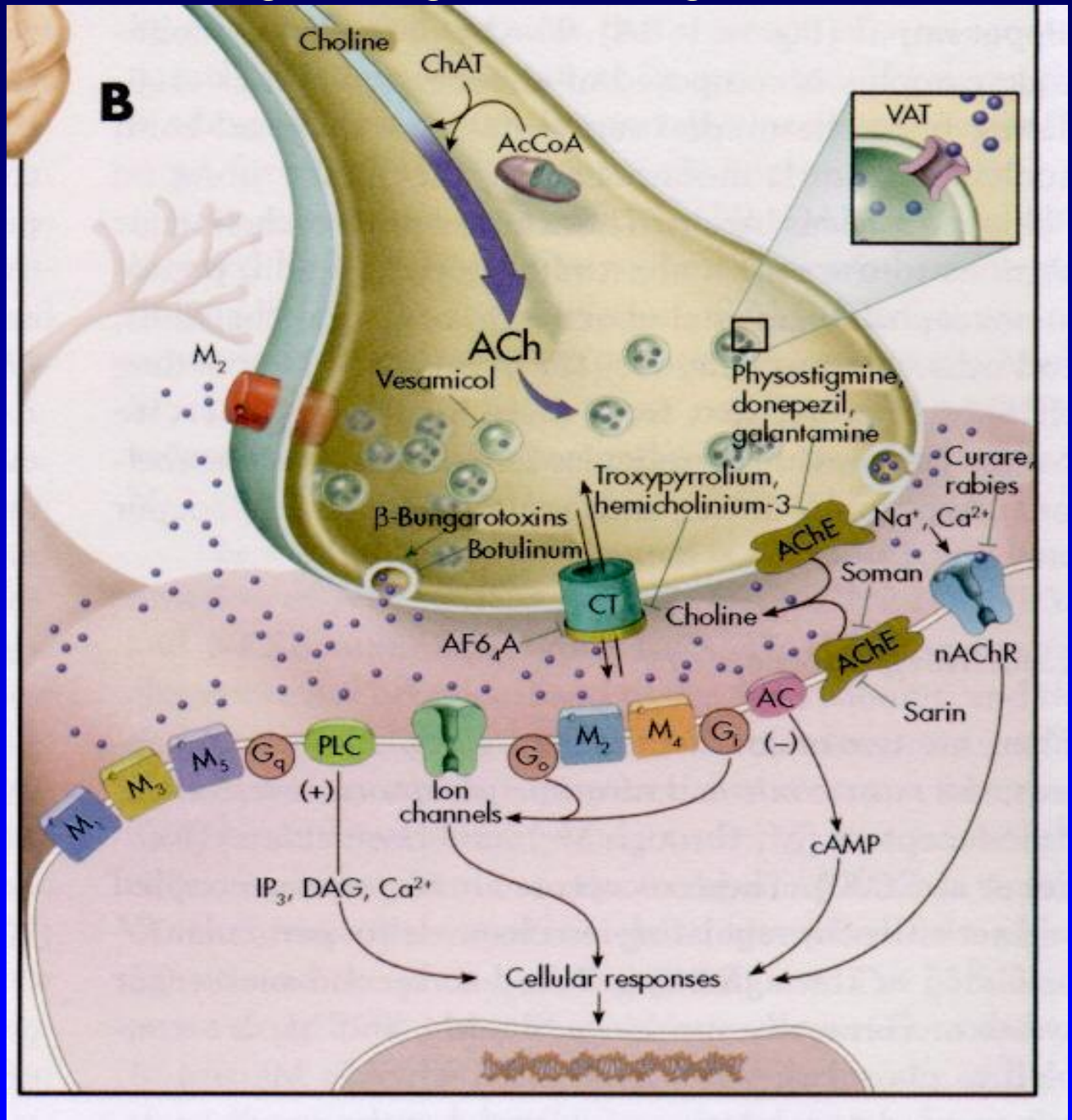
Acetylcholine receptors



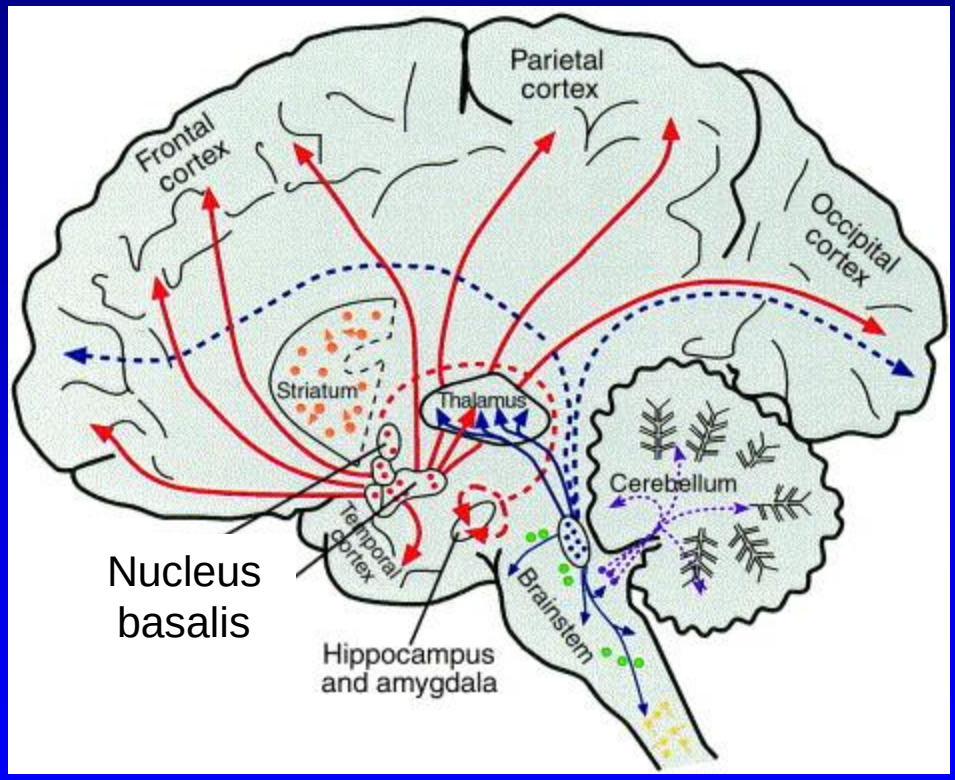
Acetylcholine receptors



Drugs acting at cholinergic terminal

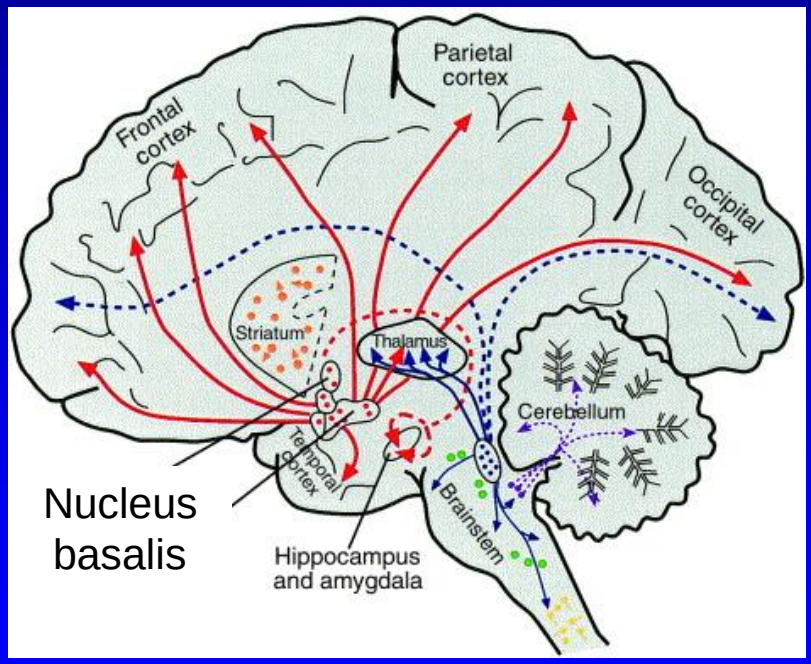


Acetylcholine Pathway



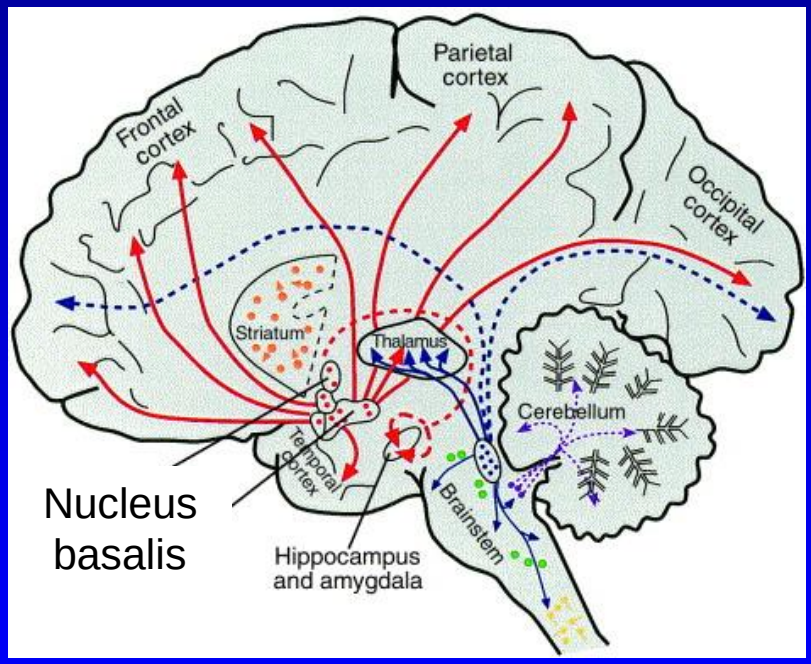
Acetylcholine Pathway

- arousal and reward
- enhancement of sensory perceptions
- sustaining attention



Acetylcholine Pathway

- arousal and reward
- enhancement of sensory perceptions
- sustaining attention



Alzheimer's disease – loss of cholinergic cells in nucleus basalis

Neuromodulators

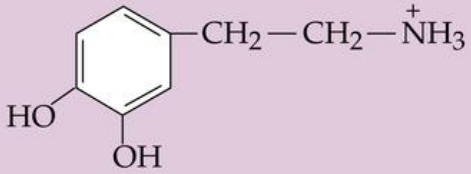
Biogenic Amines

SMALL-MOLECULE NEUROTRANSMITTERS

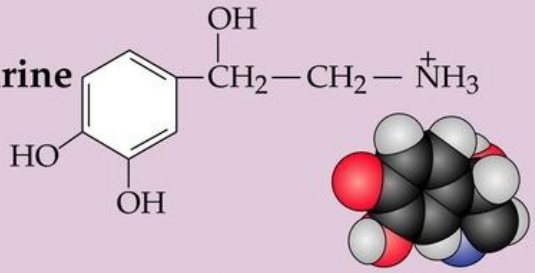
BIOGENIC AMINES

CATECHOLAMINES

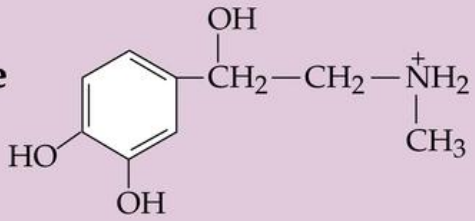
Dopamine



Norepinephrine

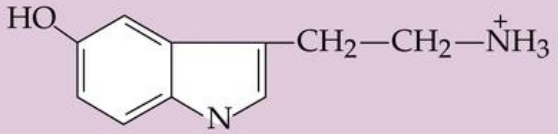


Epinephrine

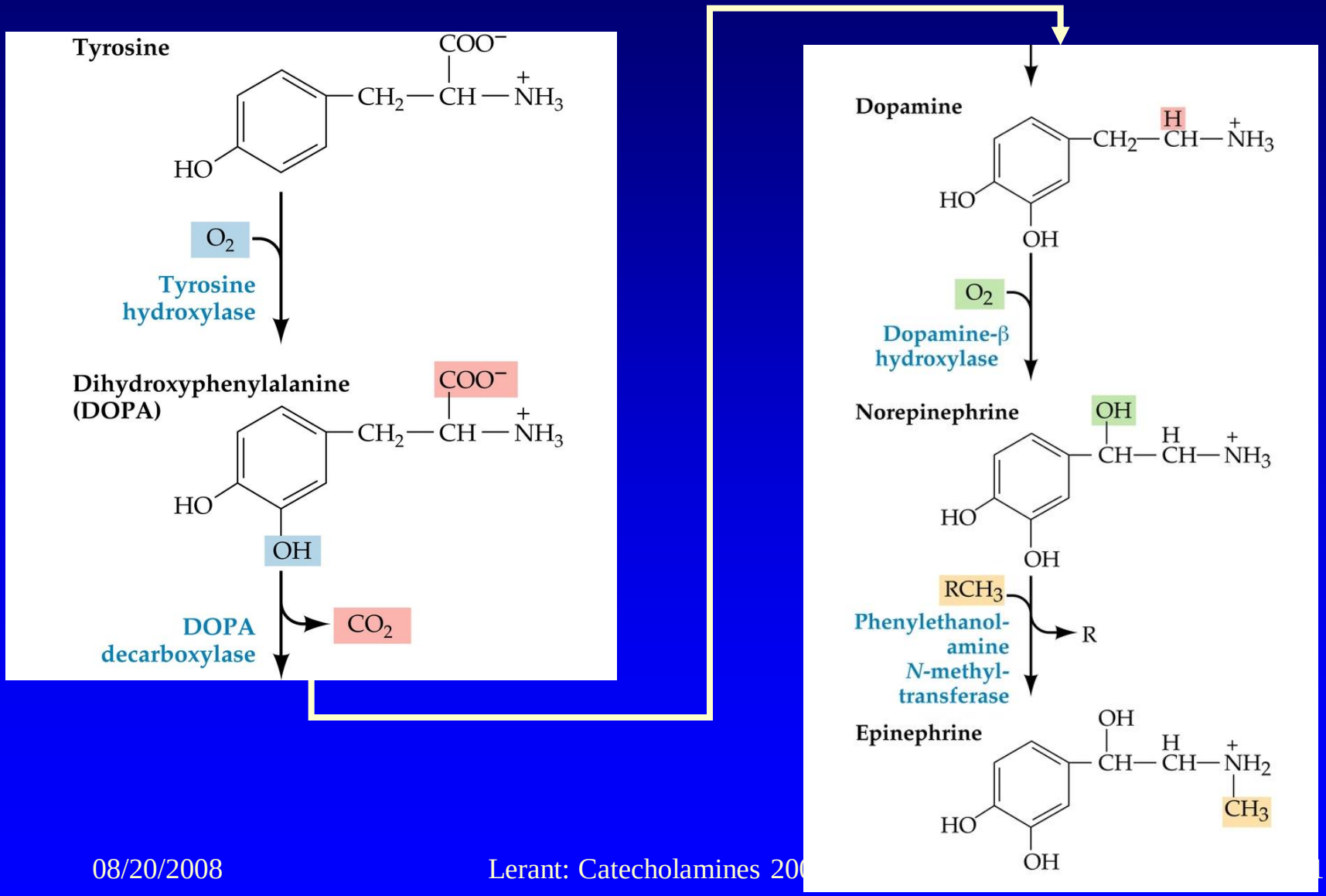


INDOLEAMINE

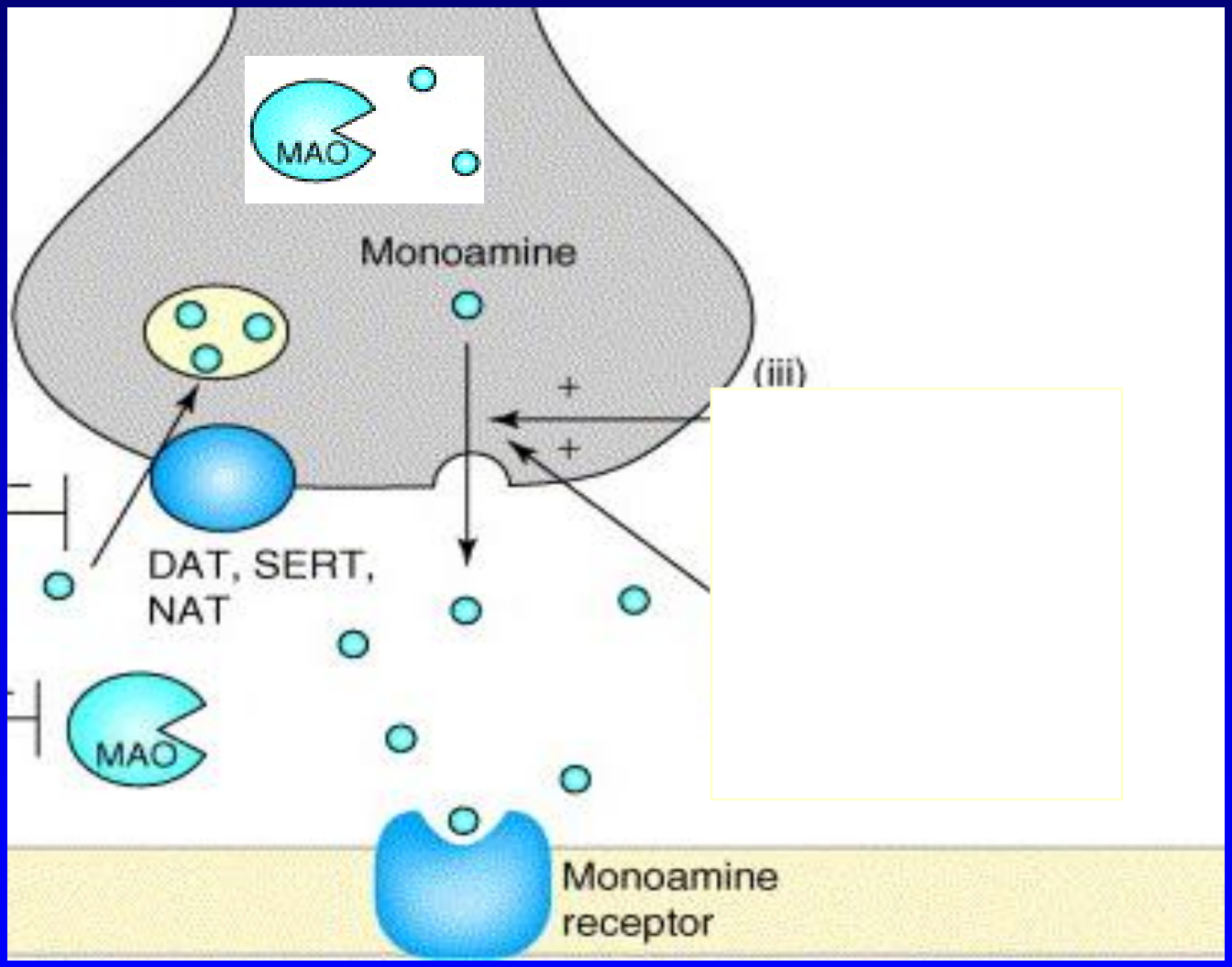
Serotonin



The biosynthetic pathway for the catecholamine neurotransmitters



Biogenic Amines Synapses



MAO : Monoamine Oxidase

Dopamine

Dopamine receptors

- G protein-coupled receptors

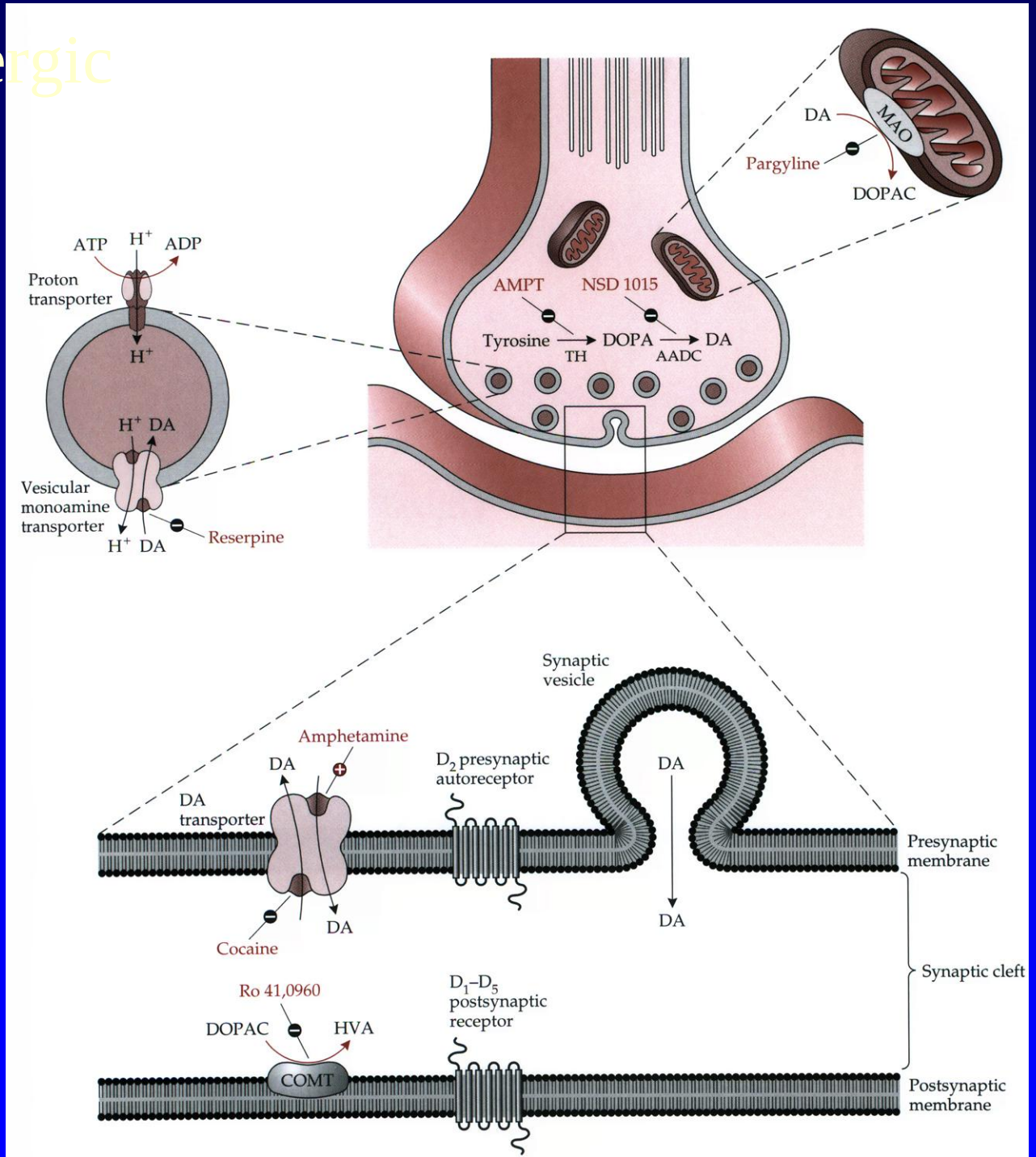
Dopamine receptors

- G protein-coupled receptors
- D1 → excite
- D2 → inhibit
- D3 → inhibit
- D4 → inhibit
- D5 → excite

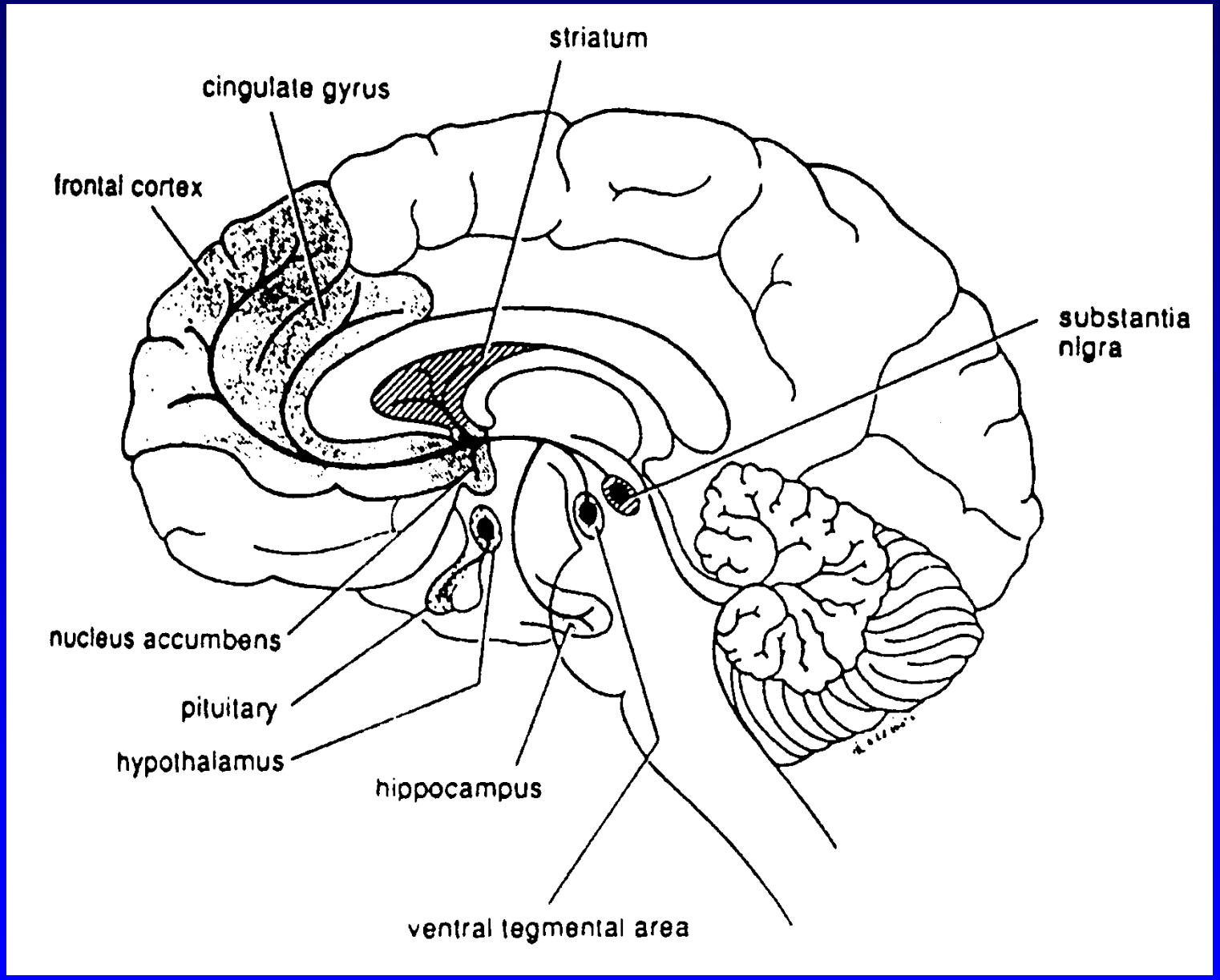
Dopamine receptors

- G protein-coupled receptors
- D1 → excite
- D2 → inhibit ★ Mainly presynabtic (Autoreceptor)
- D3 → inhibit
- D4 → inhibit
- D5 → excite

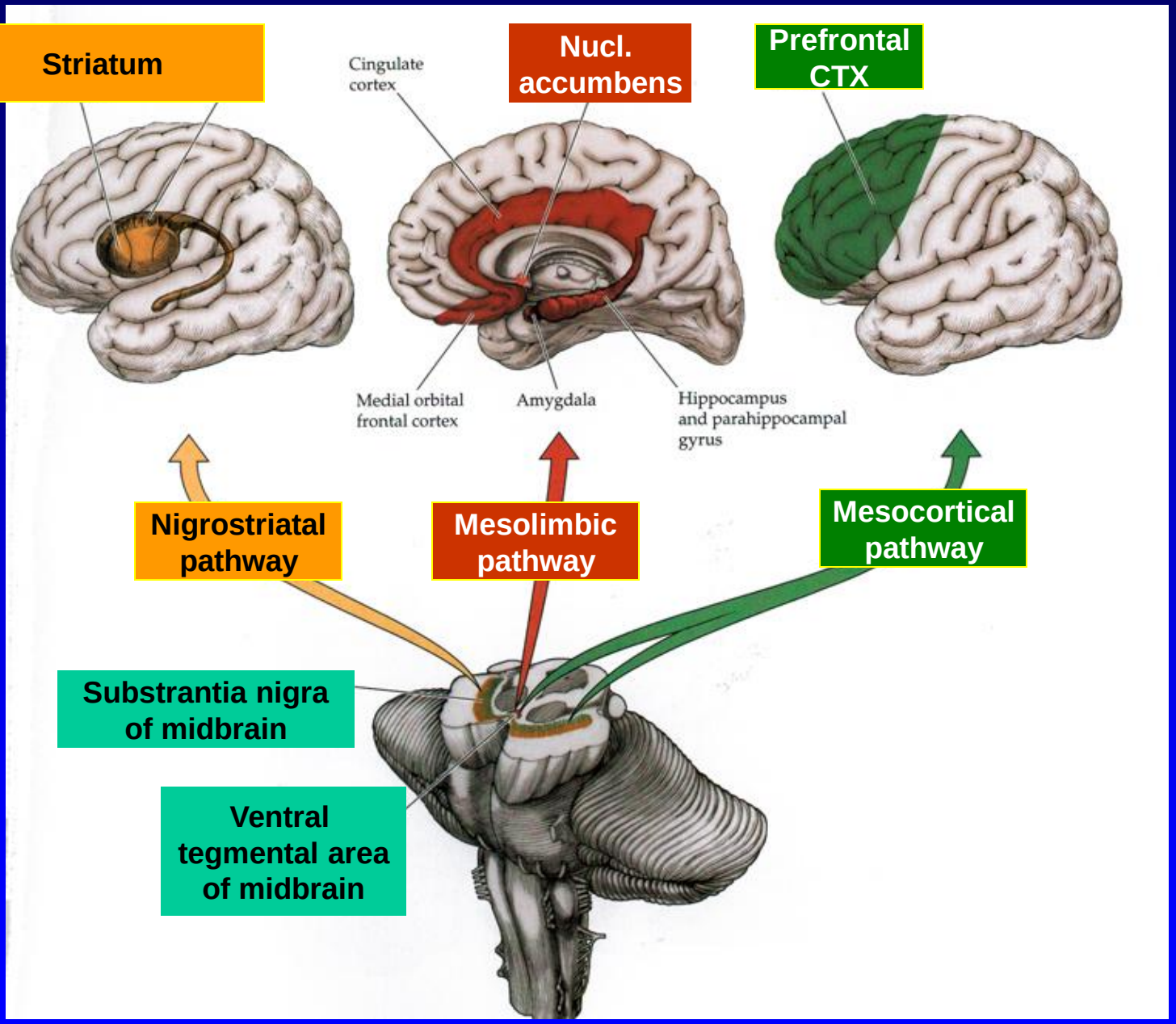
3. Dopaminergic (DA) synapse



Dopamine Pathways



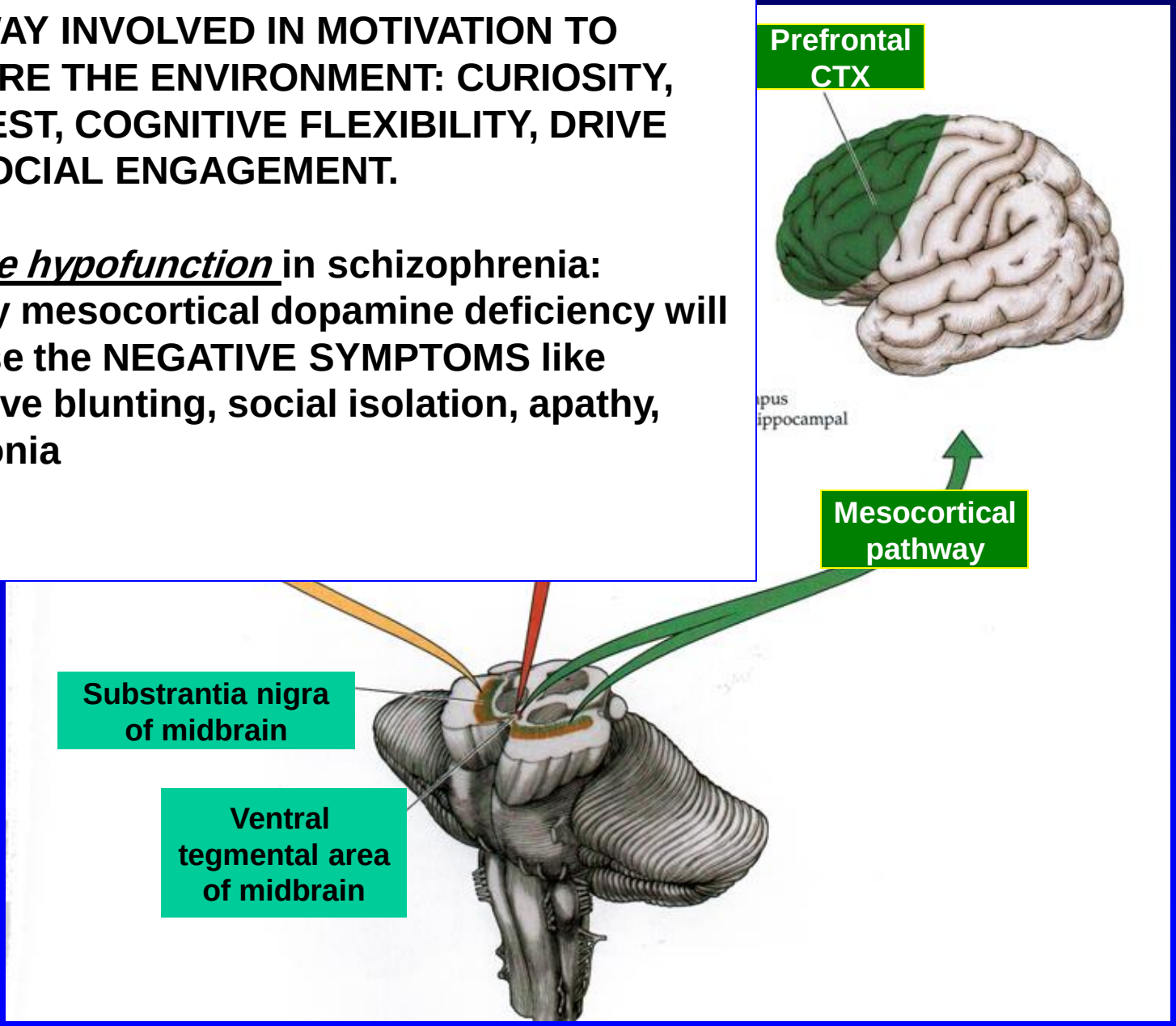
DOPAMINERGIC PATHWAYS



DOPAMINERGIC PATHWAYS

PATHWAY INVOLVED IN MOTIVATION TO EXPLORE THE ENVIRONMENT: CURIOSITY, INTEREST, COGNITIVE FLEXIBILITY, DRIVE FOR SOCIAL ENGAGEMENT.

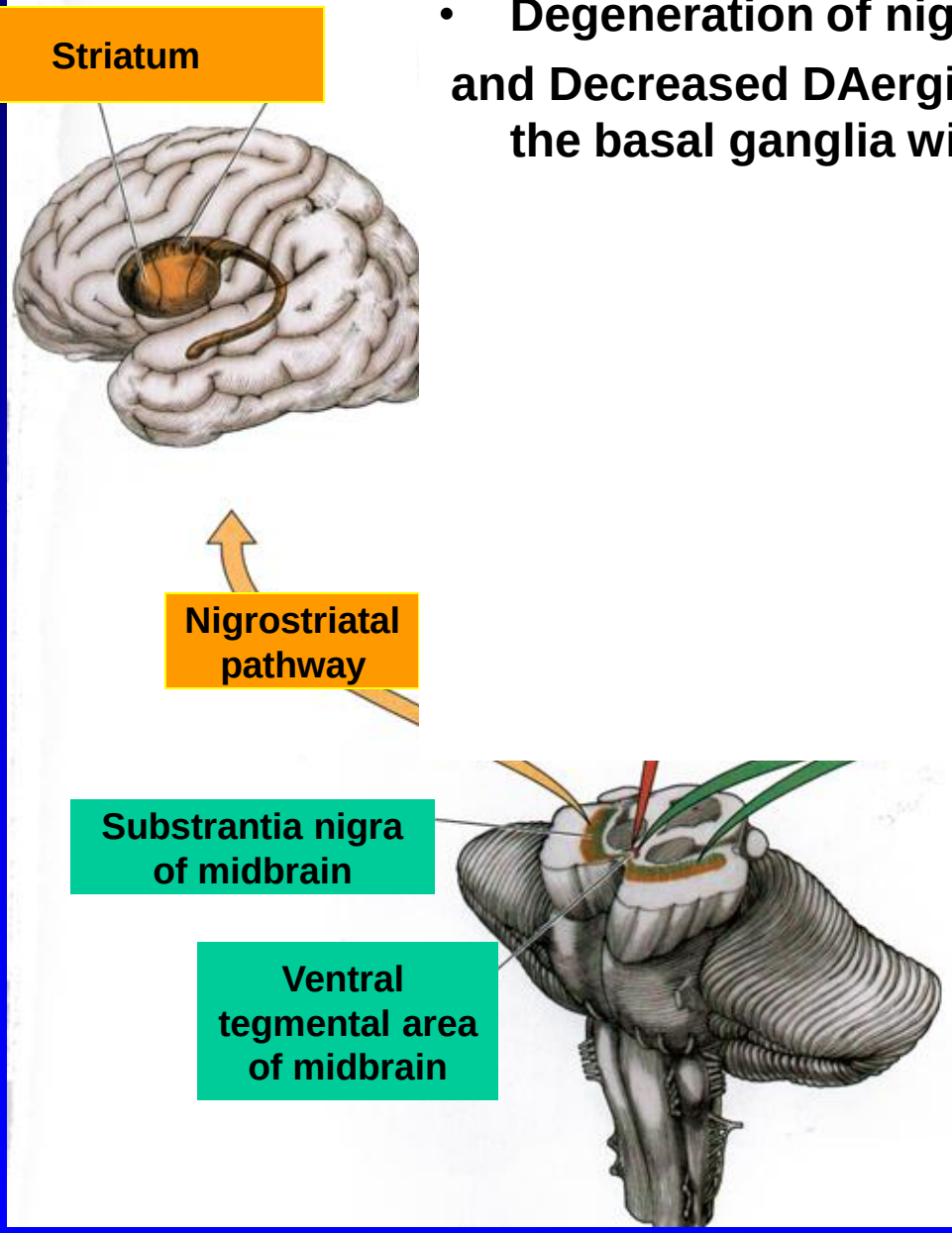
Relative hypofunction **in schizophrenia: Primary mesocortical dopamine deficiency will increase the NEGATIVE SYMPTOMS like Cognitive blunting, social isolation, apathy, anhedonia**



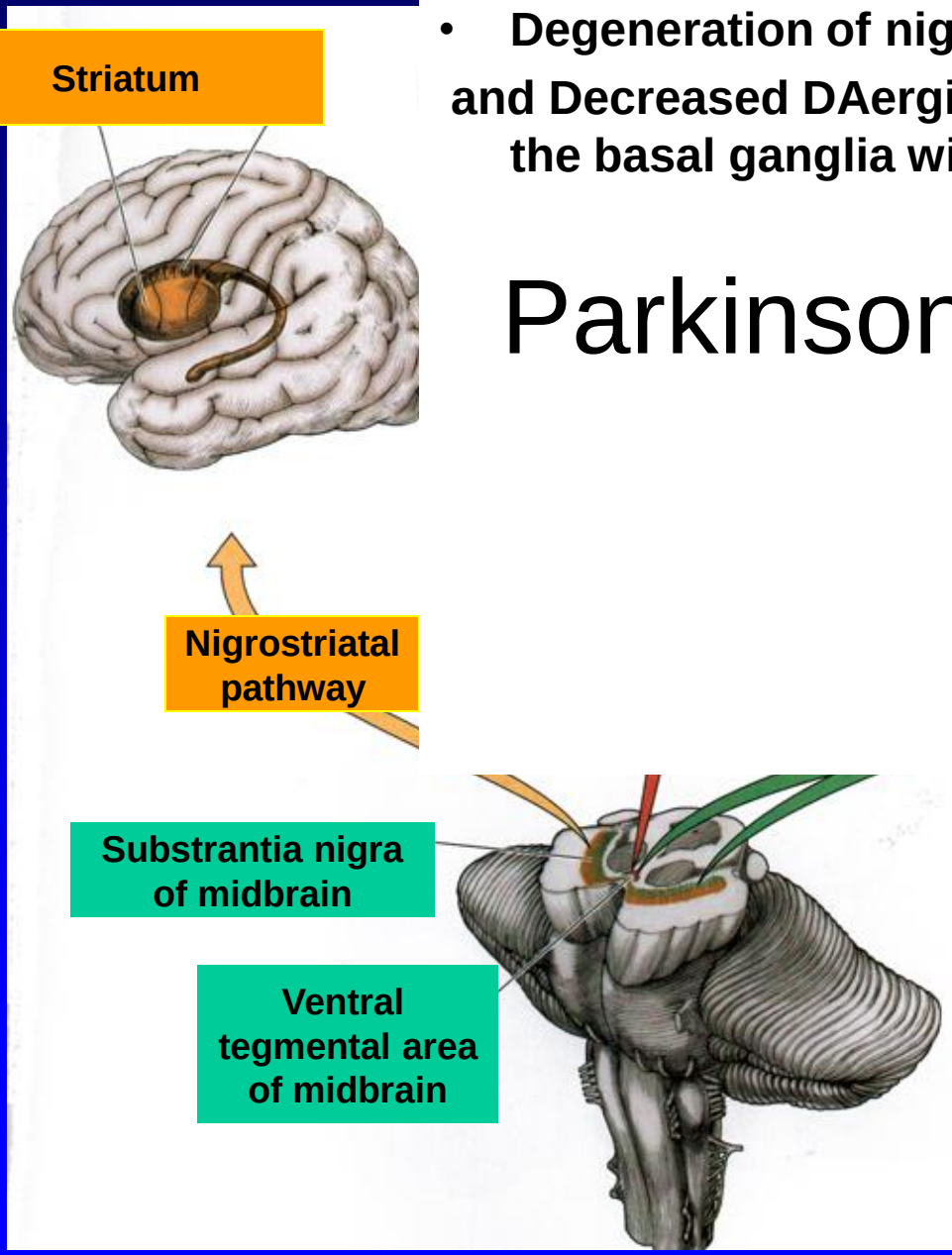
DOPAMINERGIC PATHWAYS

- **Degeneration of nigro-striatal DA system**

and Decreased DAergic trans-mission in the basal ganglia will lead to



DOPAMINERGIC PATHWAYS



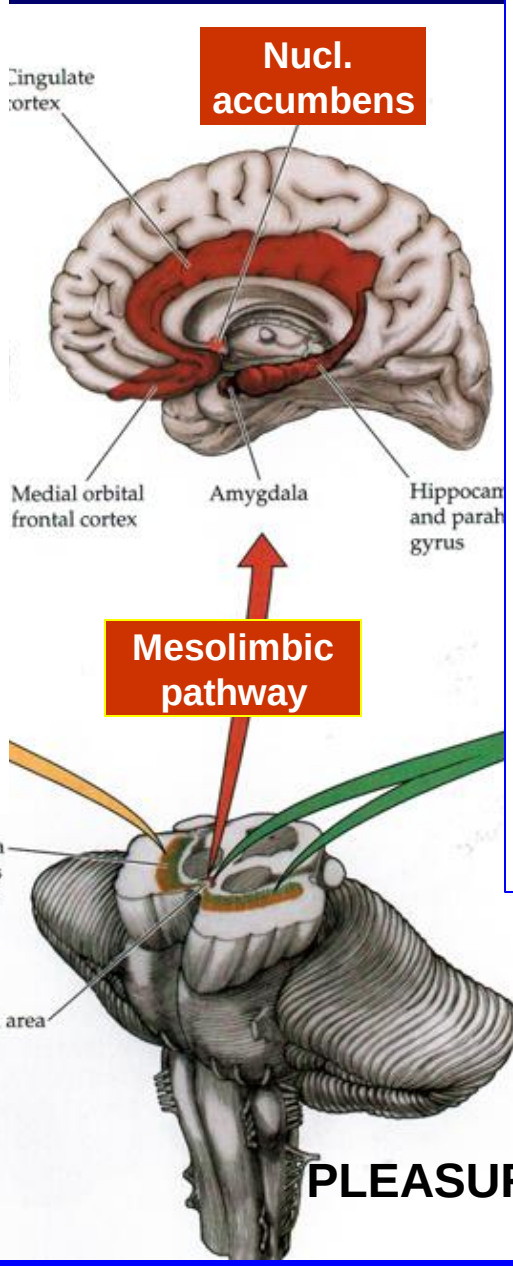
- **Degeneration of nigro-striatal DA system**

and Decreased DAergic trans-mission in the basal ganglia will lead to

Parkinson Disease

DOPAMINERGIC PATHWAYS

PLEASURE, REWARD AND BEHAVIOR REINFORCING PATHWAY



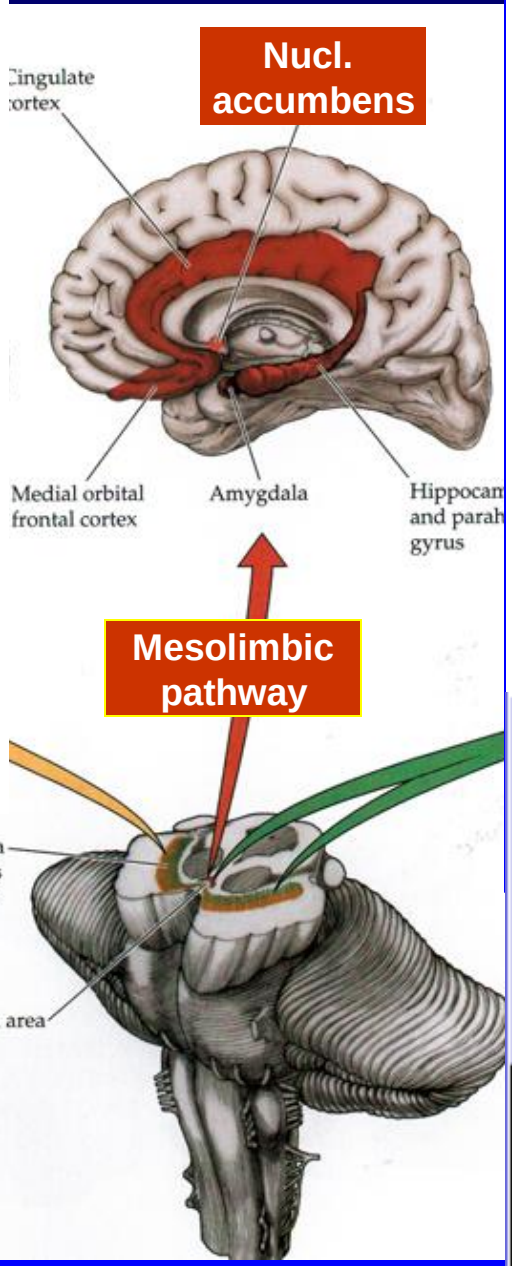
Substrantia nigra of midbrain

Ventral tegmental area of midbrain

PLEASURE, REWARD AND BEHAVIOR

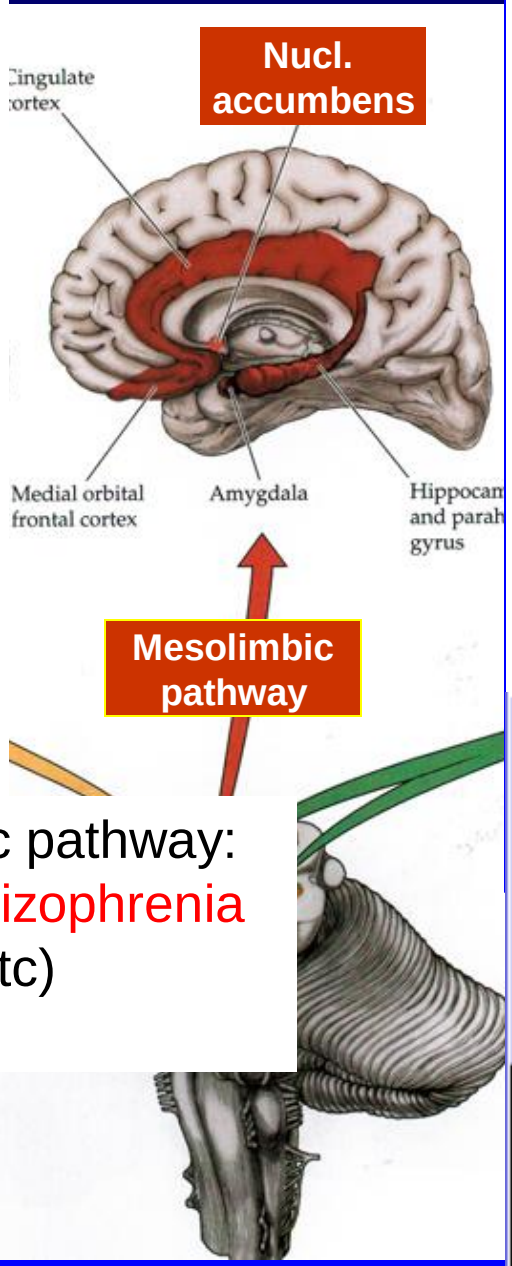
DOPAMINERGIC PATHWAYS

PLEASURE, REWARD AND BEHAVIOR REINFORCING PATHWAY



DOPAMINERGIC PATHWAYS

PLEASURE, REWARD AND BEHAVIOR REINFORCING PATHWAY



Hyperactivity of mesolimbic pathway:
- positive symptoms of schizophrenia
(hallucinations, etc)