Neurochemistry

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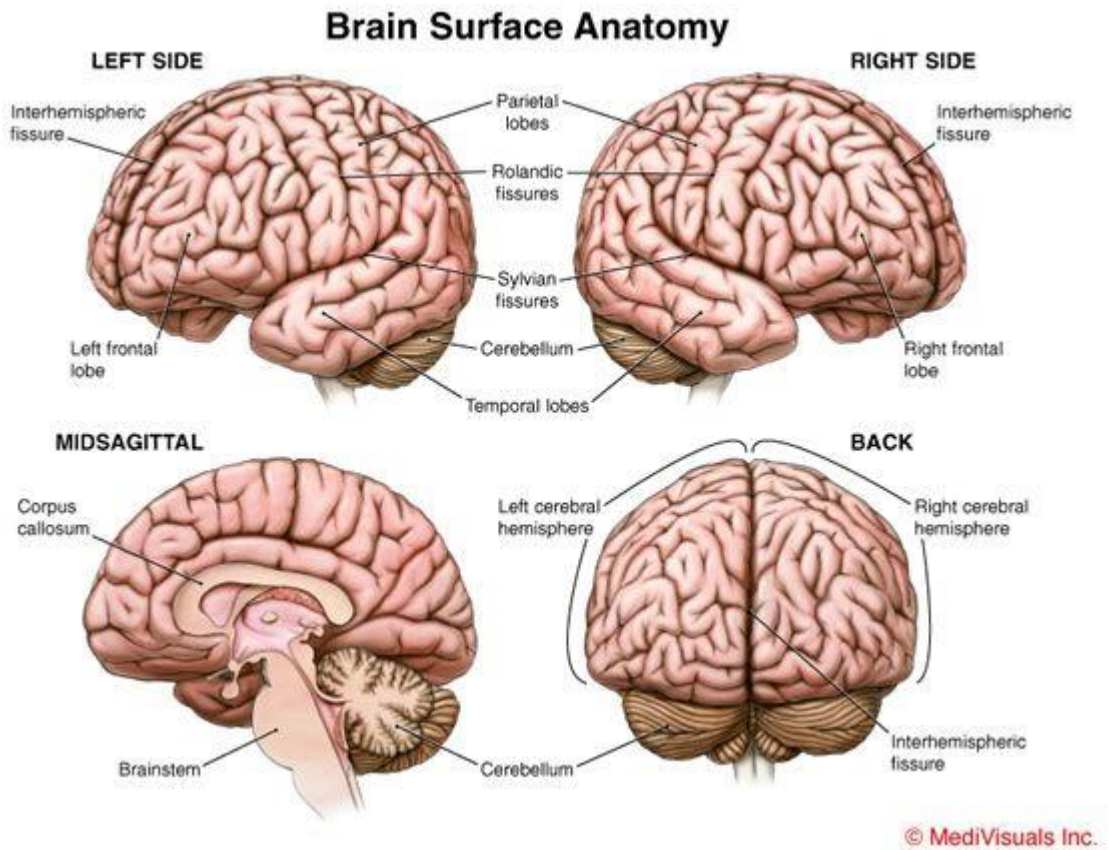
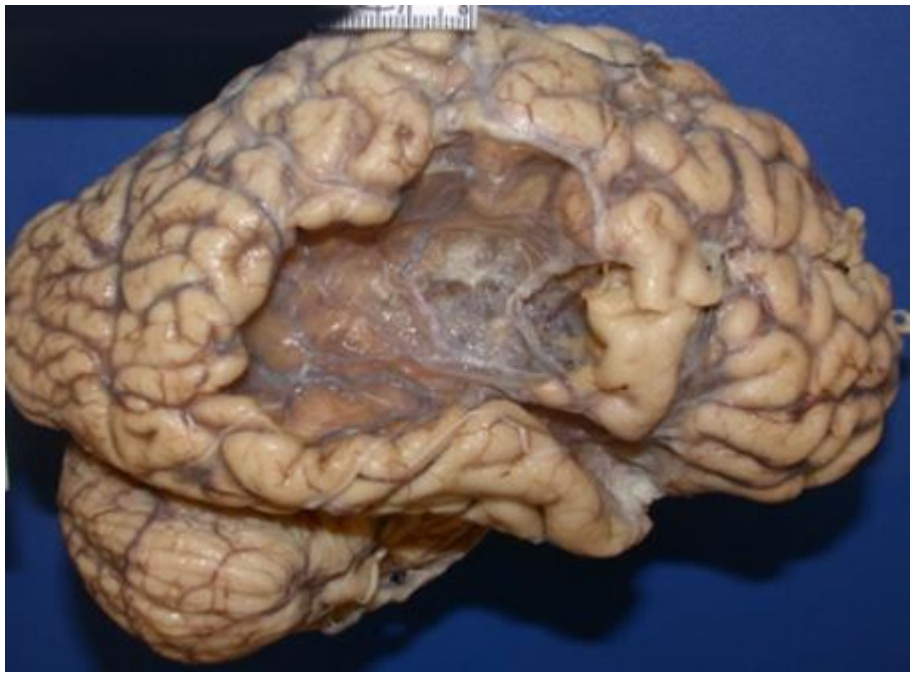
2019

As Psychiatrists, we need to see the brain in a different light

How the brain is considered in Neurology & Radiology in general

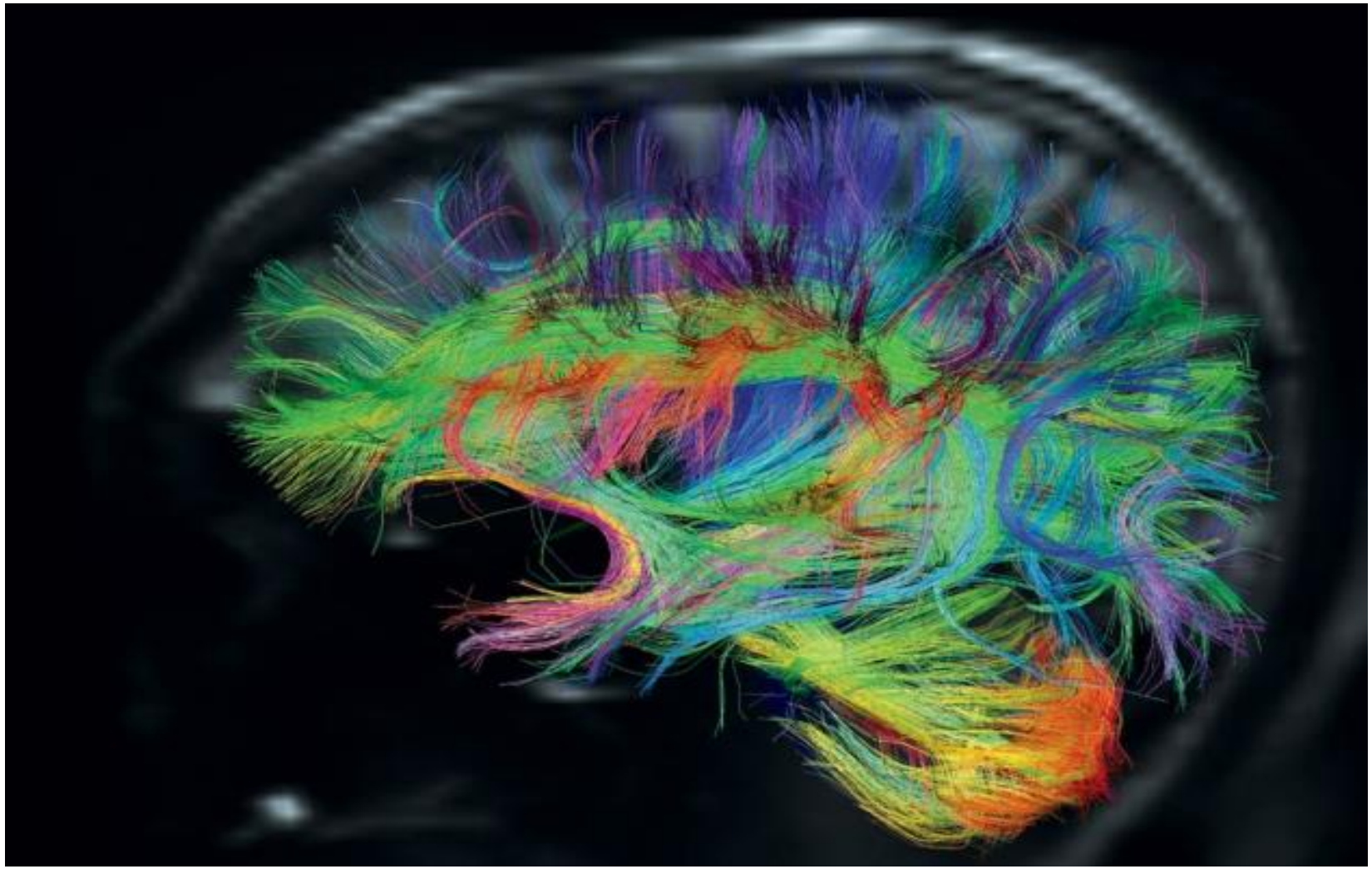




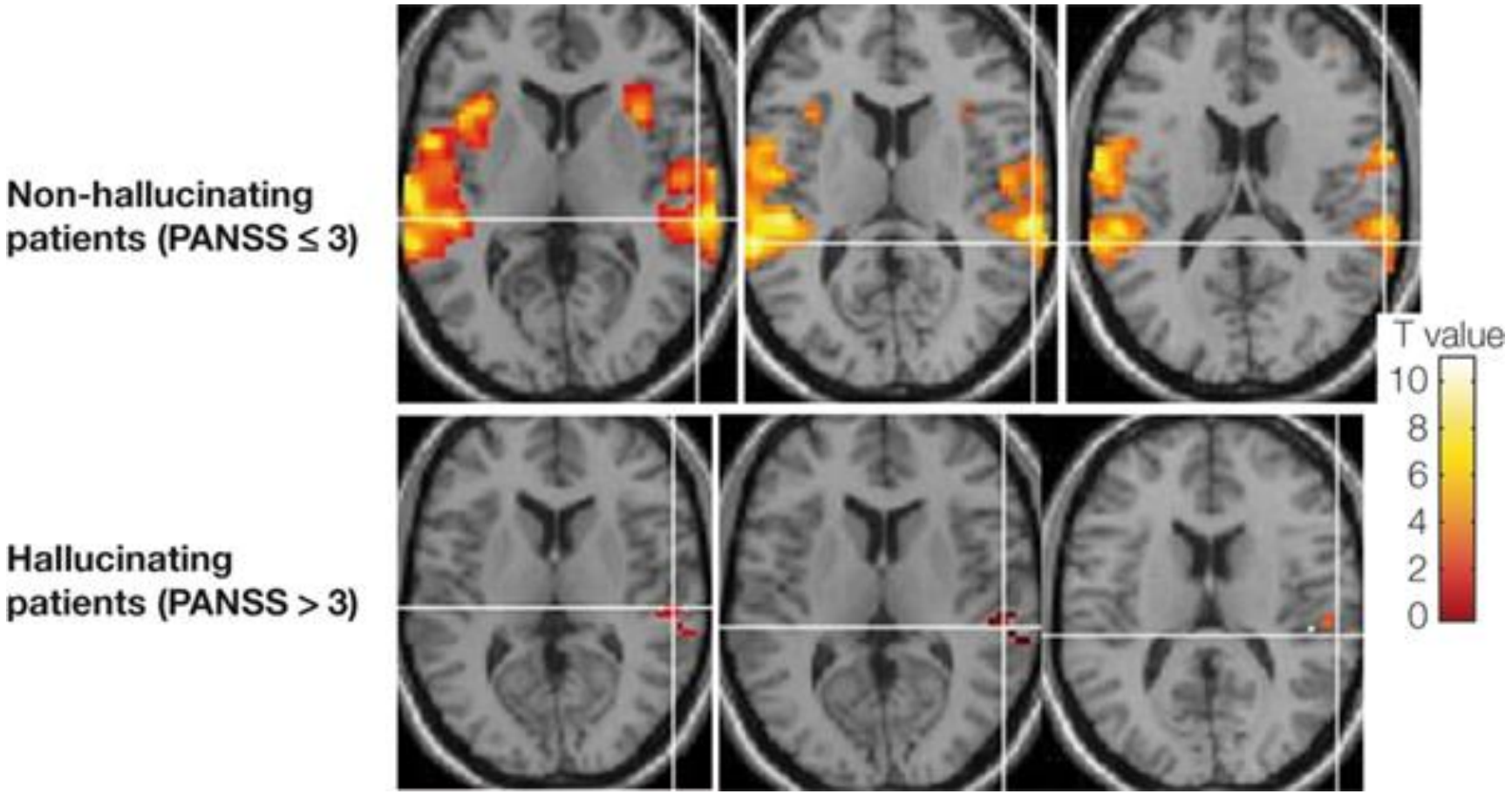
Using a city as metaphor for the brain in non-psychiatry thought:

How we should view the brain in Psychiatry

It is about macro as well as micro-anatomy, most importantly, connections and function!



Functional MRI of the brain in control group (upper) and schizophrenia group (lower)



Learning Objectives Stage I

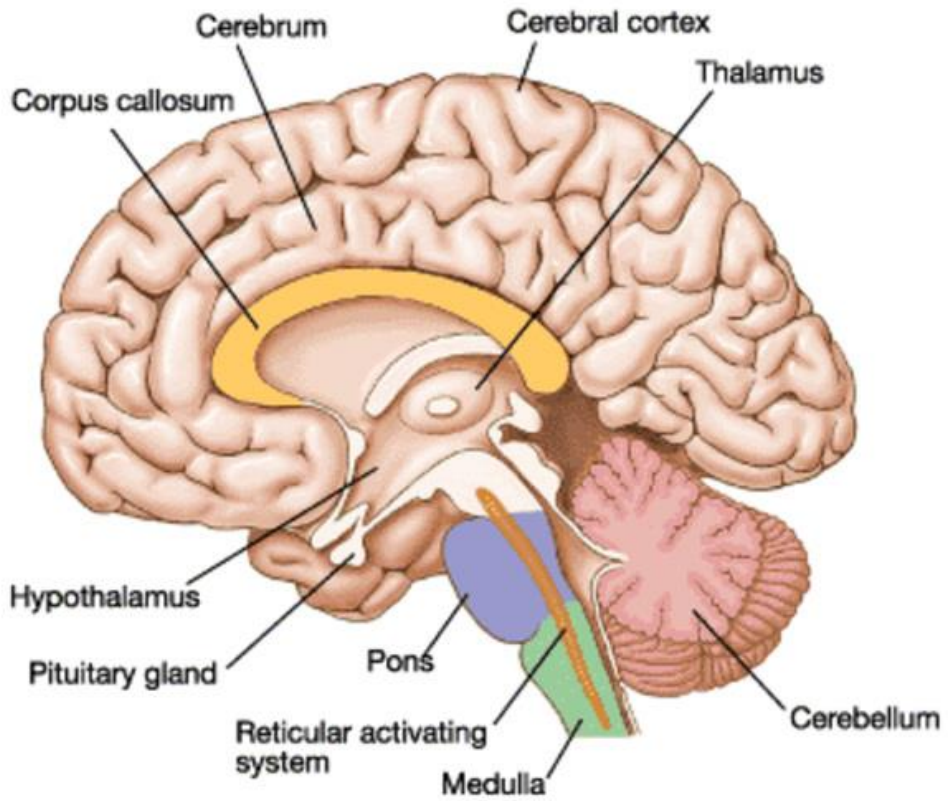
a. Brief overview (refresher) of macro-anatomy of the Central Nervous System (CNS) – *20 minutes*
b. Brief overview (refresher) of micro-anatomy of the CNS – *10 minutes*
c. Neuro-transmission (in depth)
d. Neurodevelopment and neuronal plasticity
e. Neurodevelopmental & Chemical Neurotransmission as Mediators of Disease
f. Concepts of neuropsychopharmacology, focusing on:
    i. Schizophrenia
    ii. Bipolar Disorder
    iii. Major Depressive Disorder
    iv. Anxiety Disorders

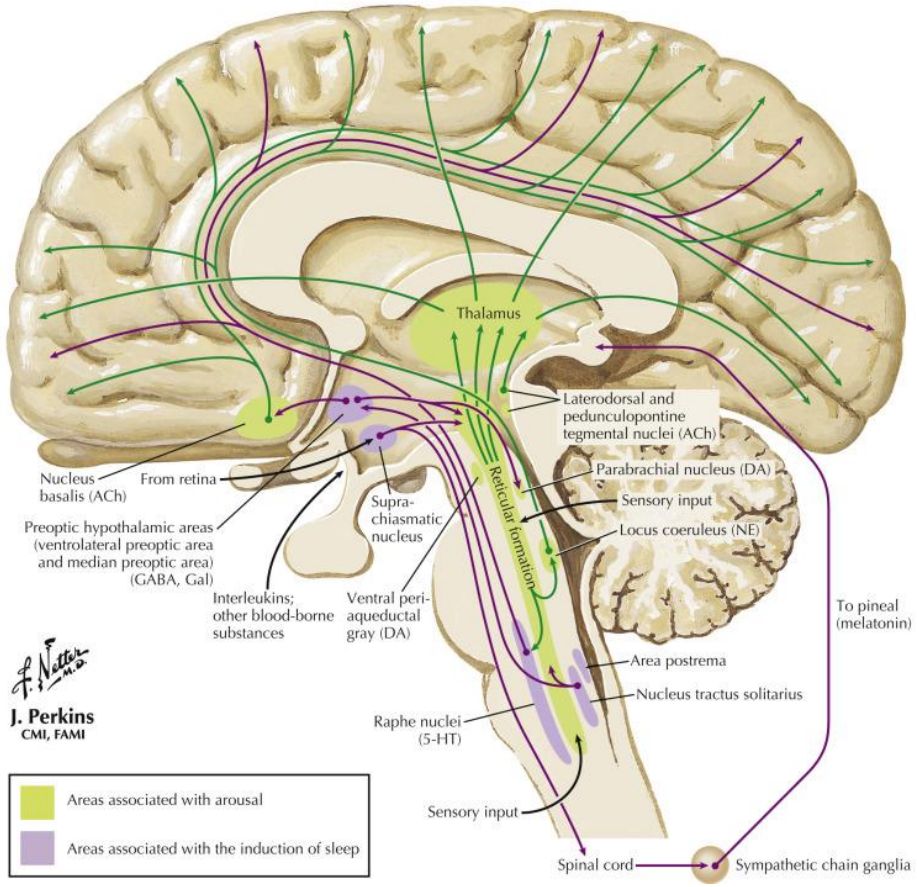
a. **Brief overview (refresher) of macro-anatomy of the Central Nervous System (CNS) – *20 minutes***

- Mid-brain, pons, medulla oblongata and their projections via the Thalamus as part of the reticular Activating System (consciousness)
- The Limbic System (emotion and memory)
- The Basal ganglia (as per role in psychotropic side effects & motivation, decision-making & working memory).
- The cortices (frontal, parietal, temporal, occipital)
- Cerebellum in relation to cerebellar cognitive affective syndrome.

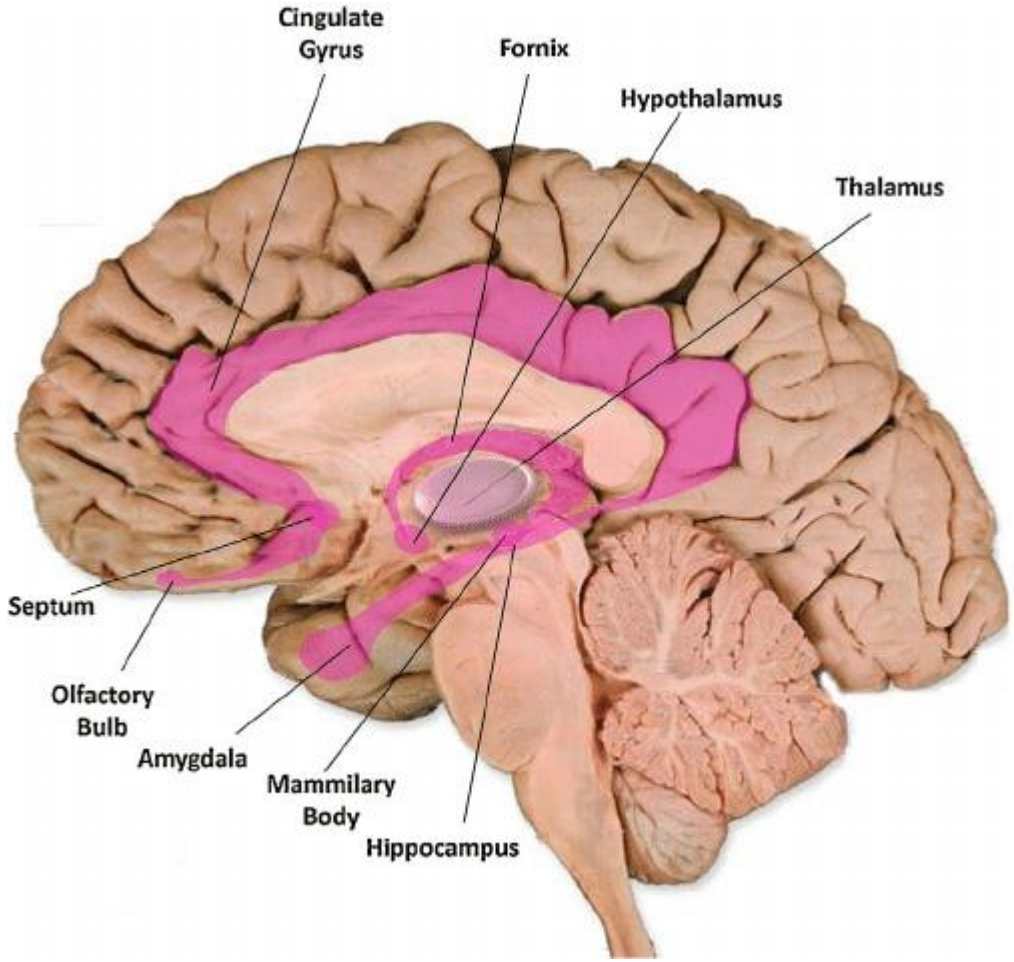
- Mid-brain, pons, medulla oblongata and their projections via the Thalamus as part of the

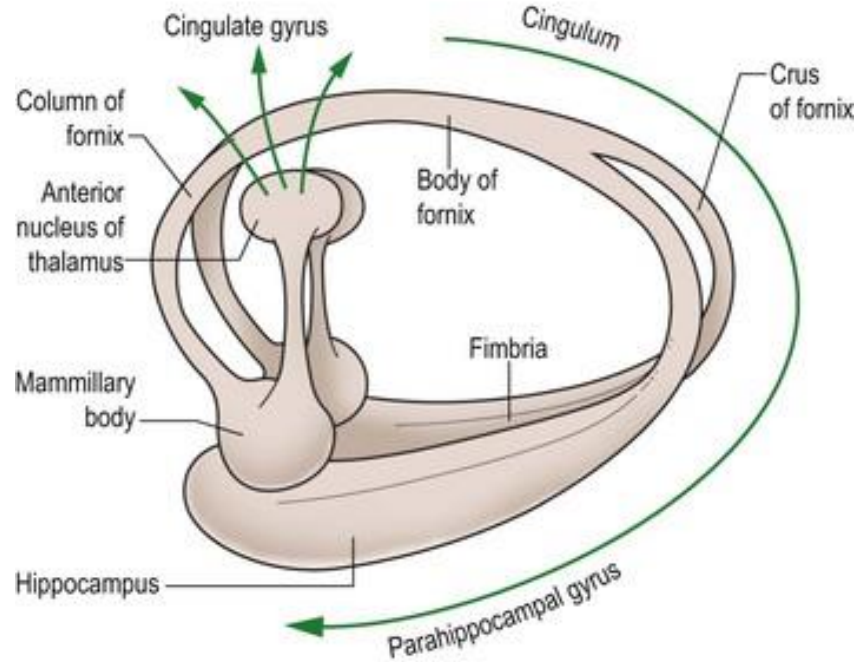
  Reticular Activating System RAS (consciousness)

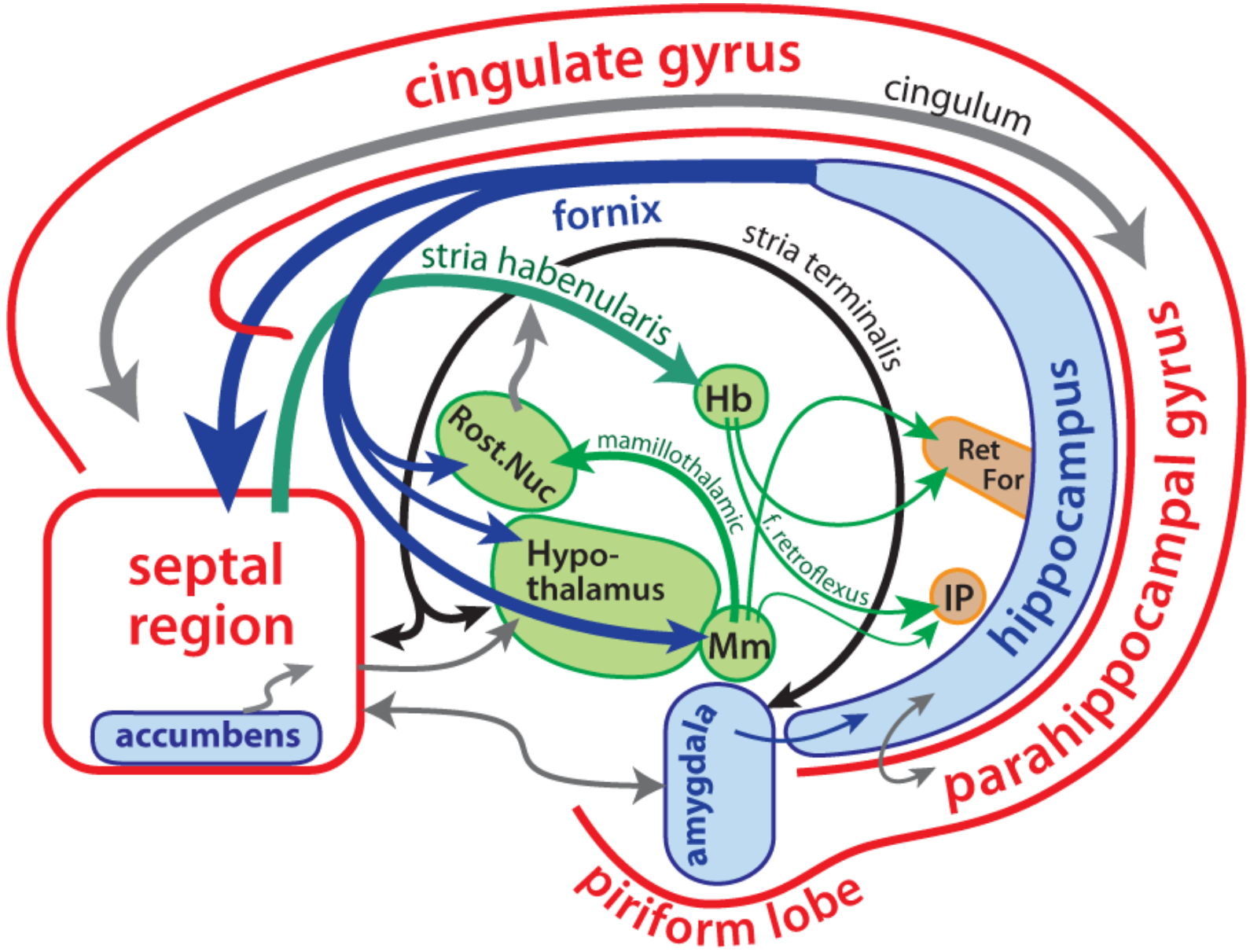




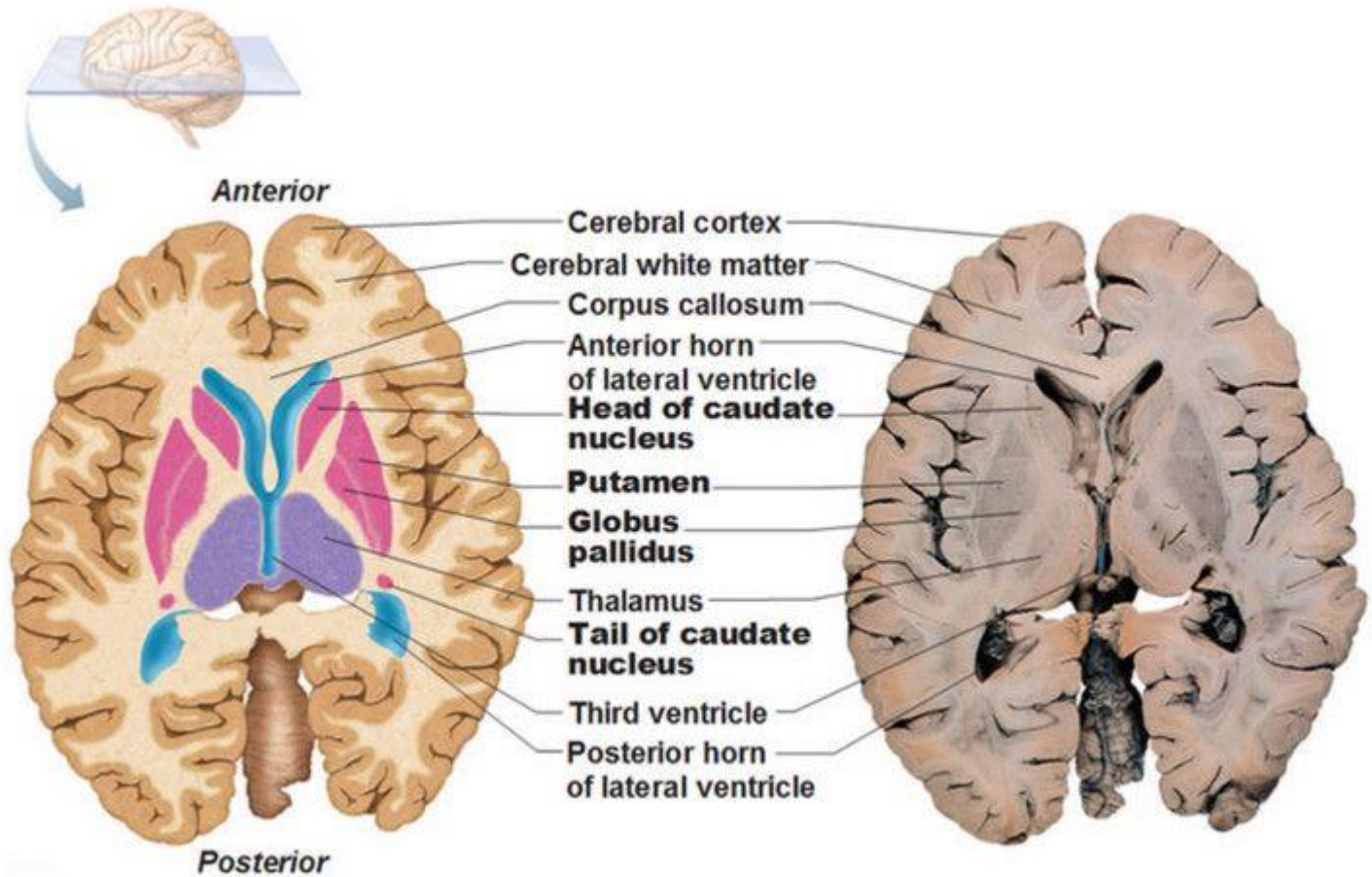
- The Limbic System (emotion and memory)

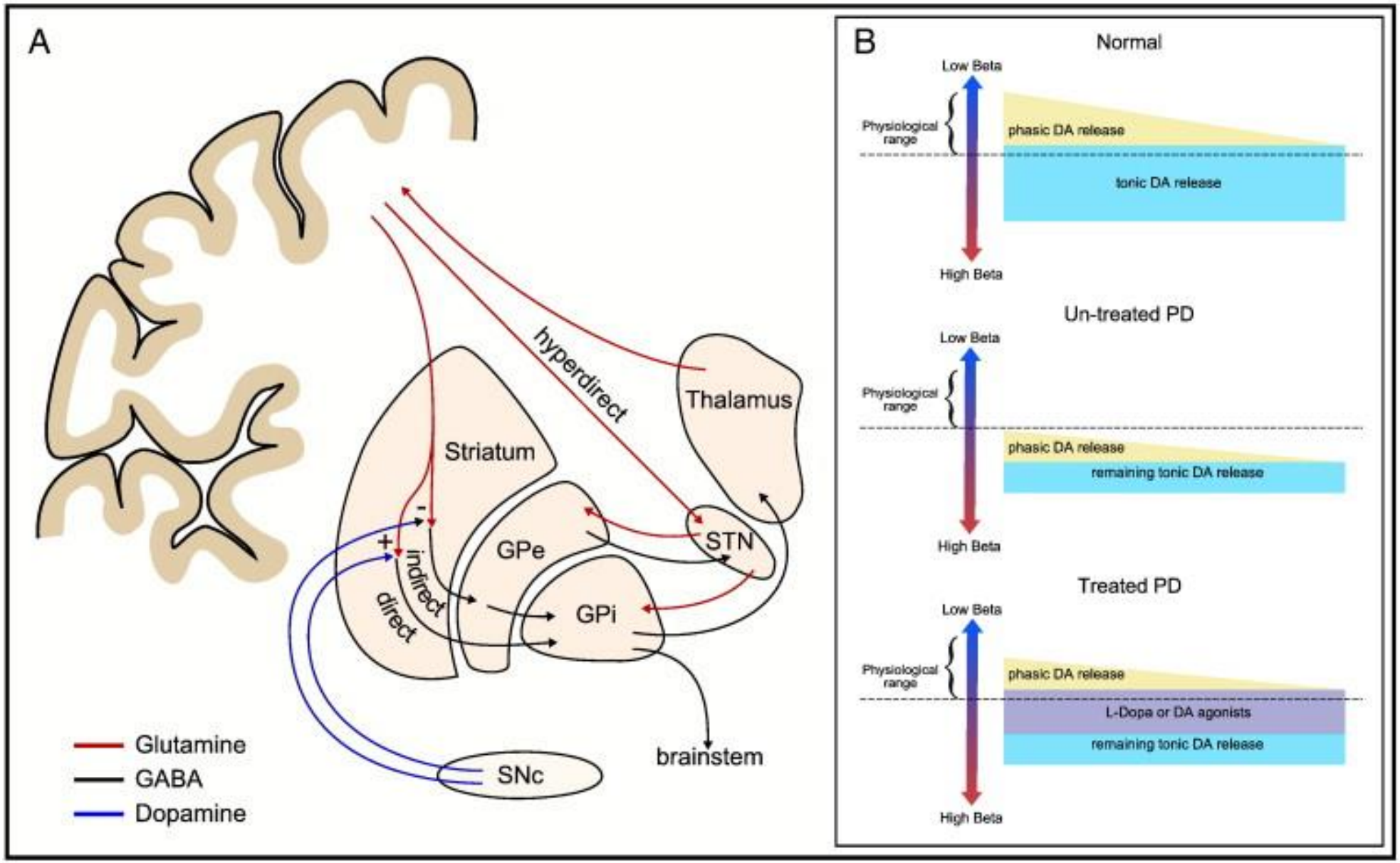


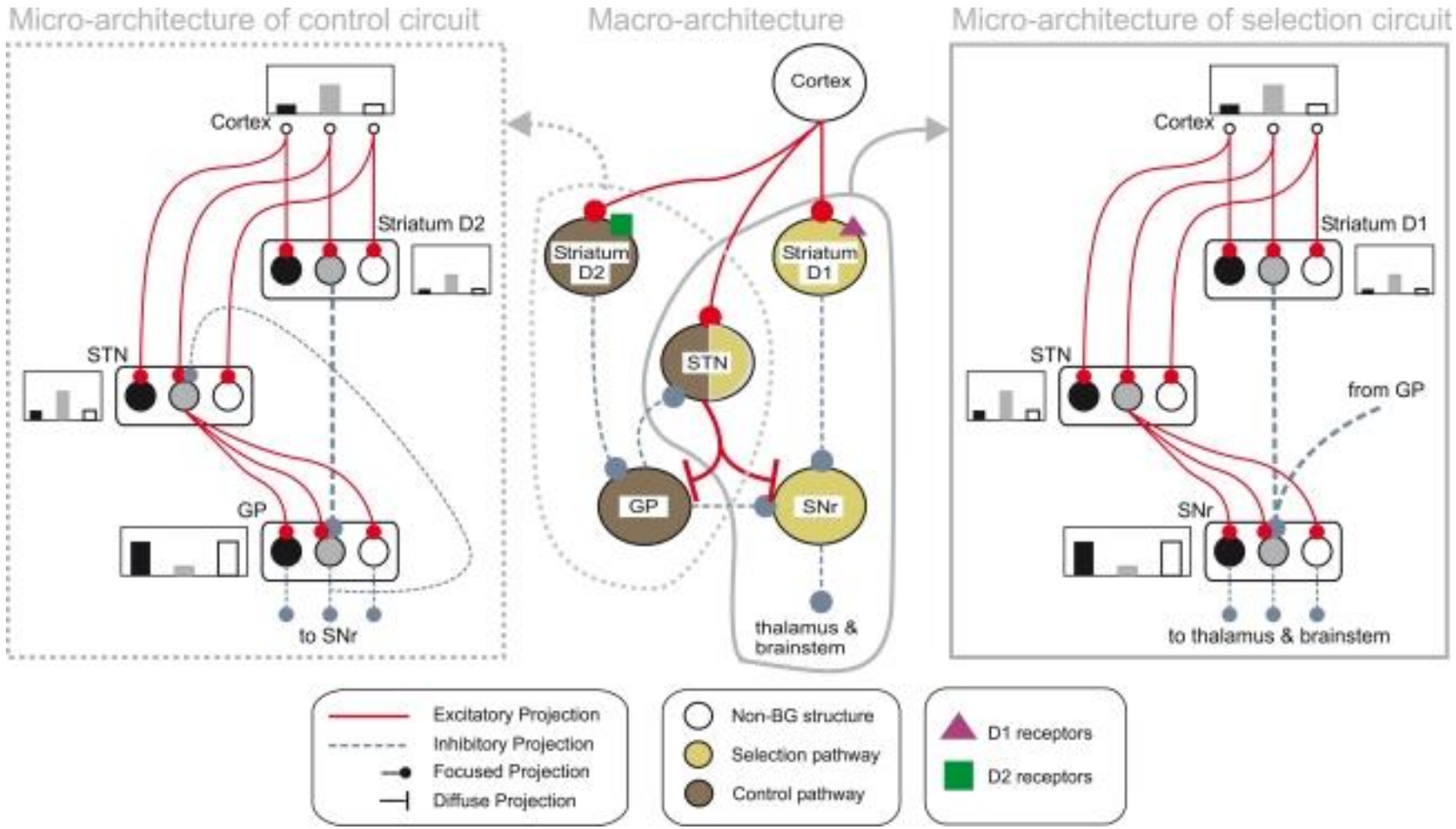



cingulate gyrus
cingulum
fornix
stria habenularis
stria terminalis
Hb
Rost.Nuc
mamillothalamic
Ret
For
f. retroflexus
Hypo-
thalamus
IP
Mm
hippocampus
septal
region
accumbens
amygdala
parahippocampal gyrus
piriform lobe

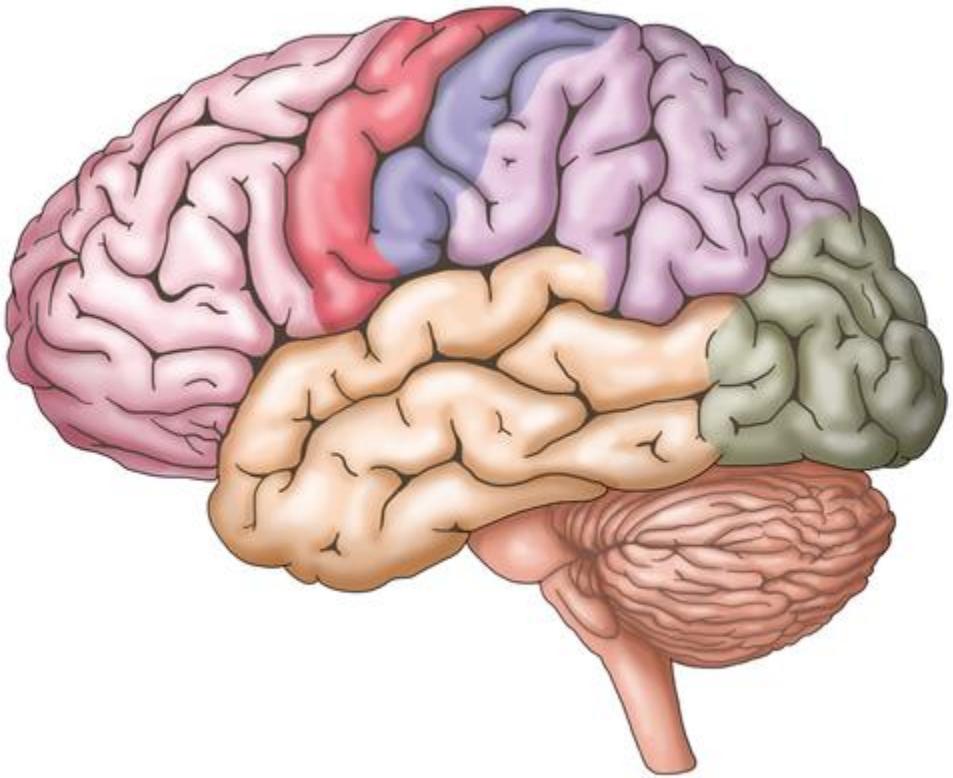
- The Basal ganglia (as per role in psychotropic side effects & motivation, decision-making & working memory).

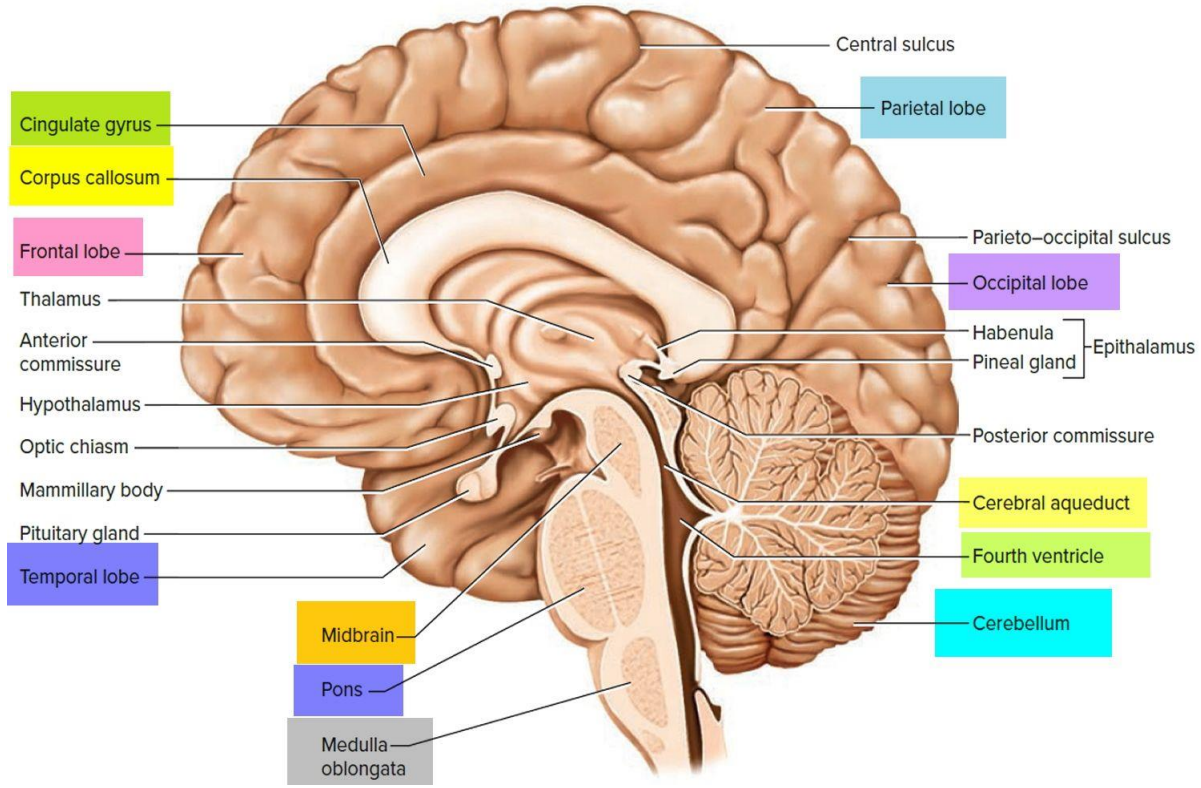



A
hyperdirect
Thalamus
Striatum
GPe
STN
GPi
indirect
direct
brainstem
SNc
Glutamine
GABA
Dopamine
B
Normal
Low Beta
Physiological range
phasic DA release
tonic DA release
High Beta
Un-treated PD
Low Beta
Physiological range
phasic DA release
remaining tonic DA release
High Beta
Treated PD
Low Beta
Physiological range
phasic DA release
L-Dopa or DA agonists
remaining tonic DA release
High Beta


Micro-architecture of control circuit
Cortex
Striatum D2
STN
GP
to SNr
Macro-architecture
Cortex
Striatum D2
Striatum D1
STN
GP
SNr
thalamus & brainstem
Micro-architecture of selection circuit
Cortex
Striatum D1
STN
from GP
SNr
to thalamus & brainstem
Excitatory Projection
Inhibitory Projection
Focused Projection
Diffuse Projection
Non-BG structure
Selection pathway
Control pathway
D1 receptors
D2 receptors

- The cortices (frontal, parietal, temporal, occipital) & Cerebellum



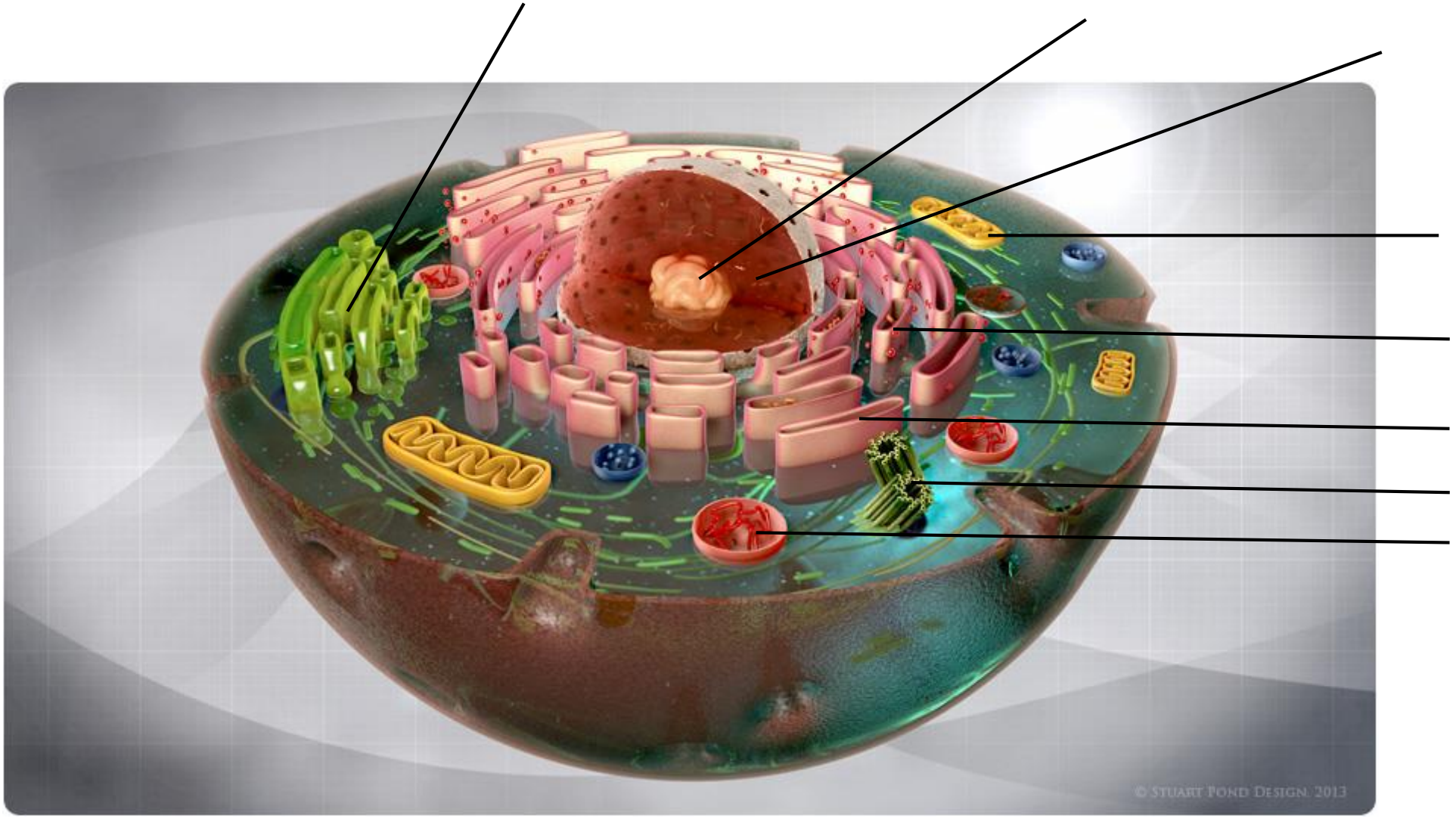


b. Brief overview (refresher) of micro-anatomy of the CNS – *10 minutes*

- A very brief overview of the generic Cell as preparation for the Neuron's 2nd dimension of neurotransmission
  >> DNA changes/ gene expression equating to neuropathway & learning changes in the brain, or 'neuroplasticity'

- Neurons

- Glial cells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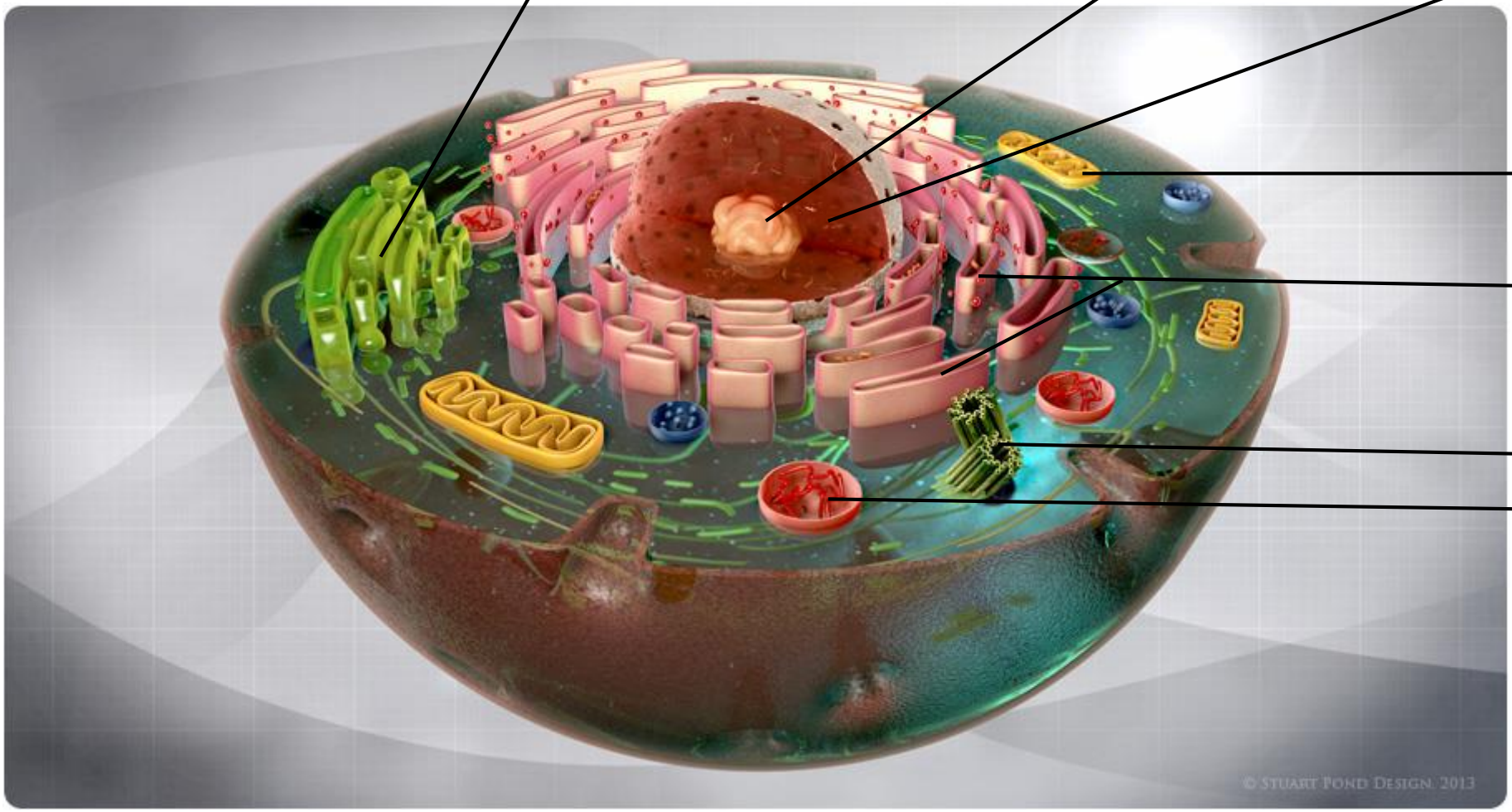
Golgi Apparatus (protein folding)
Nucleolus (Ribosomes & rRNA
Nucleus with DNA in chromosomes
Mitochondria (energy)
Smooth & Rough Endoplasmic Reticulum (protein synthesis
Centriole (division)
Vacuole (storage)
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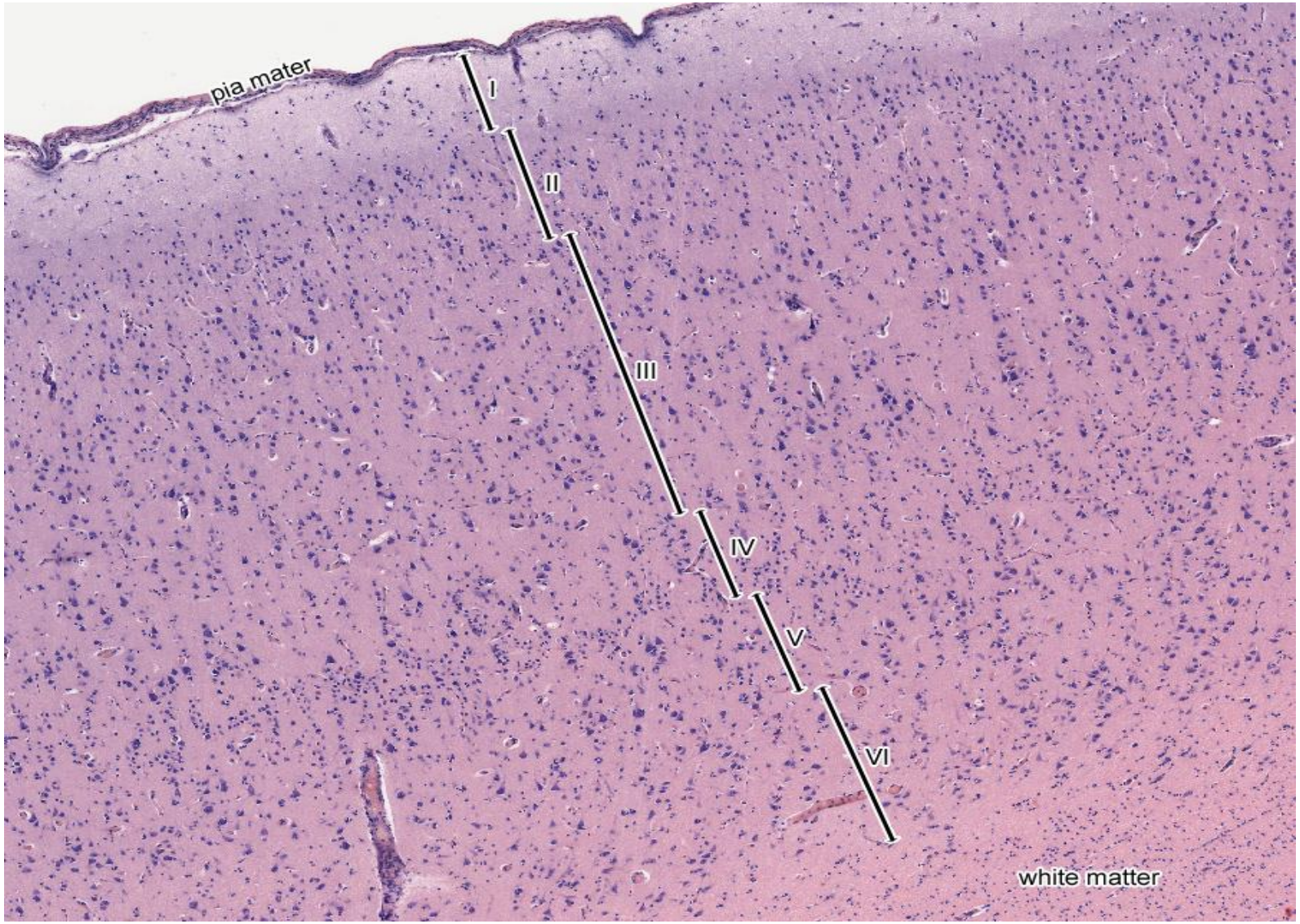
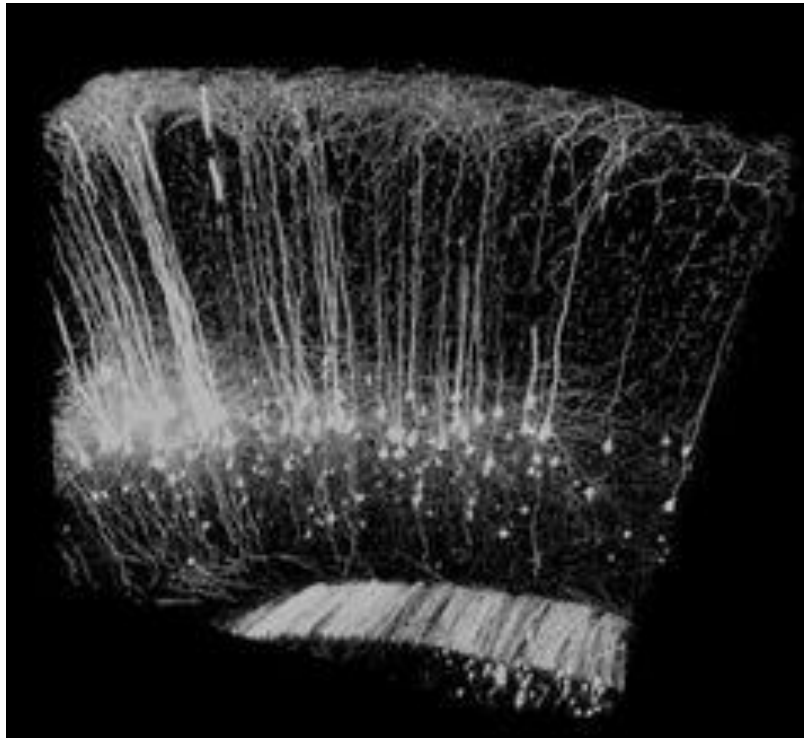
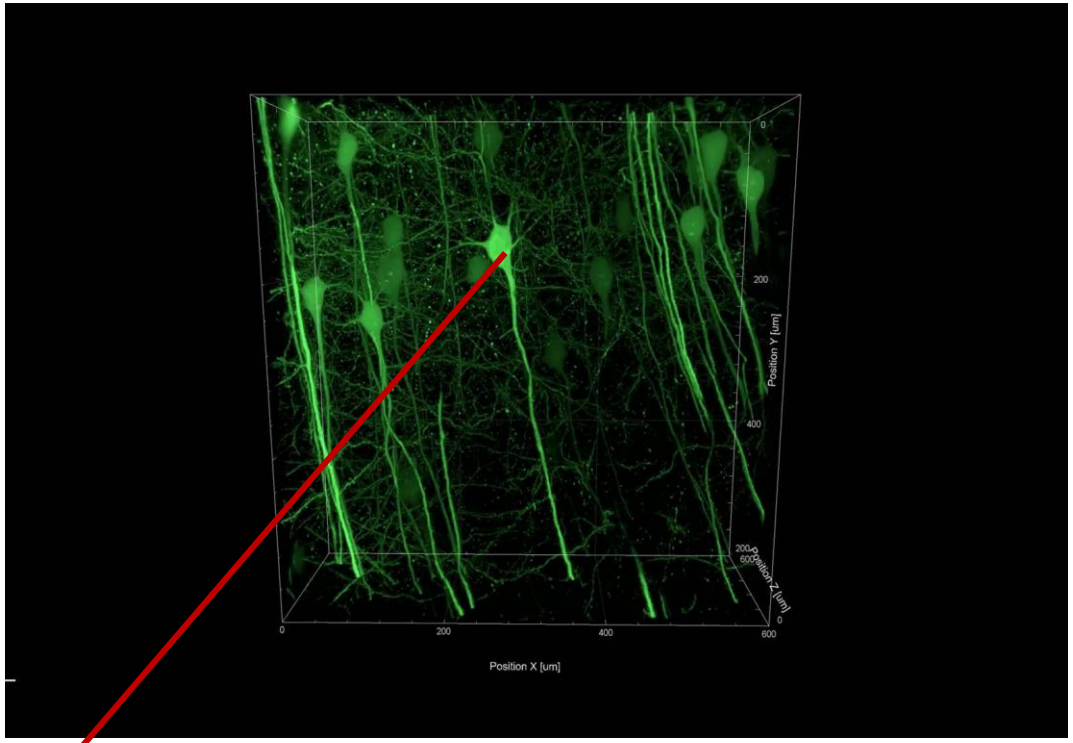
Cross Section of Cortex: layers I – VI of grey matter, shaping into white matter



Three Dimensional imaging of grey matter layers (neuron somae and connections)

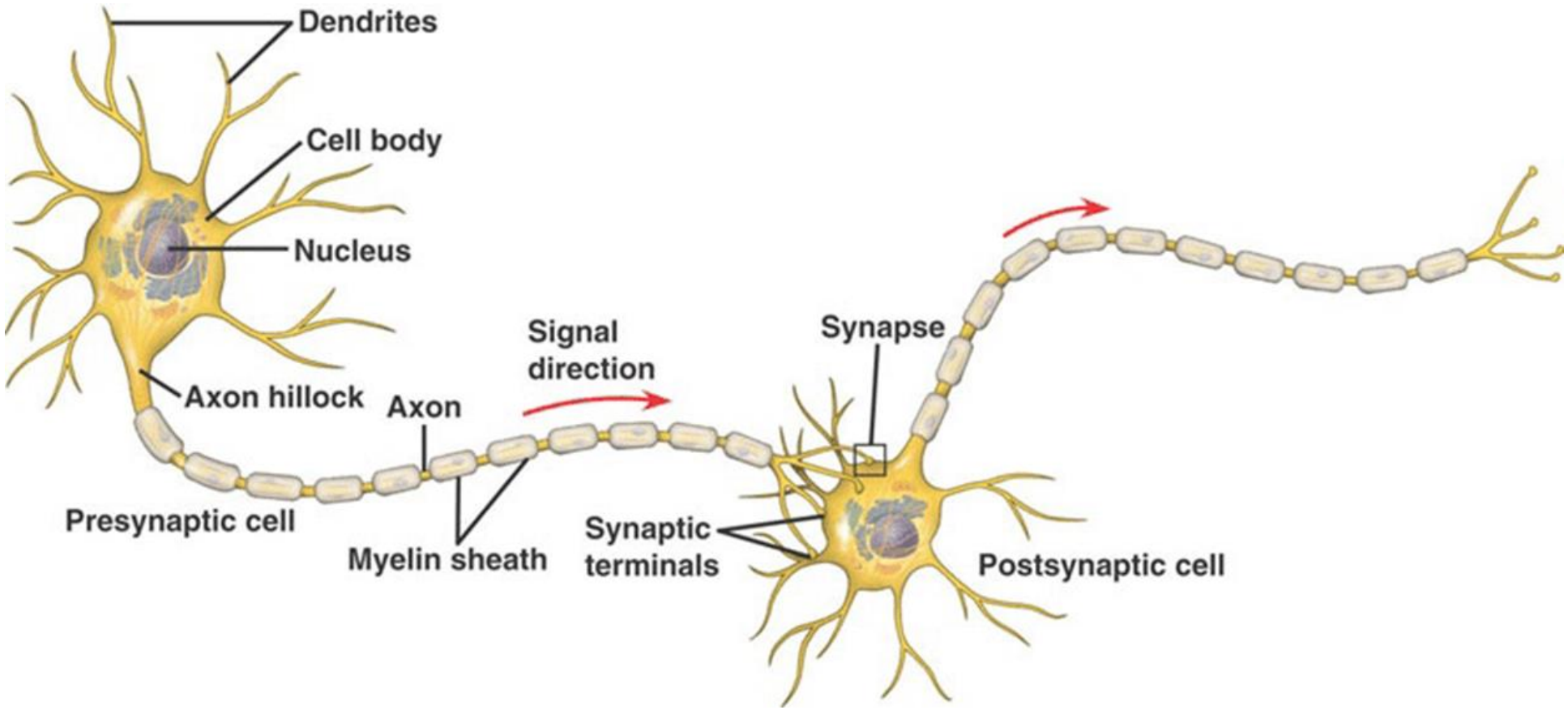


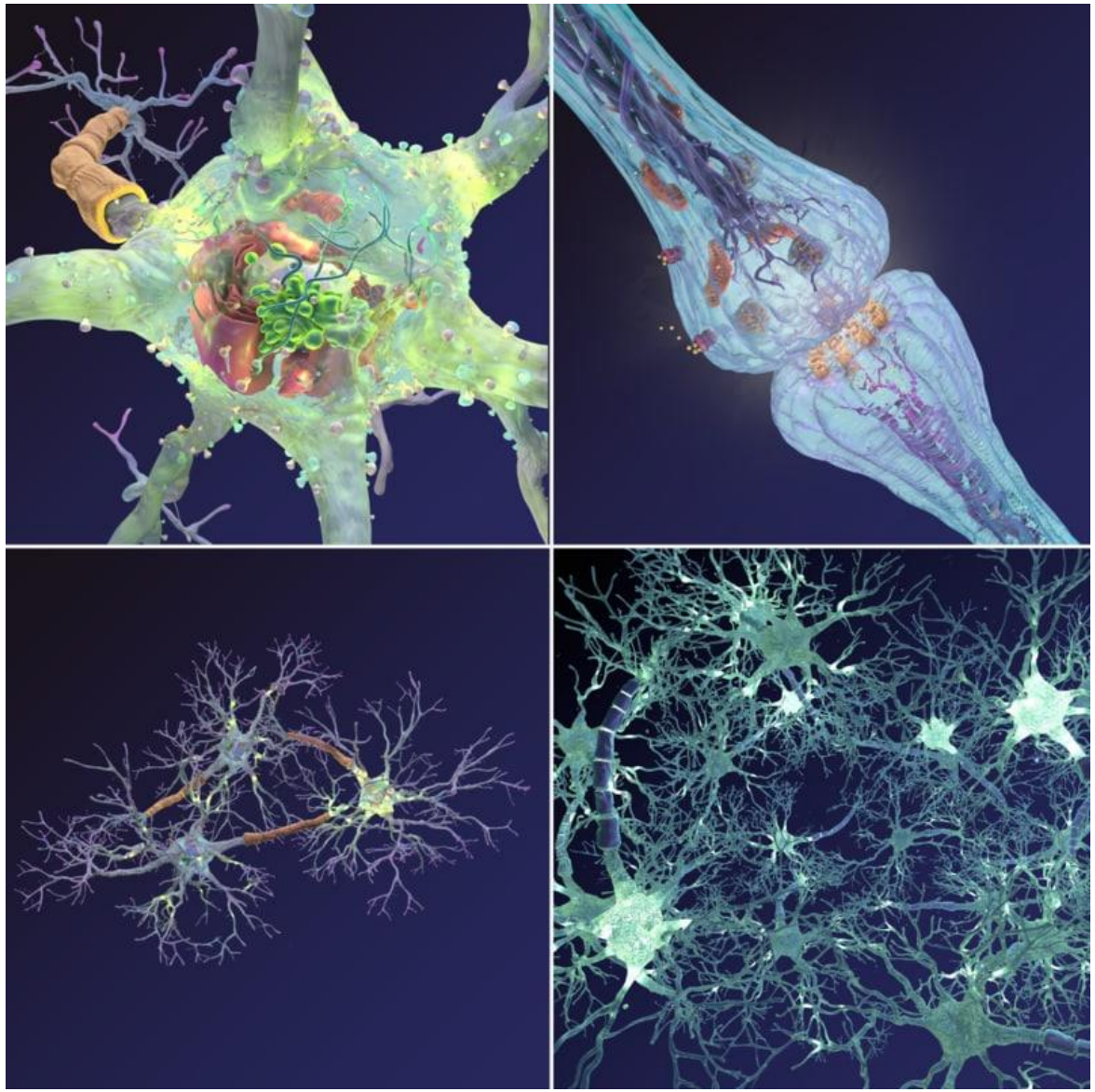


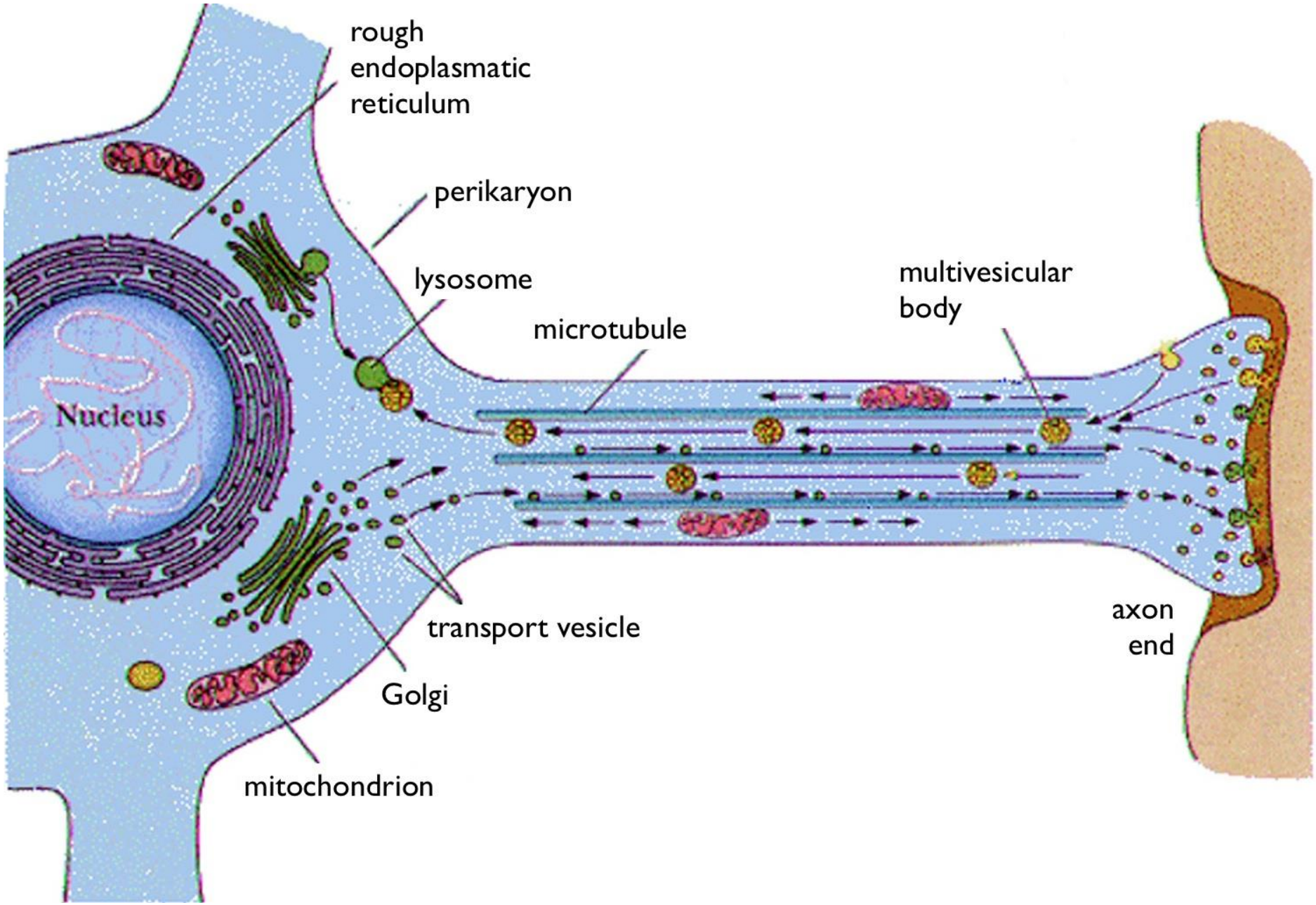
Neurons

- 100 billion neurons (approximately)
- 100 trillion neural connections (1000 times more than the number of stars in our galaxy)
- Approximately 40% of our genes participate in CNS formation, with 7% involved in synapse formation.
- Cell body manufactures proteins and poly-peptides (for integrity of neuron & secretory vesicles with neuro-transmitters destined for terminal/ synapses -> neurotransmission.
- Transported anterograde (to terminals) via microtubules in axon by Kinesin proteins.
- Transported retrograde (recycled vesicles from terminals) via by Dynein proteins.
- Neurons supported by Glial cells.

Neurons (diagram)






rough
endoplasmatic
reticulum
perikaryon
lysosome
microtubule
multivesicular
body
Nucleus
transport vesicle
axon
end
Golgi
mitochondrion

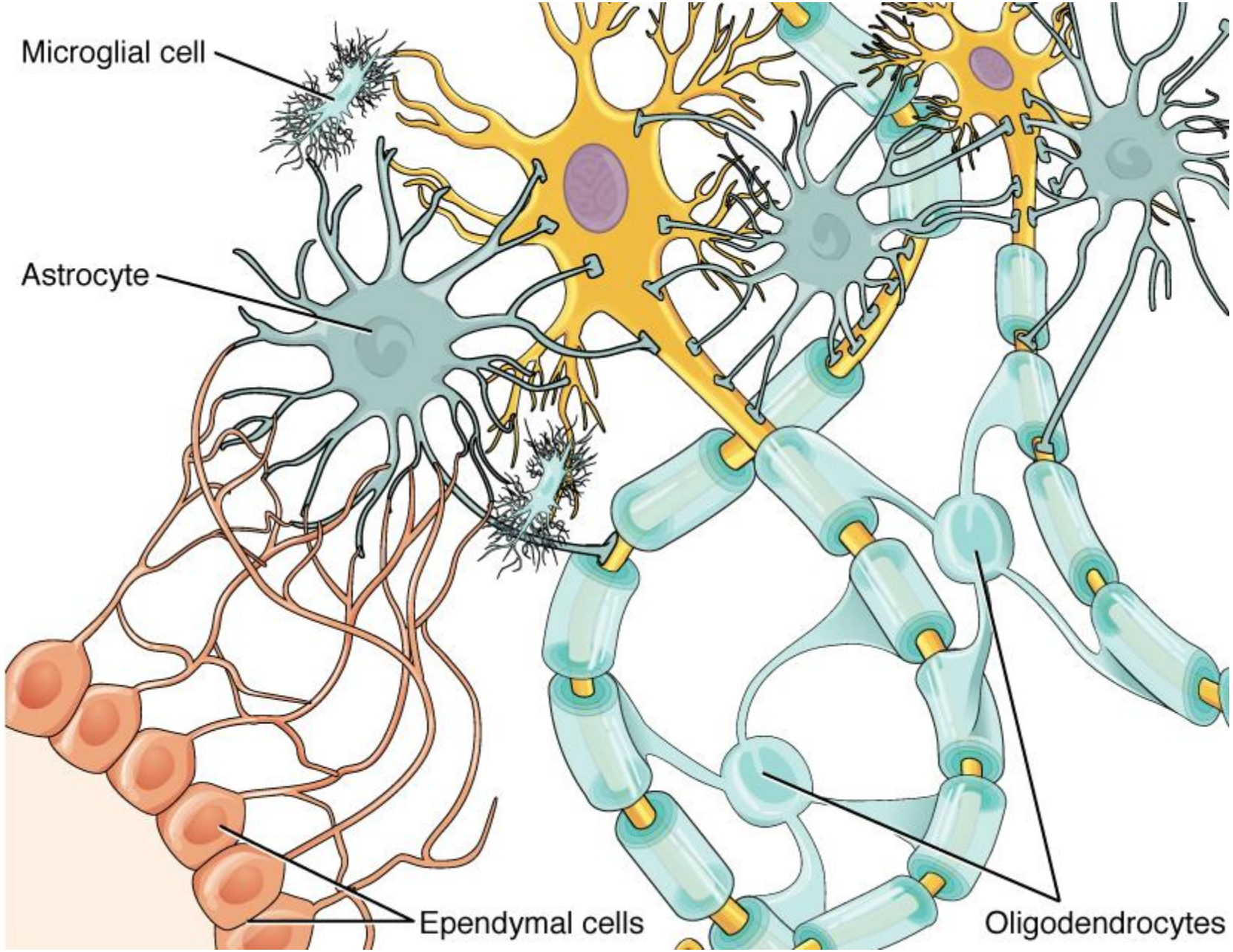
Glial Cells

- ‘Glia’ Greek for ‘glue’
- In partnership with neurons for communication
- Unlike Neurons, can undergo division for recovery of CNS such as post trauma/ stroke etc.

2 Types

- Microglia
  ‘Scavenger’ cells (macrophage)

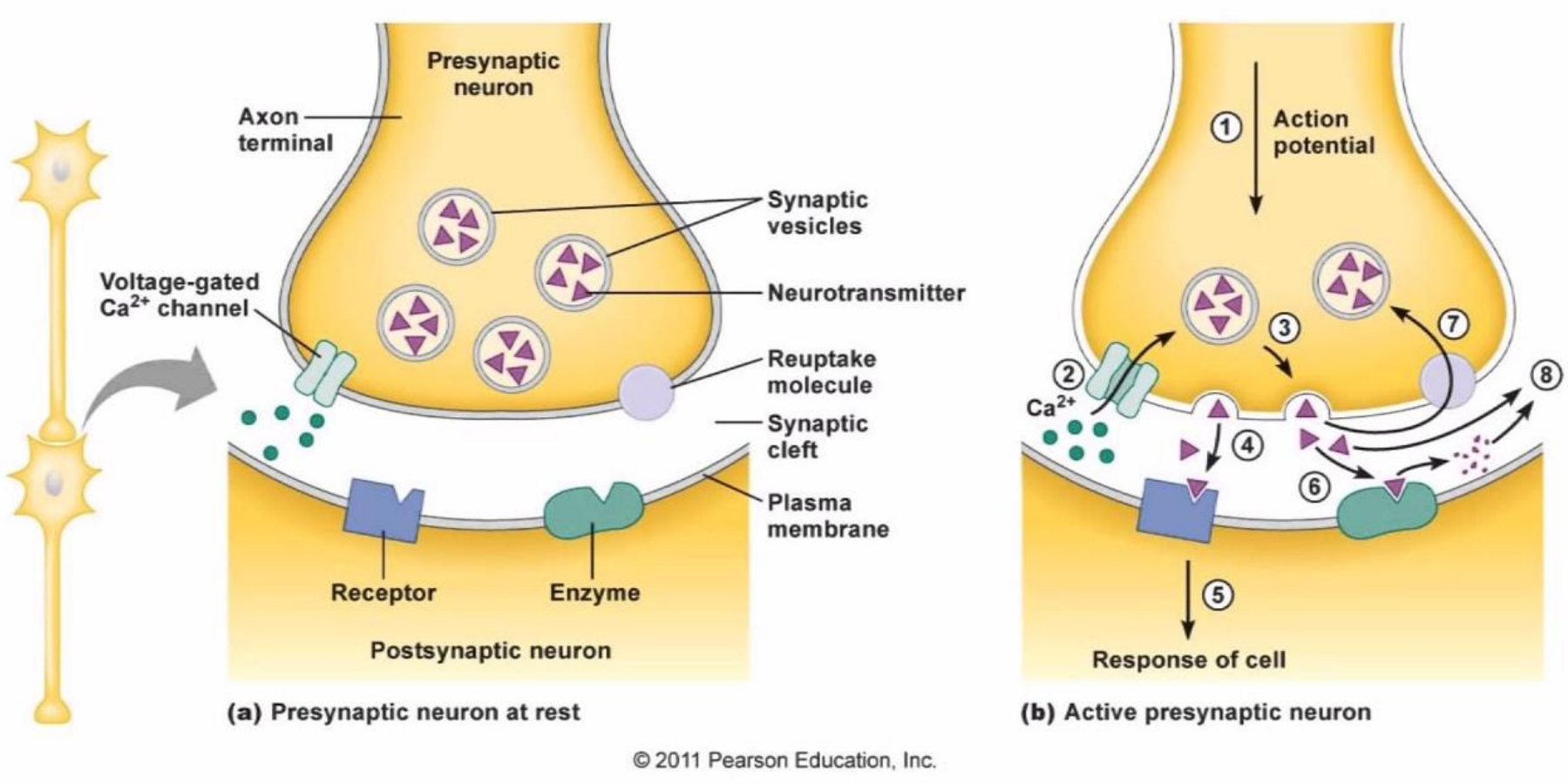
- Macroglia
  a. Oligodendrocytes -> myelin formation
  b. Schwann Cells -> neurotrophins
  c. Astrocytes:
  Biochemical support, provision of nutrients, ion balance, repair post injury, Blood Brain Barrier
  i. Fibrous Astrocytes (white matter)
  ii. Protoplasmic Astrocytes (grey matter)

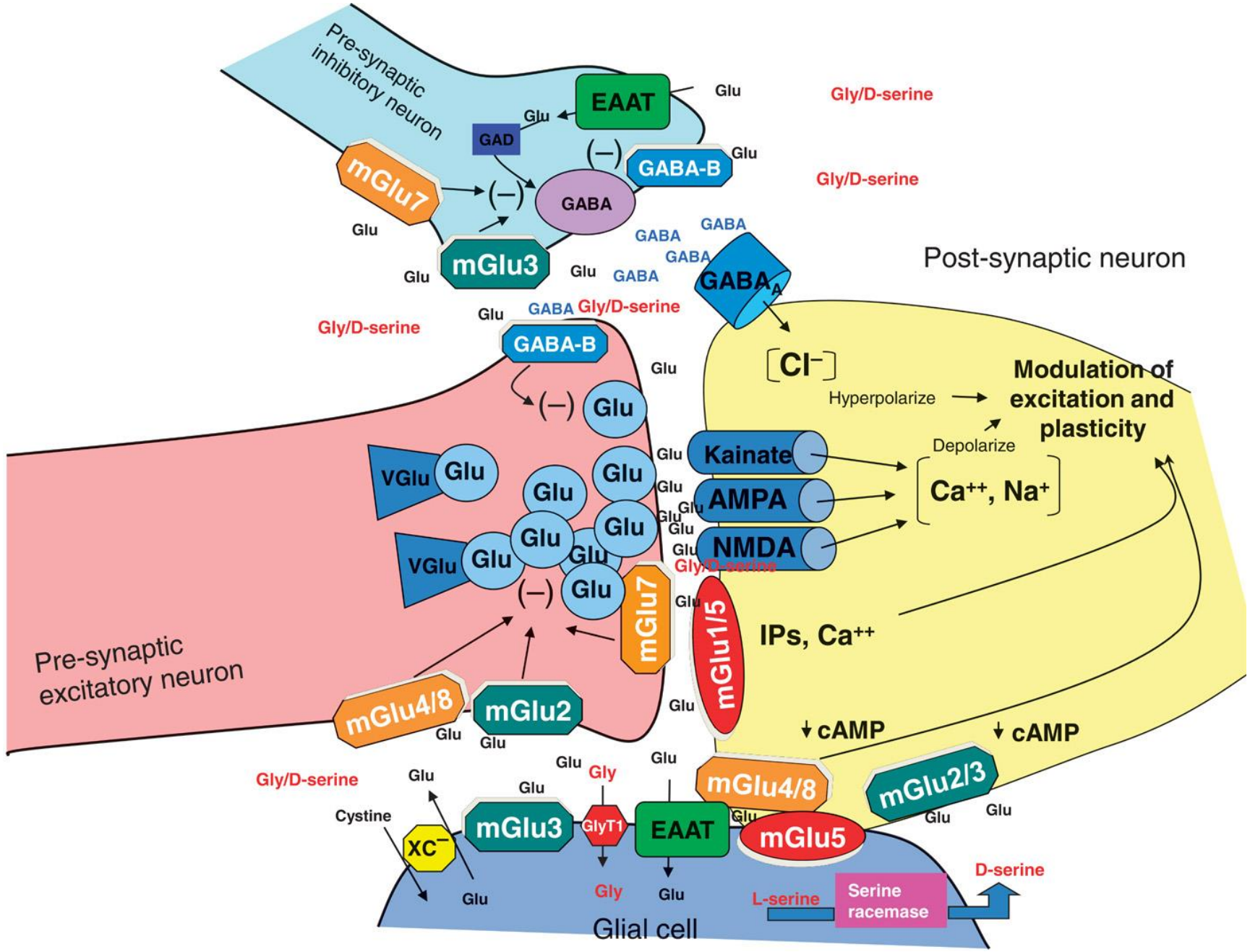

Microglial cell
Astrocyte
Ependymal cells
Oligodendrocytes

Neurotransmission

- Synapse
- 3 dimensions: space, time & function
- Neurotransmitters (types & function)
- Receptors (types & function relating to psychopharmacology)

Synapse (simple)




Pre-synaptic inhibitory neuron
EAAT
Glu
Gly/D-serine
GAD
Glu
(–)
GABA-B
Glu
Gly/D-serine
mGlu7
(–)
GABA
Glu
GABA
GABA
mGlu3
Glu
Glu
GABA
GABA
Post-synaptic neuron
GABA$_A$
Gly/D-serine
Glu
GABA
Gly/D-serine
GABA-B
Glu
[Cl$^-$]
Hyperpolarize
Modulation of excitation and plasticity
(–)
Glu
Depolarize
Glu
Kainate
VGlu
Glu
Glu
Glu
Glu
AMPA
Ca^{++}, Na$^+$
Glu
Glu
Glu
Glu
Glu
VGlu
Glu
Glu
Glu
NMDA
Gly/D-serine
(–)
Glu
mGlu7
Glu
mGlu1/5
IPs, Ca^{++}
Pre-synaptic excitatory neuron
mGlu4/8
mGlu2
Glu
Glu
Glu
↓cAMP
↓cAMP
Gly/D-serine
Glu
Glu
Glu
Gly
Glu
mGlu4/8
mGlu2/3
Glu
Glu
Glu
Cystine
XC$^-$
mGlu3
GlyT1
EAAT
mGlu5
Glu
Glu
Gly
Glu
D-serine
L-serine
Serine racemase
Glial cell

The Three Dimensions of Neurotransmission

I. Space

a. Anatomically addressed system

-> The anatomical orientation of the brain can be viewed as a ‘wire & plug’ system (axon – synapse)

-> 100 billion neurons with 100 trillion connections

-> Information starts electrical (depolarization at soma) with transmission then being chemical (synapse)

b. Chemically addressed system

-> Chemical neurotransmission not limited to synapse: can diffuse to more distant areas of CNS and trigger receptors. Can be seen as ‘wireless’ system.

-> Non-synaptic diffusion neurotransmission

-> Brain thus ‘bathed’ in neurochemical solution (endocrine system is chemical system)

II. Time

A. Fast onset (milli-seconds)

- Stimulatory (+) Glutamate
- Inhibitory (-) Gamma-Aminobutyric Acid (GABA)

B. Slower onset (long term)

- Mono-amines
- 5 – HT (serotonin)
- Neuropeptides

Slower, long term effects via cascades
Multi-modal, modulatory.

III. Function

A. Pre-Synaptic Events

a. Cell body creates neuro-transmitters via DNA > mRNA > tRNA > protein synthesis

Storing neurotransmitters in vesicles > transported via Kinesin to Synapse, awaiting:

b. Electrical impulse from Soma via axon to terminal/ synapse with nodes of Ranvier

causing fast electrical transmission via saltatory conduction (leaping)

c. Depolarization of terminal, Calcium influx, triggering release of NT's via vesicles into

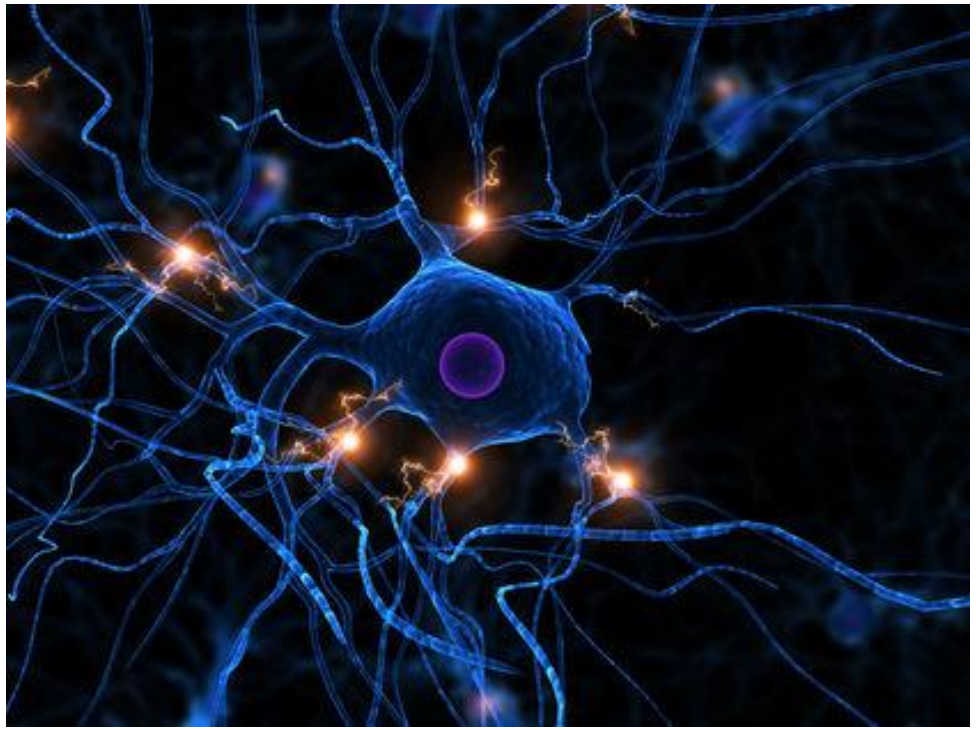
synaptic space.

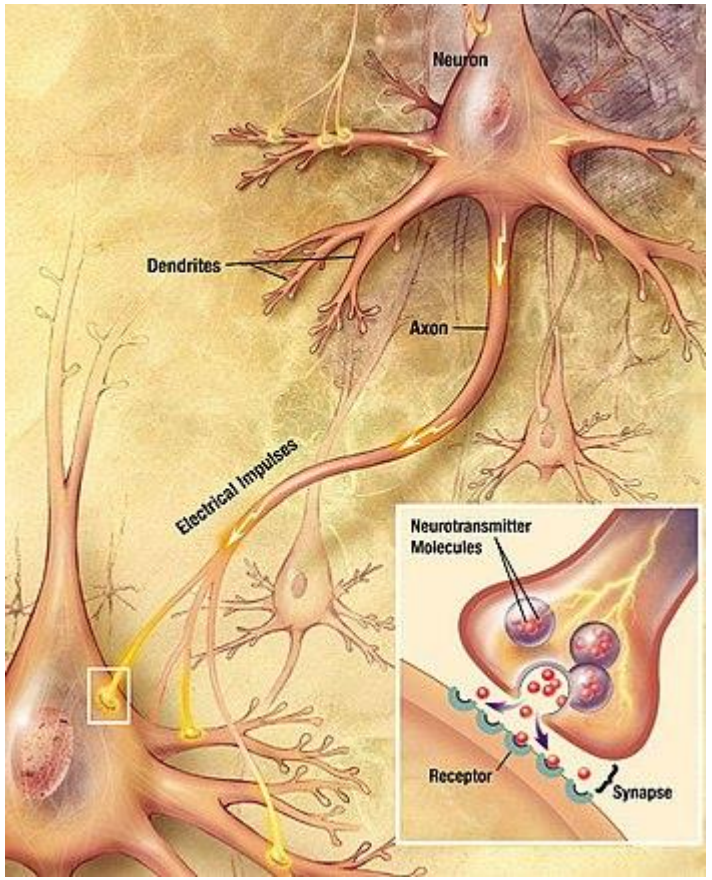
d. Empty vesicles either filled locally by re-uptake, or transported retrograde to soma to

via Dynein to be refilled by manufactured NT's.

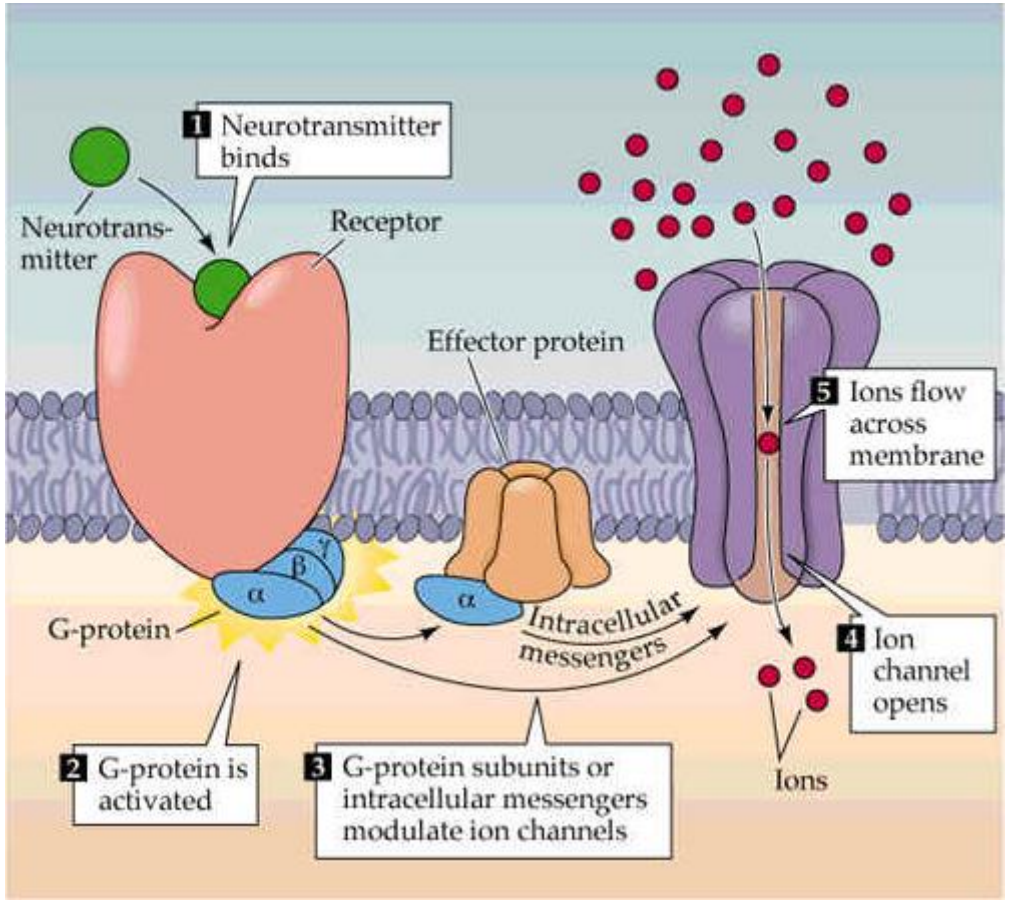
B. Post Synaptic Event (2- dimensional event)

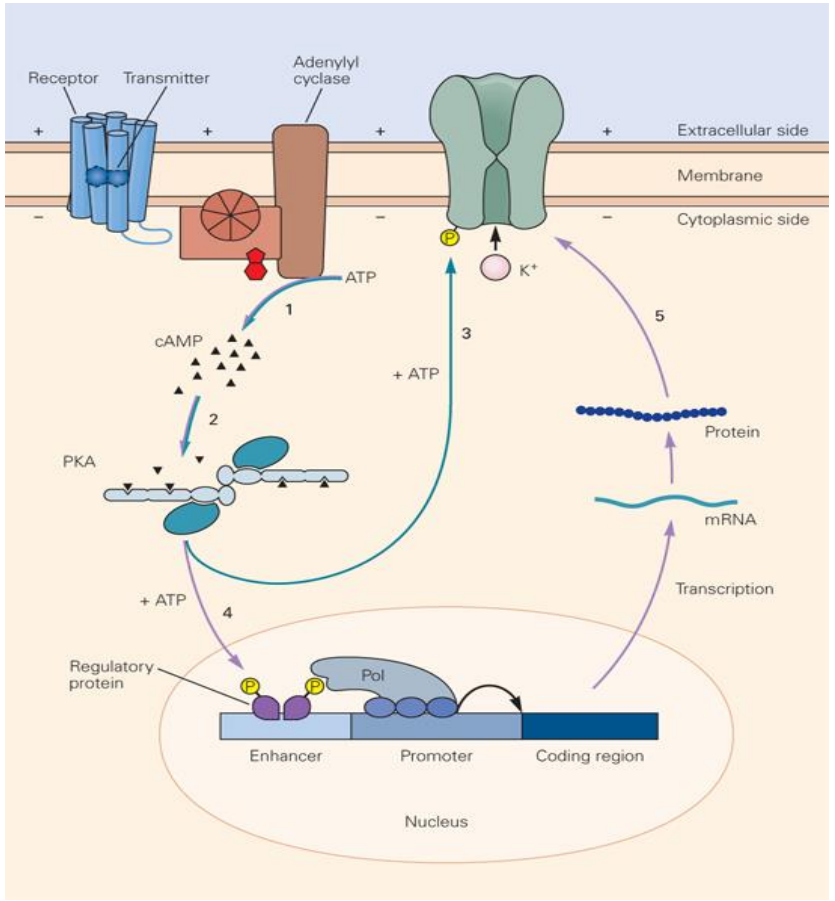
a. Depolarization and continuation of electrical impulse (+/-)



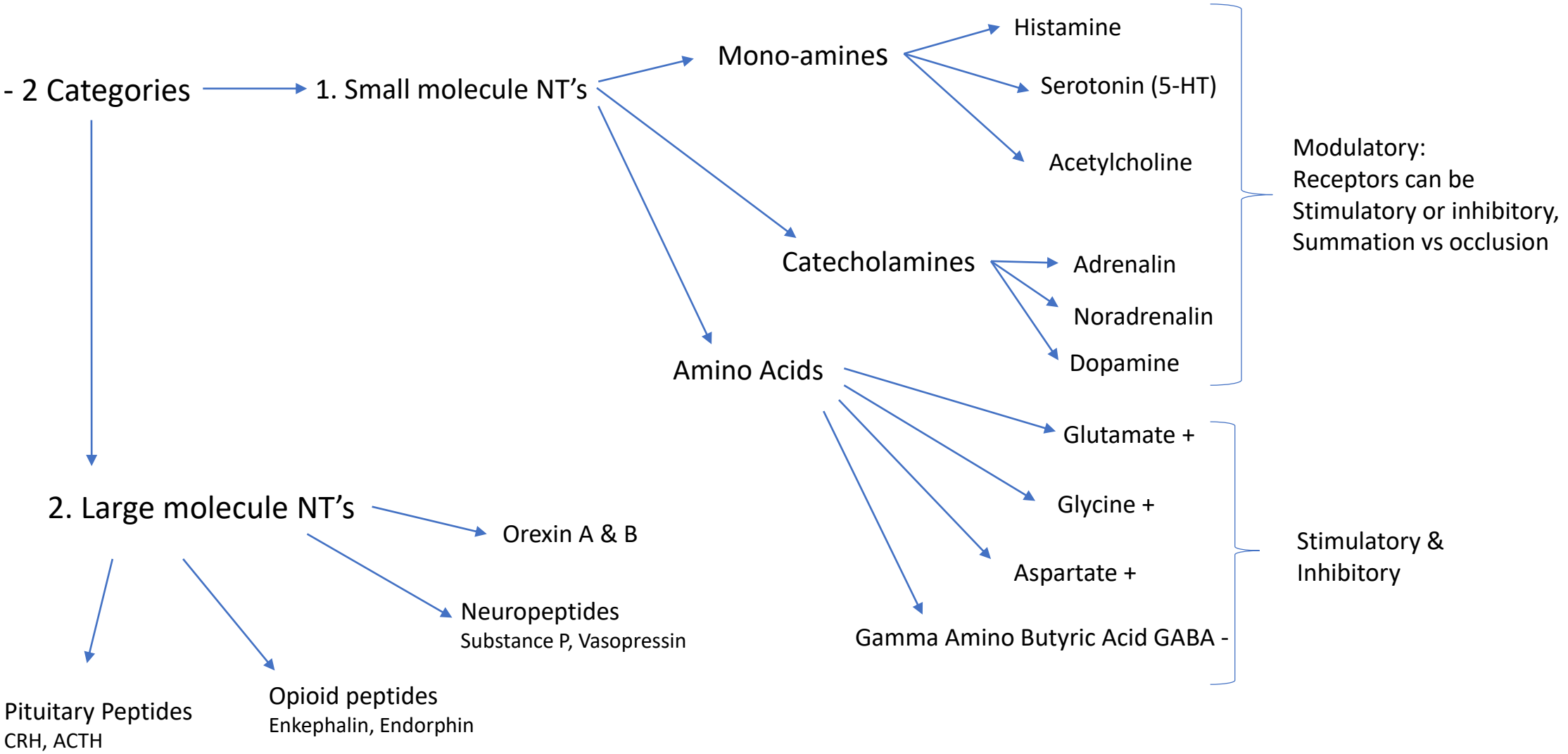


b. NT binds to specific receptor like ‘key and lock’ as 1st messenger, activating chemical cascade:
G – protein (2nd messenger) -> Cyclic AMP -> Protein Kinase A -> DNA to RNA to Protein transcription.
Proteins are structural as well as functional. Genotypal brain transcribing to phenotypal brain
in response to environmental stimuli.





Neurotransmitters (types and function)



Receptors (types & function)

- Each ligand (NT or 1st messenger) has different receptor subtypes
- Receptors can be -> pre-synaptic (mostly inhibitory or modulatory)

  -> post-synaptic (mostly excitatory)
- Receptors group in families as far as function concerned
- Prolonged exposure to ligands can lead to unresponsiveness (homologous or heterologous)

  With glutamate, can lead to excitotoxicity, Ca 2+ disruption and cell death

Ligand	Receptor	2nd Messenger	Effect
ACH	Nicotinic Post and Pre-synaptic excitation, attention enhancing and reward		↑ Na+ & K+
Septal Nucleus	M1/ M2/ M3	IP3 & DAG	↑ Ca2+
Basal Nucleus	M2/ M4	C-Amp	↑ K+
Serotonin	5-HT 1A addiction, aggression, anxiety, appetite, blood pressure sleep, etc	C-Amp	↑ K+
Raphe Nuclei	1B as above + learning, memory, penile erection, sexual behaviour	C-Amp	↓ K+
	2A anxiety, autoreceptor, locomotion, vasoconstriction	IP3 & DAG	K+
	2C addiction modulation, anxiety, GI motility, thermoregulation		
	etc		
Dopamine	D1, D5 motivation, cognition, learning, pleasure, fine motor control		
VTA	D2 ADHD, addiction, path gambling, schizophrenia, parkinsons	C-Amp	K+, Ca2+
SN	D3		

IP3: Inositol-tri-phosphate DAG: diacylglycerol C-Amp: cyclic adenosine monophosphate

Ligand	Receptor	2nd Messenger	Effect
Noradrenalin	α1,2 anxiety, panic, depression, Parkinson's	IP3, DAG	↓ K+
Locus Coeruleus	B1,2,3		↑K+ , Ca2+ ↓
Glutamate Basal ganglia et al	N-methyl-D-aspartate receptor (NMDA r) Excitatory, excitotoxicity, neural plasticity, LTP, LTD		↑ Na+, K+/ Ca2+↓
GABA	GABA A & B, mainly inhibitory	IP3, DAG	↑ K+, Ca2+↓
Basal ganglia et al			

LTP: Long Term Potentiation -> persistent strengthening of synapses based on recent patterns of activity
LTD: Long term Depression -> long lasting decrease in synaptic strenth

Re-uptake

After release into synaptic area, the NT's will undergo:

a. Re-uptake

-> transporter proteins using trans-membrane ion gradients, will move NT's from synapse back into terminal

-> 5HT, NA, Dop, Ach, GABA, glycine: transported by 1 'family' of transporter proteins.

-> Glutamate transported by another family of transporter proteins, role in excitatory toxicity.

-> Selective Re-Uptake Inhibitors (SSRI, SNRI, DRI) decreases re-uptake, increases amount of NT available in synaptic cleft, more potential for binding and thus increase in function.

Question: immediate action, why does it take 2 weeks before response?

BUT, with Bipolar Disorder, rapid transition to manic episode?

b. Metabolized by enzymes.

Neuro-development & Neuronal Plasticity

- Neuronal migration starts right after conception and ends just before birth.
- Most dynamic brain development happens before birth.
- Starting with 1 trillion cells at birth > apoptosis > reduced to 100 billion cells by birth.
- Apoptosis is controlled cell death (vs necrosis), natural process controlled by gene expression.
- Approximately 95% of brain volume by the age of 5 years with,
- myelination & arborization peaking at adolescence, then steadily decreasing into further adulthood.
- Synaptogenesis continues into adulthood, but slowly decreases past mid 20’s.

- Neurotrophic factors regulate development throughout life:

  -> DNA coding for correct NTF at the right time/ stage

  -> apoptosis, neuroprotective, adhesion, growth repulsion or attraction

  -> neuronal migration > fixation > axonal sprouting & migration > axonal fixation > synapse formation > pruning of unwanted/ unused synapses and apoptosis (if not used, lost).

- Brain constantly interacting with environment

  -> leading to depolarization and actions AS WELL AS activation of 2nd messenger > protein synthesis (cell structures, receptors, neurotrophins), with synaptogenesis.

  Genotypal brain -> phenotypal brain, thus, cognitive therapy can change architecture of brain.

- Neurotrophic factors -> Nerve growth function &

  -> Brain Derived Neurotrophic factor (BDNF):

  differentiation/ neurogenesis/ maintenance

  Plays role in regeneration of hippocampal cells

Neurodevelopment & Chemical Neurotransmission as Mediators of Disease

Normal neurotransmission is essential for:

-> primary stimulus reaction communicated to secondary, tertiary etc stimulation, information processing and reaction (motor, sensory, emotional, behaviour)

-> activating 2nd messenger systems, leading to protein synthesis in CNS and beyond, creating NT's receptors, neurotrophic factors etc, to ensure healthy brain development, activity and behaviour.

-> Disruption to this system will lead to pathology.

2 Hit or 'multiple hit' hypothesis:

-> Genetic & epi-genetic predisposition to specific psychiatric disorder (hit 1) } Disruption in neuronal migration & fixation

-> Exposure to substances/ virus/ toxins in utero (hit 2)

-> Traumatic birth (oxygen deprivation etc) with low Apgar (hit 3)

-> Meningitis leading to encephalitis as child (hit 4)

-> Traumatic brain injury as adolescent such as concussion (hit 5) } Leading to abnormal sprouting, pruning

-> Trying cannabis and methamphetamine as adolescent (hit 6)

-> First Episode in Psychosis

Concepts of neuropsychopharmacology, focusing on:

1. **Schizophrenia**

-> Chronic neurocognitive/ mental disorder characterized by episodes of psychosis (so called positive symptoms) and disorganized thought processes to various degrees, suffered by about 1% worldwide.

-> High co-morbid medical conditions & social dysfunction.

-> Very complex disorder with genetic heritability and multiple theories as pathophysiology:

I. **Neurochemical**

a. Dopamine hypothesis

- Overactivity of meso-limbic (positive sx) and meso-cortical (negative sx) pathways
- Believed this overactivity leads to abnormal LTD & LTP in combined pathways.
- Dopaminergic agonists such as amphetamine and even Bupropion can lead to psychosis.
- Thus dopamine antagonists (especially D2 and D4 receptor antagonists) successful in reducing psychotic symptoms in most cases.
- Some shortcomings in this theory as a standalone theory:
  > DA antagonism at 90% almost immediate, with slow to sometimes no effect.
  > Atypical anti-psychotic have a lower affinity for DA receptors, equally effective.
  > Other substances such as DMT, psilocybin, salvia divinorum (acting on 5HT 2A) cause profound hallucinations

b. Glutamate hypothesis

- NMDA receptor hypo-activity (NMDA receptor antagonists) cause schizophrenia-like symptoms (+/-)
- NMDA r encephalitis causes psychotic illness.
- Lower amount of NMDA r found post-mortem in brains of patients with schizophrenia.
- BUT, methamphetamine (NMDA r agonist) can cause psychosis.

c. 5-HT 2A

- LSD, psilocybin, DMT have affinity for this receptor, causing hallucinations
- Clozapine and other atypicals have agonistic effect on this receptor.

II. Neurodevelopmental theories
III. Disconnection hypothesis
IV. Neurodegenerative theory etc

As it is a complex disorder, with multiple genes and epi-genetic areas identified as well, the best hypothesis thus far is

- a multiple hit hypothesis, where multiple genes and epigenetic areas cause genetic vulnerability, with
- multiple environmental stressors causing abnormal neurodevelopment, and this disorder eventually
- precipitated by the final 'hit' , with all neurotransmitter systems malfunctioning to some extent.

>> Multiple studies showed decreases in fronto-temporal grey matter thickness over years.

2. **Bipolar Disorder**

-> A chronic mental disorder (mood disorder) characterized by episodes of mood abnormalities such as manic episodes (decreased need for sleep, pressure of speech, grandiosity, disorganized thoughts) and depressive episodes (with sleep disturbance, psychomotor retardation, thoughts of hopelessness and thoughts of death and suicide).

-> Like schizophrenia, a complex disorder with genetic heritability and pathophysiology theories:

- Meta-analyses of structural MRI studies report decreased volume in left rostral anterior cingulate cortex fronto-insular cortex, ventral prefrontal cortex, and claustrum.
- Dopamine shown to have increased transmission in manic episodes. Increase in DA = homeostatic = down regulation in receptors (G protein coupled) leading to depressive phase.
- Glutamate significantly increased within the left dorsolateral prefrontal cortex during manic phase, decreasing post mania (glutamate toxicity = kindling effect with following worse manic episodes?)
- Anti-psychotic treatment in manic episodes shown my Cipriani et al 2011, to be most effective
- Depressive phase most likely different pathophysiology vs MDD, thus anti-depressant not effective or cause manic/ mixed episodes.
- Mechanism for mood stablizers as maintenance therapy (especially Lithium) unclear.

3. **Major Depressive Disorder**

-> Mental disorder, characterized by episode/s of depressed mood, thoughts of death and suicide emptiness, lack of pleasure, decreased volition and sleep disturbances.

-> Yet again, a complex disorder with multiple causative factors.

-> Mono-=amine hypothesis

- Involving abnormal neurotransmission, especially serotonin, dopamine and noradrenalin
  Serotonin -> regulator of others neurotransmission systems, if depleted, or NT systems faulty (permissive hypothesis).
- Noradrenalin relates to anxiety, attention and interest abnormalities in MDD.
- Dopamine relating to motivation and lack of pleasure abnormalities in MDD.

>> STAR*D: showed a 1/3d of patients will respond to first line antidepressant treatment
a 1/3d will need augmentation, and a 1/3d will be treatment resistant
-> MDD vs BPAD vs other medical conditions missed?

-> HPA axis theory:

- Stress = over secretion of ACTH by hypothalamus.
- Over secretion of cortisol with hippocampal hypotrophy and mood dysregulation.
- Chronic increased states of cortisol will increase pro-inflammatory cytokines (IL 1, IL 6, TNFα damaging endothelium and leading to cardiovascular illness) .
- NB to treat MDD!

4. Anxiety Disorders (focusing on GAD)

-> A mental disorder characterized by continued excessive, uncontrollable and sometimes irrational fear about events (GAD) or specific things (phobias), causing social dysfunction.

-> Amygdala the centre for flight/ fight, regulated by pre-frontal cortex.
With anxiety disorders, amygdala and medial pre-frontal cortex as well as basolateral complex disrupted functional connectivity with abnormal processing of fear and anxiety.

-> Regulation of these connections seem to be increased by SSRI and SNRI medications.
(bottom to top approach)

-> Cognitive Behavioural Therapy addresses this connection dysfunction over months to years with a top to bottom approach.

References

1. Ganong's Review of Medical Physiology, 24th Edition – Mc Graw Hill
2. Stahl’s Essential Psychopharmacology 3d edition – Cambridge, UK
3. Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 10th edition - LWW