Neuromodulation

Neurotransmitters

Excitatory

Glutamate

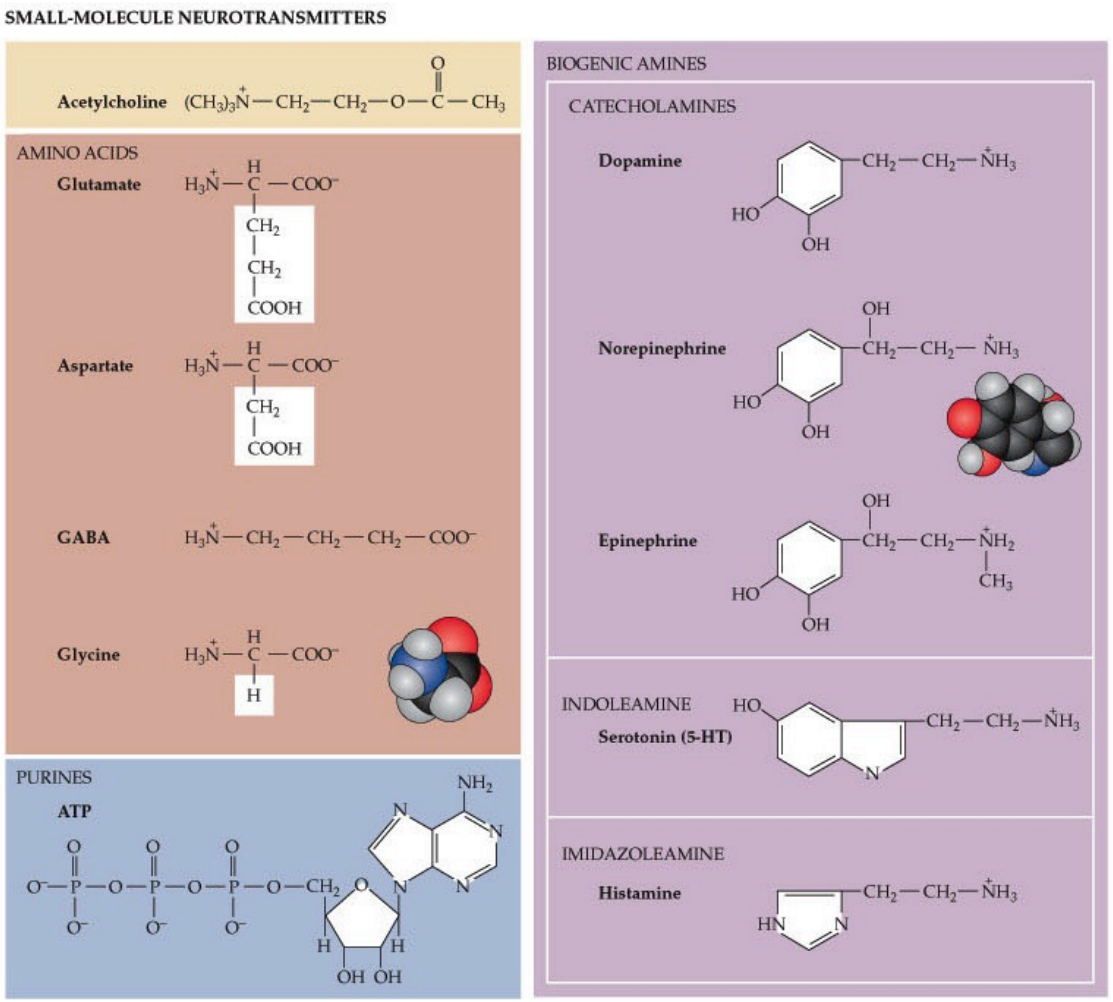
Inhibitory

GABA
glycine

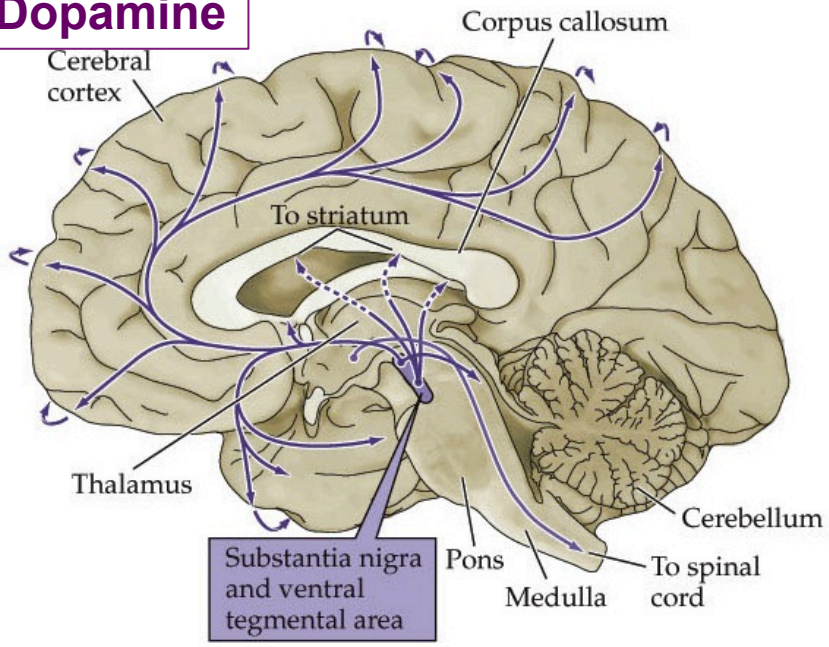
Modulatory

Dopamine
Norepinephrine
Serotonin
Acetylcholine

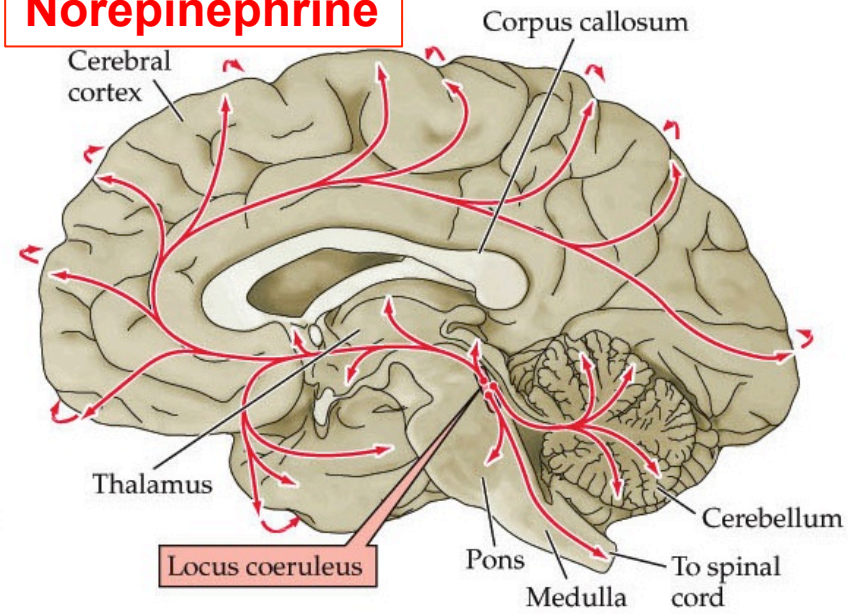
Neuropeptides



Dopamine



Norepinephrine

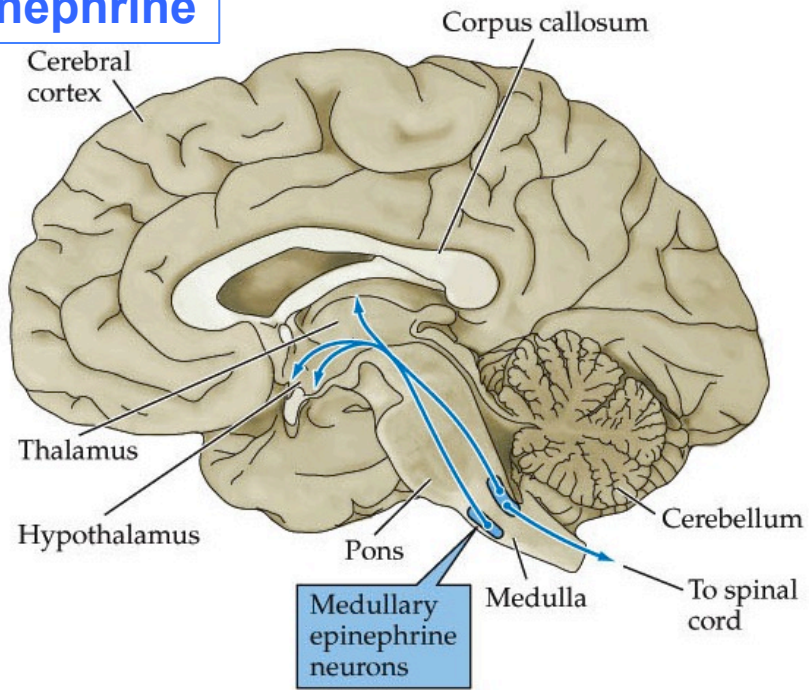


Neuromodulators have global effects!

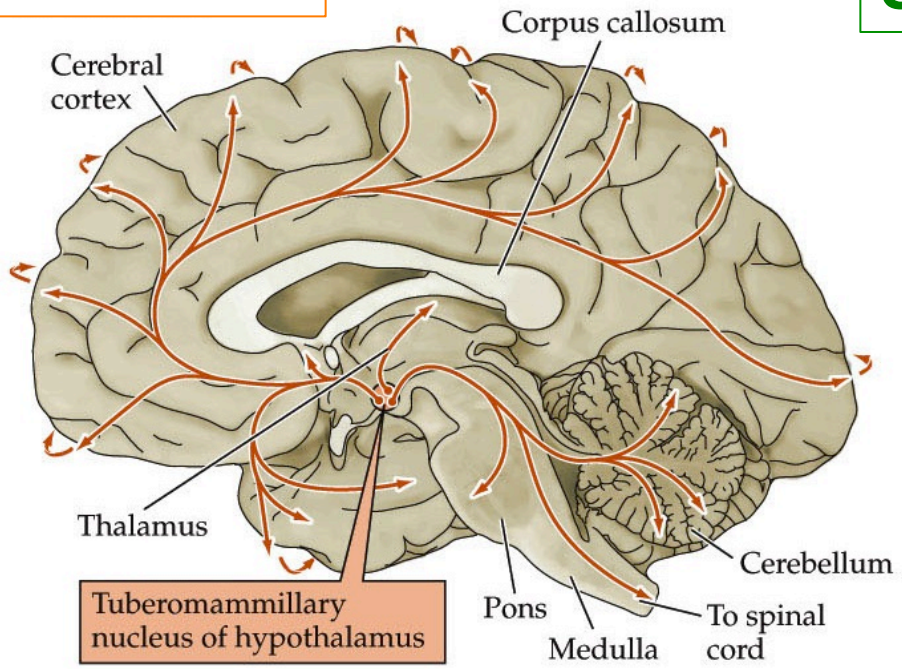
made by small clusters of cells (nuclei) in brain stem or midbrain

project axons to many areas of brain

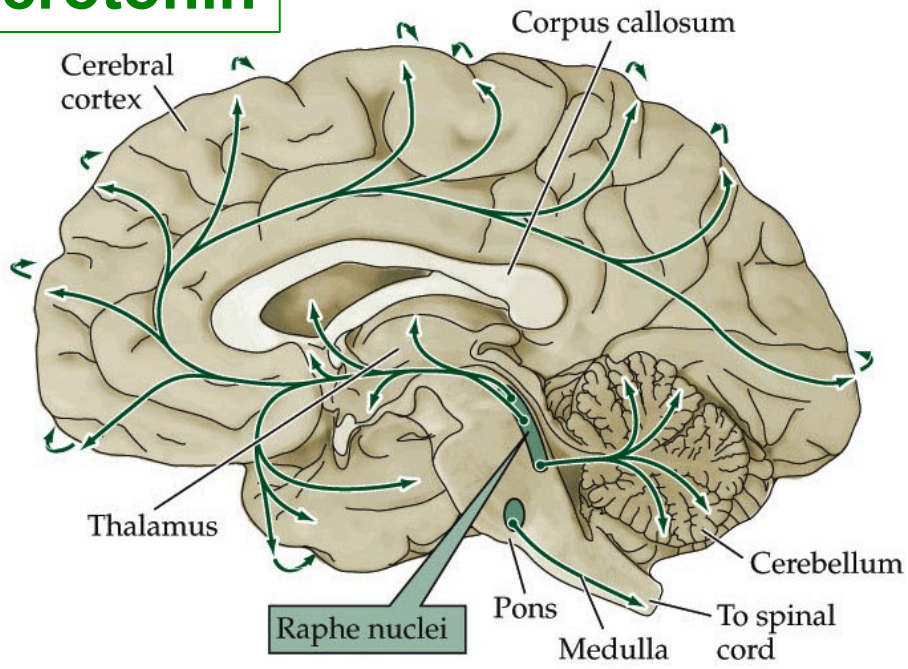
Epinephrine



Histamine



Serotonin

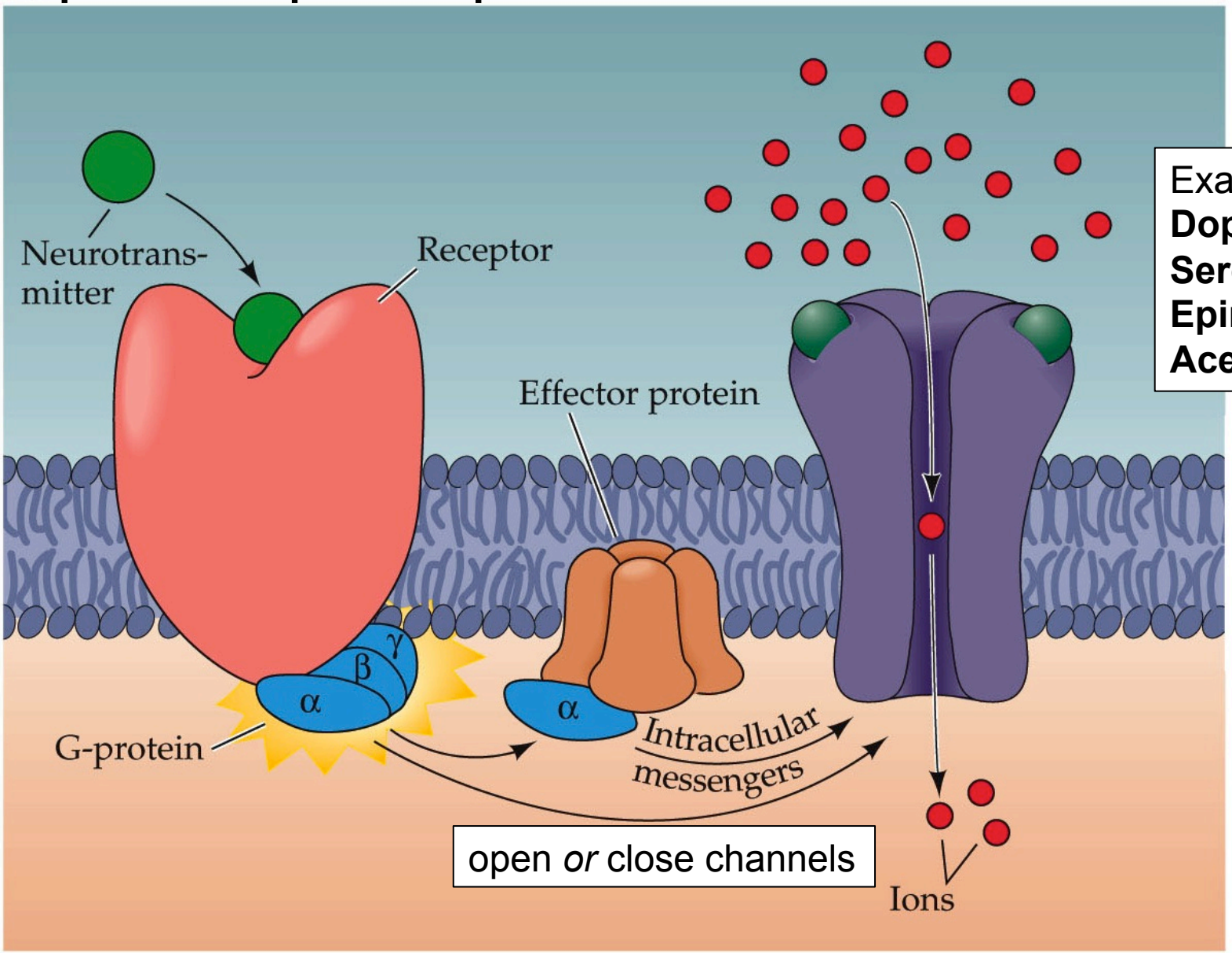


Neuromodulators have global effects!

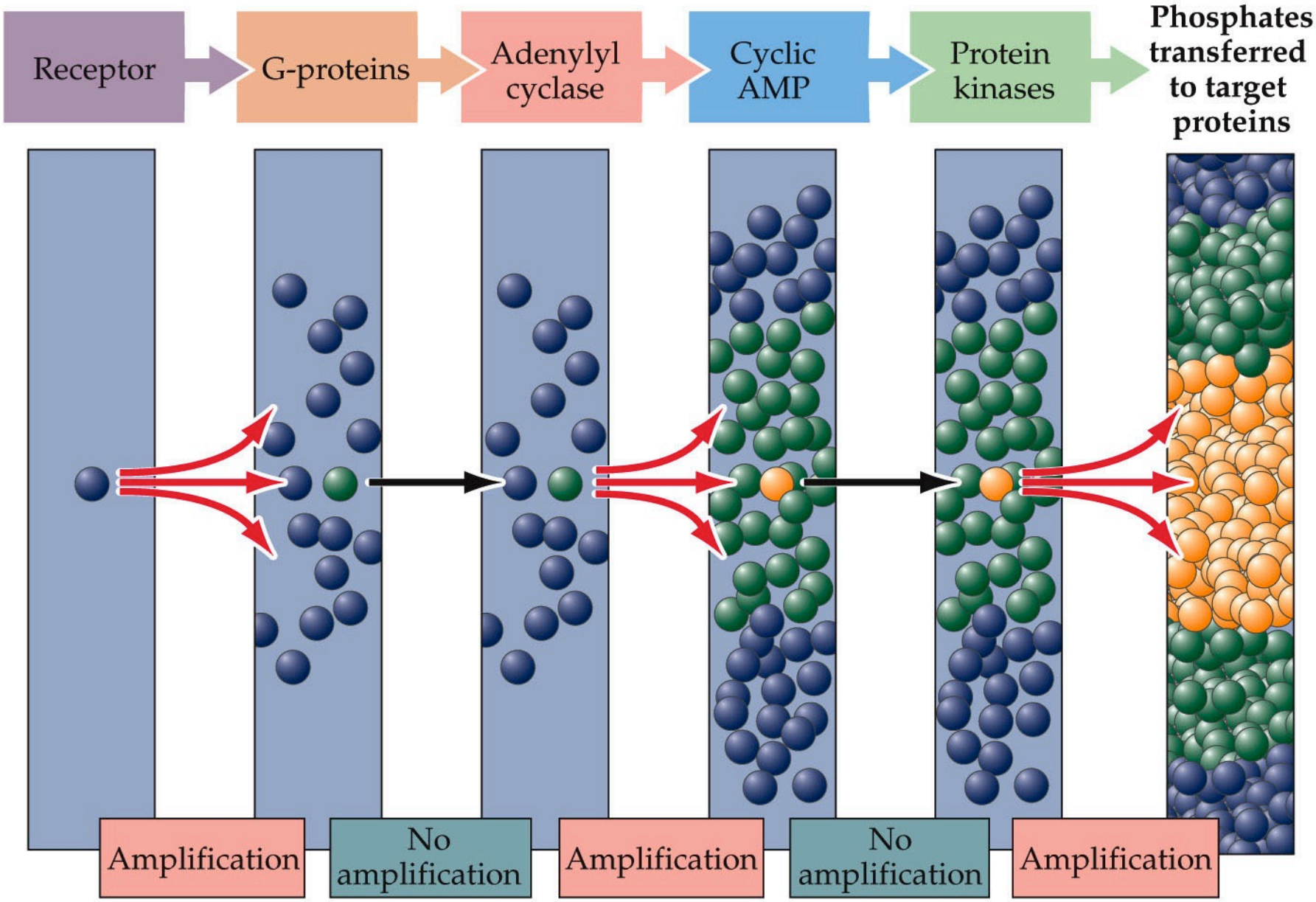
made by small clusters of cells (nuclei)
in brain stem or midbrain

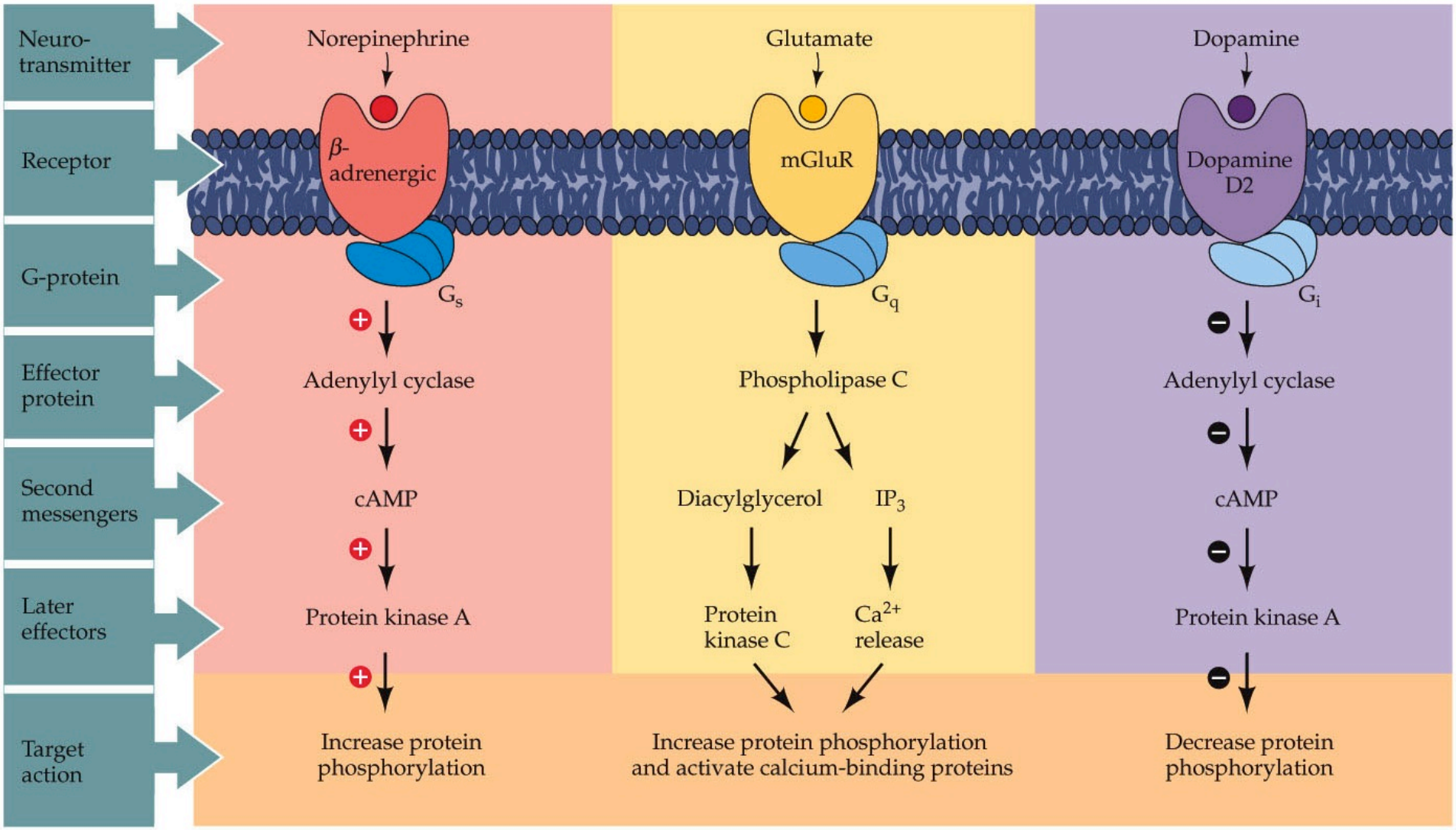
project axons to many areas of brain

G-protein-coupled receptors

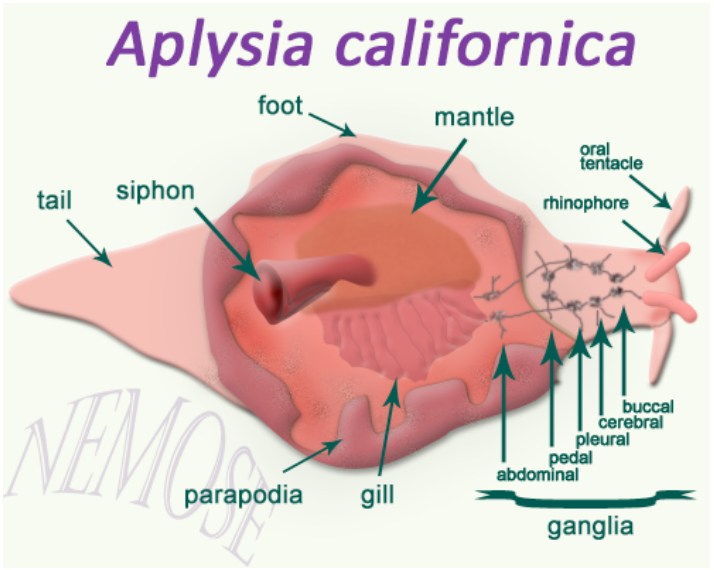


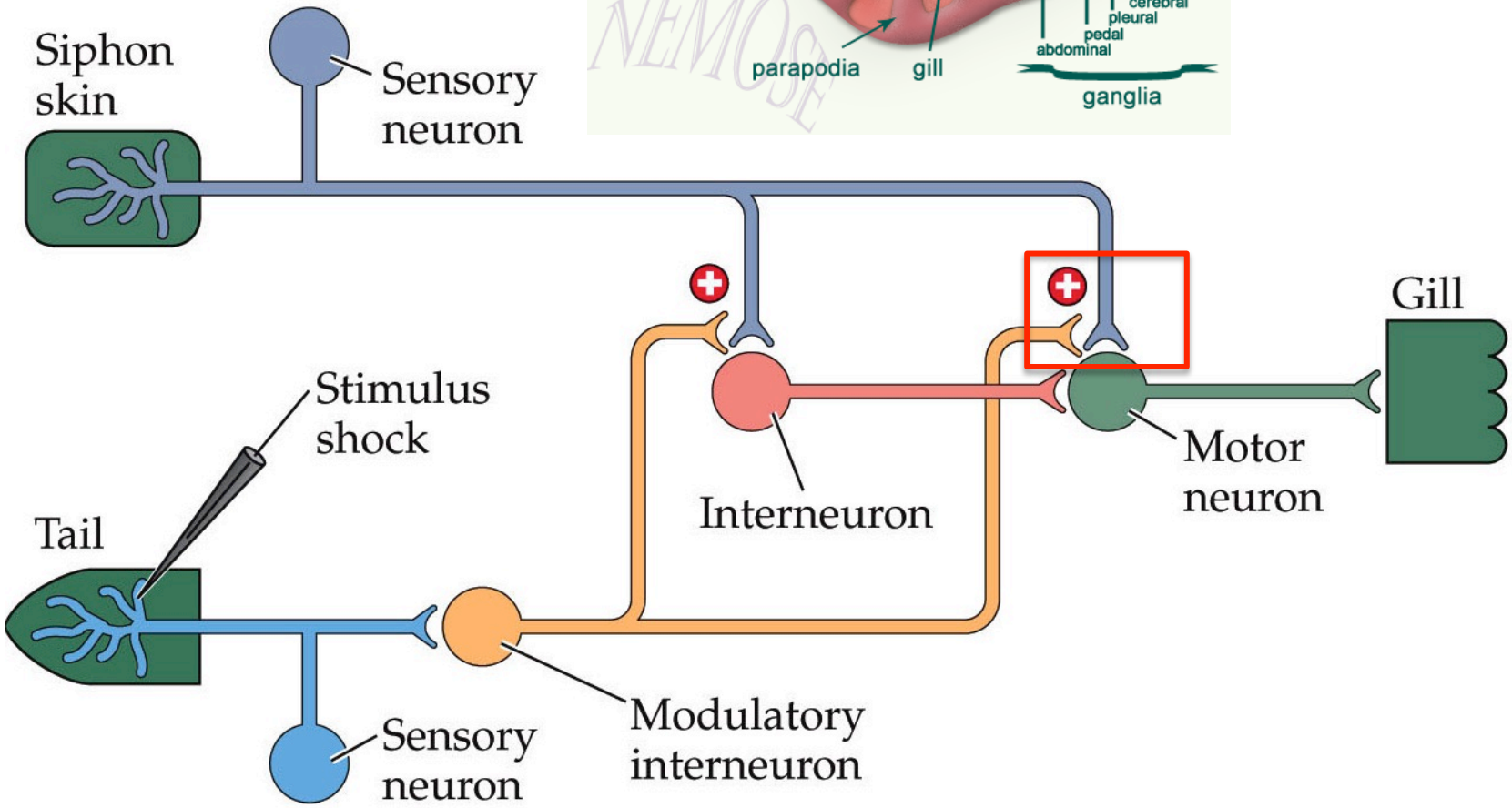
Examples:
Dopamine
Serotonin
Epinephrine
Acetylcholine

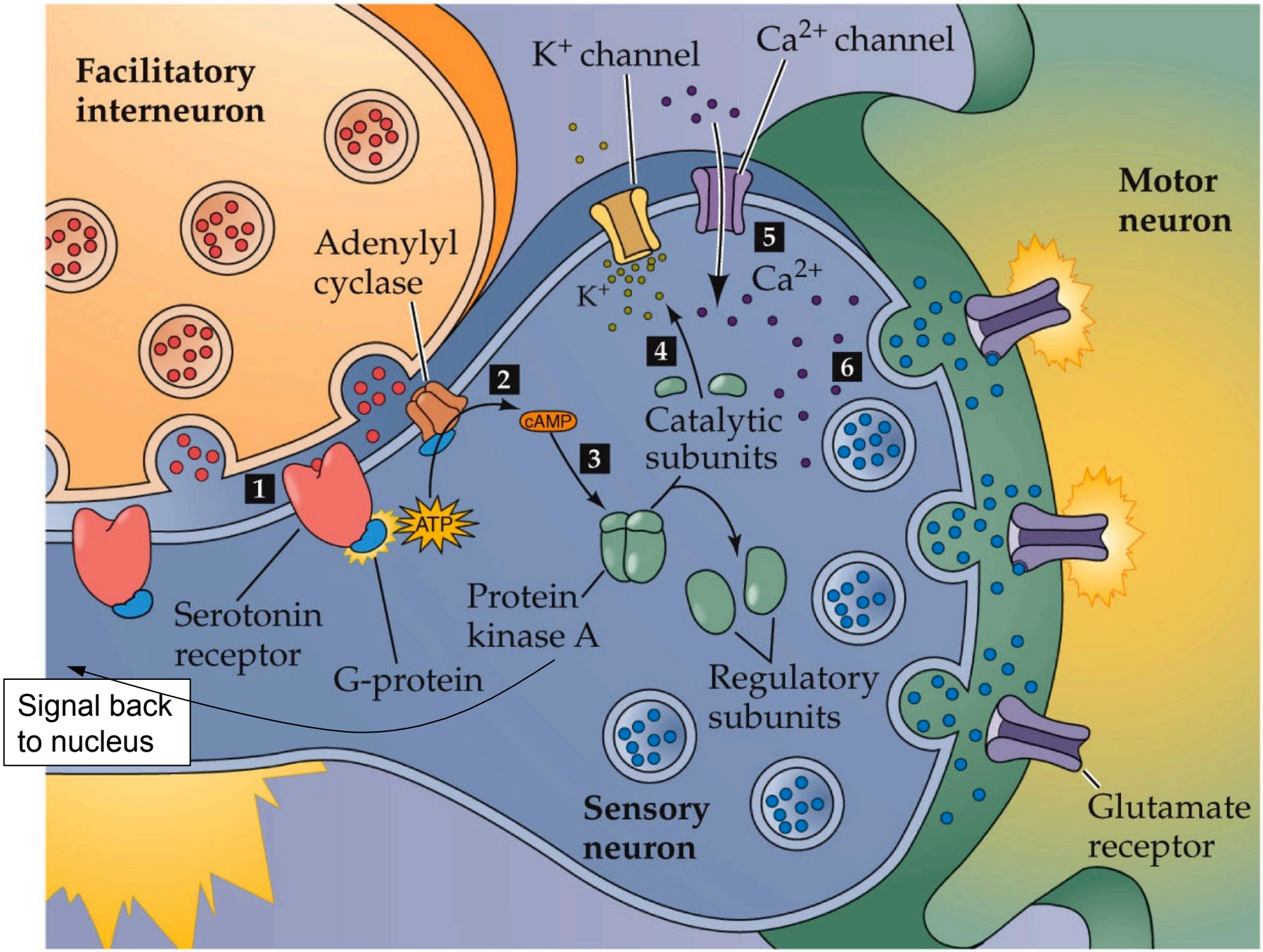

Receptor
G-proteins
Adenylyl cyclase
Cyclic AMP
Protein kinases
Phosphates transferred to target proteins
Amplification
No amplification
Amplification
No amplification
Amplification

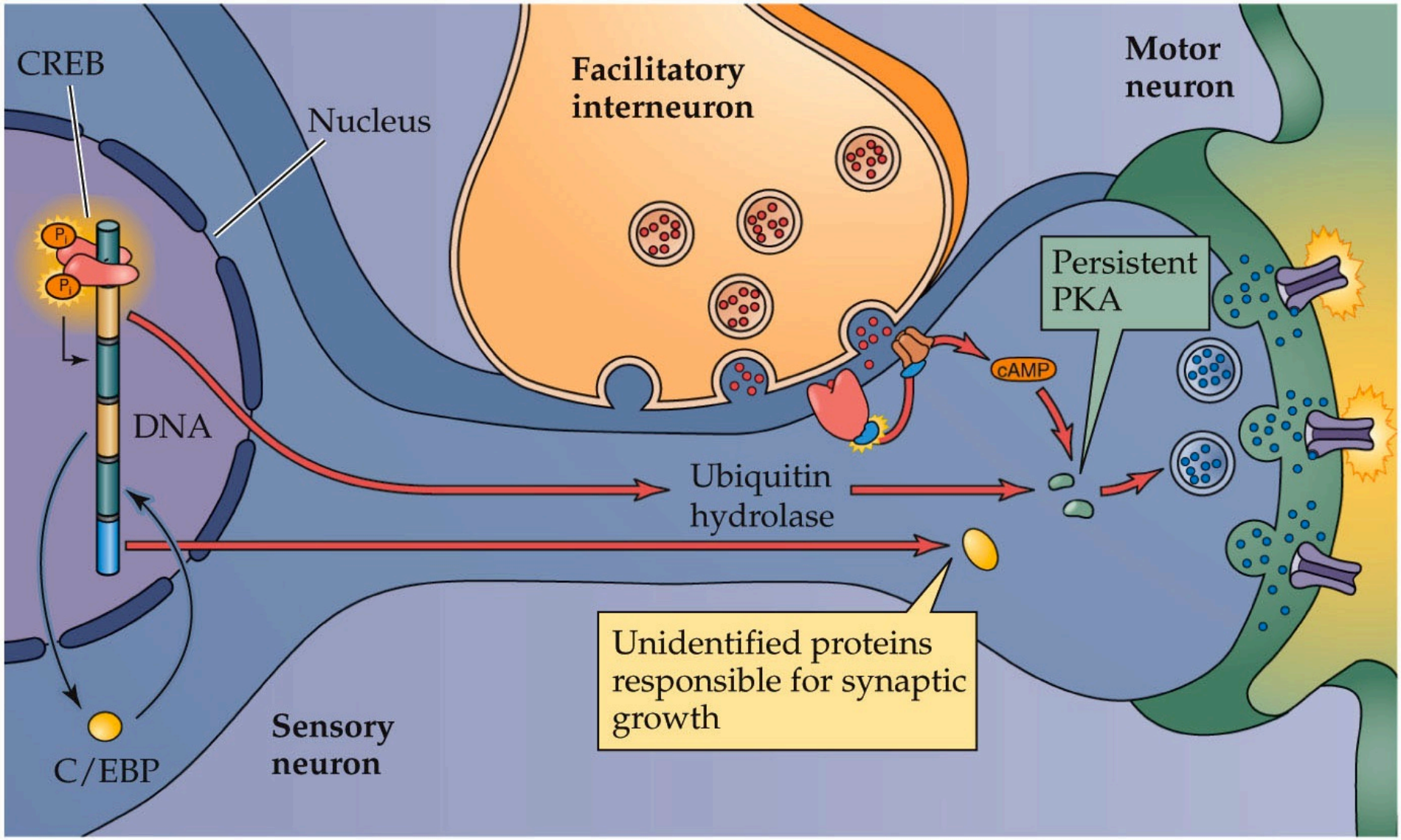


open/close ion channels
change gene expression
…


Aplysia californica
foot
mantle
oral tentacle
tail
siphon
rhinophore
buccal
cerebral
pleural
pedal
abdominal
parapodia
gill
ganglia
NEMOSE


Siphon skin
Sensory neuron
Stimulus shock
Tail
Interneuron
Motor neuron
Gill
Sensory neuron
Modulatory interneuron


Facilitatory interneuron
K+ channel
Ca2+ channel
Motor neuron
Adenylyl cyclase
5
Ca2+
K+
4
6
2
cAMP
Catalytic subunits
3
1
ATP
Serotonin receptor
G-protein
Protein kinase A
Regulatory subunits
Signal back to nucleus
Sensory neuron
Glutamate receptor


CREB
Nucleus
Facilitatory interneuron
Motor neuron
Persistent PKA
cAMP
DNA
Ubiquitin hydrolase
Unidentified proteins responsible for synaptic growth
C/EBP
Sensory neuron

Depression

Major Depressive Disorder

≥ 5 of following symptoms:

Depressed mood

Loss of interest or pleasure in most or all activities

Insomnia or hypersomnia

Change in appetite or weight

Psychomotor retardation or agitation

Low energy

Poor concentration

Thoughts of worthlessness or guilt

Recurrent thoughts about death or suicide

S Sleep disturbance

I Interest/pleasure reduction

G Guilt, feelings or thoughts of worthlessness

E Energy changes/fatigue

C Concentration/attention impairment

A Appetite/weight changes

P Psychomotor disturbances

S Suicidal thoughts

Depression

Affective (mood)

- depressed mood
- loss of interests or pleasure
- blunted emotion

Cognitive (ideations)

- feelings of worthlessness
- unjustified guilt
- thoughts of death/suicide

Somatic (physical)

- sleep (insomnia, hypersomnia)
- appetite or weight changes
- agitation
- concentration

Depression

8 - 12% incidence of major depressive episode

2:1 females-to-males (diagnosis bias?)

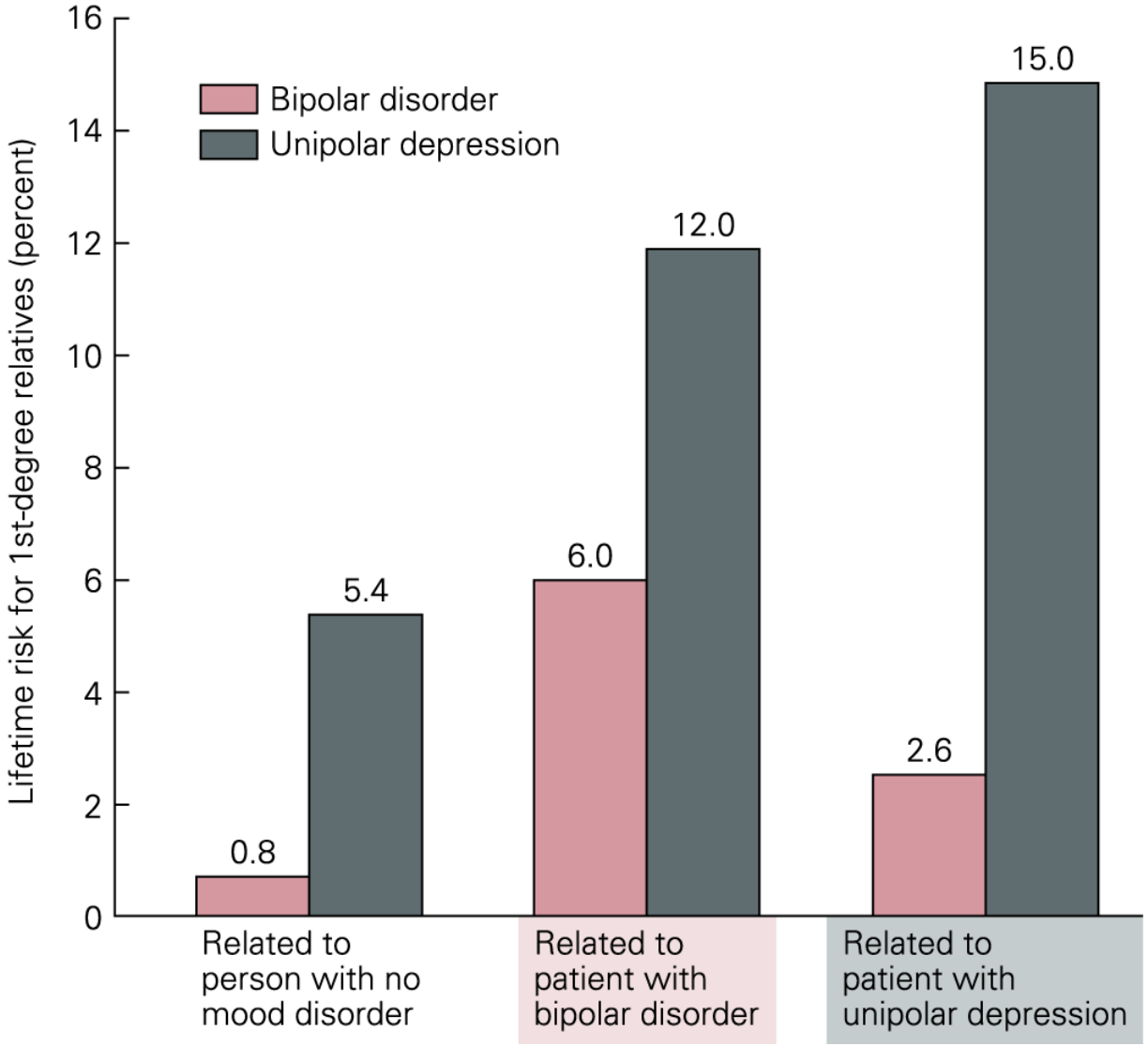
Suicide 3rd leading cause of death for 15-24 year olds

Bipolar Disorder (Manic Depression)

- Decreased need for sleep
- Talkativeness
- Racing thoughts or flight of ideas
- Distractibility
- Increased self-esteem or grandiosity

Depression

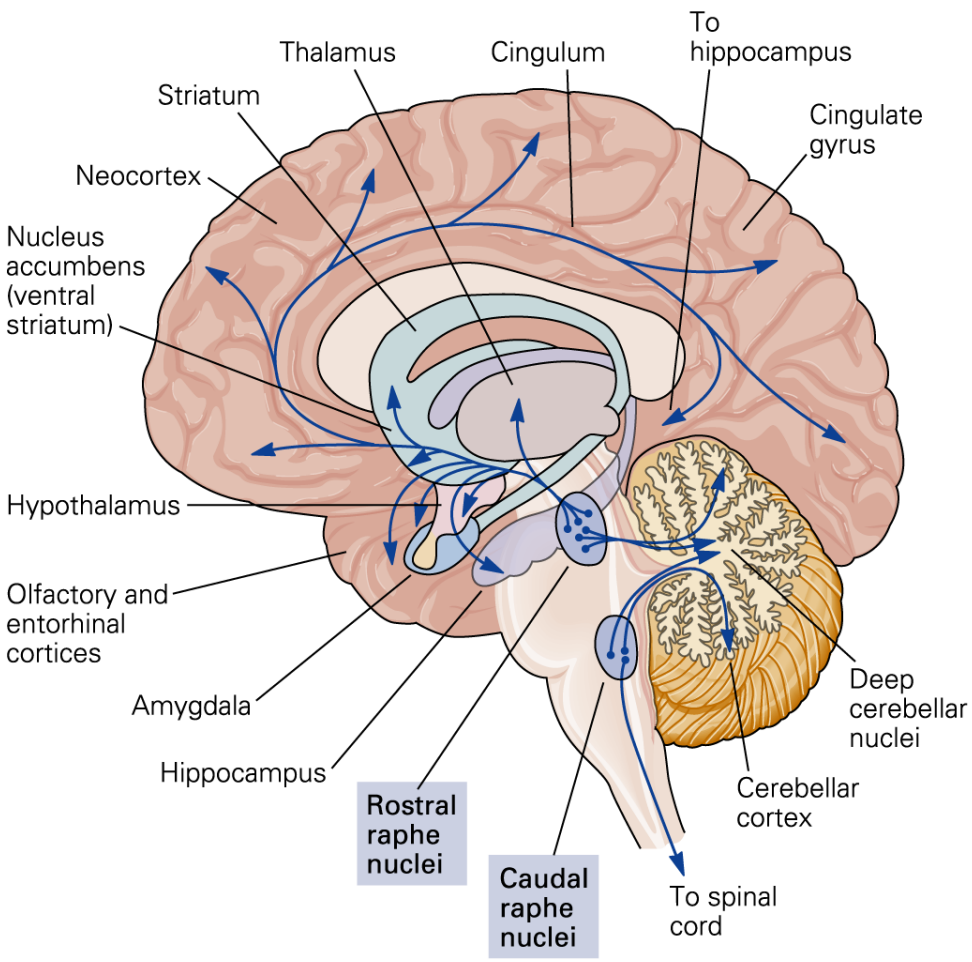
Strong genetic component



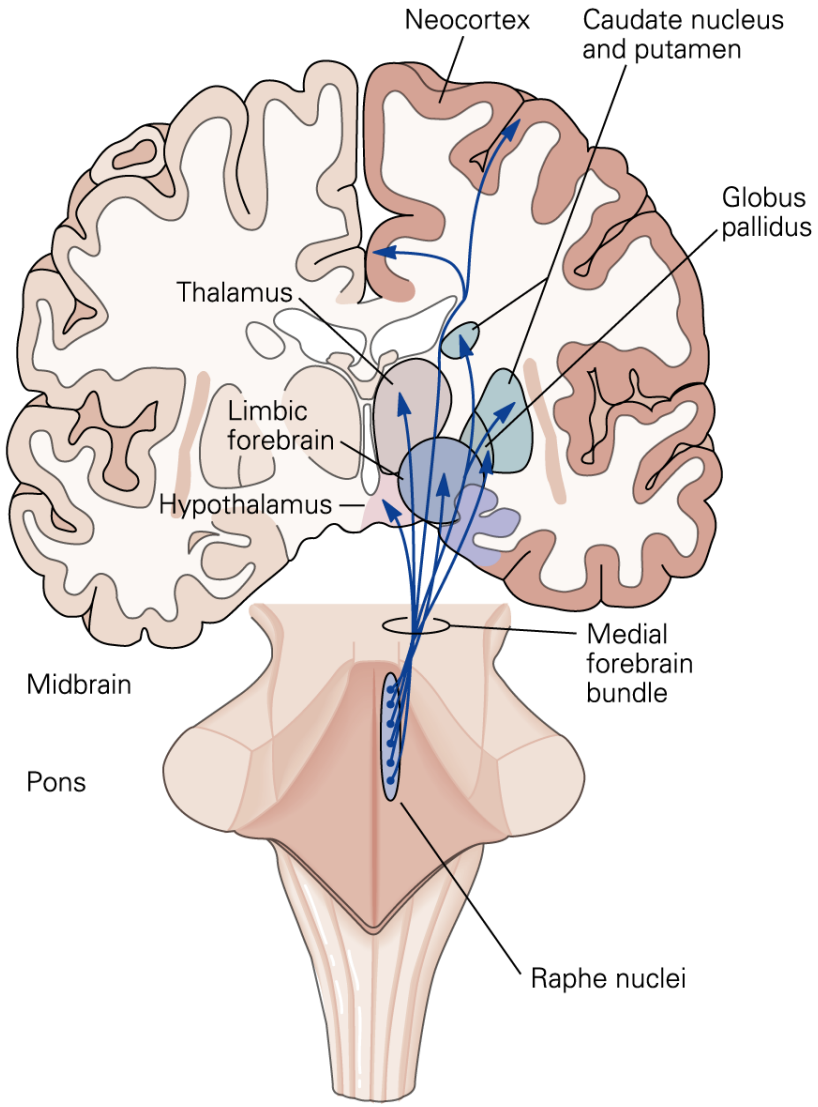
Depression

Serotonin System

A Pathways

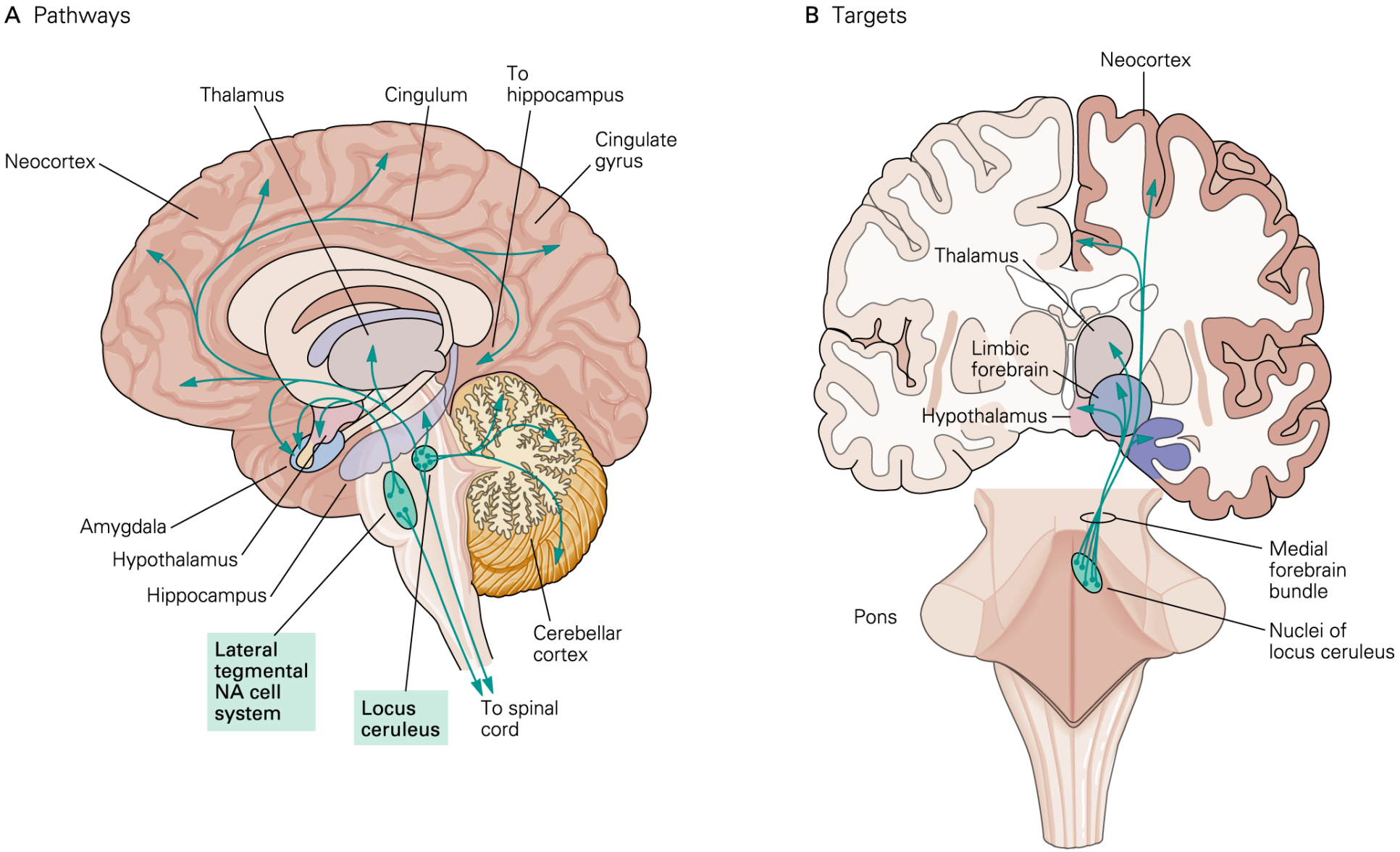


B Targets



Depression

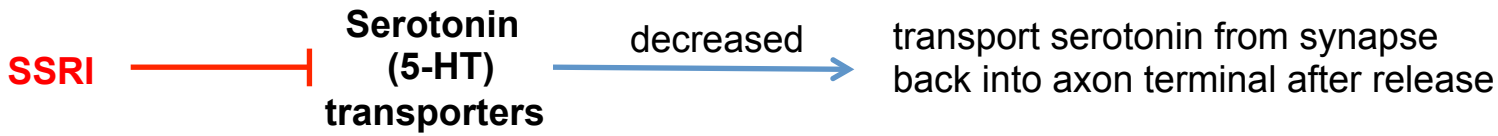
Norepinephrine System



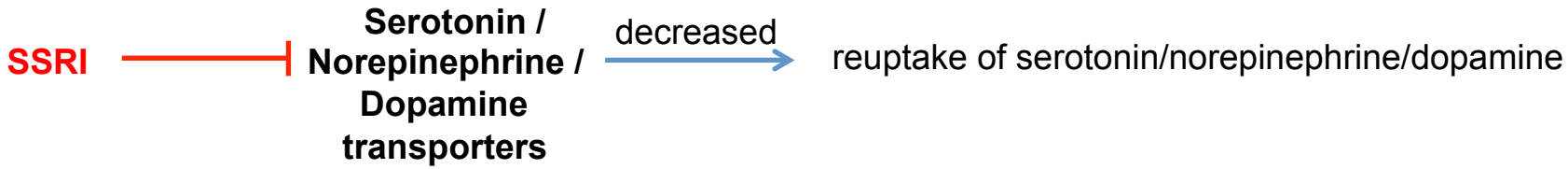
Treatment for Depression

Classes of Antidepressants

Selective Serotonin Reuptake Inhibitors (**SSRIs**)



Non-selective Serotonin Reuptake Inhibitors (**NSRIs**)



Monoamine Oxidase Inhibitors (**MAOIs**)

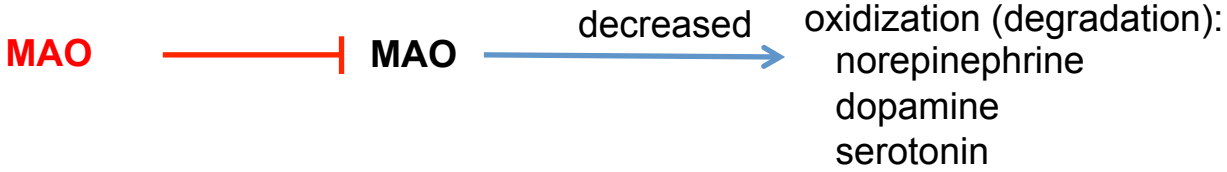
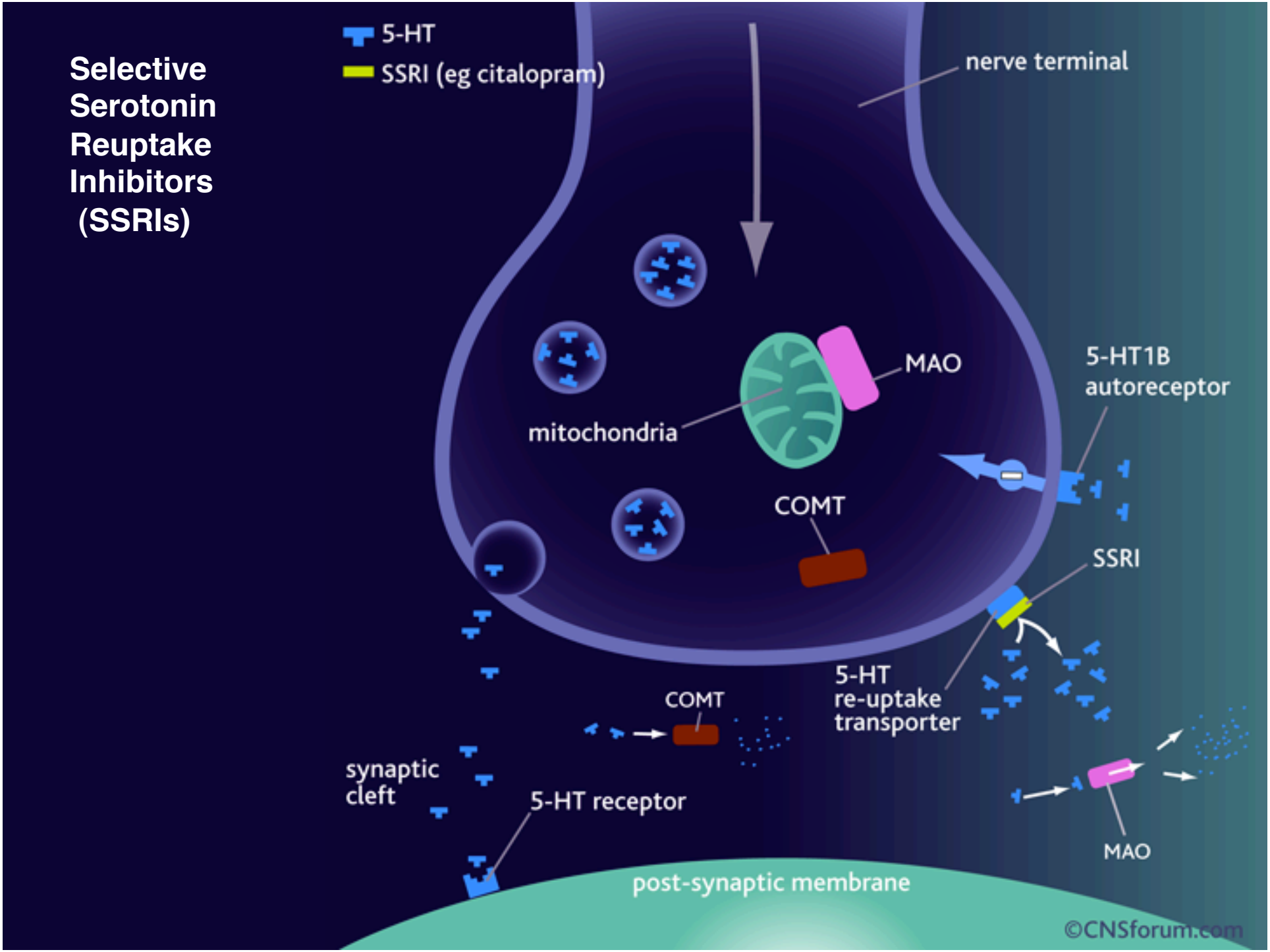


Table 1 | **Currently available antidepressant treatments**

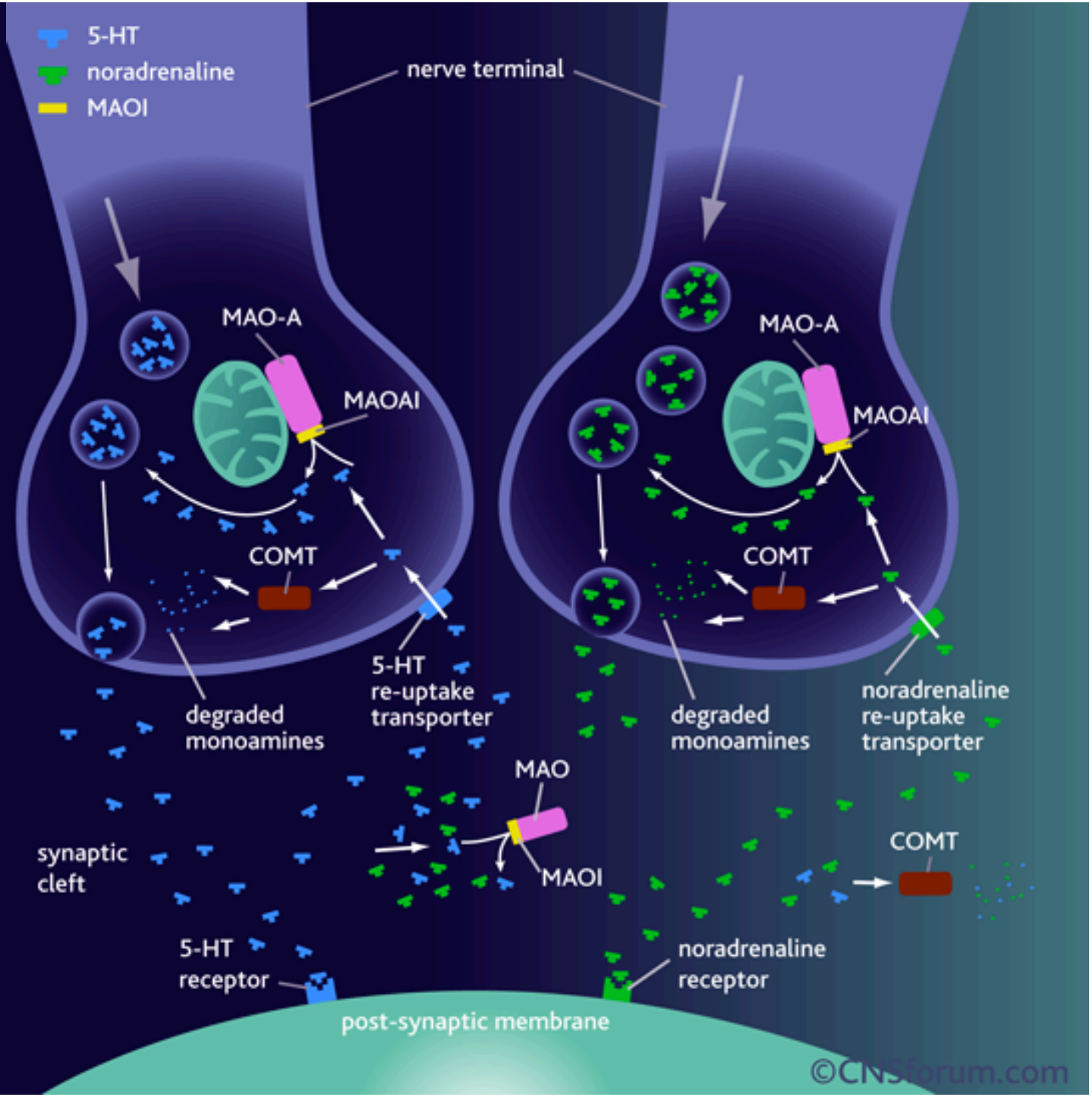
Type of treatment	Mode of action	Examples
*Medication**		
Tricyclics	Inhibition of mixed noradrenaline and serotonin reuptake	Imipramine, desipramine
Selective serotonin reuptake inhibitors (SSRIs)	Inhibition of serotonin-selective reuptake	Fluoxetine, citalopram
Noradrenaline reuptake inhibitors (NRIs)	Inhibition of noradrenaline-selective reuptake	Atomoxetine, reboxetine
Serotonin and noradrenaline reuptake inhibitors (SNRIs)	Inhibition of mixed noradrenaline and serotonin reuptake	Venlafaxine, duloxetine
Monoamine oxidase inhibitors (MAOIs)	Inhibition of monoamine oxidase A (MAO_A). Inhibition of MAO_B does not have antidepressant effects	Tranylcypromine, phenelzine
Lithium	Lithium has many molecular actions (for example, inhibition of phosphatidylinositol phosphatases, adenylyl cyclases, glycogen synthase kinase 3β and G proteins) but which of its actions is responsible for its antimanic and antidepressant effects is unknown	
Atypical antidepressants	Unknown. Although these drugs have purported monoamine-based mechanisms (for example, bupropion inhibits dopamine reuptake, mirtazapine is an α_2-adrenergic receptor antagonist and tianeptine an activator of monoamine reuptake), these actions are not necessarily the mechanisms that underlie the drugs' therapeutic benefit	Bupropion, mirtazapine, tianeptine
Non-medication		
Electroconvulsive therapy (ECT)	General brain stimulation	
Magnetic stimulation	General brain stimulation? A magnetic field is thought to affect the brain by inducing electric currents and neuronal depolarization	
Vagal nerve stimulation (VNS)	Unknown	
Psychotherapies	Exact mechanism is uncertain, but is thought to involve learning new ways of coping with problems	Cognitive-behavioural therapy, interpersonal therapy
Deep brain stimulation	In severely ill patients, stimulation of a region of the cingulate cortex found to function abnormally in brain imaging scans reportedly has antidepressant effects[84]	

Berton & Nestler 2006

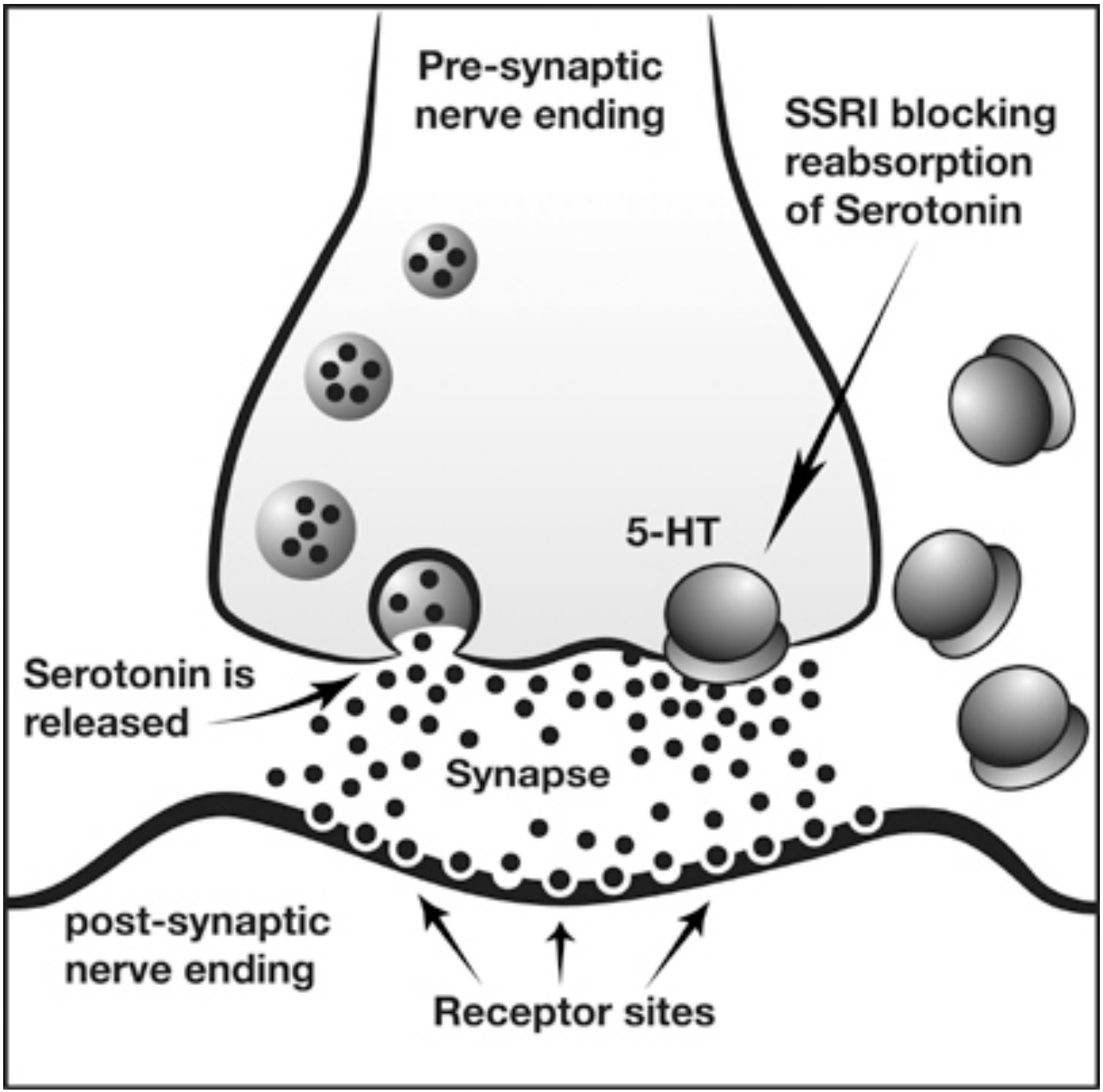
Selective Serotonin Reuptake Inhibitors (SSRIs)



Monoamine Oxidase Inhibitors (MAOIs)



Selective Serotonin Reuptake Inhibitors (SSRIs)

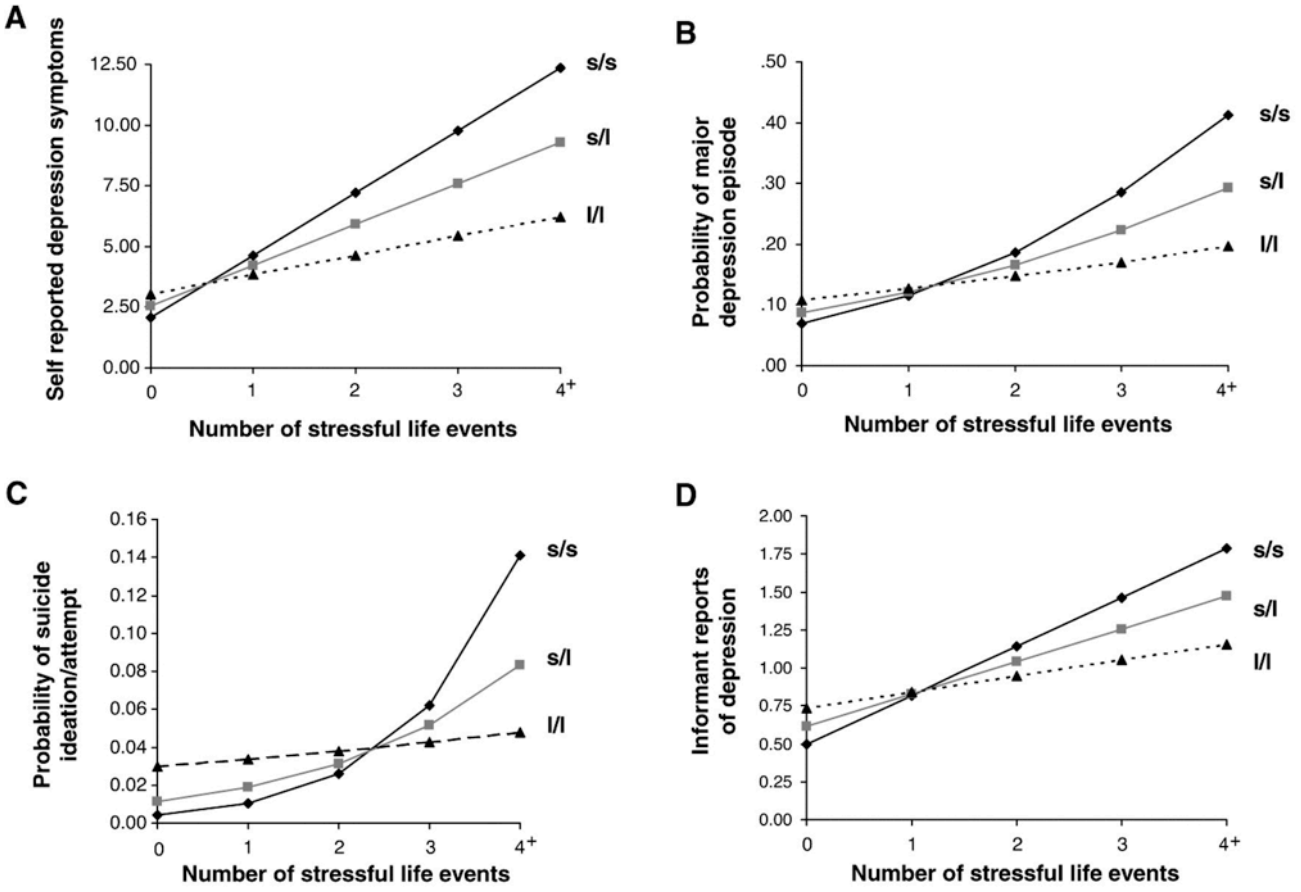


Genetic predisposition to depression

5-HTT gene
serotonin transporter

2 forms { long "l" — "normal form"
short "s" — lower transcriptional efficiency

life stressors {
- employment
- financial
- housing
- health
- relationship

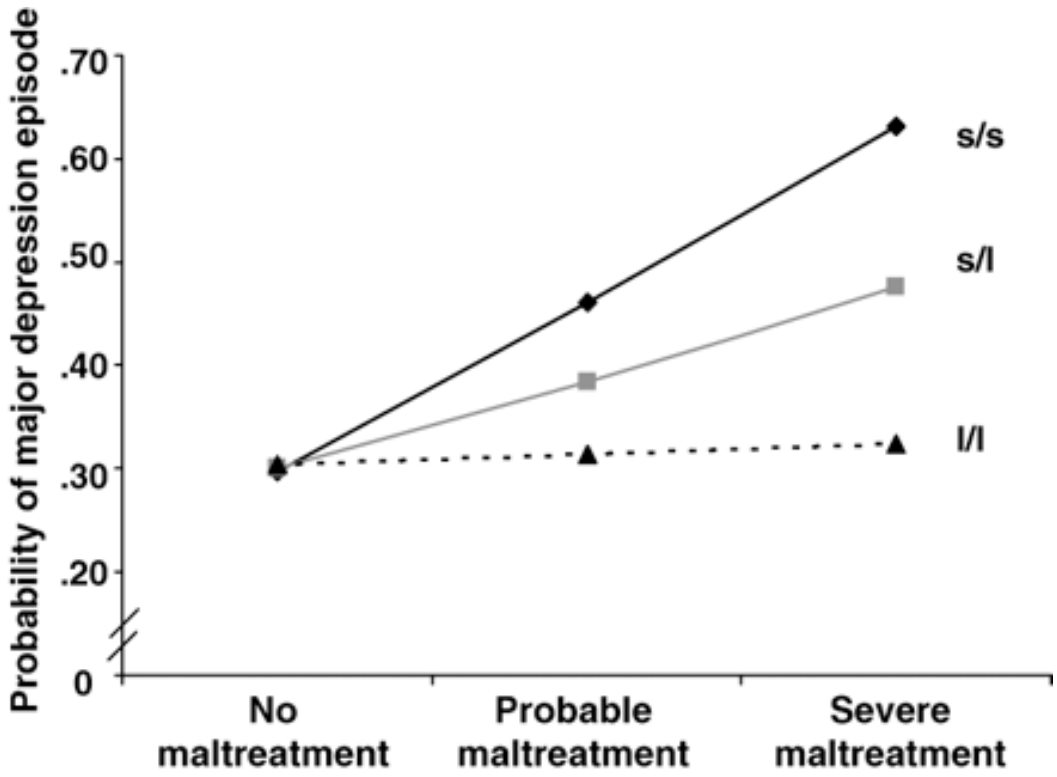


Caspi *et al.* 2003

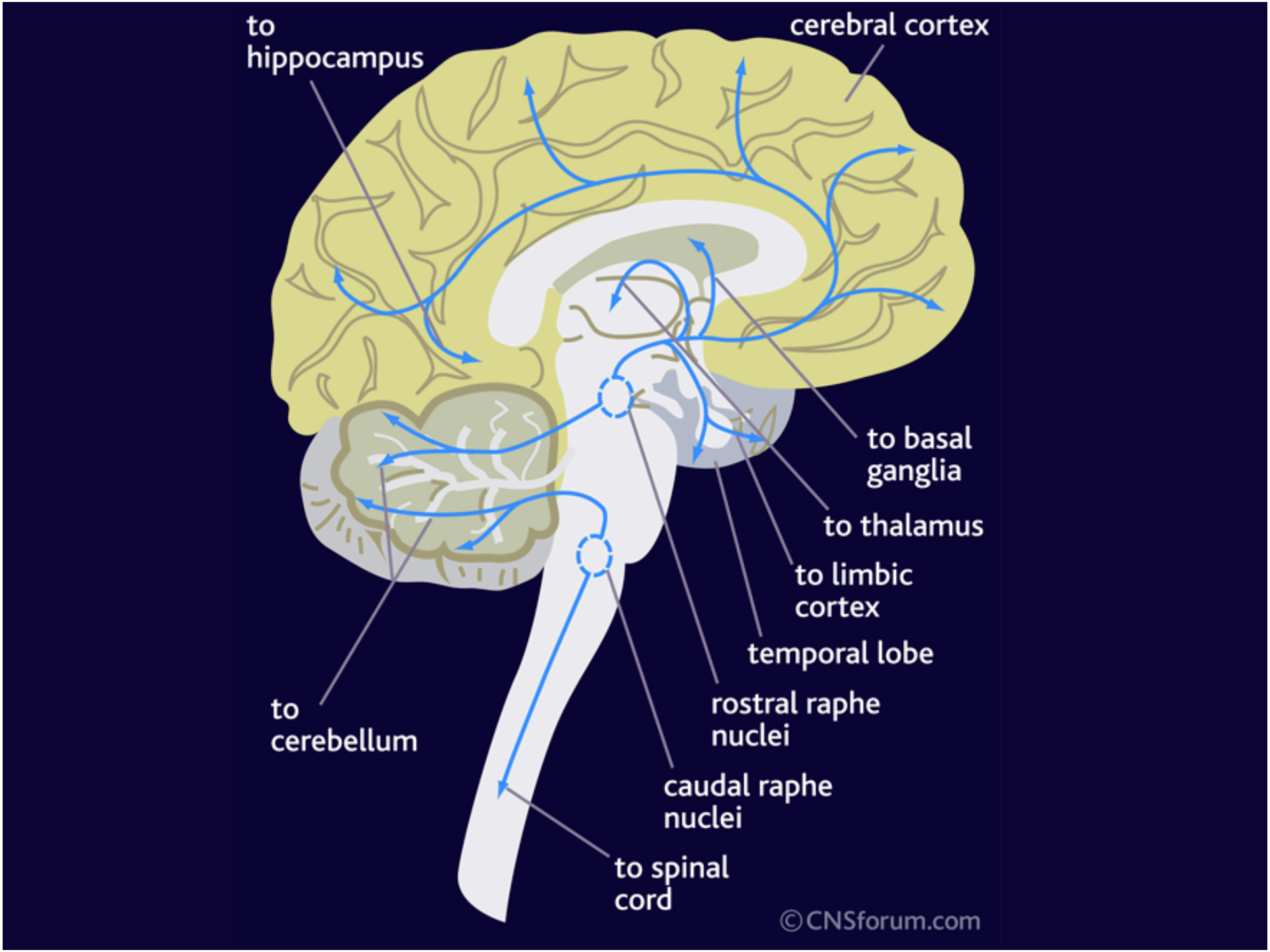
Genetic predisposition to depression

5-HTT gene
serotonin transporter

2 forms { long "l" — "normal form"
short "s" — lower transcriptional efficiency



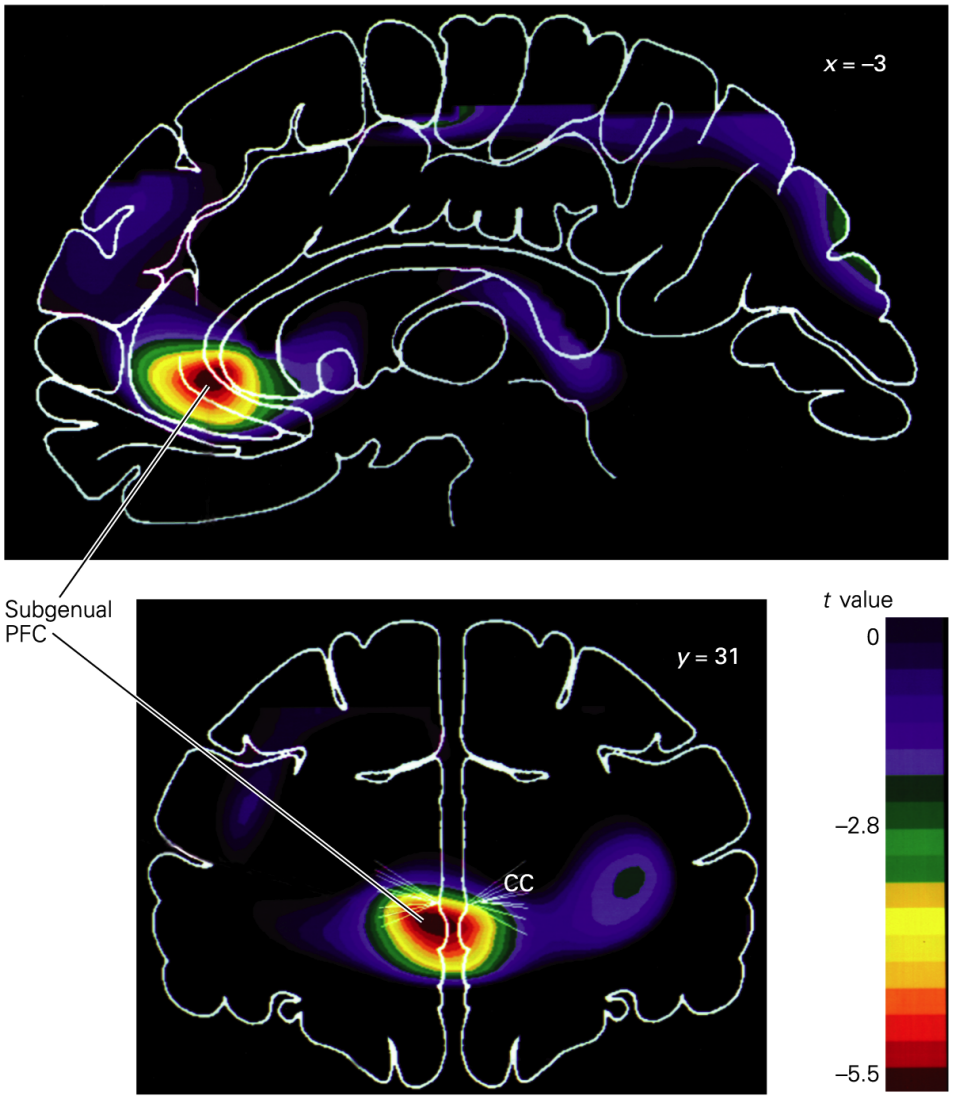
Caspi *et al.* 2003


to
hippocampus
cerebral cortex
to basal
ganglia
to thalamus
to limbic
cortex
temporal lobe
rostral raphe
nuclei
caudal raphe
nuclei
to spinal
cord
to
cerebellum
©CNSforum.com

Abnormal activity in prefrontal cortex

↑activity during manic phase

↓activity during depressive phase



To get at what is really going on, need to get at the circuitry

How?

Fundamental Problem in Making Mouse Models

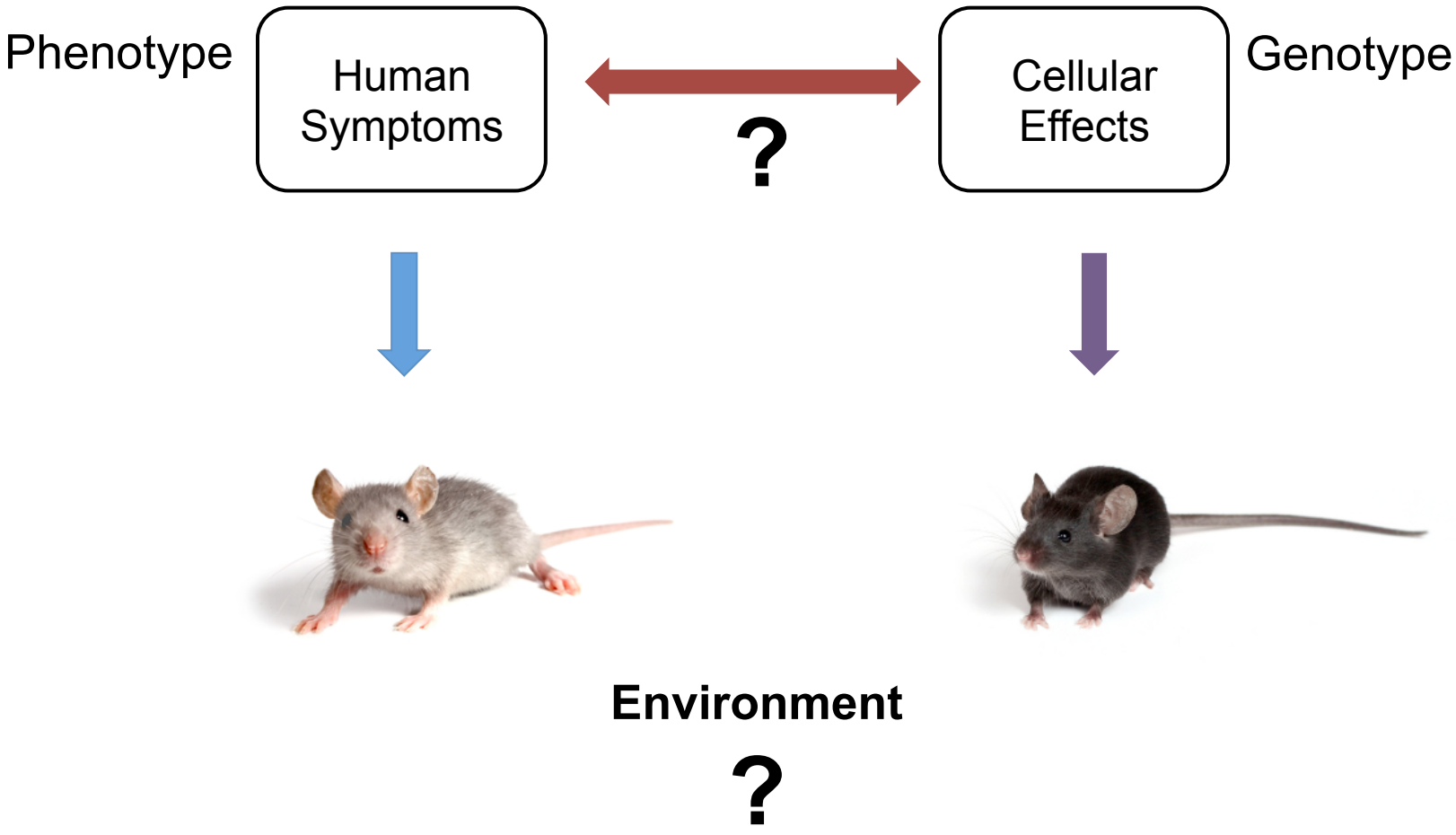
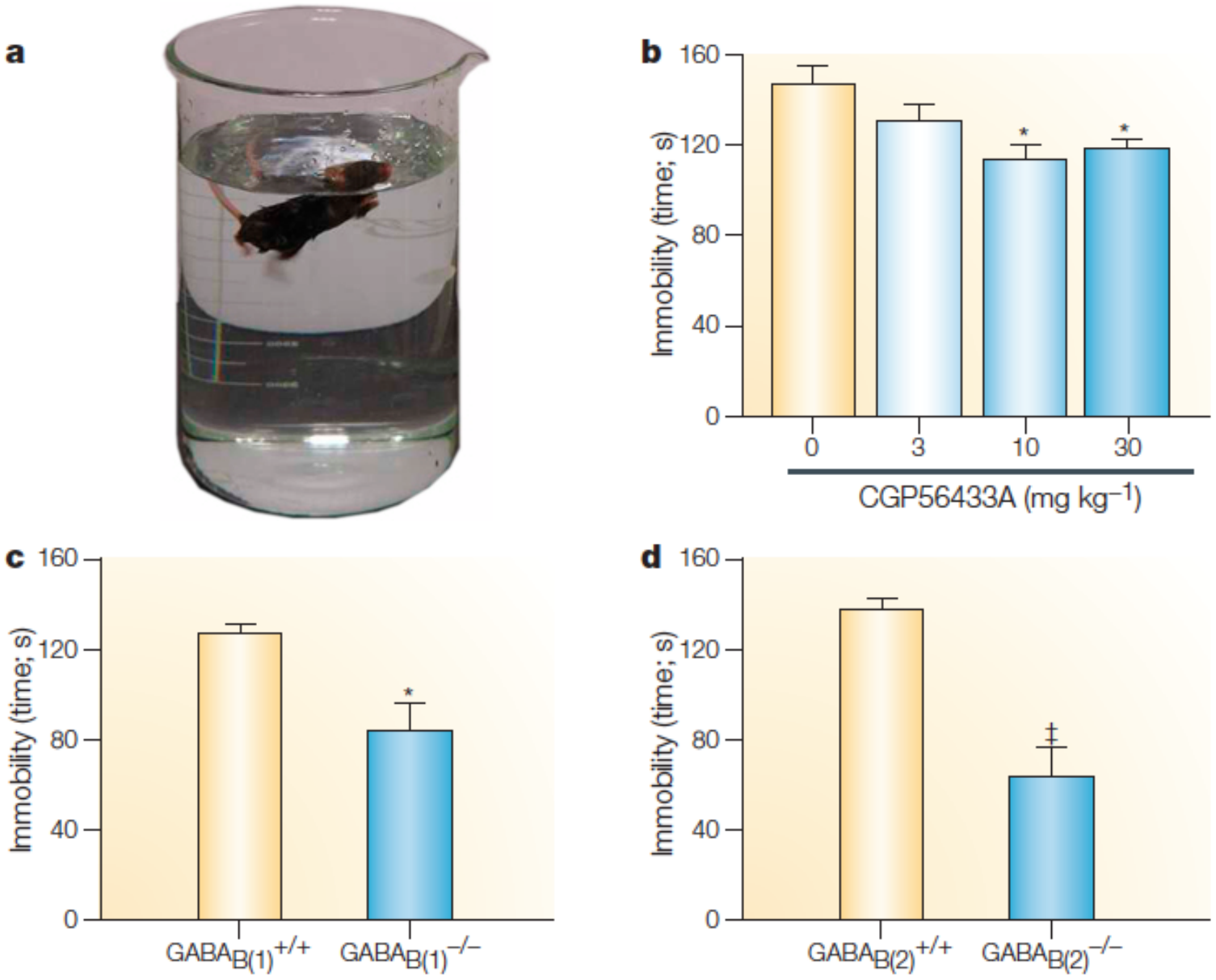


Table 1 | **Modelling symptoms of major depression* in mice**

Symptom	How might symptom be modelled in mice?
Markedly diminished interest or pleasure in everyday activities (anhedonia)	Reduced intracranial self-stimulation, progressive ratio responding for positive reward (for example, sucrose) and social withdrawal
Large changes in appetite or weight gain	Abnormal loss in body weight after exposure to chronic stressors
Insomnia or excessive sleeping	Abnormal sleep architecture (measured using electroencephalogy)
Psychomotor agitation or slowness of movement	Difficulty in handling and alterations in various measures of locomotor activity and motor function
Fatigue or loss of energy	Reduced activity in home cage, treadmill/running-wheel activity, nest building and active waking electroencephalogram
Indecisiveness or diminished ability to think or concentrate	Deficits in working and spatial memory and impaired sustained attention
Difficulty performing even minor tasks, leading to poor personal hygiene	Poor coat condition during chronic mild stress
Recurrent thoughts of death or suicide	Cannot be modelled
Feelings of worthlessness or excessive or inappropriate guilt	Cannot be modelled

*Symptoms used in the *Diagnostic and Statistical Manual-IV* diagnosis of major depression.

Forced Swim Test

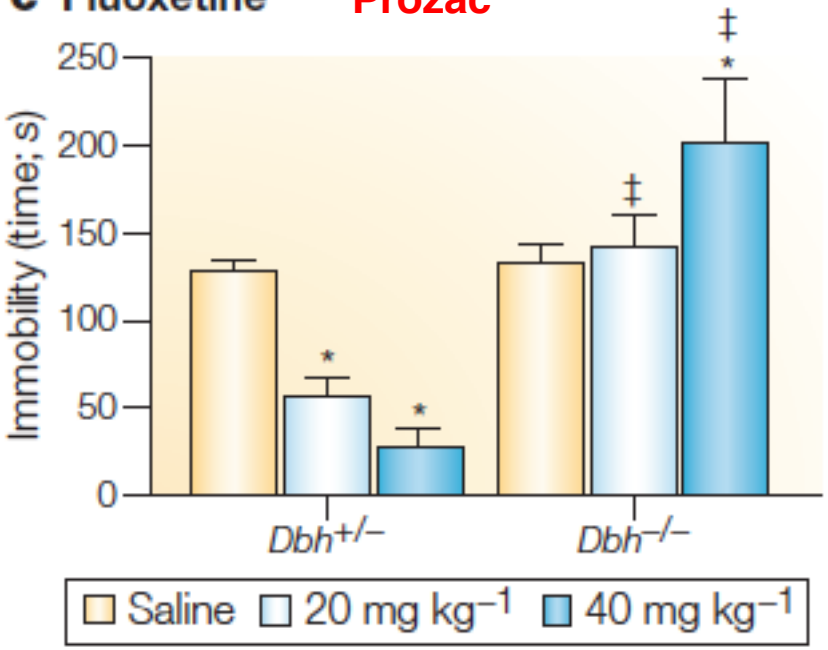


Tail Suspension Test

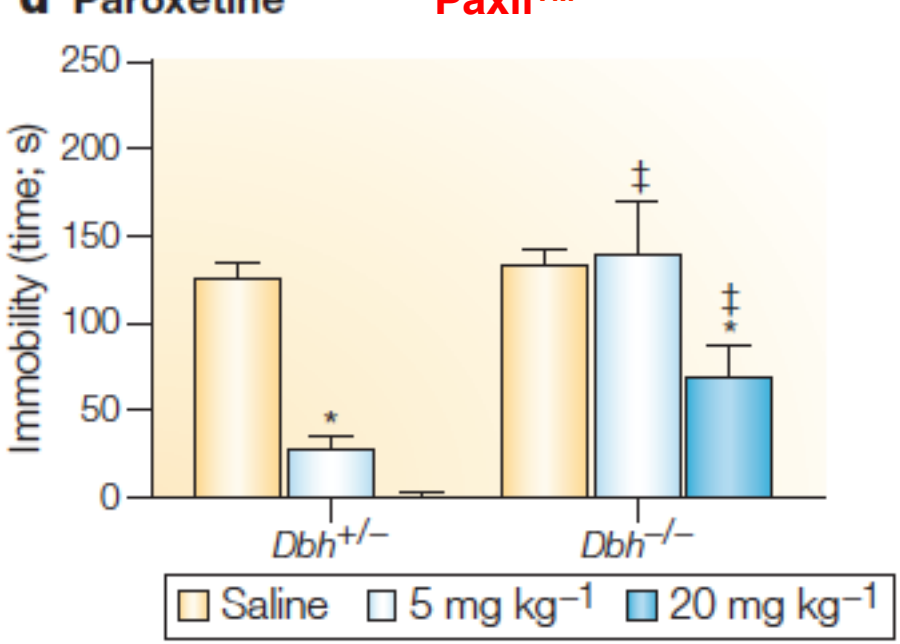
a

(*DBh-/-* lack noradenaline)

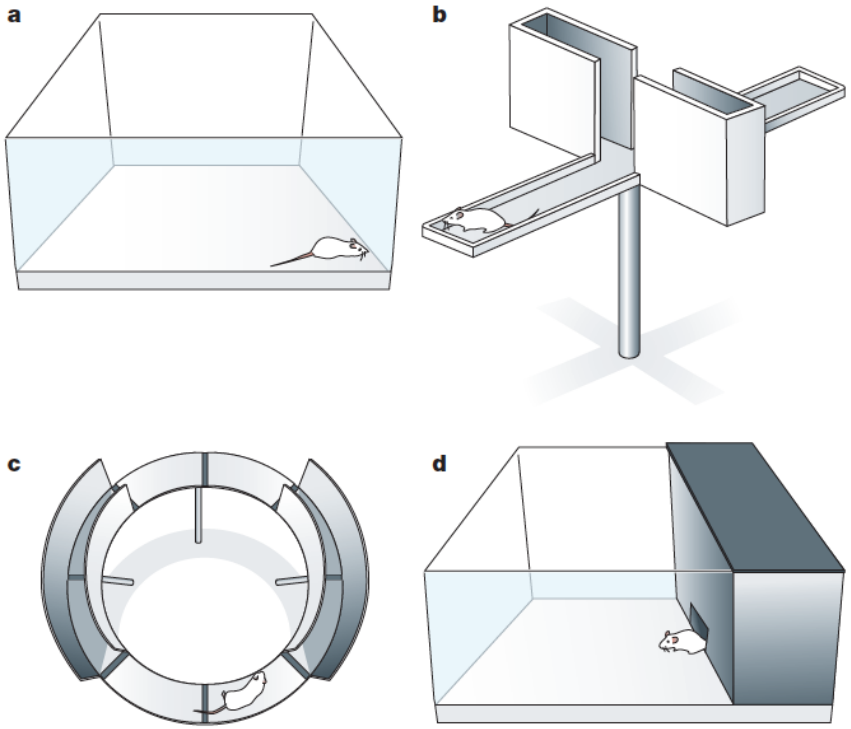
c Fluoxetine **Prozac™**

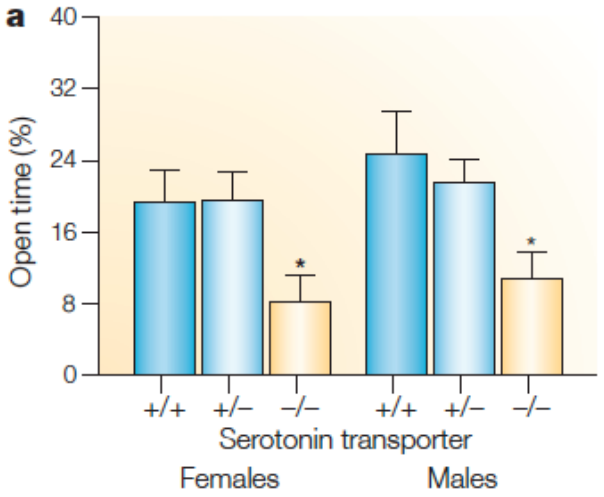


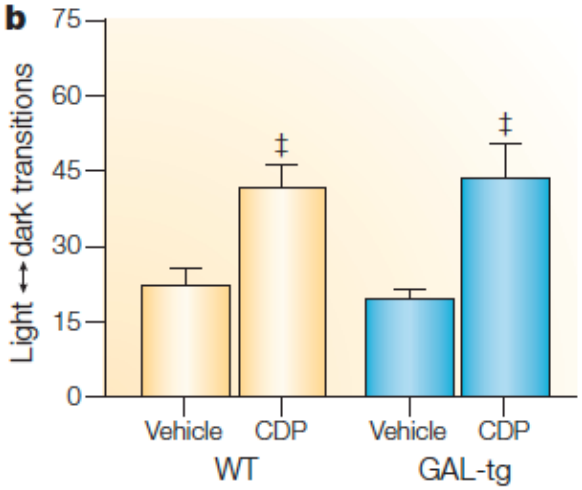
d Paroxetine **Paxil™**



Tests for anxiety

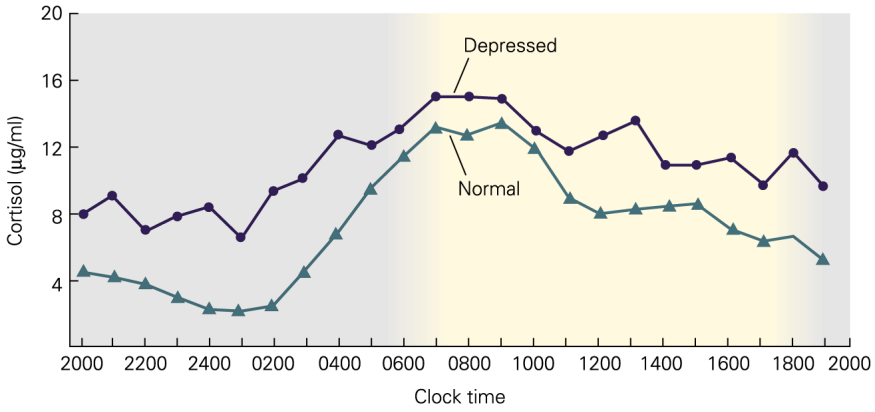






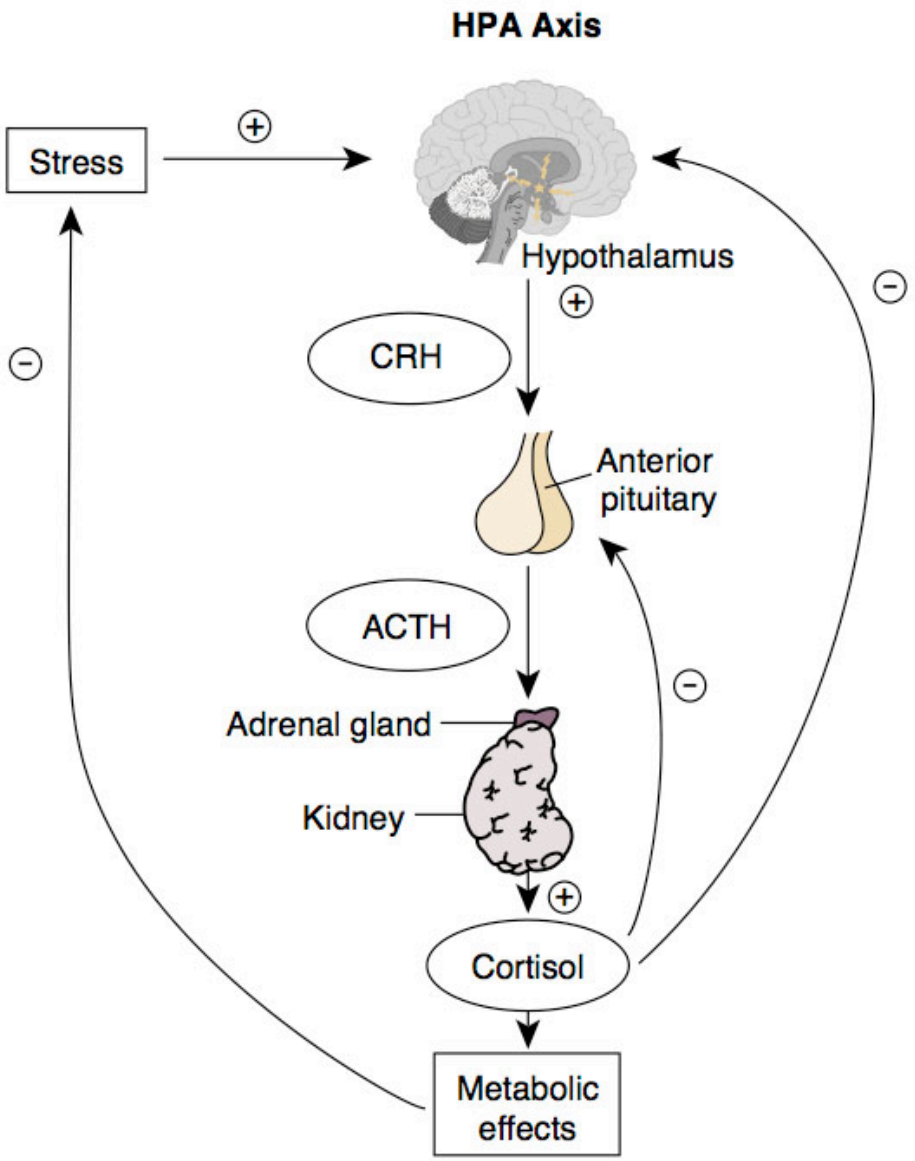
CDP similar to Valium

Stress & Depression

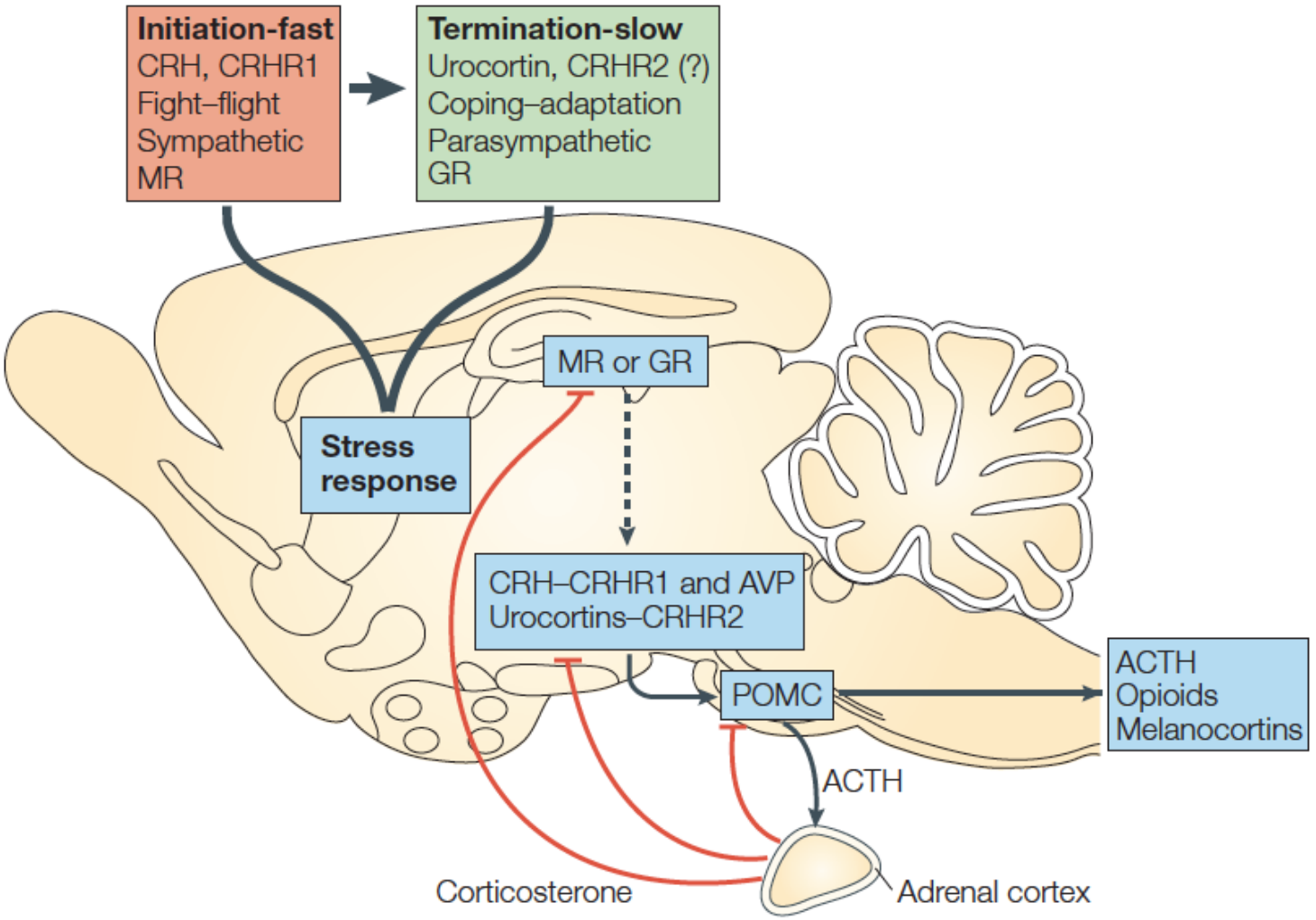


Glucocorticoids
Cortisol
ACTH

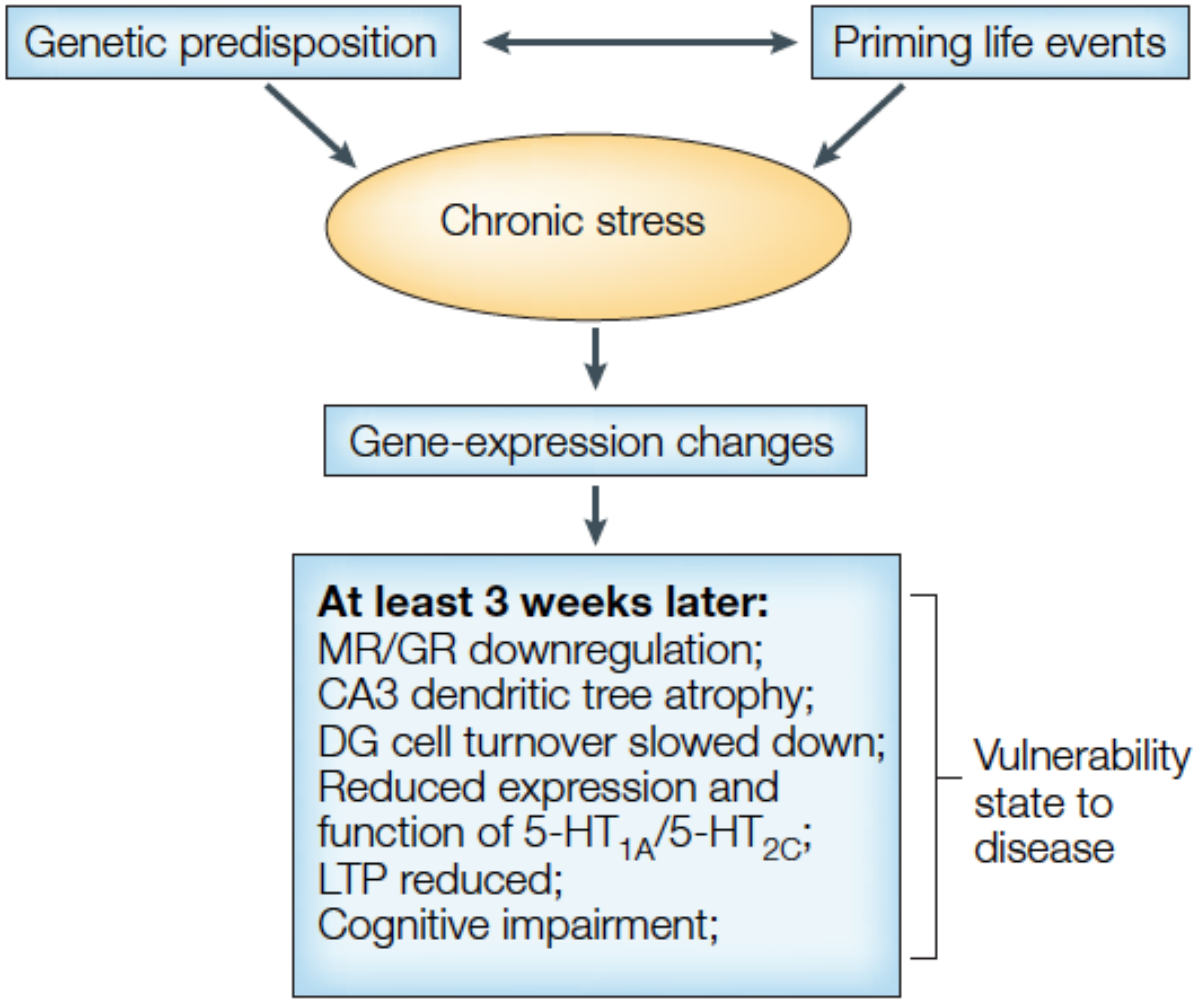
} Stress Hormones



Stress Hormones in the Brain

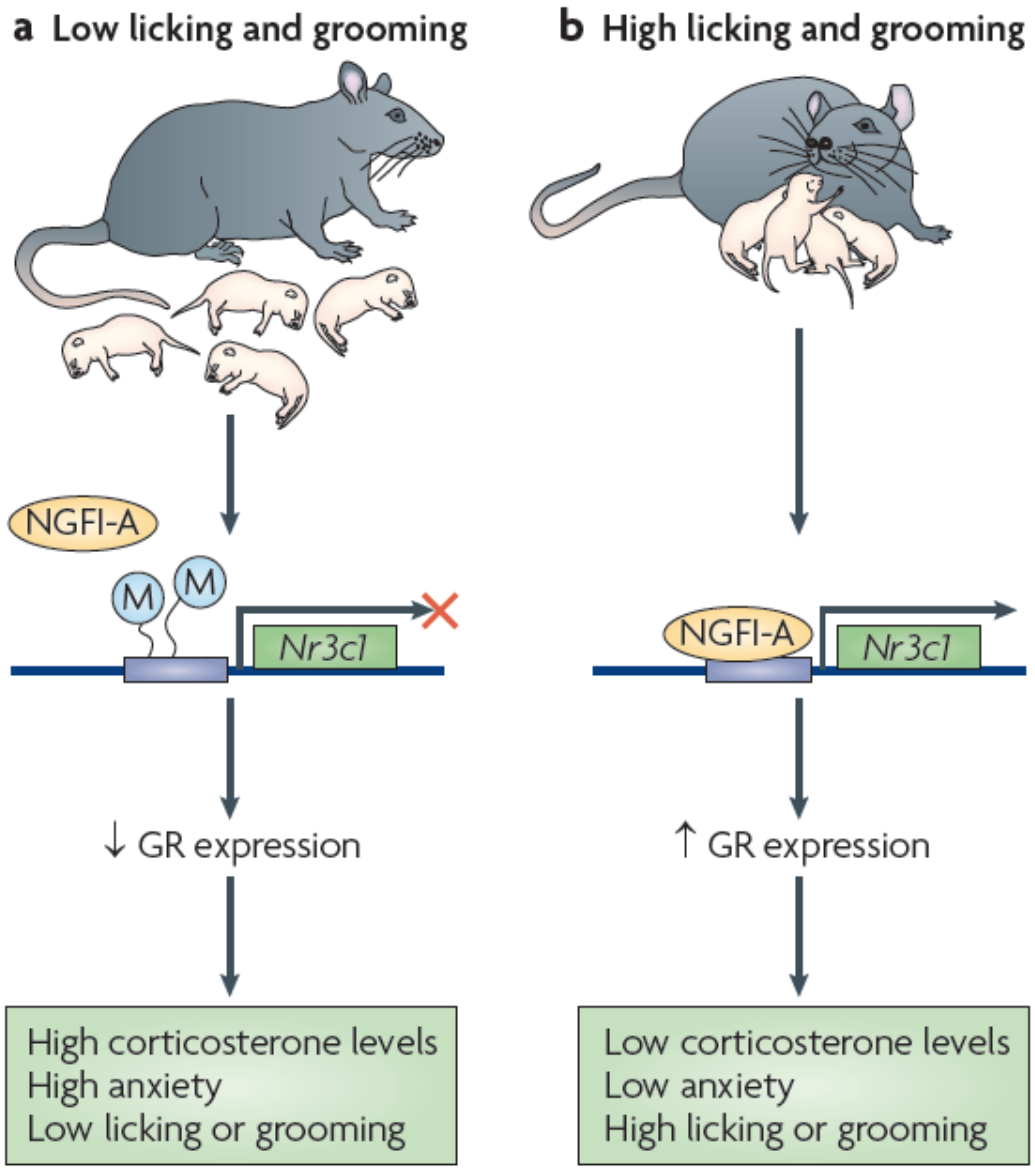


Stress Leads to Vulnerability to Depression

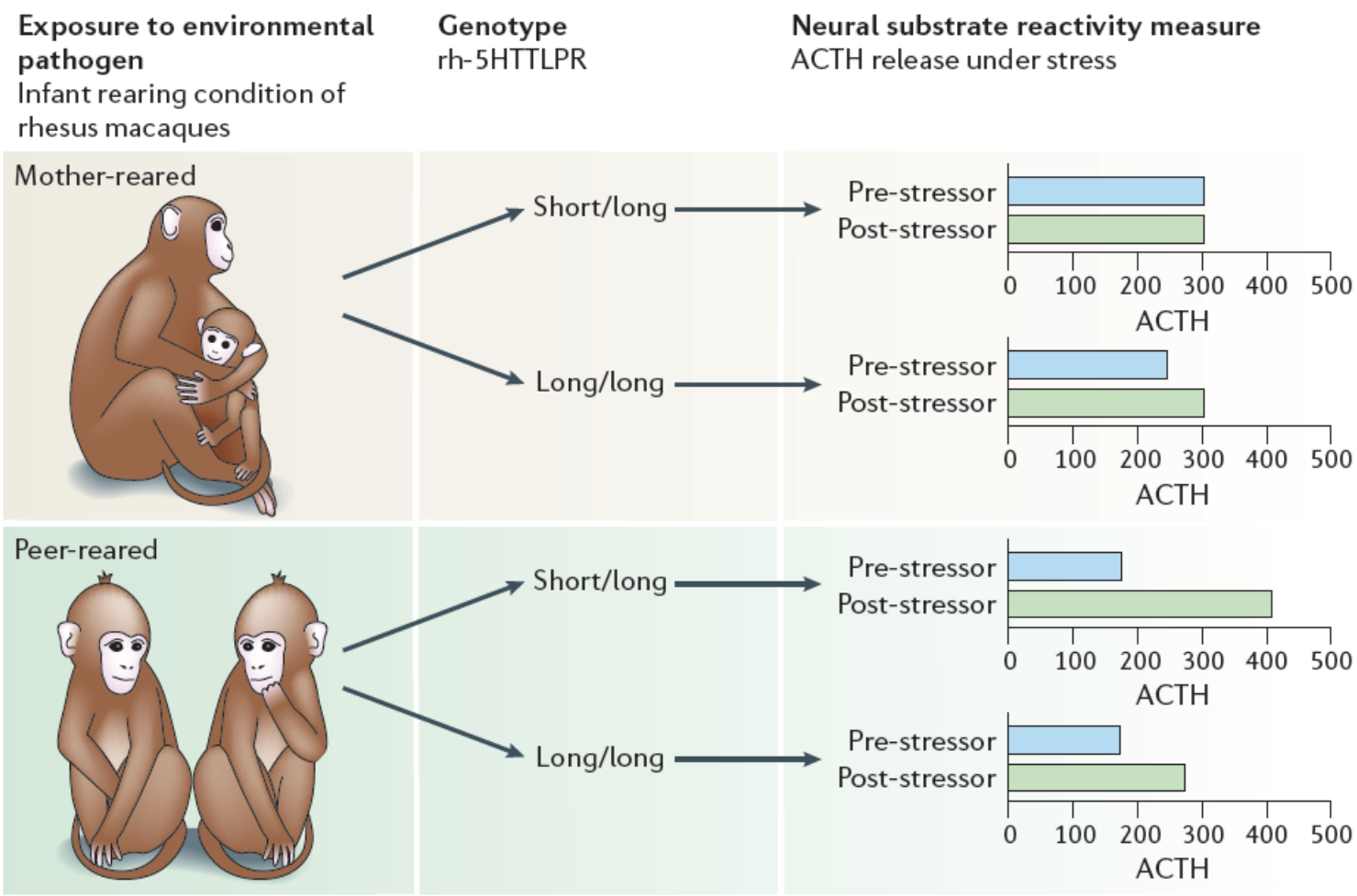


Stress Has Long-term Effects on Genes

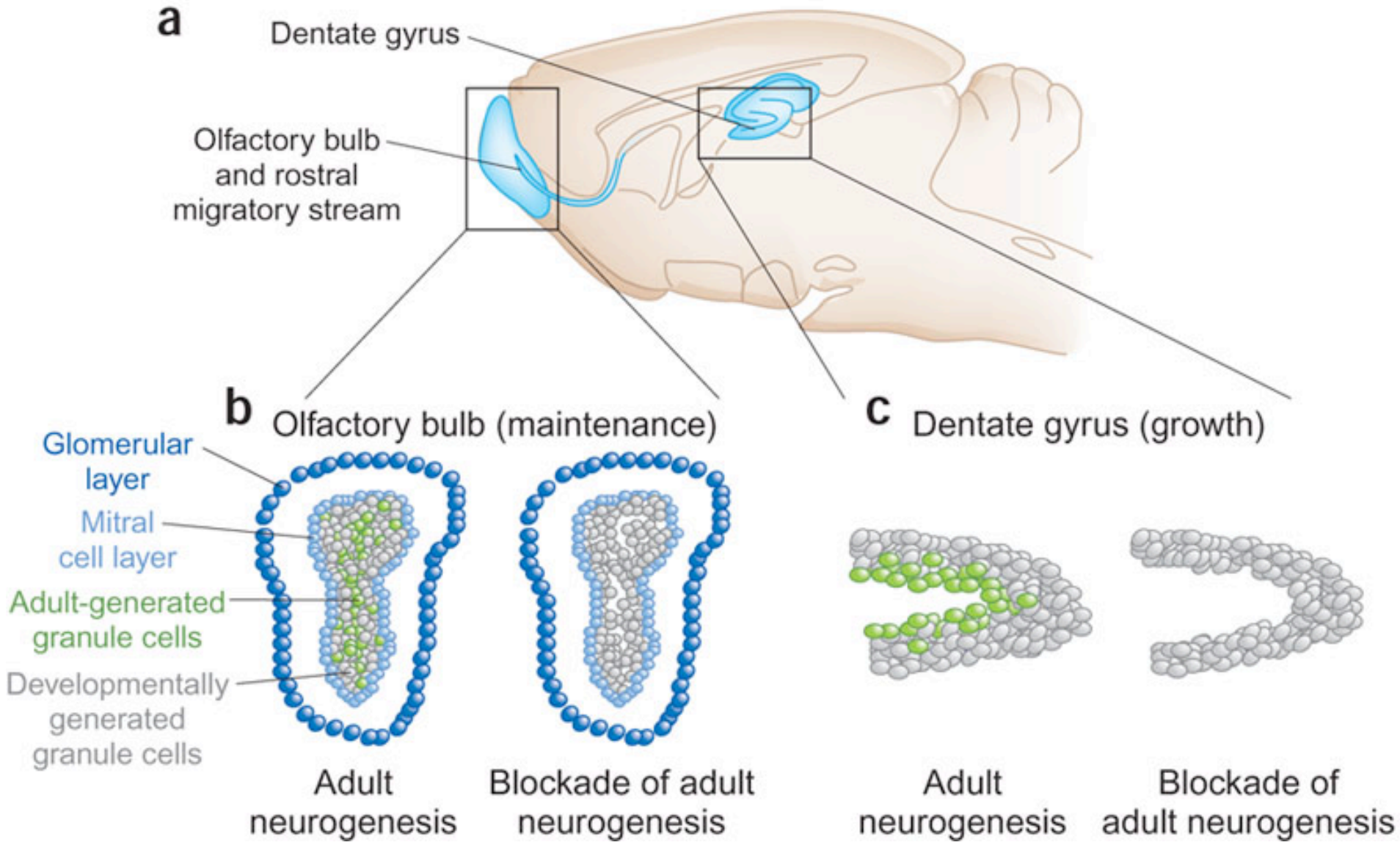
Epigenetics

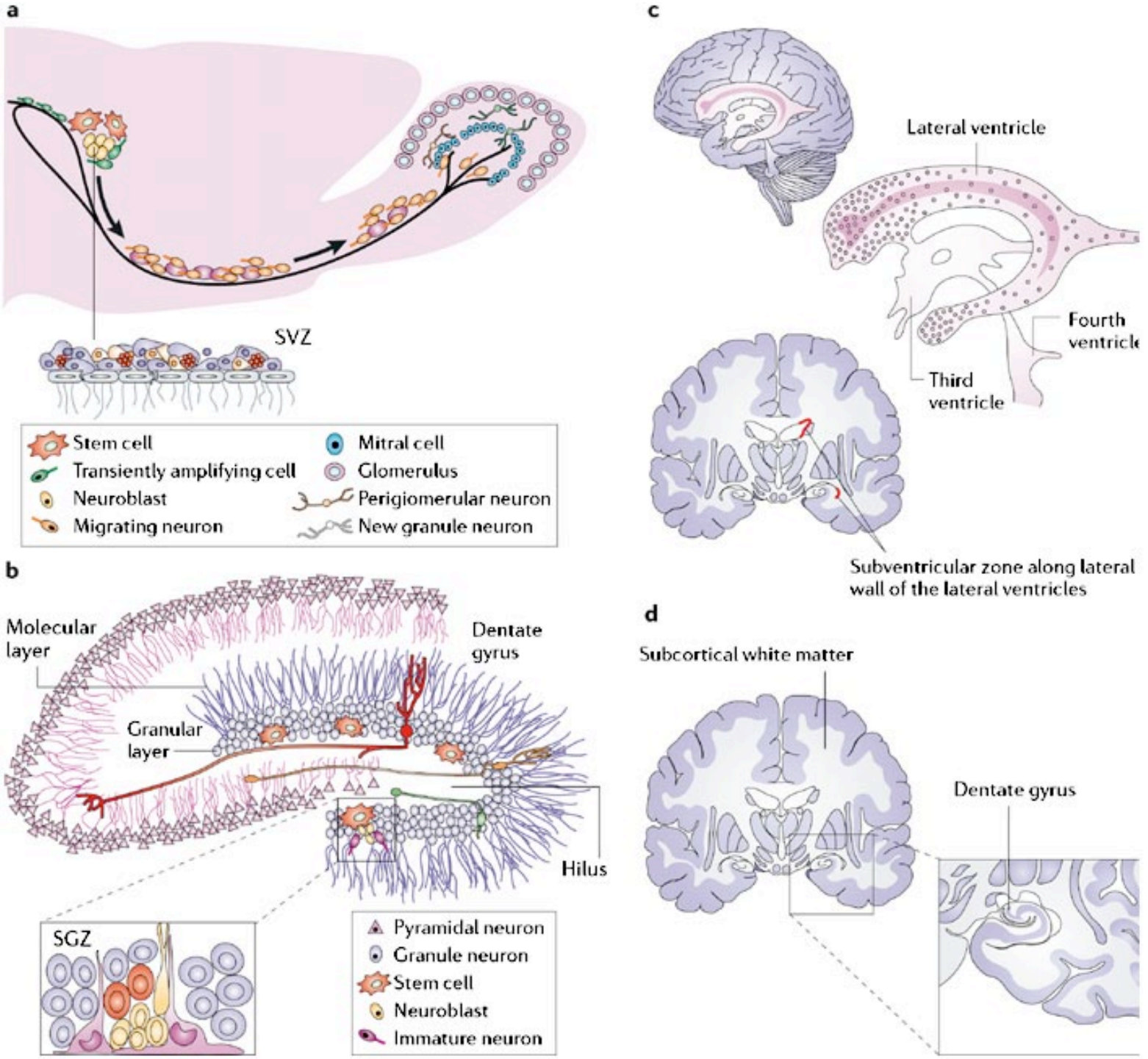


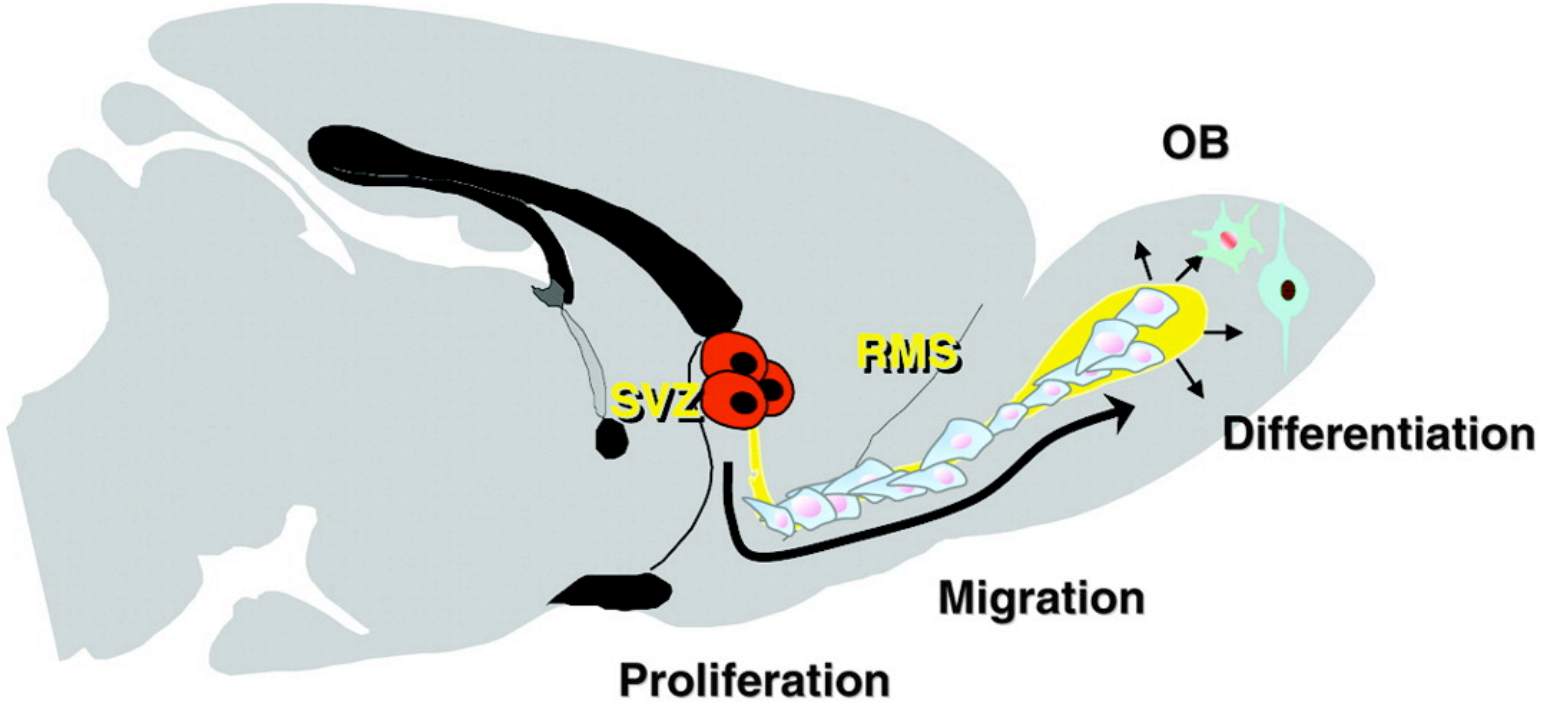
Feder, Nestler, & Charney 2009


Exposure to environmental pathogen
Infant rearing condition of rhesus macaques
Genotype
rh-5HTTLPR
Neural substrate reactivity measure
ACTH release under stress
Mother-reared
Short/long
Long/long
Pre-stressor
Post-stressor
0 100 200 300 400 500
ACTH
Peer-reared
Short/long
Long/long
Pre-stressor
Post-stressor
0 100 200 300 400 500
ACTH

Adult Neurogenesis

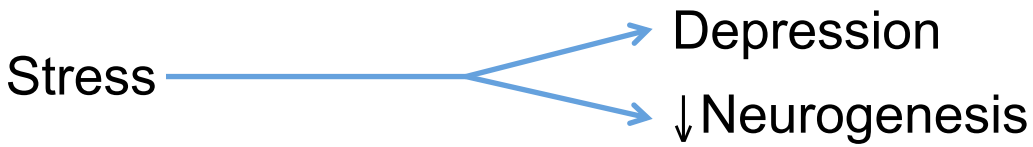

a
Dentate gyrus
Olfactory bulb
and rostral
migratory stream
b
Olfactory bulb (maintenance)
c
Dentate gyrus (growth)
Glomerular
layer
Mitral
cell layer
Adult-generated
granule cells
Developmentally
generated
granule cells
Adult
neurogenesis
Blockade of adult
neurogenesis
Adult
neurogenesis
Blockade of
adult neurogenesis

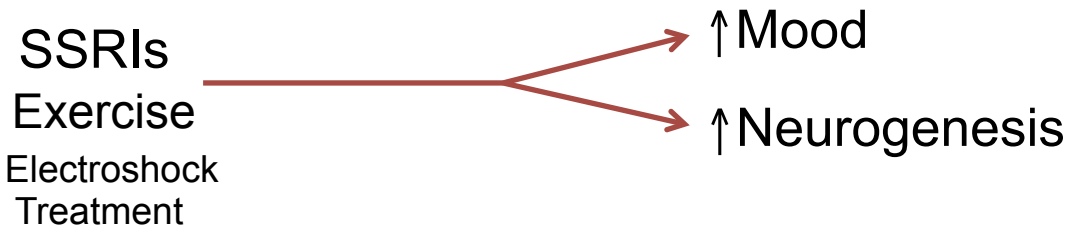

a
SVZ
Stem cell
Transiently amplifying cell
Neuroblast
Migrating neuron
Mitral cell
Glomerulus
Perigiomerular neuron
New granule neuron
b
Molecular layer
Granular layer
Dentate gyrus
Hilus
SGZ
Pyramidal neuron
Granule neuron
Stem cell
Neuroblast
Immature neuron
c
Lateral ventricle
Fourth ventricle
Third ventricle
Subventricular zone along lateral wall of the lateral ventricles
d
Subcortical white matter
Dentate gyrus

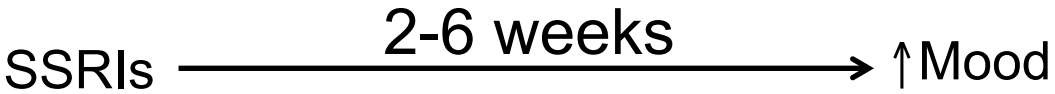


Neuronal lineage	B	C	A	
Cell identity	SVZ astrocyte Putative stem cell	Transit amplifying progenitor	Migrating neuroblast	Immature and mature neurons
Identified markers	**GFAP** Vimentin Nestin	**Dlx2** Nestin	**PSA-NCAM** **Dlx2** Tuj1 Hu	DCX, calretinin NeuN TH Calbindin GAD65

Evidence for role of neurogenesis in depression







Similar to the amount of time required for increased neurogenesis and maturation of neurons

Finally, depressed patients have *decreased* hippocampal volume

Schizophrenia

Schizophrenia

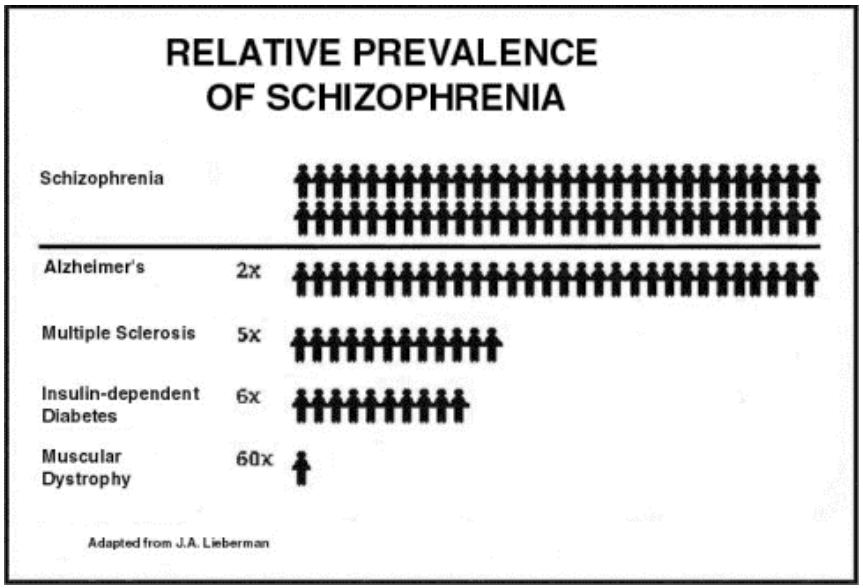
1.1% population >18yo, 51 million people worldwide

Male-to-Female 1.4:1

Though occurs earlier and with worse prognosis in males

Usually presents in early twenties

Estimated 30-40% of homeless population



Schizophrenia

Positive Symptoms

Hallucinations

- Auditory
- Visual
- Somatic

Delusions

- Bizarre
- Grandiose
- Paranoid
- Nihilistic
- Erotomanic

Disorganization

- Tangential speech
- Circumstantial speech
- Derailment
- Neologisms
- Word salad

Schizophrenia

Negative Symptoms

- Decreased expressiveness
- Apathy
- Lack of energy
- Lack of emotion

Cognitive Impairment

- Processing speed
- Attention
- Learning & memory
- Reasoning
- Verbal comprehension
- Social cognition

And finally, can also have mood or anxiety symptoms

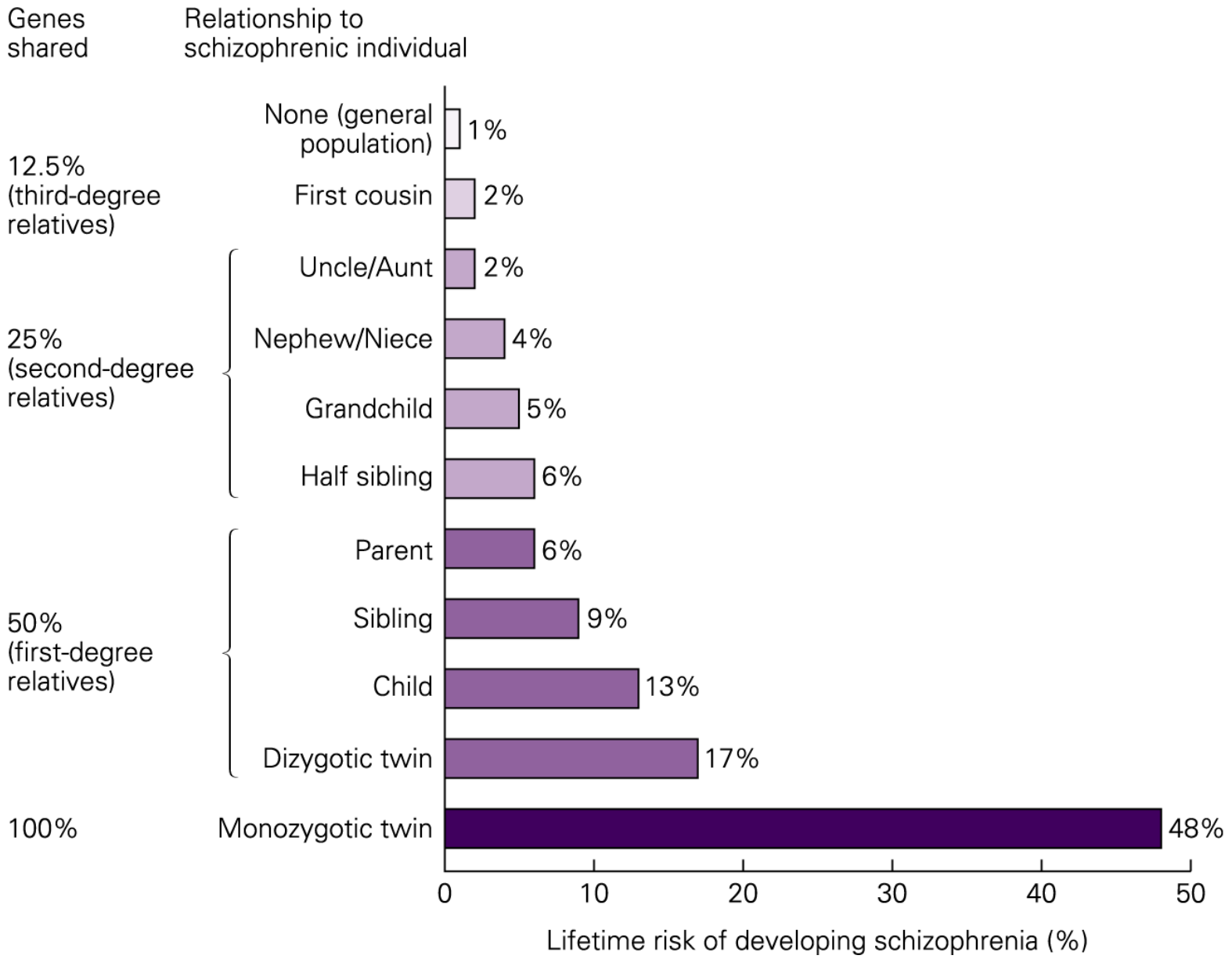
Table 1 | **Examples of positive symptoms of schizophrenia**

Symptom	Example
Audible thoughts	The patient would think 'I must put the kettle on', and after a pause of not more than one second would hear a voice say 'I must put the kettle on'.
Voices arguing	Patient G.T. heard one voice say 'G.T. is a bloody paradox'; another say 'He is that, he should be locked up'; and a third say 'He is not, he is a lovely man'.
Voices commenting on one's actions	A voice in a flat monotone describing everything the patient was doing: 'She is peeling potatoes, got hold of the peeler, she does not want that potato…'
An influence on the body (somatic passivity)	'X-rays enter the back of my neck, where the skin tingles and feels warm, they pass down the back in a hot tingling strip about six inches wide to the waist.'
Thought withdrawal	'I am thinking about my mother, and suddenly my thoughts are sucked out of my mind by a phrenological vacuum extractor, and there is nothing in my mind.'
Thought insertion	'The thoughts of Eamonn Andrews come into my mind. He treats my mind like a screen and flashes his thoughts on to it like you flash a picture.'
Thought broadcasting	'My thoughts leave my head on a type of mental ticker-tape. Everyone around me has only to pass the tape through their mind and they know my thoughts.'
'Made' feelings	'It is not me who is unhappy, but they are projecting unhappiness into my brain. They project upon me laughter for no reason.'
'Made' impulses	'It came to me from the X-ray department. It was nothing to do with me, they wanted it so I picked up the bottle and poured it.'
'Made' volitional acts (delusions of control)	'It is my hand and arm that move, and my fingers pick up the pen, but I don't control them. What they do is nothing to do with me.'
Delusional perception	One of the lodgers pushed the salt cellar towards him, and the patient knew that he must return home 'to greet the Pope who is visiting Ireland to see his family and reward them'.

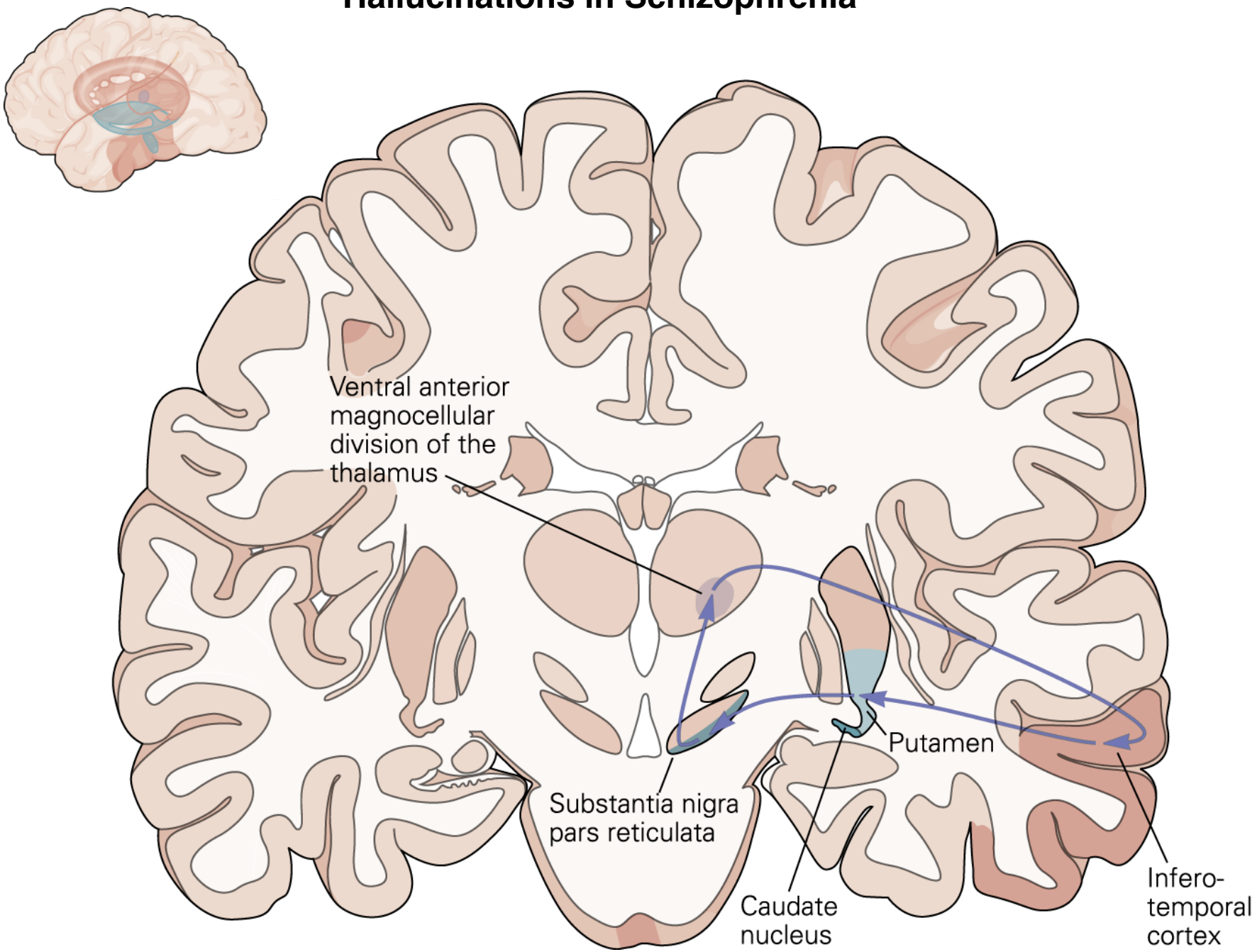
The examples are taken from Schneider's first rank symptoms of schizophrenia[114].

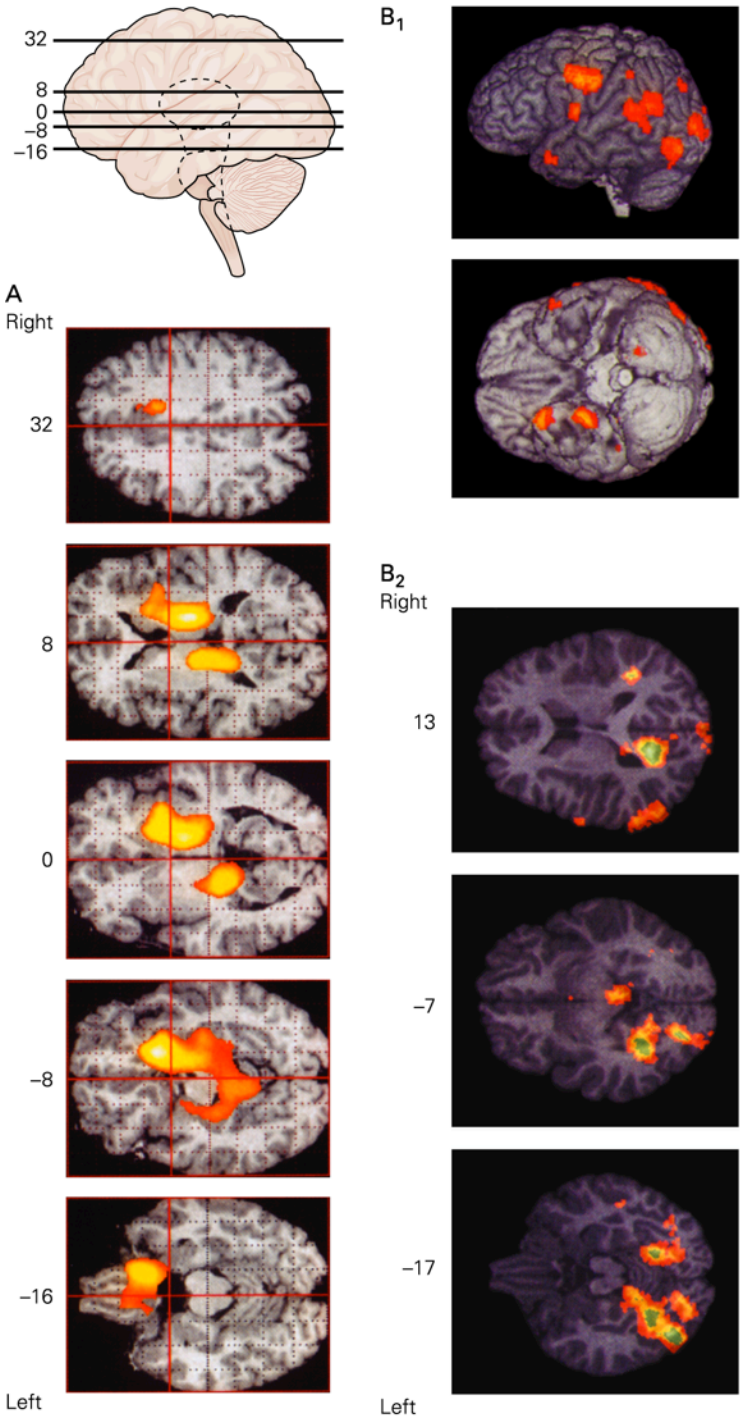
Schizophrenia

Strong genetic component

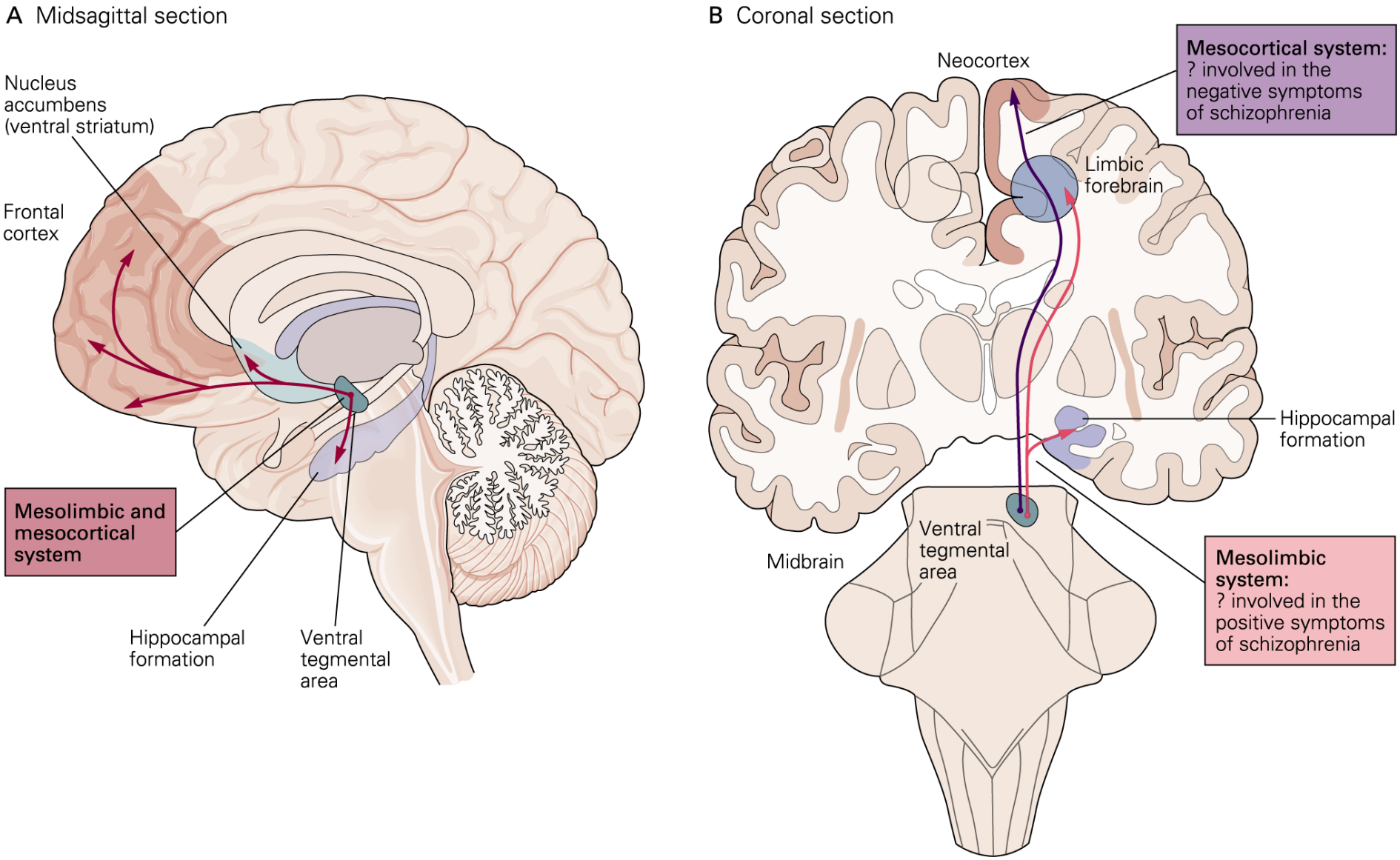


Hallucinations in Schizophrenia

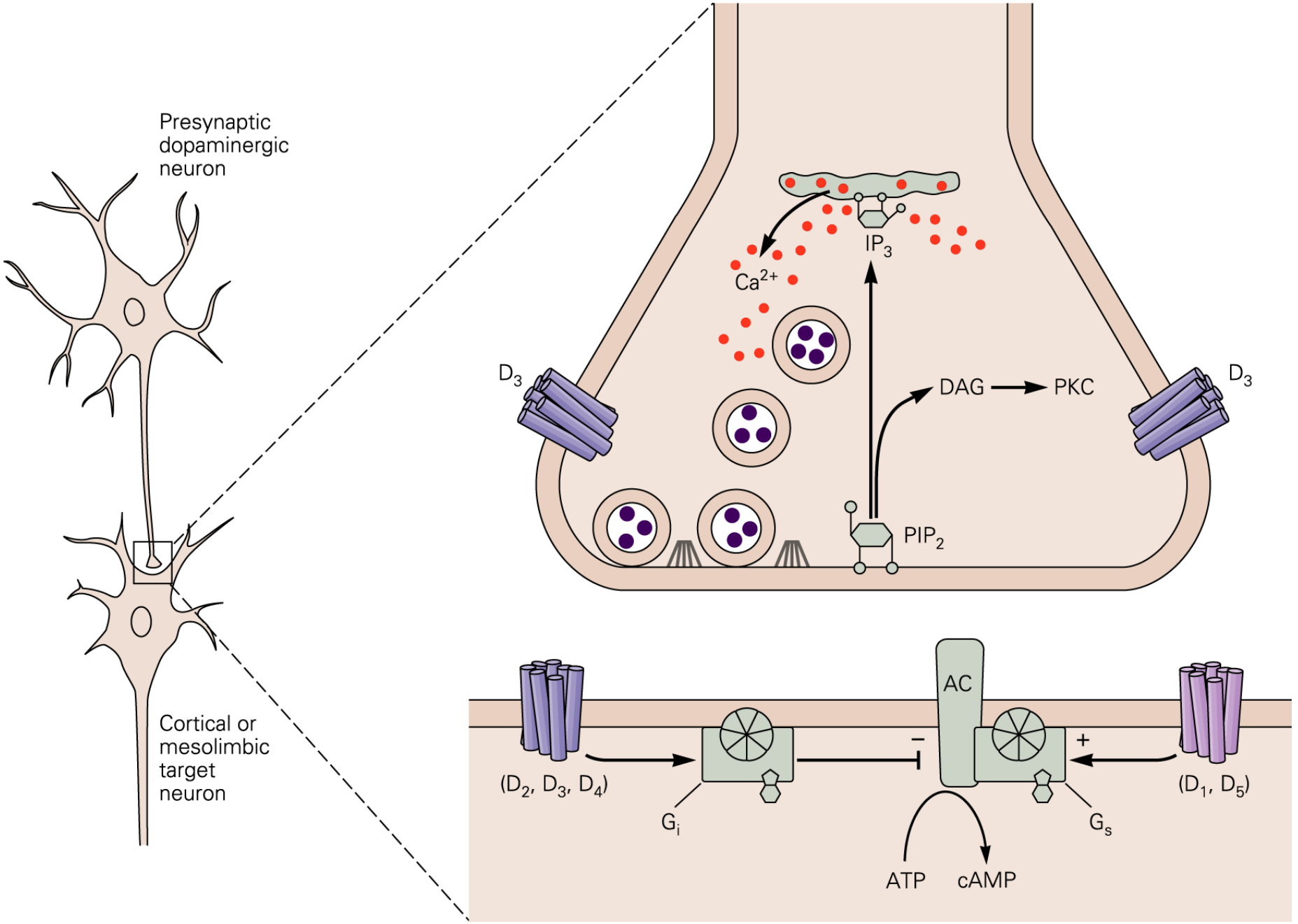



32
8
0
−8
−16
A
Right
32
8
0
−8
−16
Left
B1
B2
Right
13
−7
−17
Left

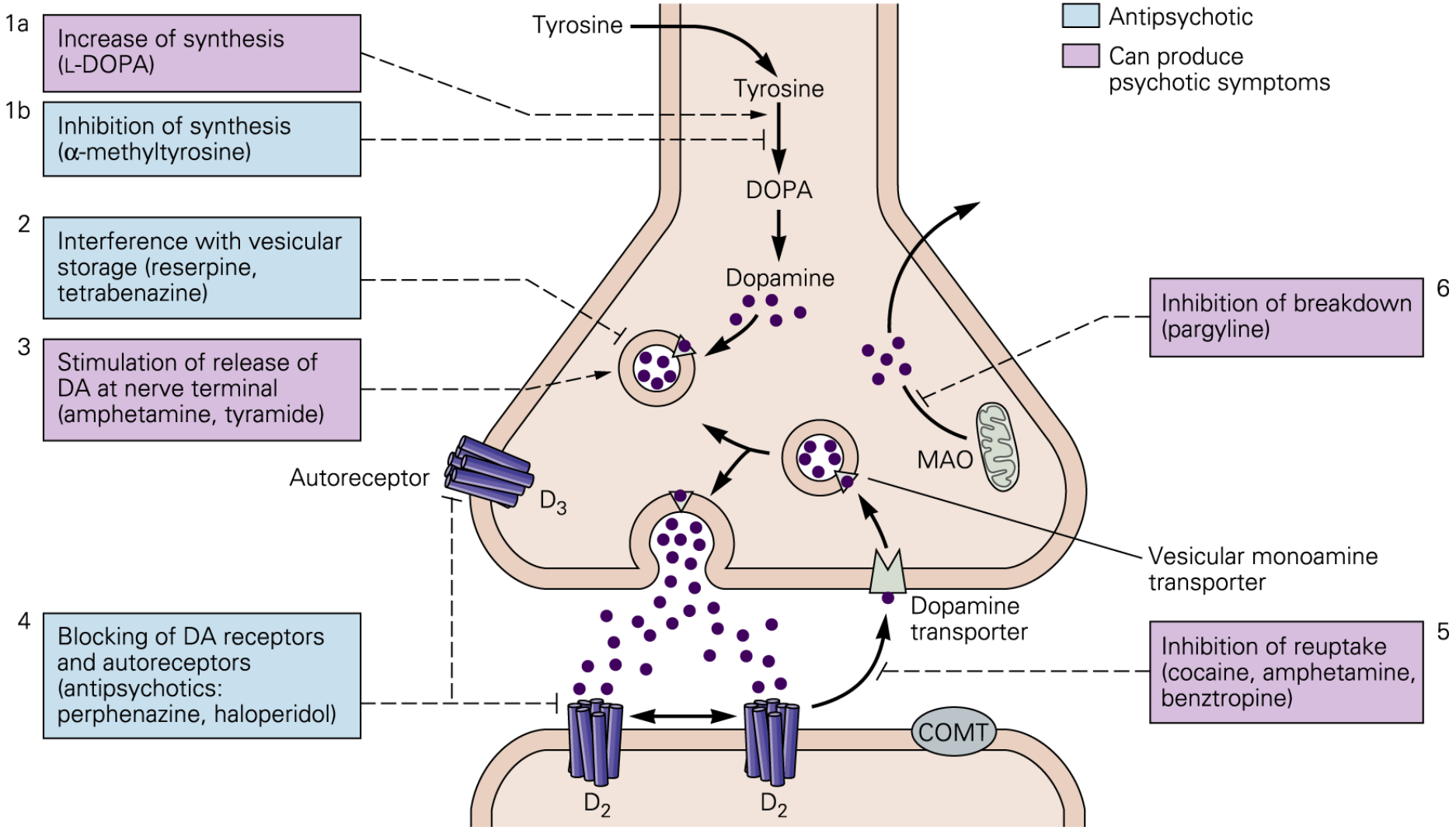
Dopaminergic systems in the brain

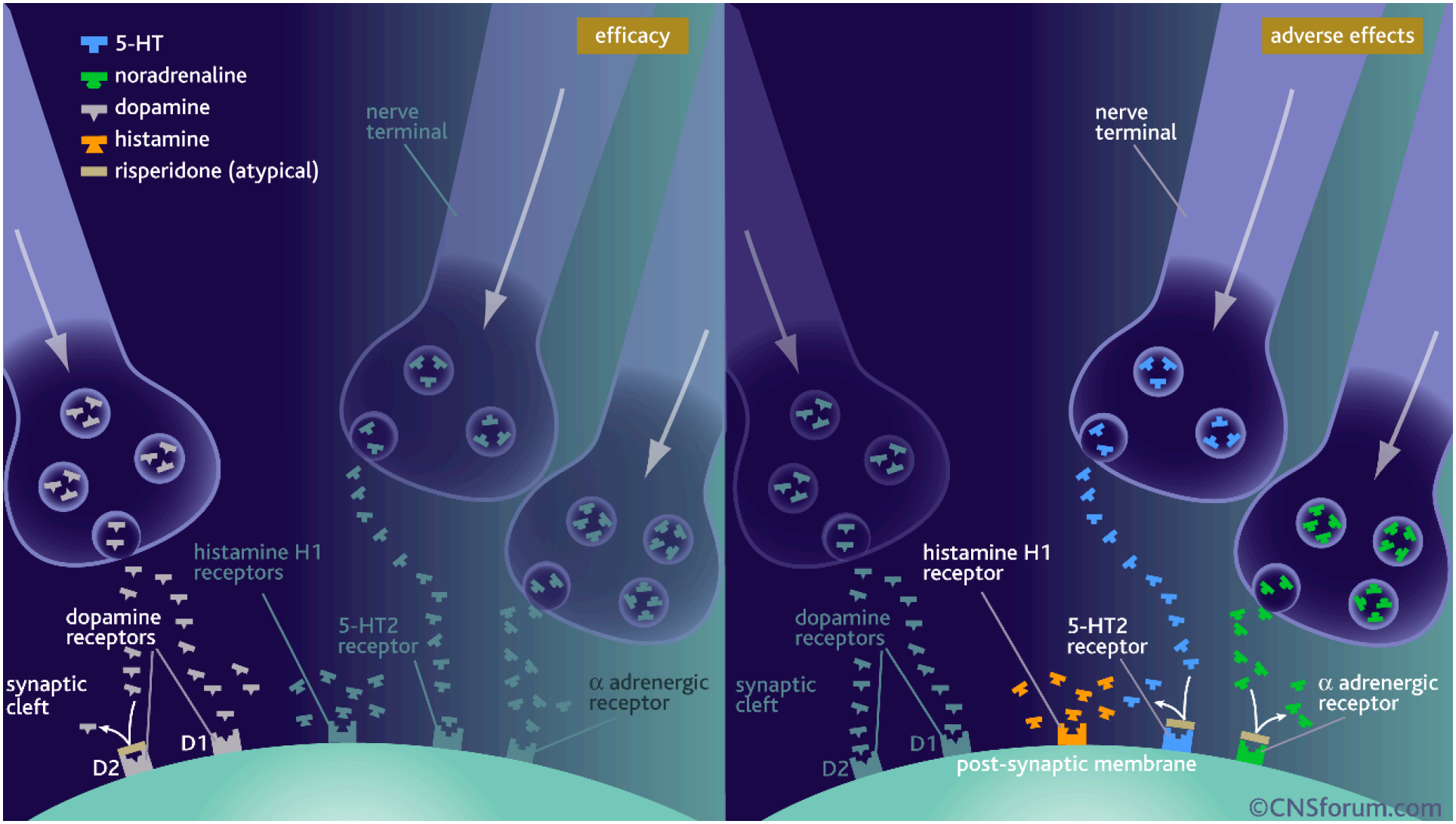


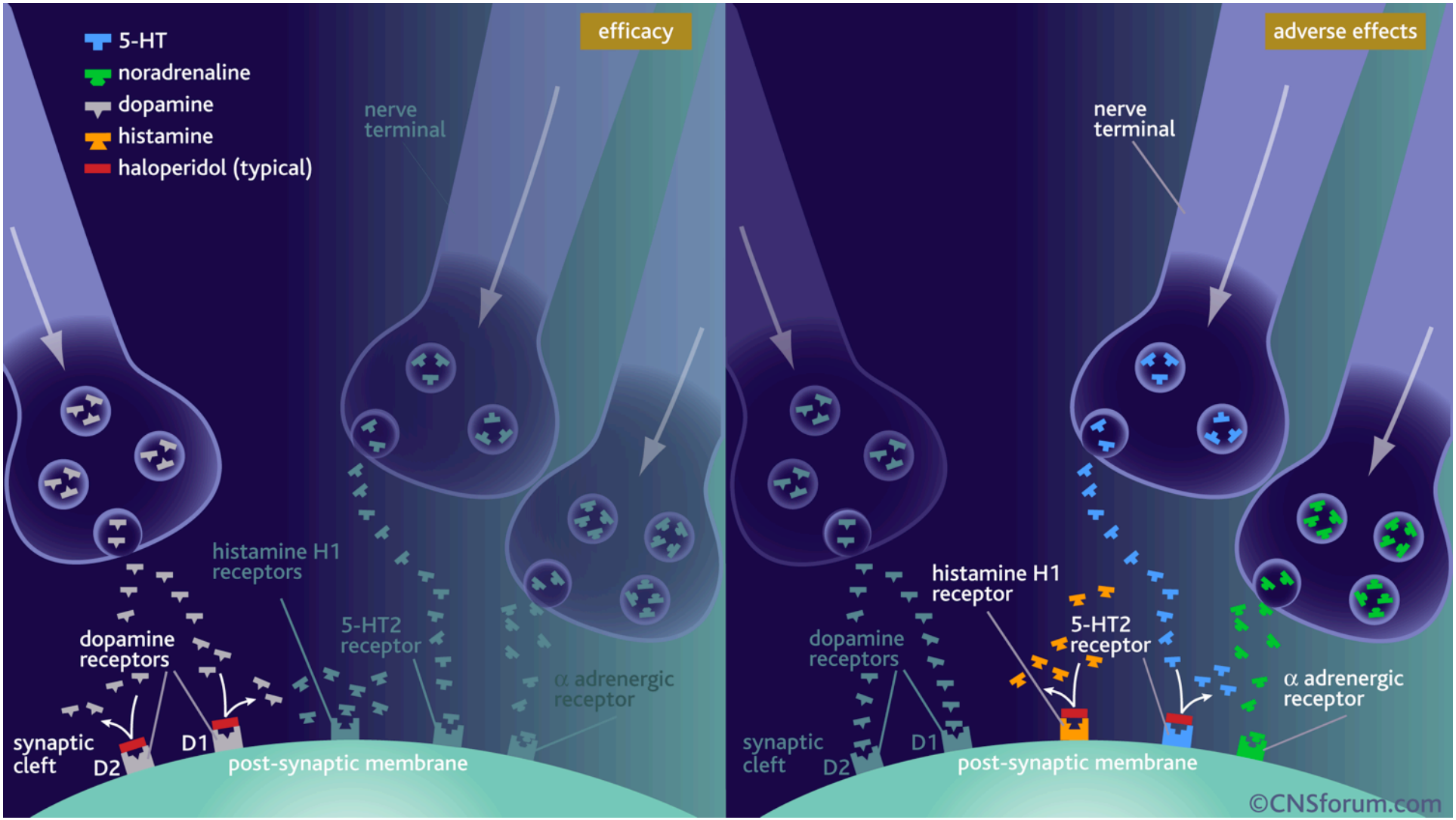
Dopaminergic Receptors



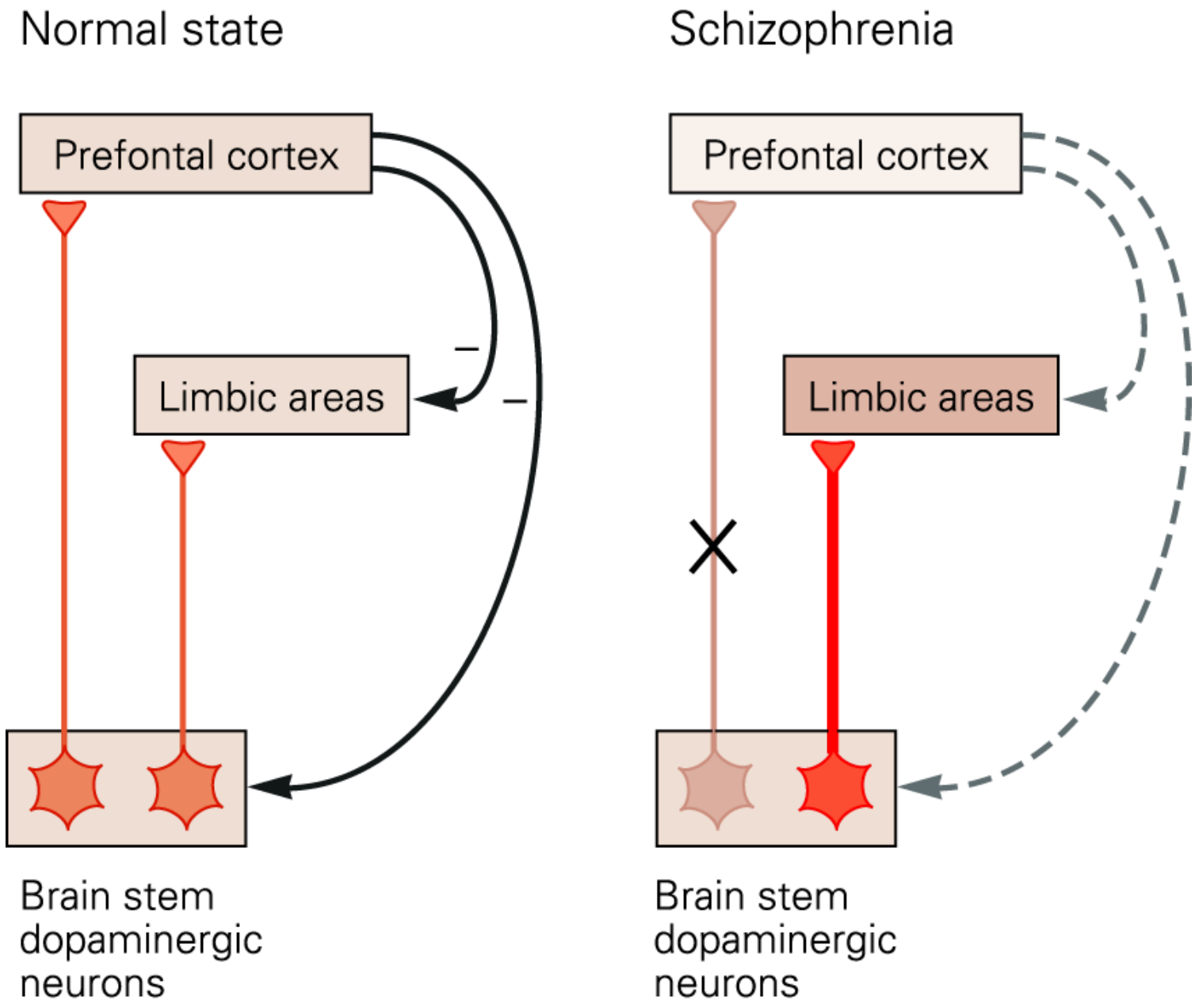
Actions of anti-psychotics at dopaminergic synapses




5-HT
noradrenaline
dopamine
histamine
risperidone (atypical)
efficacy
nerve terminal
histamine H1 receptors
dopamine receptors
5-HT2 receptor
α adrenergic receptor
synaptic cleft
D1
D2
adverse effects
nerve terminal
histamine H1 receptor
dopamine receptors
5-HT2 receptor
α adrenergic receptor
synaptic cleft
D1
D2
post-synaptic membrane
©CNSforum.com

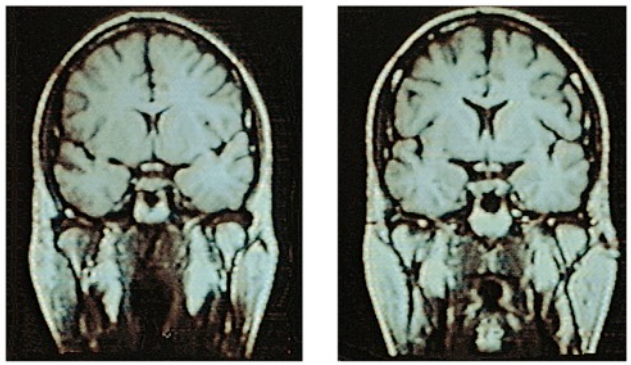

5-HT
noradrenaline
dopamine
histamine
haloperidol (typical)
efficacy
nerve terminal
histamine H1 receptors
dopamine receptors
5-HT2 receptor
α adrenergic receptor
synaptic cleft
D2
D1
post-synaptic membrane
adverse effects
nerve terminal
histamine H1 receptor
5-HT2 receptor
dopamine receptors
α adrenergic receptor
synaptic cleft
D2
D1
post-synaptic membrane
©CNSforum.com

Just One Working Model of Schizophrenia



Modeling Schizophrenia in Mouse

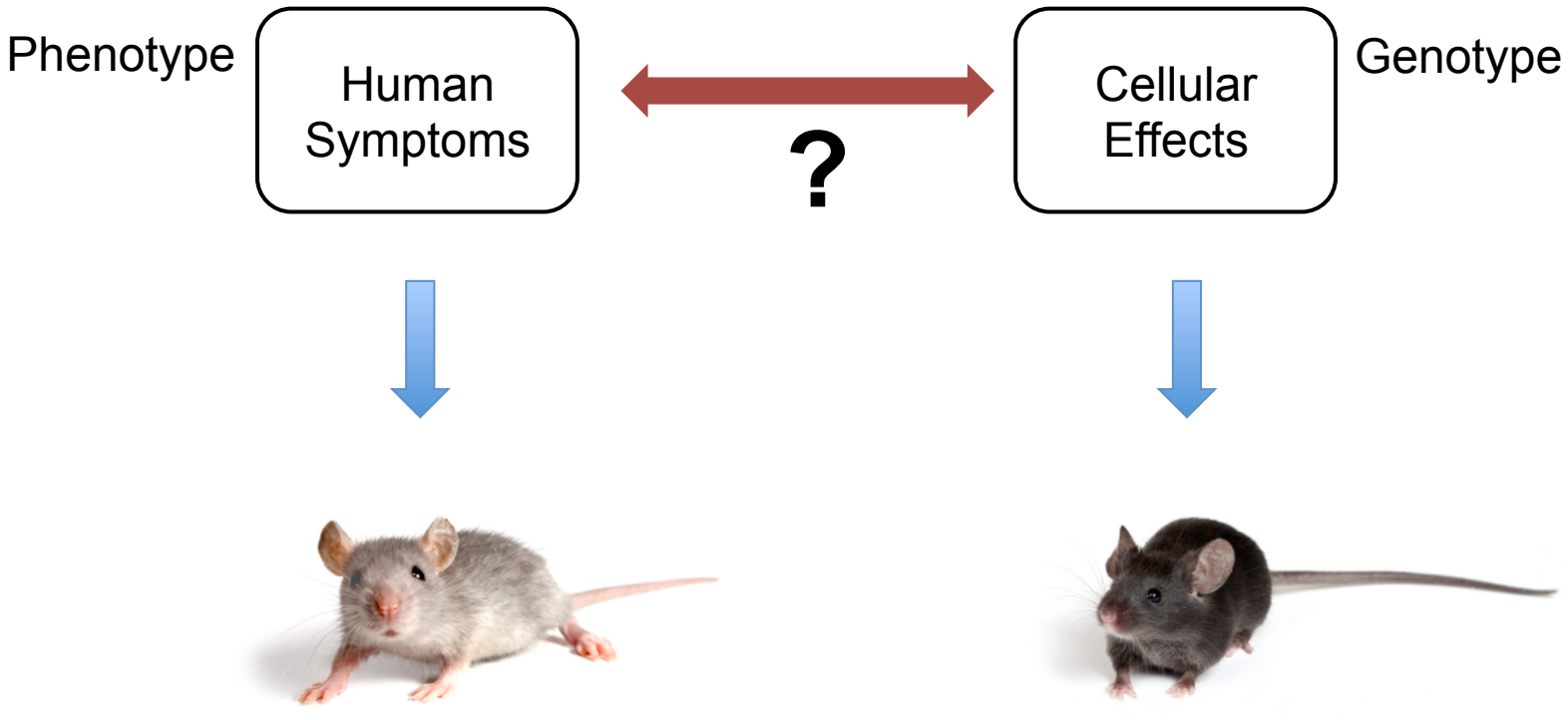
Human Trait	Mouse Trait
Social withdrawal	Deficits in reciprocal grooming or huddling
Psychomotor agitation	Increased locomotor activity
Stereotypic behaviors	Repetitive grooming
Learning, memory deficits	Impaired learning (fail in mouse school)
Cognitive rigidity	After learning one task, cannot relearn a slightly different tasl
Decreased GAD67 gene expression	…ditto
Reduced prefrontal cortical dopamine release	
Increased ventricle volume	



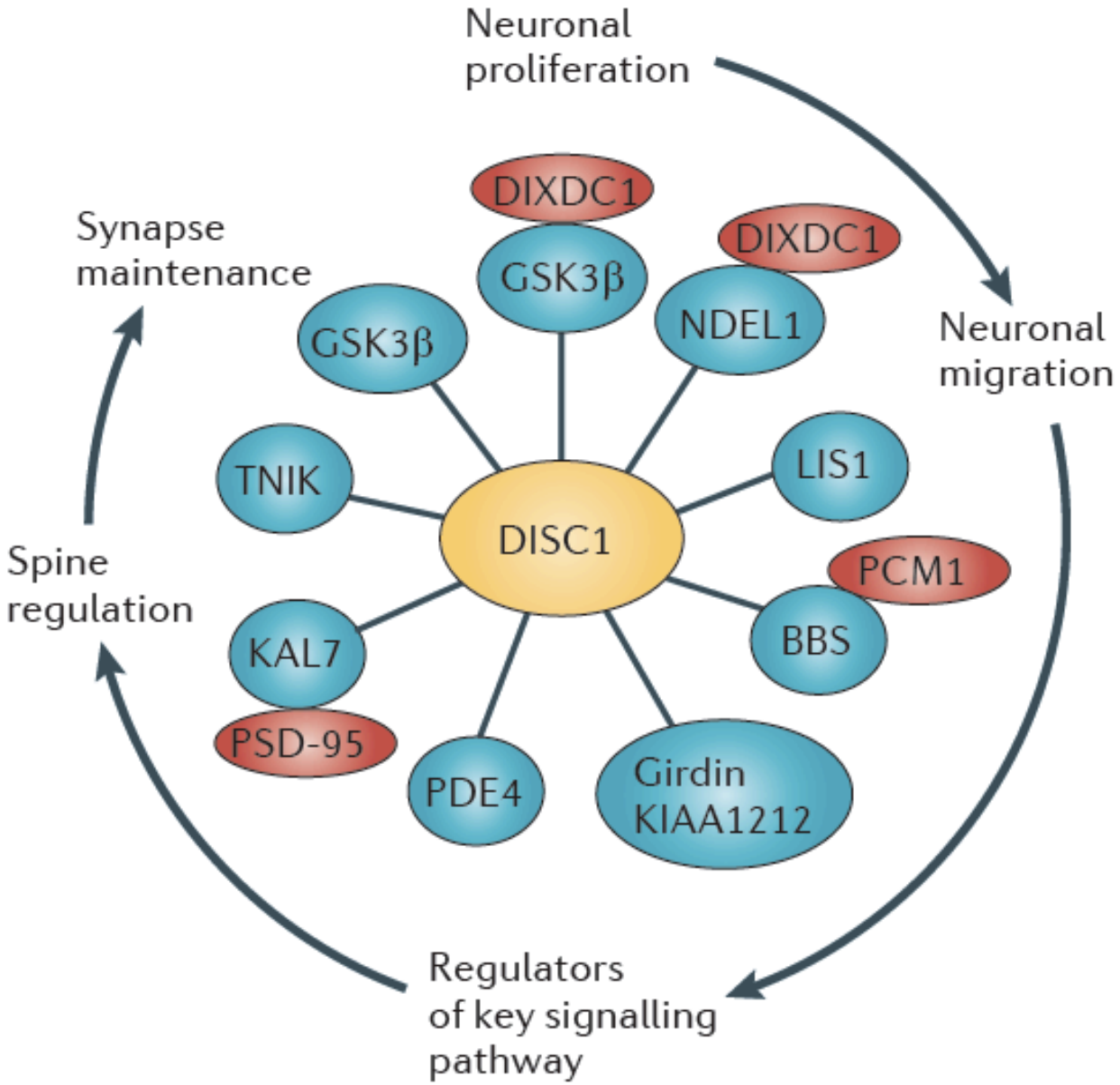
Unaffected twin

Schizophrenic twin

Fundamental Problem in Making Mouse Models



DISC1 Mutation
(Disrupted in Schizophrenia 1 gene)



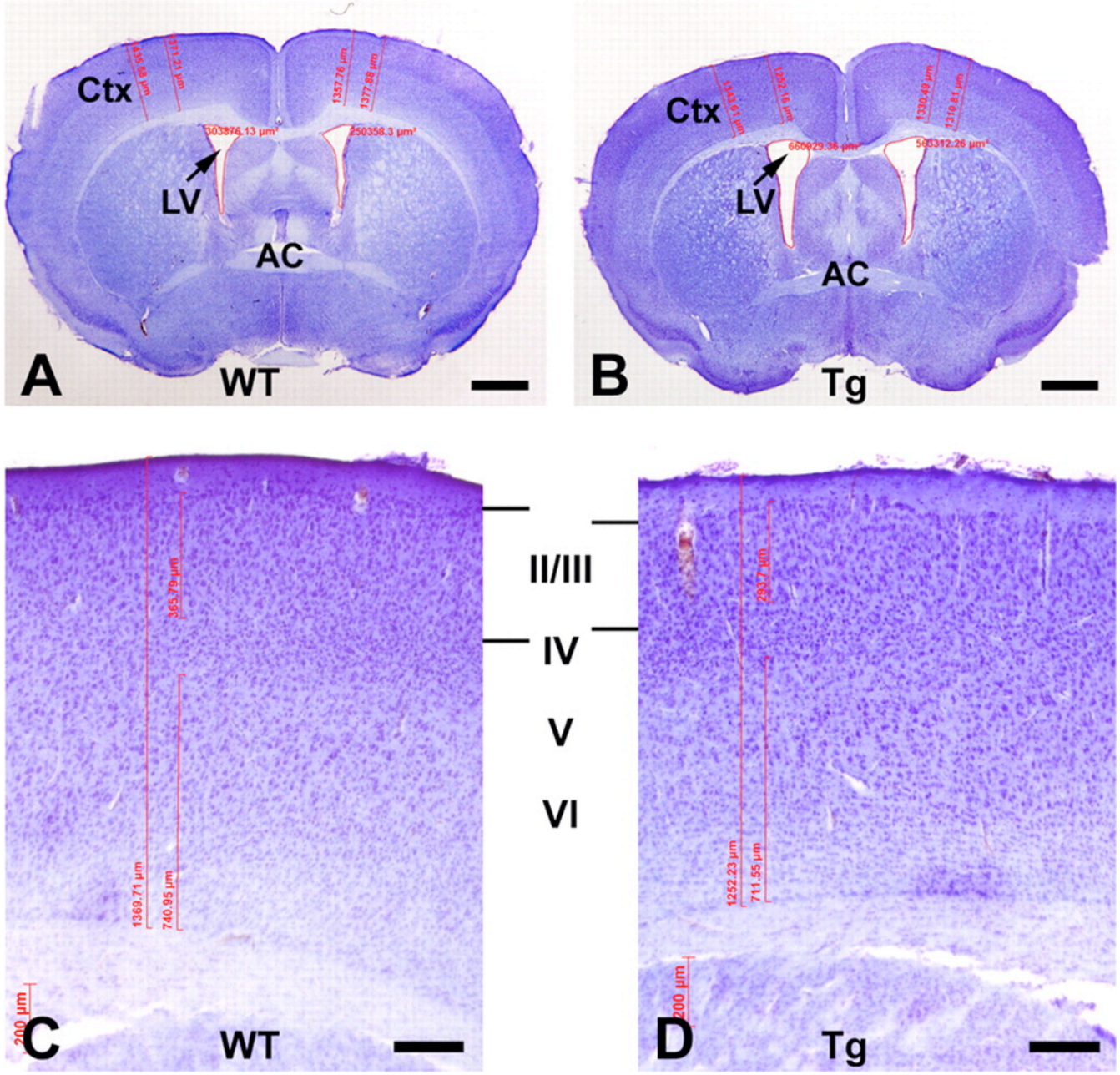
Brandon & Sawa 2011

Mutation identified in DISC1 gene of humans with schizophrenia

Genetically engineer a mouse with the same mutation:

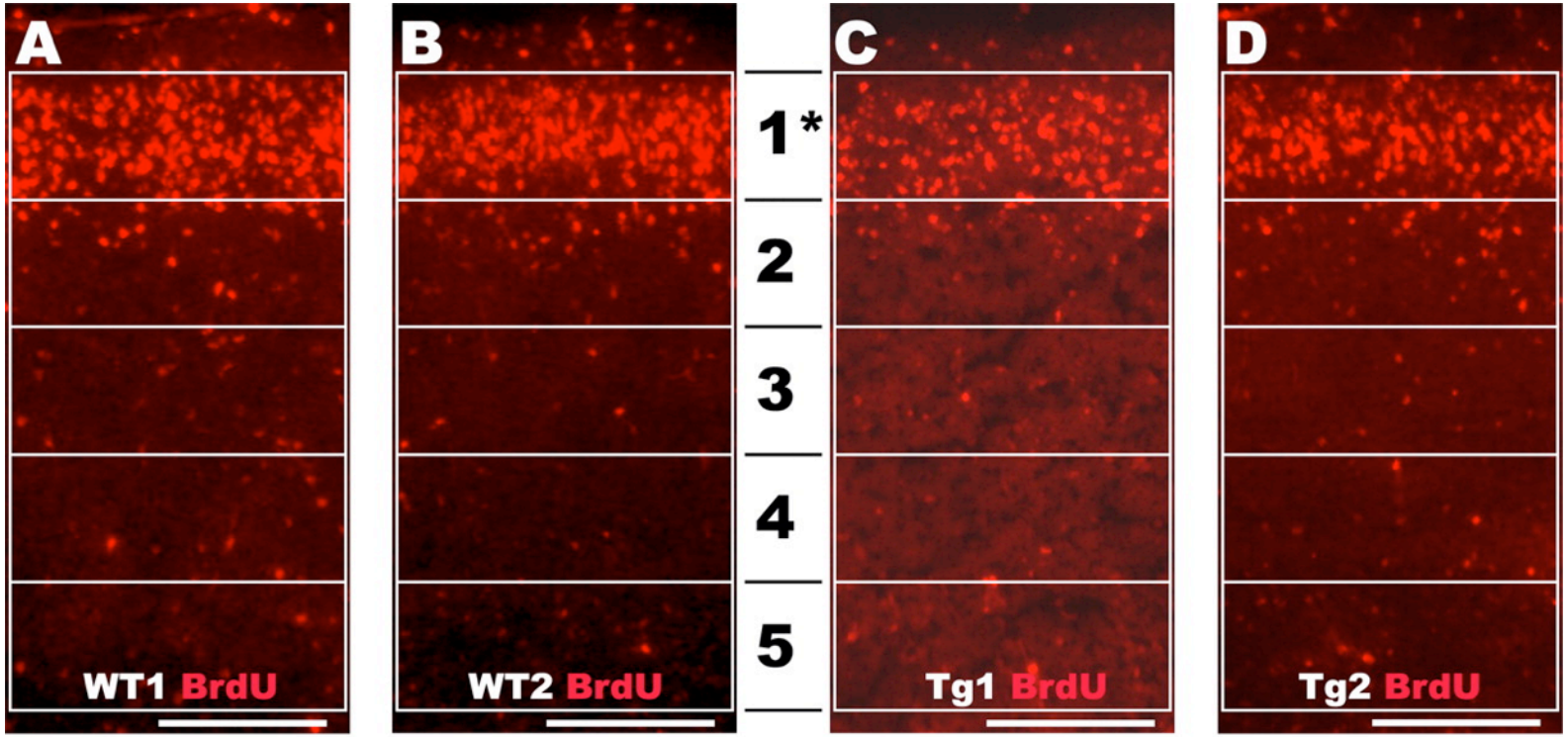
DISC1-deficient transgenic (Tg) mouse

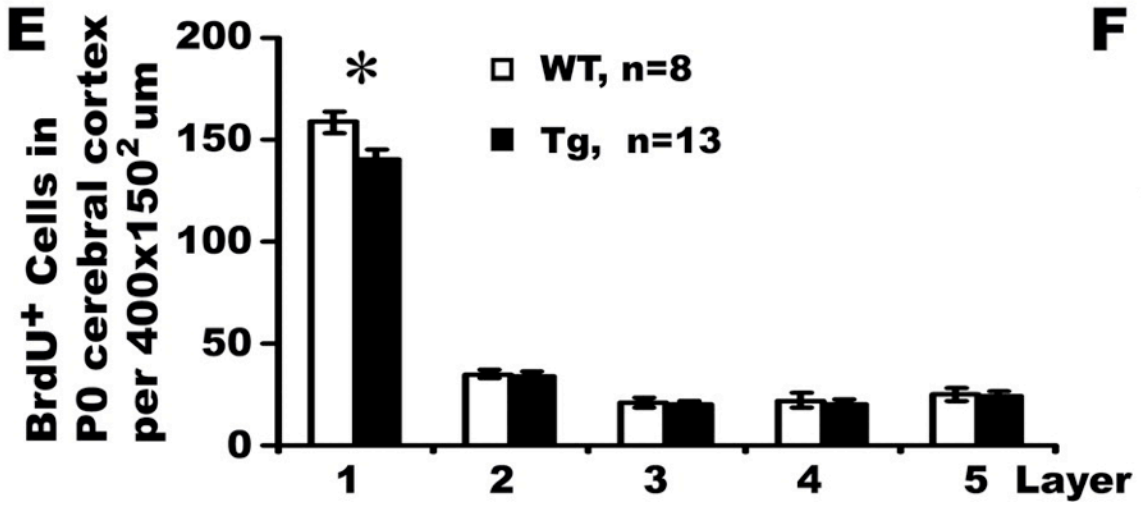
Enlarged Lateral Ventricles

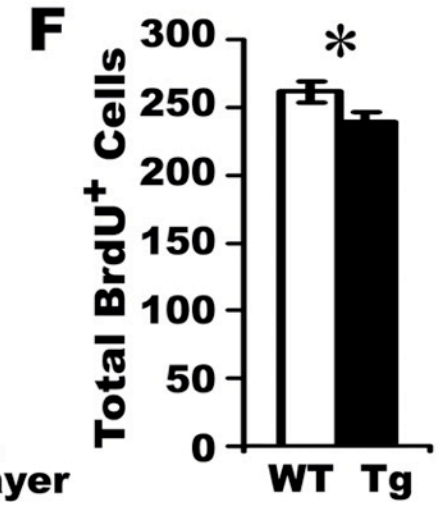


Shen *et al.* 2008

Decreased Neuron Proliferation

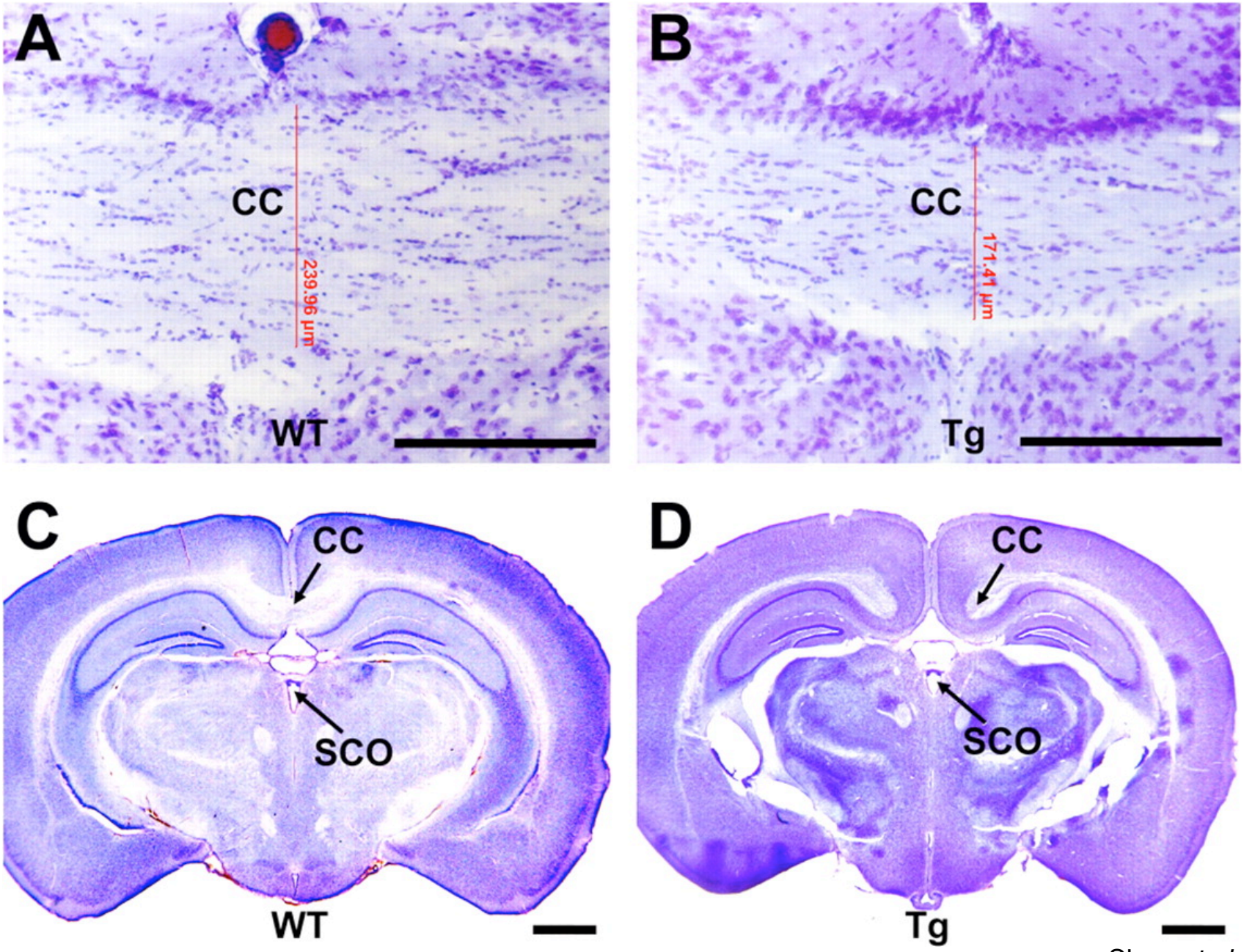






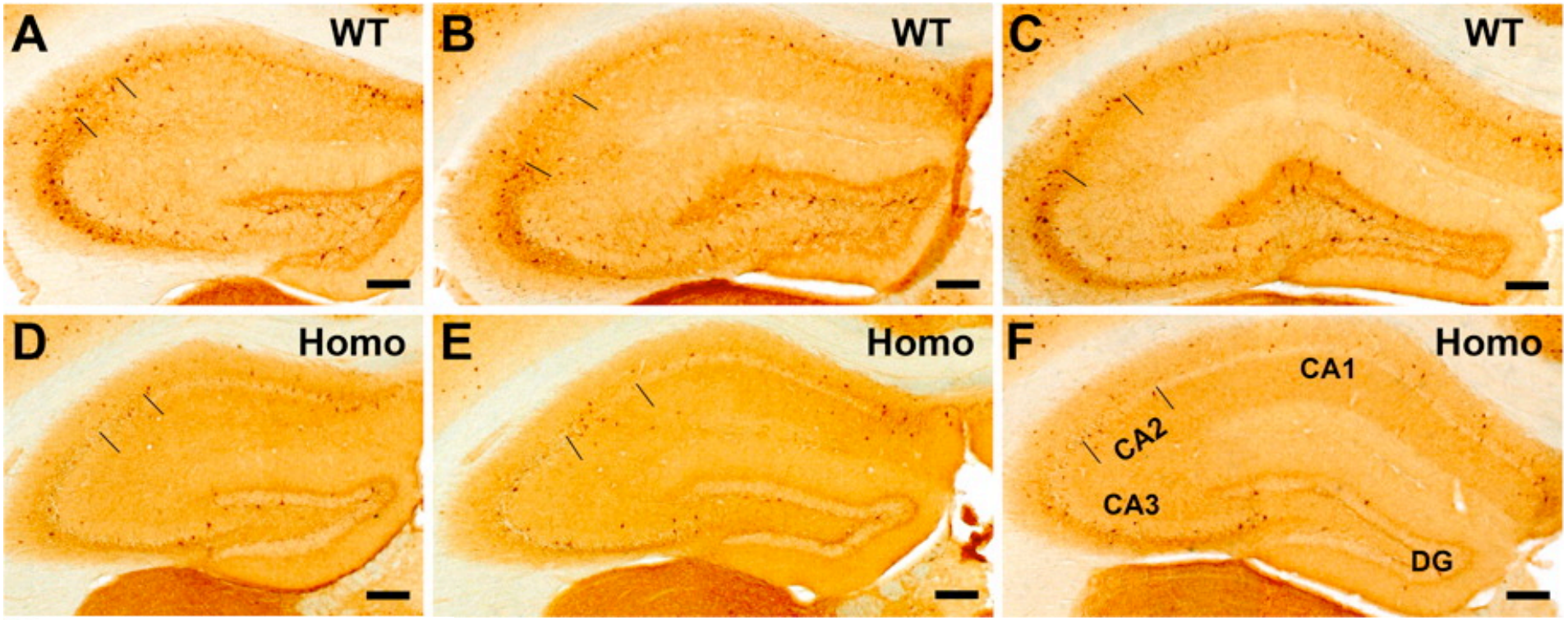
Shen *et al.* 2008

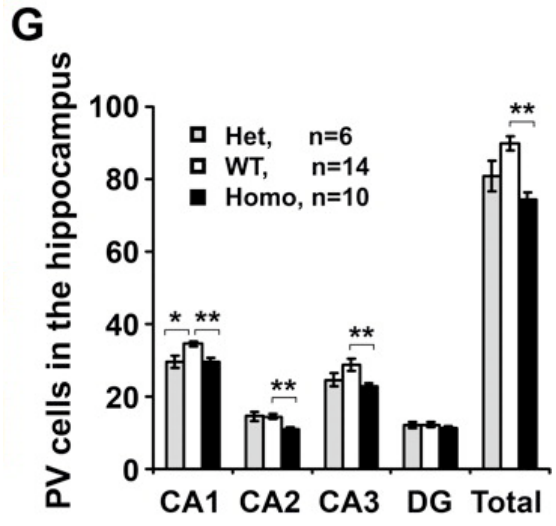
Partial Agenesis of Corpus Callosum



Shen *et al.* 2008

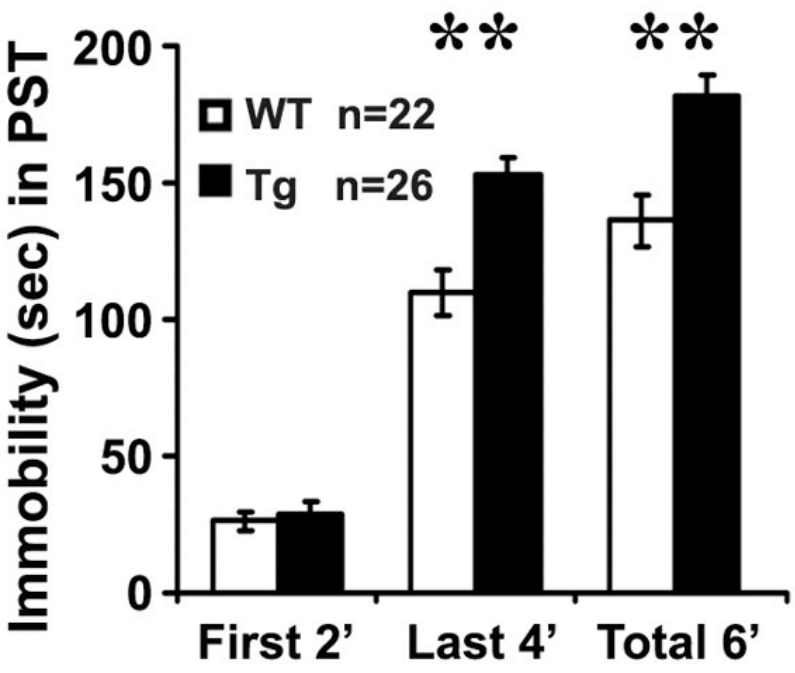
Reduced Interneurons in Hippocampus



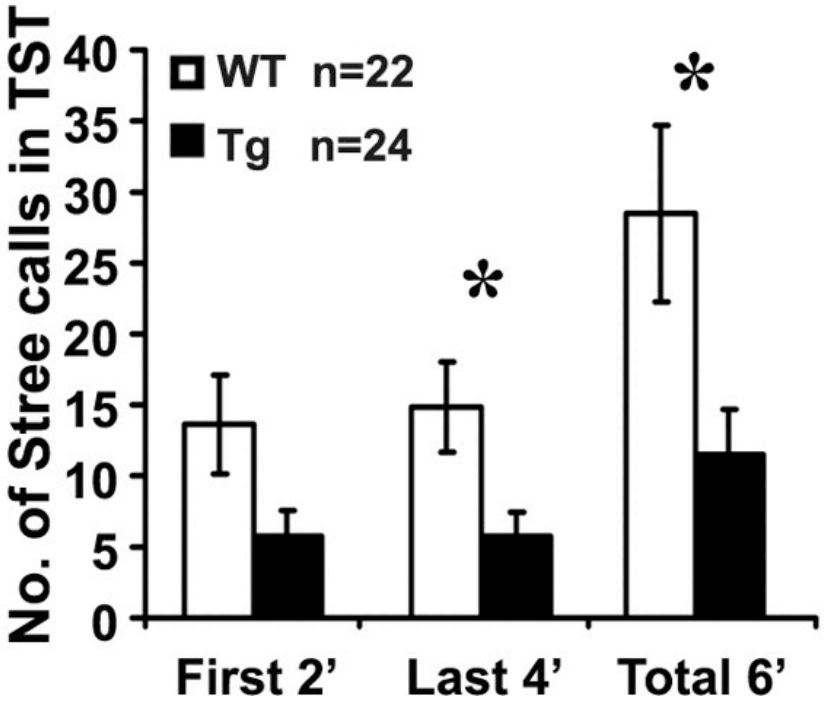


Shen *et al.* 2008

Immobility



Stress Calls



Shen *et al.* 2008