Mood disorders - Depression

Depression is a common and heterogeneous psychiatric disorder

Clinical classification (most common)
1. Major depressive disorder (unipolar depression)
2. dysthymia, a less severe but more chronic form of depression
3. bipolar disorders or maniac-depressive disorders

Affects approximately 15% of the population with high morbidity and mortality

Occurs at any age, is twice as common in women

The underlying causes of most mood disorders remain unknown

Symptoms of depression

EMOTIONAL

Lose Interest and Motivation
Lose Self Confidence / Feelings of worthlessness
Experience Feelings of Guilt
Thoughts of Suicide (7-15% commit suicide)
Loss of ambition
Little pleasure from sex or food
Excess sadness in response to loss, failure, or disappointment

BIOLOGICAL

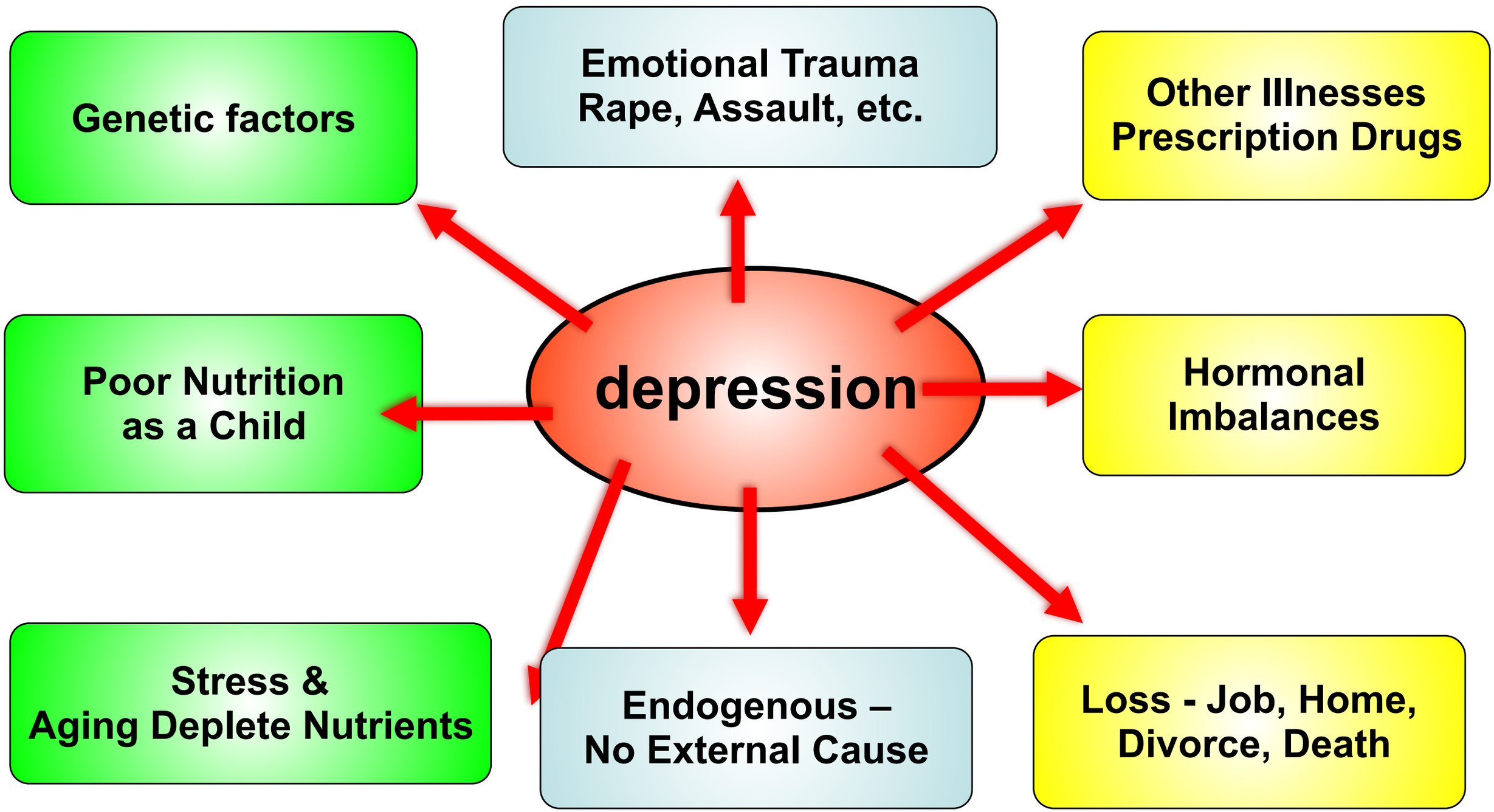
Sleep Disturbance
Appetite and Weight Change
Lack of Energy, fatigue
Poor Concentration and Memory

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV): criteria for major depression

At least five of the following symptoms for at least two weeks (symptom 1 or 2 must be present):

Depressed mood
Loss of interest or pleasure
Significant appetite or weight loss or gain
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive guilt
Impaired thinking or concentration, indecisiveness
Suicidal thoughts/thoughts of death

Depression: etiology

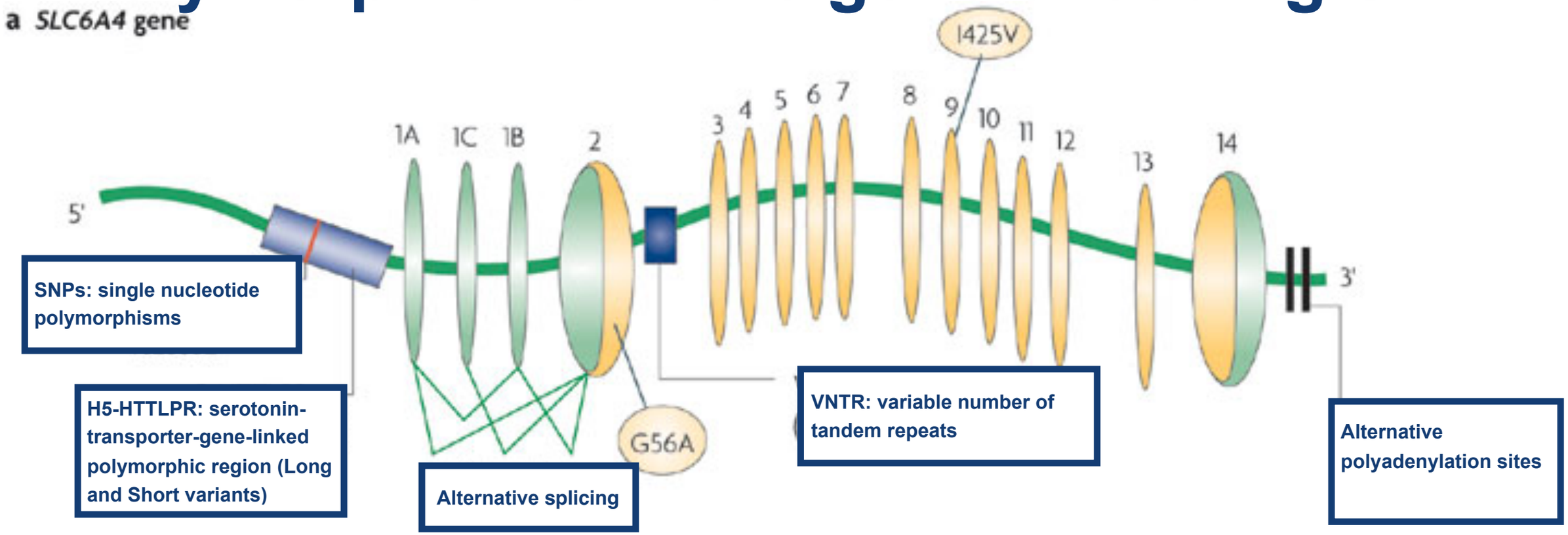


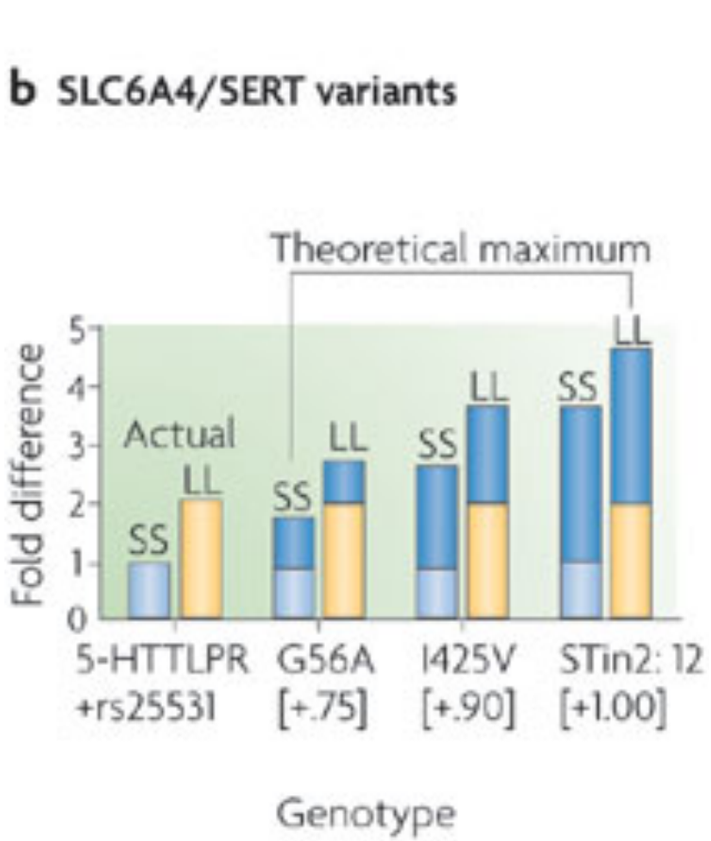
Genetic factors

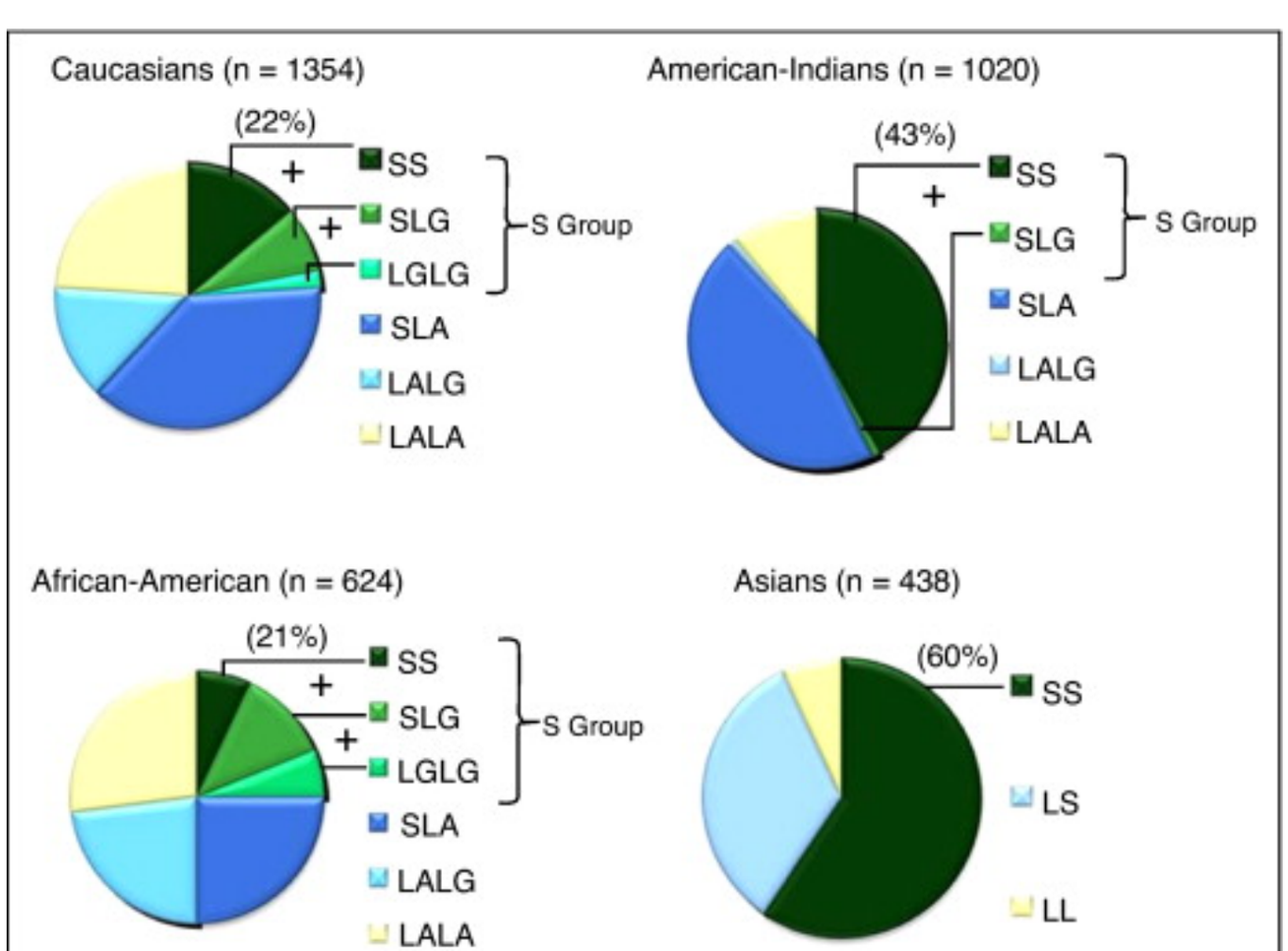
Predisposition depends on a variety of genes:

- The serotonin transporter (SERT) gene
- The serotonin 2A receptor
- FK-506 binding protein (FKBP5)

Polymorphisms in the gene encoding SERT







A

Main characteristics of the 5-HT$_{2A}$ receptor

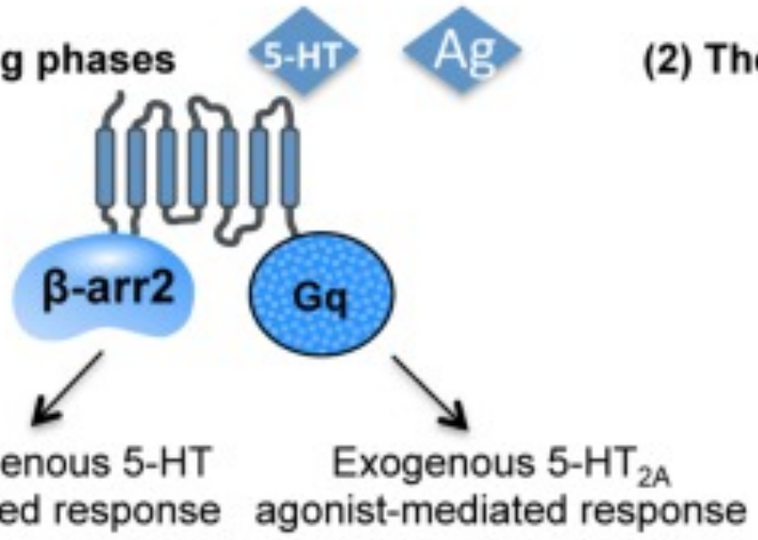
5-HT$_{2A}$ receptor in brain regions relevant to mood and epilepsy

Region:		**Cell type**:
Amygdala:	+++	Glutamatergic / GABAergic *(Bombardi, 2014)*
Neocortex:	+++	Glutamatergic / GABAergic *(Celada et al., 2013)*
Entorhinal Cortex	+++	Glutamatergic / GABAergic *(Pompeiano et al., 1994)*
Thalamus	++	Glutamatergic / GABAergic *(Li et al., 2004)*
Hippocampus:	++	Glutamatergic / GABAergic *(Tanaka et al., 2012)*
DR:	+	GABA *(Boothman and Sharp, 2005)*
LC:	+	GABA *(Szabo and Blier, 2001)*
VTA:	++	GABA & DAergic *(Cornea-Hebert et al., 1999)*

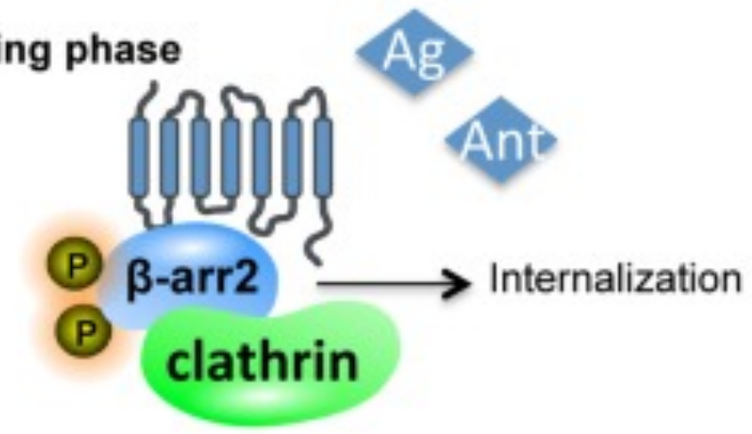
B

β-arrestin2 – dependent signaling/arresting phases

(1) The signaling phases



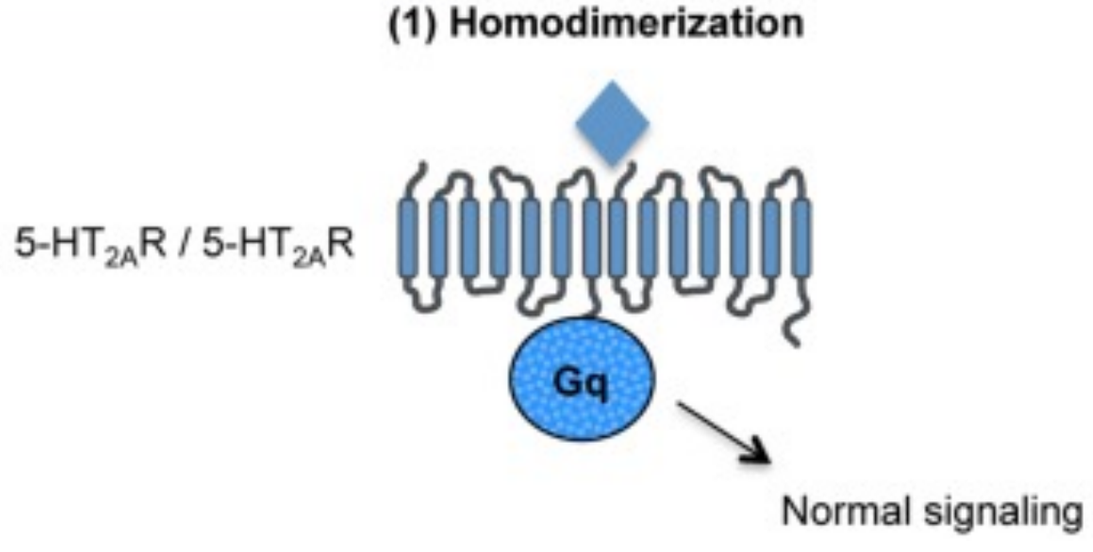
(2) The arresting phase



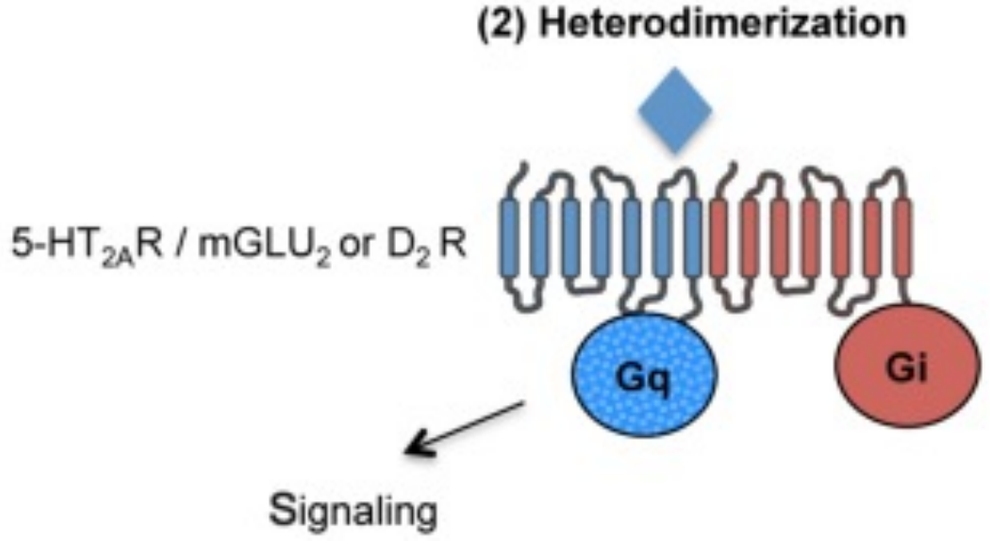
C

Dimerization

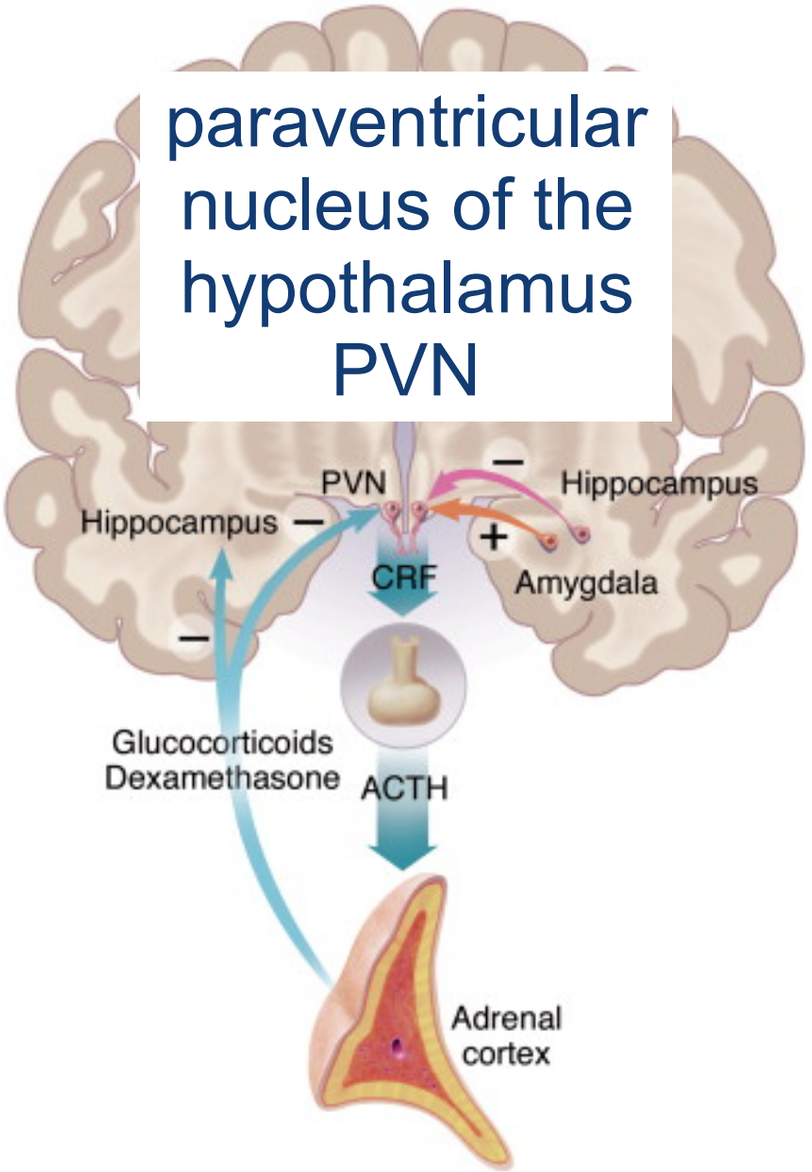
(1) Homodimerization



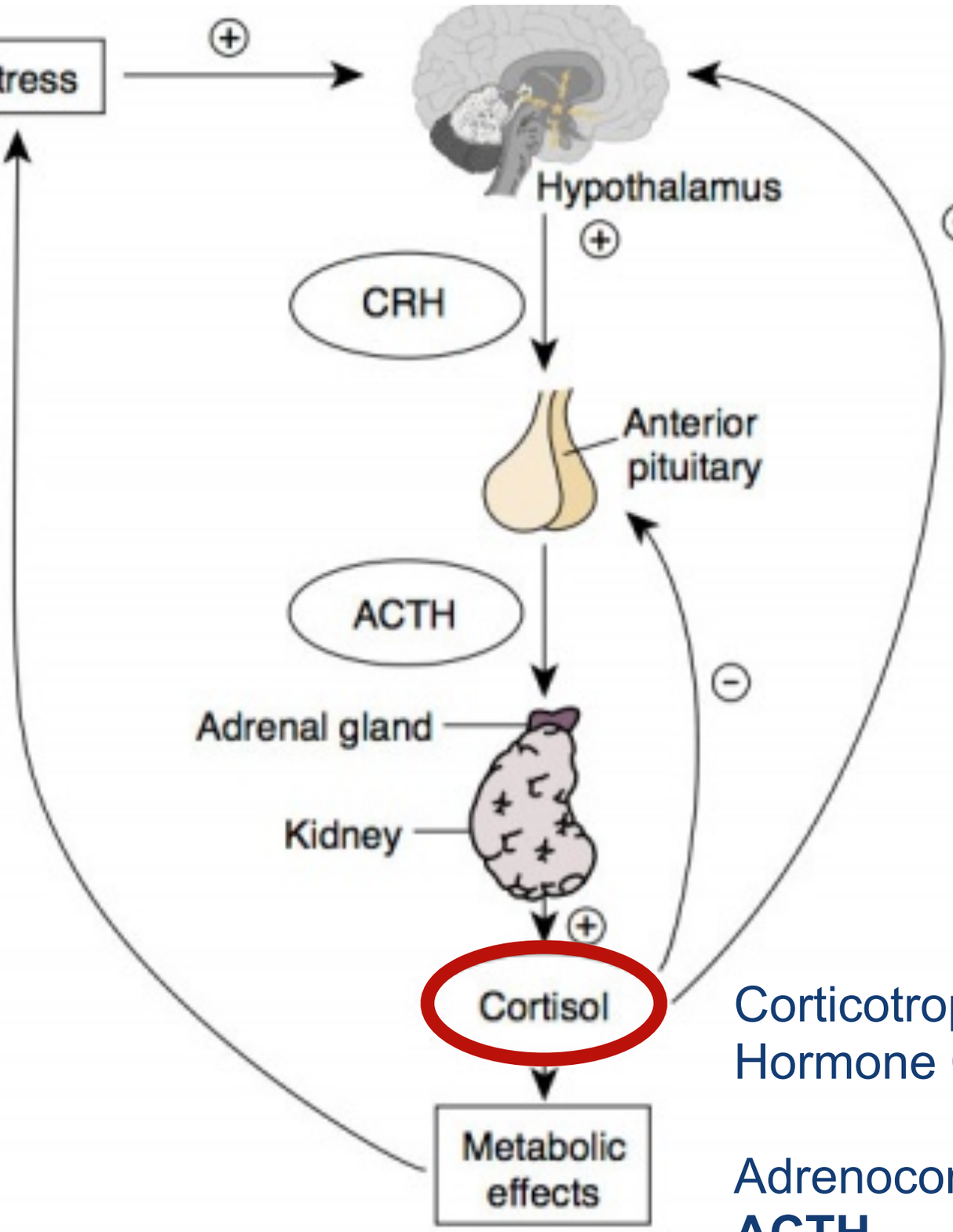
(2) Heterodimerization



The Hypotalamic - Pituitary - Adrenal Axis (HPA)



paraventricular nucleus of the hypothalamus PVN



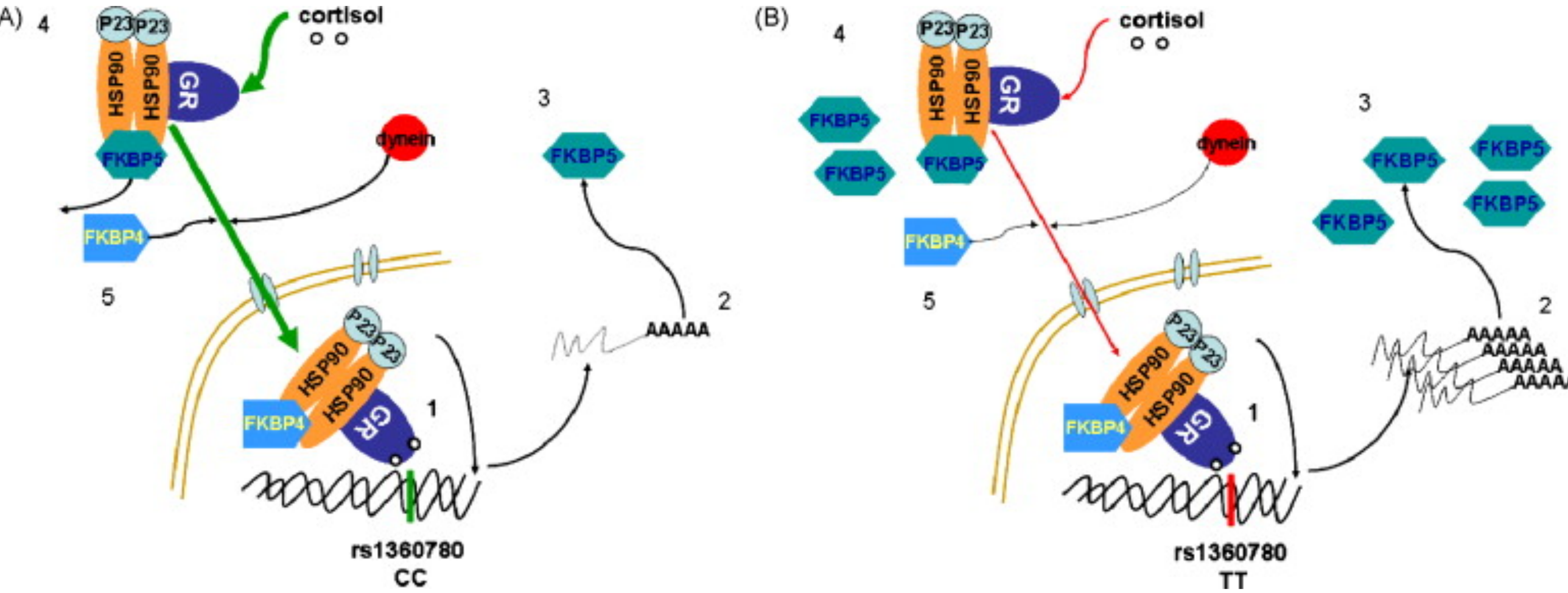
Negative feedback

Corticotropin Releasing Hormone **CRH**

Adrenocorticotrophin **ACTH**

FKBP5 regulates glucocorticoid receptor (GR) sensitivity

FKBP5 mediates an ultra-short feedback negative loop for GR-sensitivity



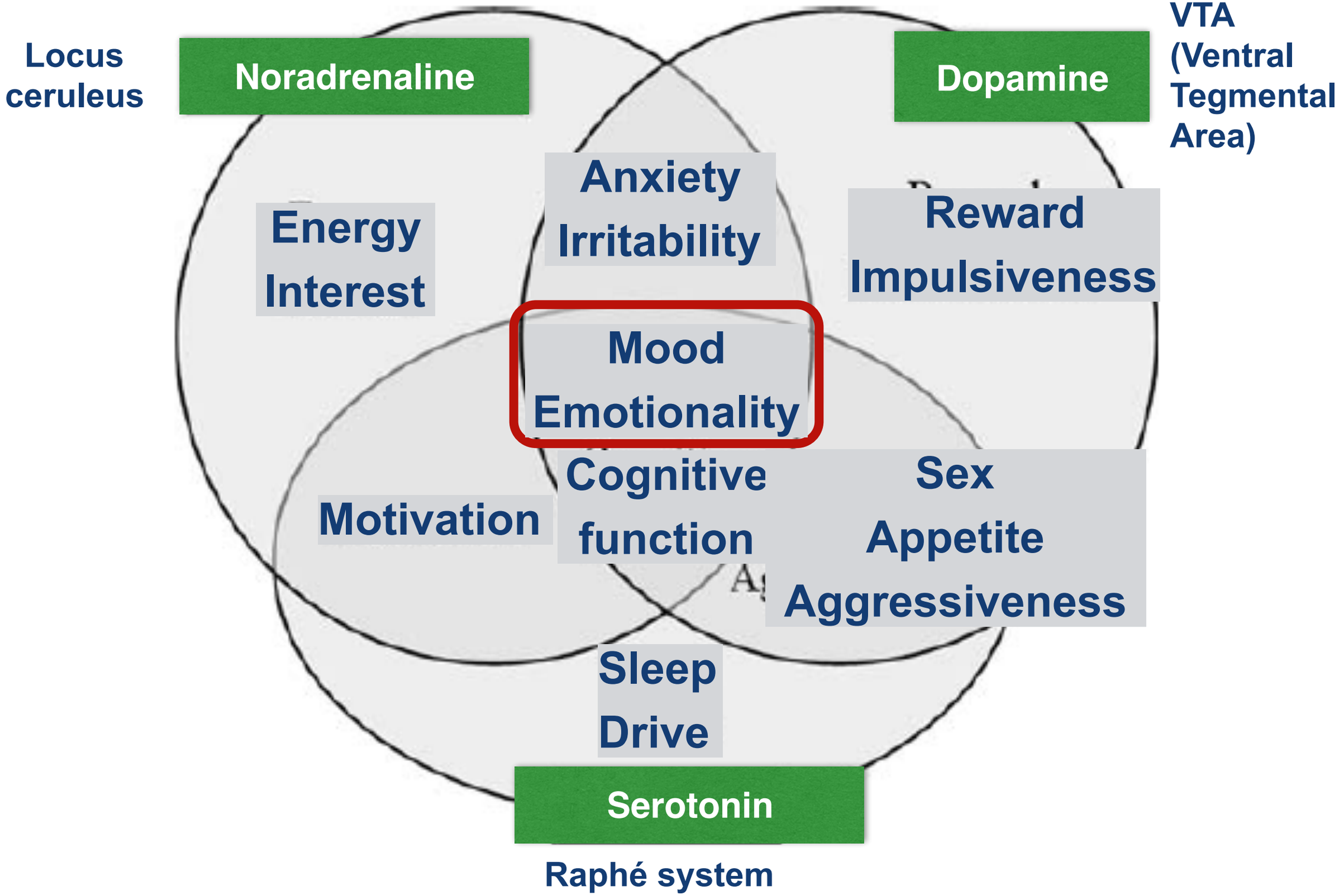
Polymorphisms in the gene encoding FKBP5 associate with differential upregulation of FKBP5 following GR activation and differences in GR sensitivity and resistance

Theories of Depression

1. Monoamine Theory of Depression
2. Stress Theory of Depression
(The neurotrophic hypothesis)

1. Mood is controlled by the level of the biogenic monoamine Serotonin, Norepinephrine and Dopamine

Relationship among noradrenaline, serotonin, and dopamine and behavior



Monoamine Theory of Depression

Most widely accepted theory:
depression may be due to **underactivity** at 5-HT and NE synapses

1. All clinically effective drugs are 5-HT and/or NE agonists
or increase 5-HT and/or NE levels

2. Certain 5-HT and/or NE receptors are **up-regulated** in untreated depressed patients (compensatory increase in receptors due to low levels of transmitters)

Criticisms

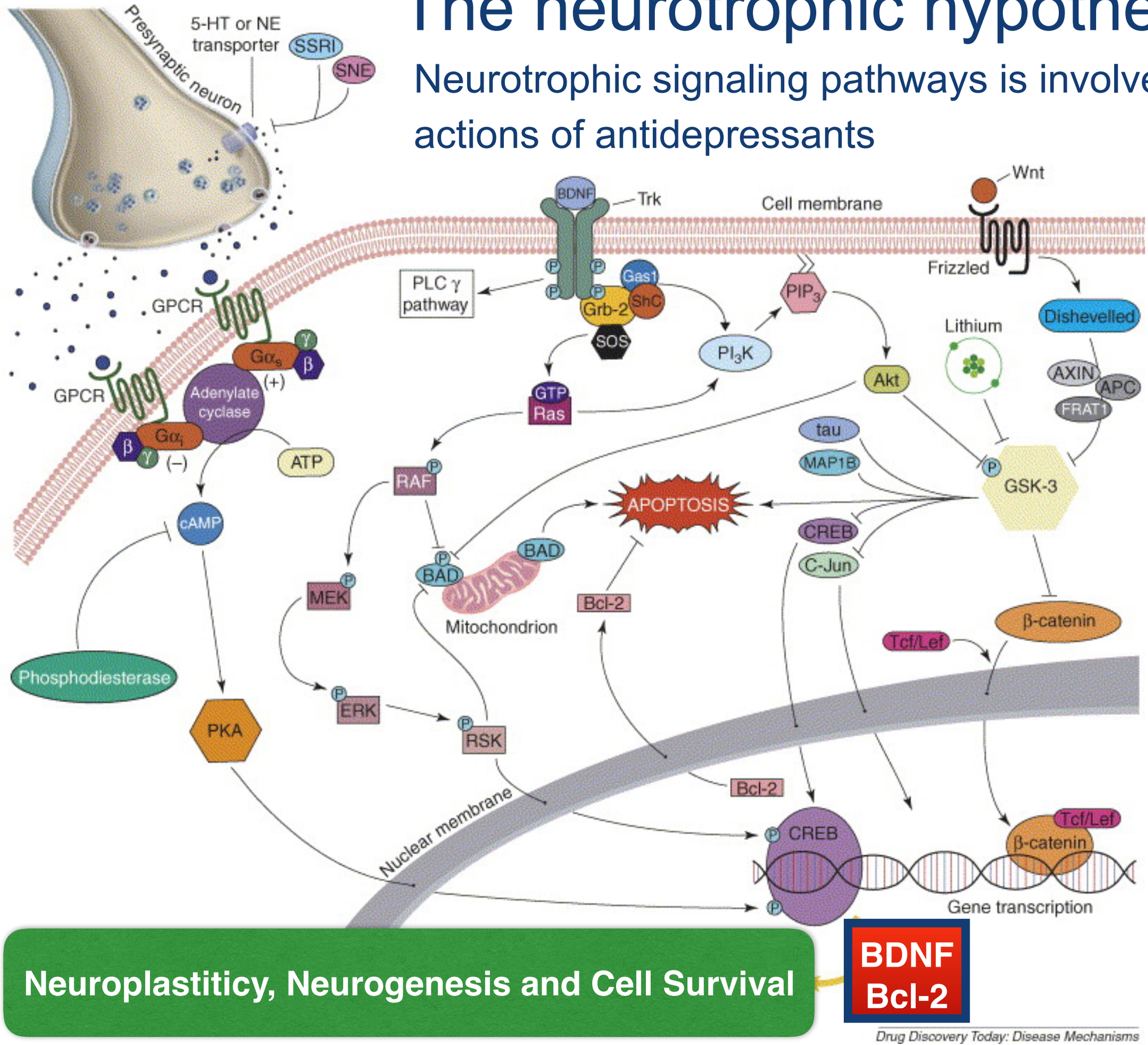
1. Neither 5-HT nor NE depletion induce clinical depression in healthy subjects

2. Antidepressants are generally effective in only about 60% of patients

3. Most antidepressants take **3 or more weeks** to take effect

The neurotrophic hypothesis

Neurotrophic signaling pathways is involved in the actions of antidepressants



Neuroplastiticy, Neurogenesis and Cell Survival

BDNF
Bcl-2

Drug Discovery Today: Disease Mechanisms

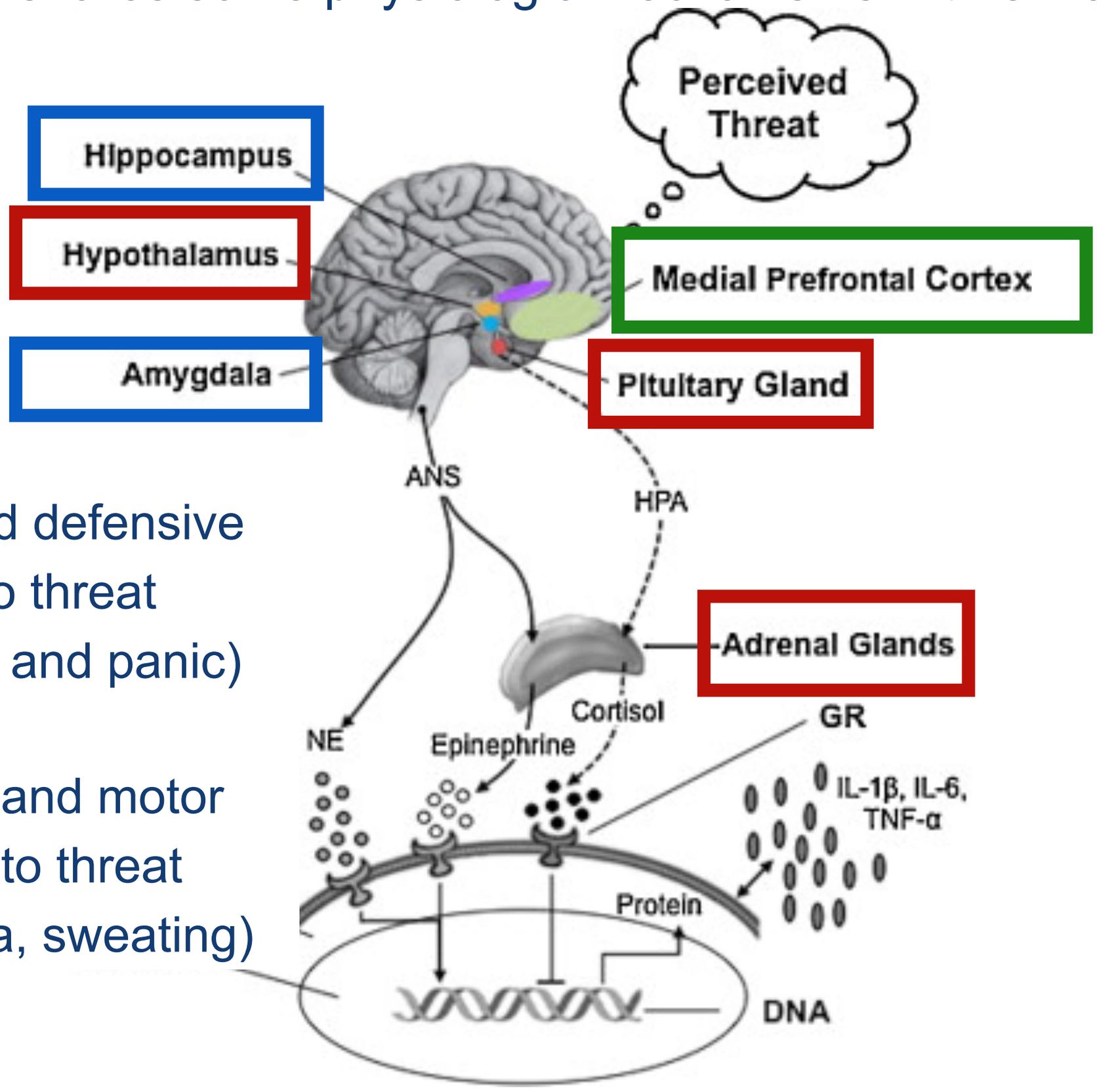
CREB (cAMP response element-binding protein)

2. Stress theory of depression

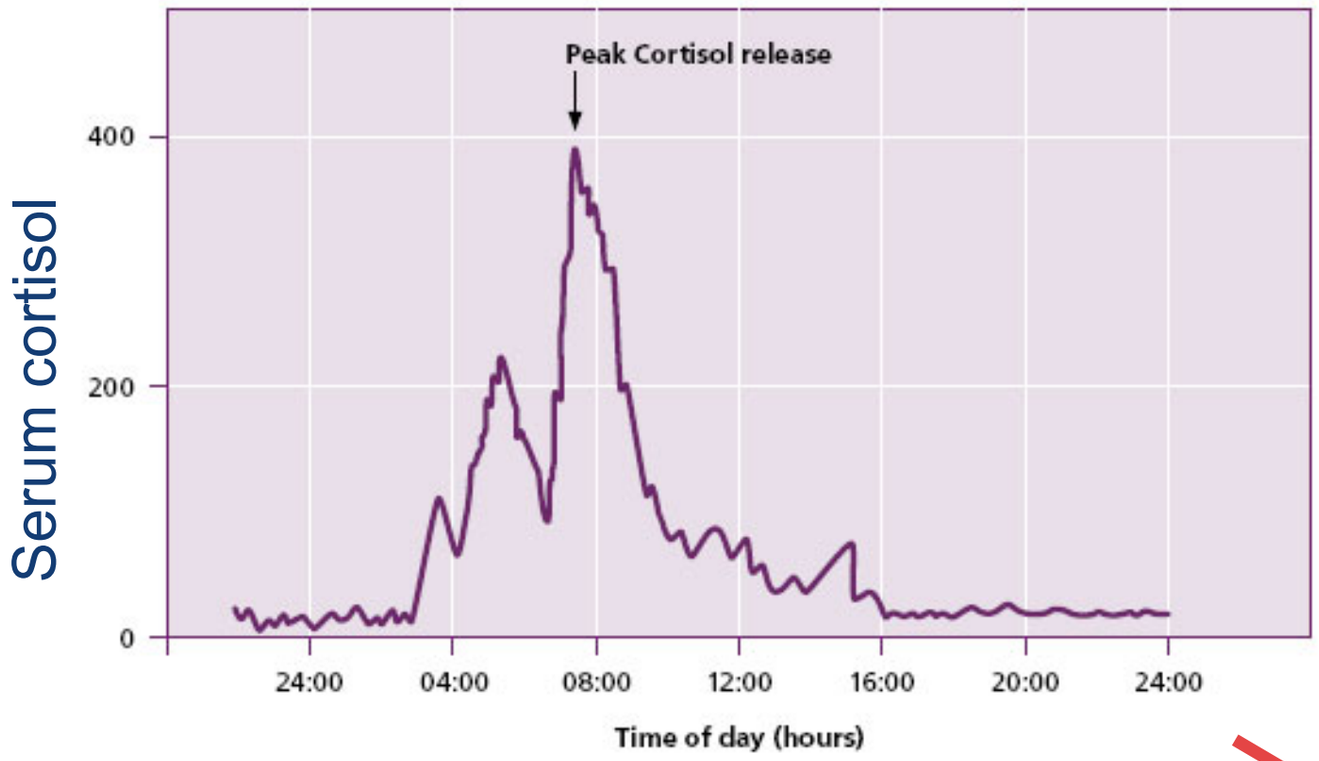
Depression shares some physiologic mechanisms with **chronic** stress

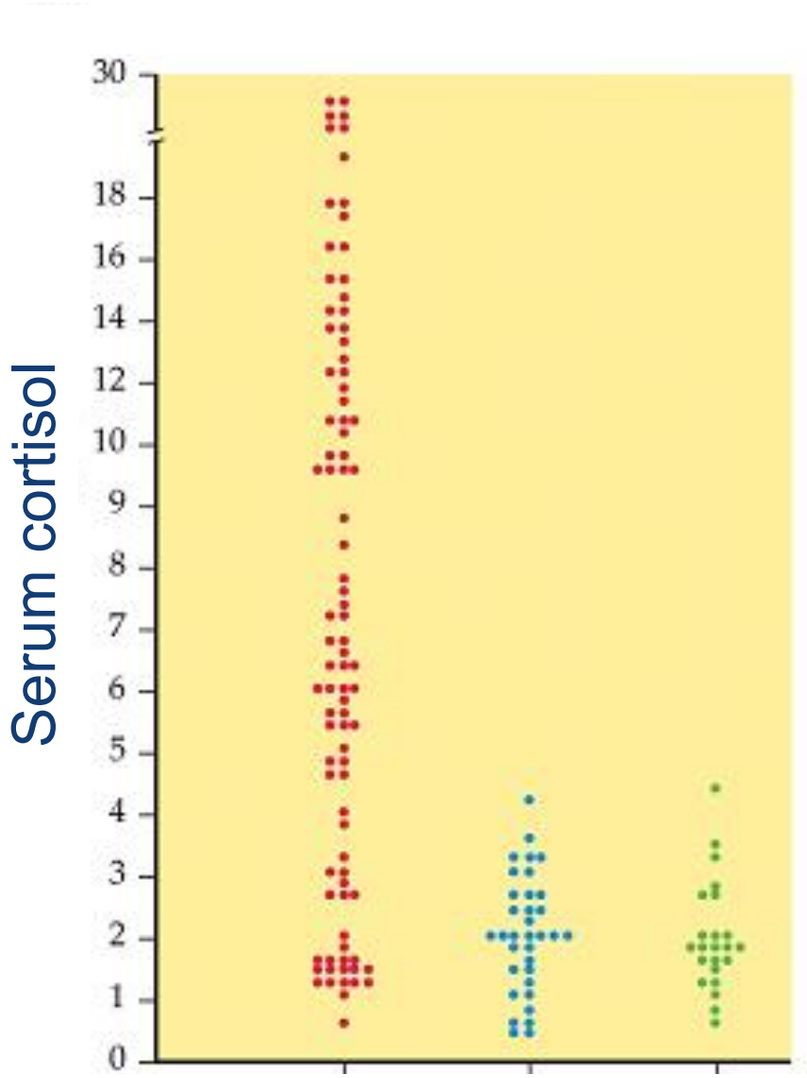
stereotyped defensive reactions to threat (immobility and panic)

autonomic and motor responses to threat (tachicardia, sweating)

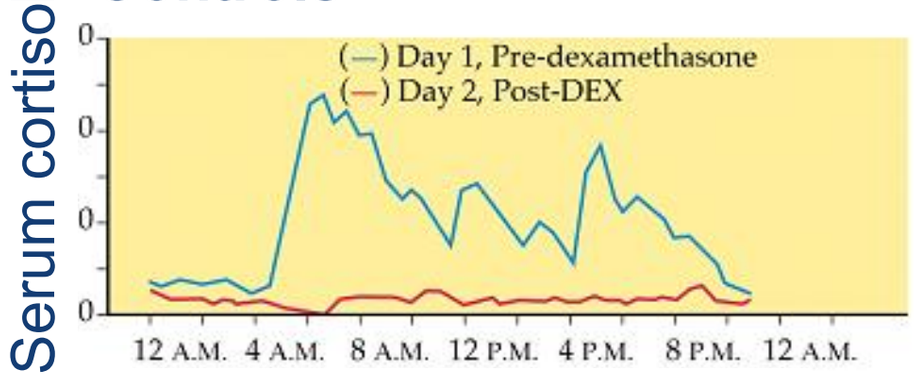


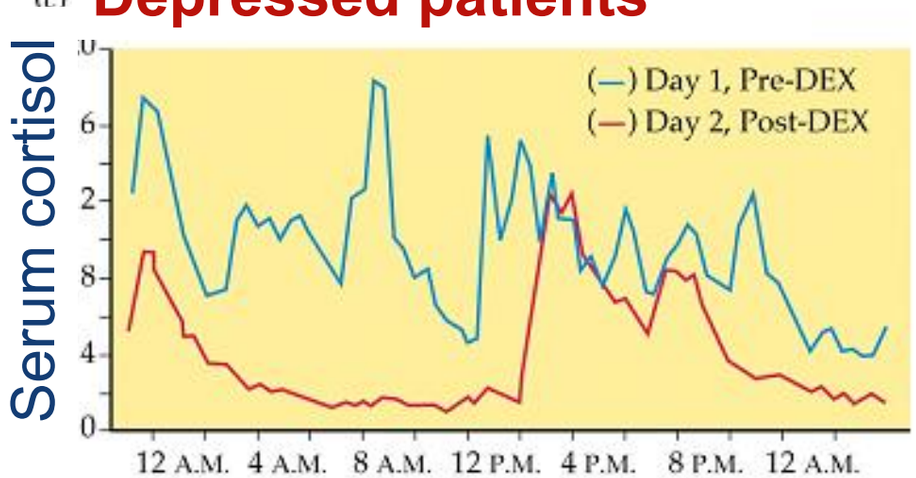
Circadian pattern of serum cortisol





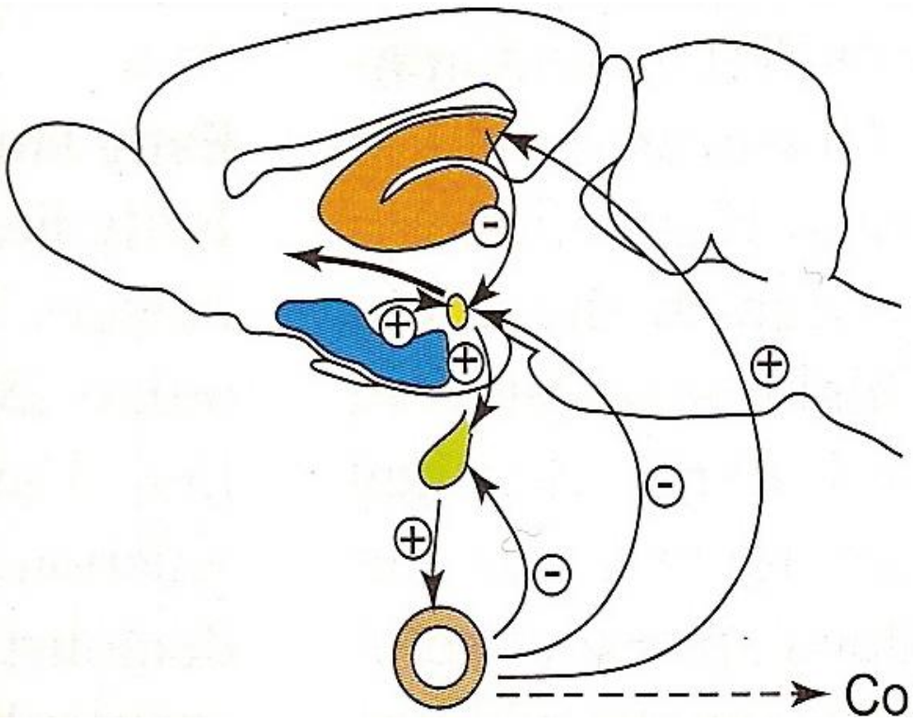
Depressed Psychiatric Normal
patients controls **controls**





Dexamethasone
Suppression test

Effect of stressors on HPA Axis

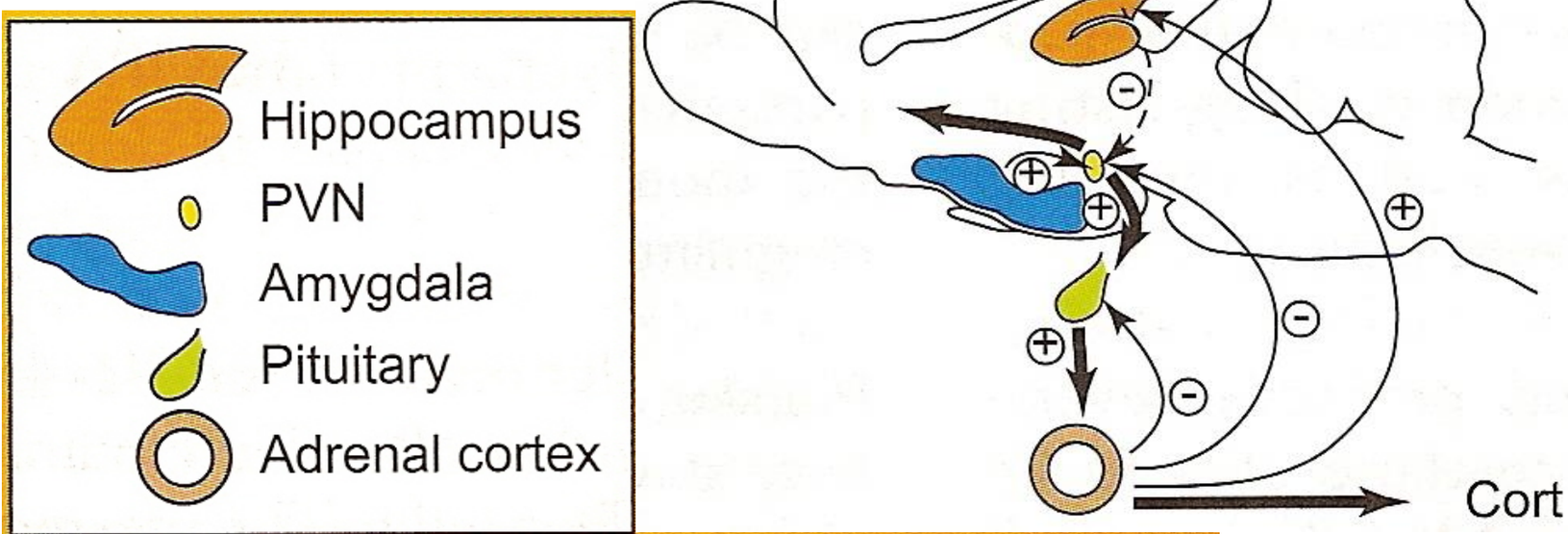


Baseline:
- depression / anxiety ↓
- hippocampal 5-HT, 5-HIA ↑
- BDNF, NGF ↑
- hippocampal neurogenesis ↑

Responses to stress:
- HPA response ↓

High levels of maternal care

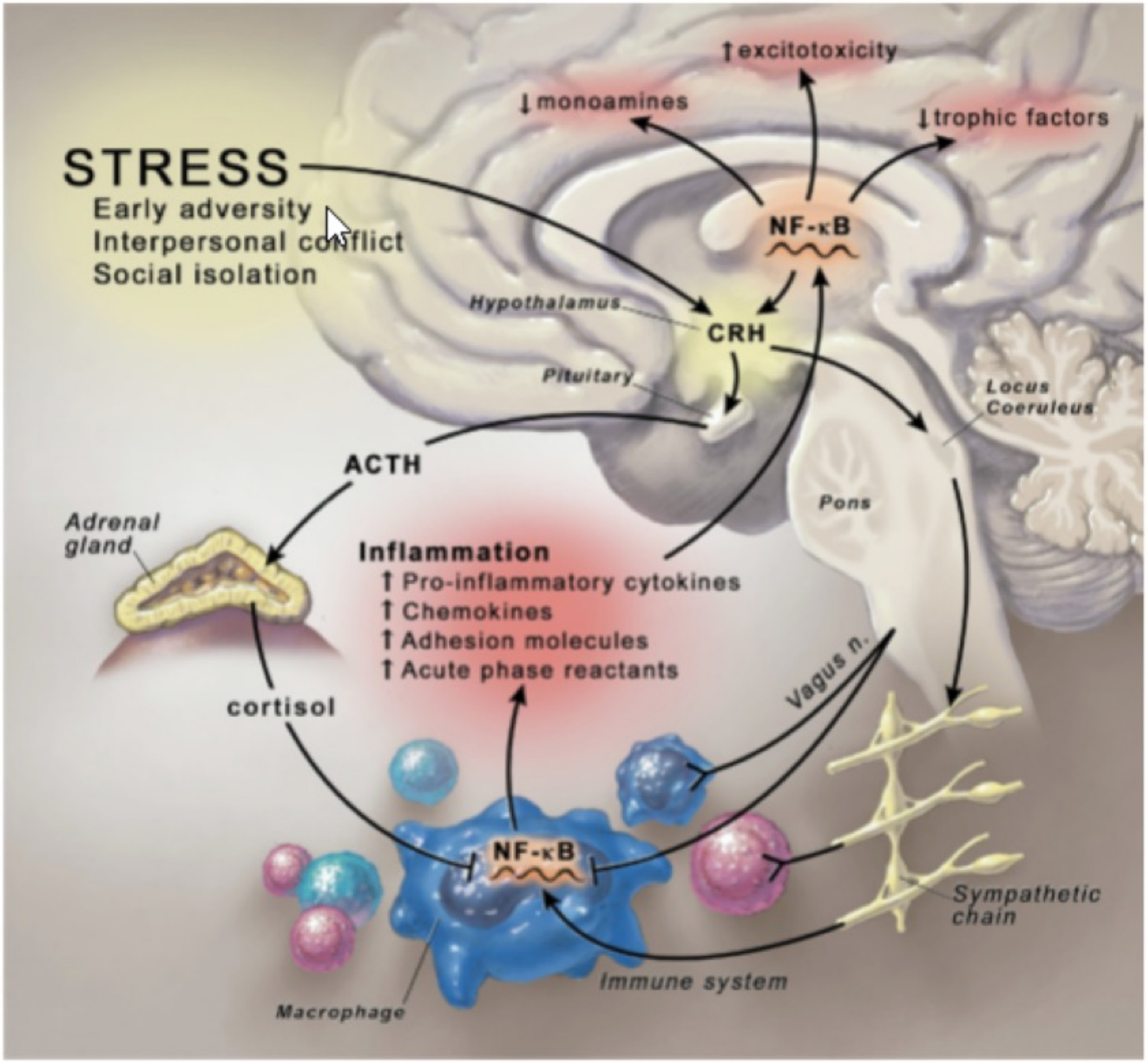
Neglect
Trauma
Chronic Stress



Baseline:
- depression / anxiety ↑
- CRF ↑
- hippocampal volume ↓
- hippocampal 5-HIAA/5-HT ratio ↑
- BDNF, NGF ↓
- hippocampal neurogenesis ↓

Responses to stress:
- HPA response ↑

Stress-induced neuroinflammation



3. Loss of the auto regulation of the HPA axis

2. Cytokines enter CNS reducing the levels of NTs and trophic factors and excitotoxicity

1. ANS activation increases NF-kB synthesis

A Unified Theory of Depression

Genetics:

G1

G2

G3

Etc

Epigenetics

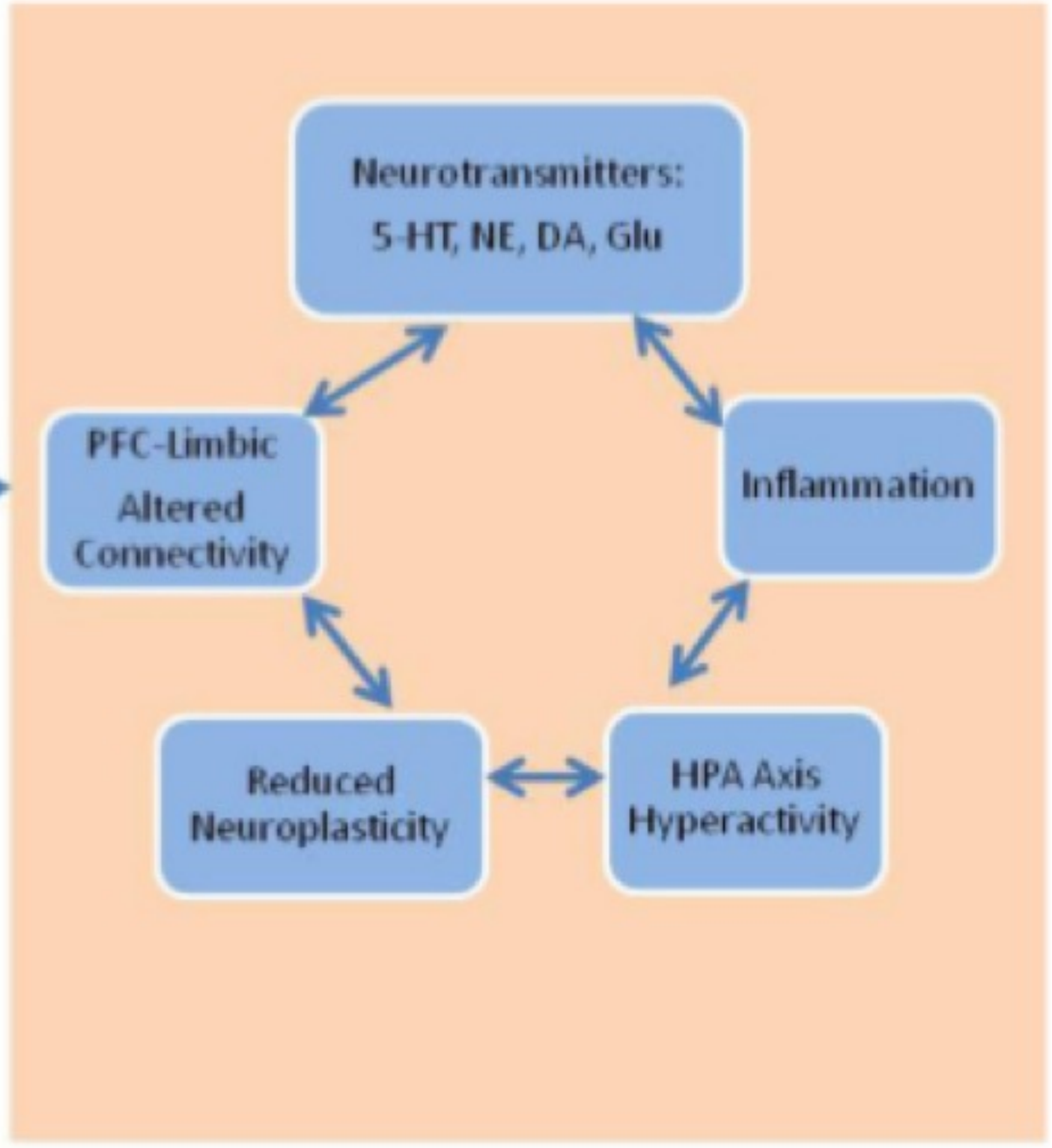
Environment

Stress

Trauma

Interpersonal Dynamics

Etc



Domains:

Negative Salience

Reward Sensitivity

Motor Activity

Impulsivity

Sleep/arousal

Symptoms:

Sadness/ Guilt

Anhedonia

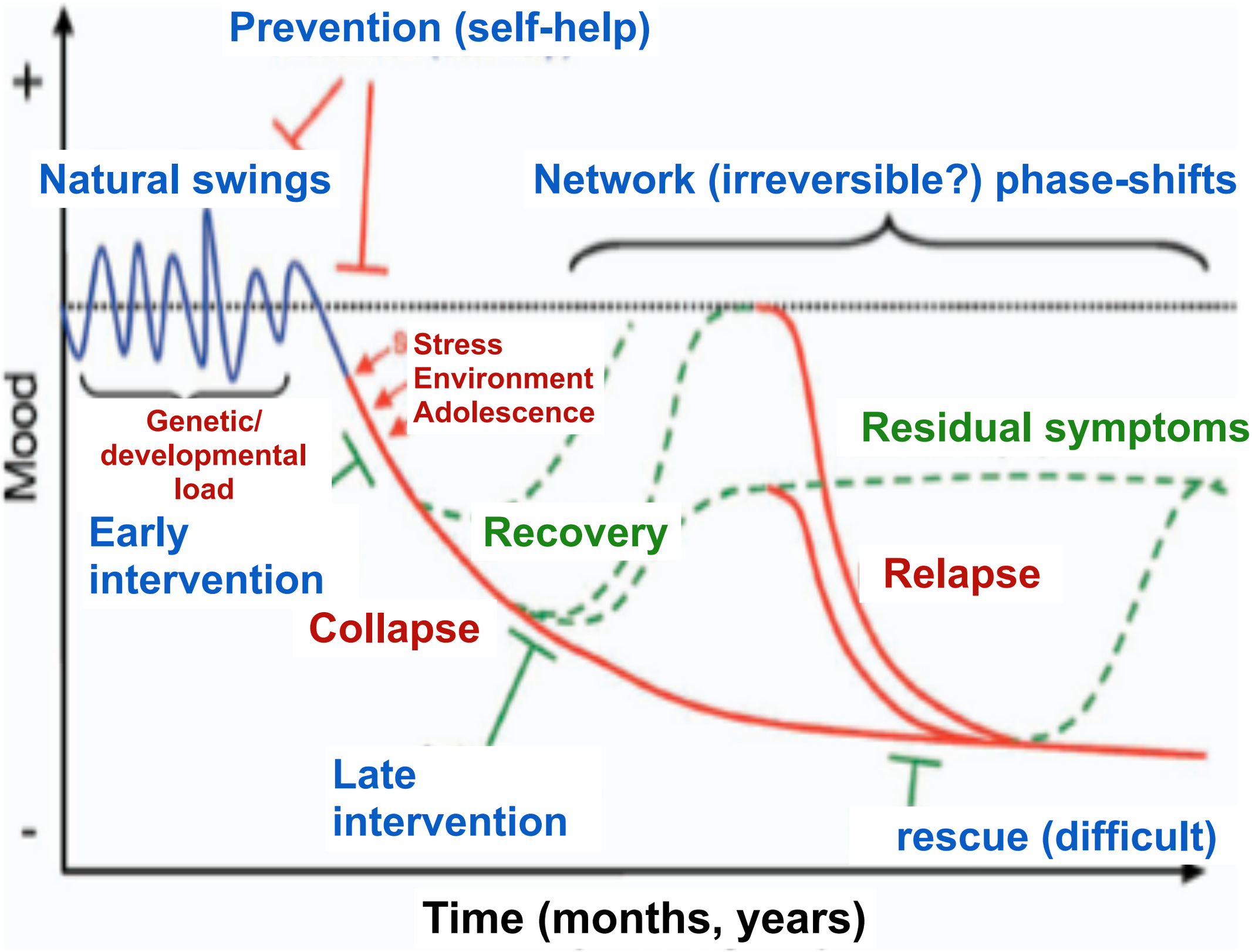
Psychomotor agitation/ Retardation

Suicidality

Sleeplessness

Etiology → **Pathophysiology** → **Clinical Phenotype**

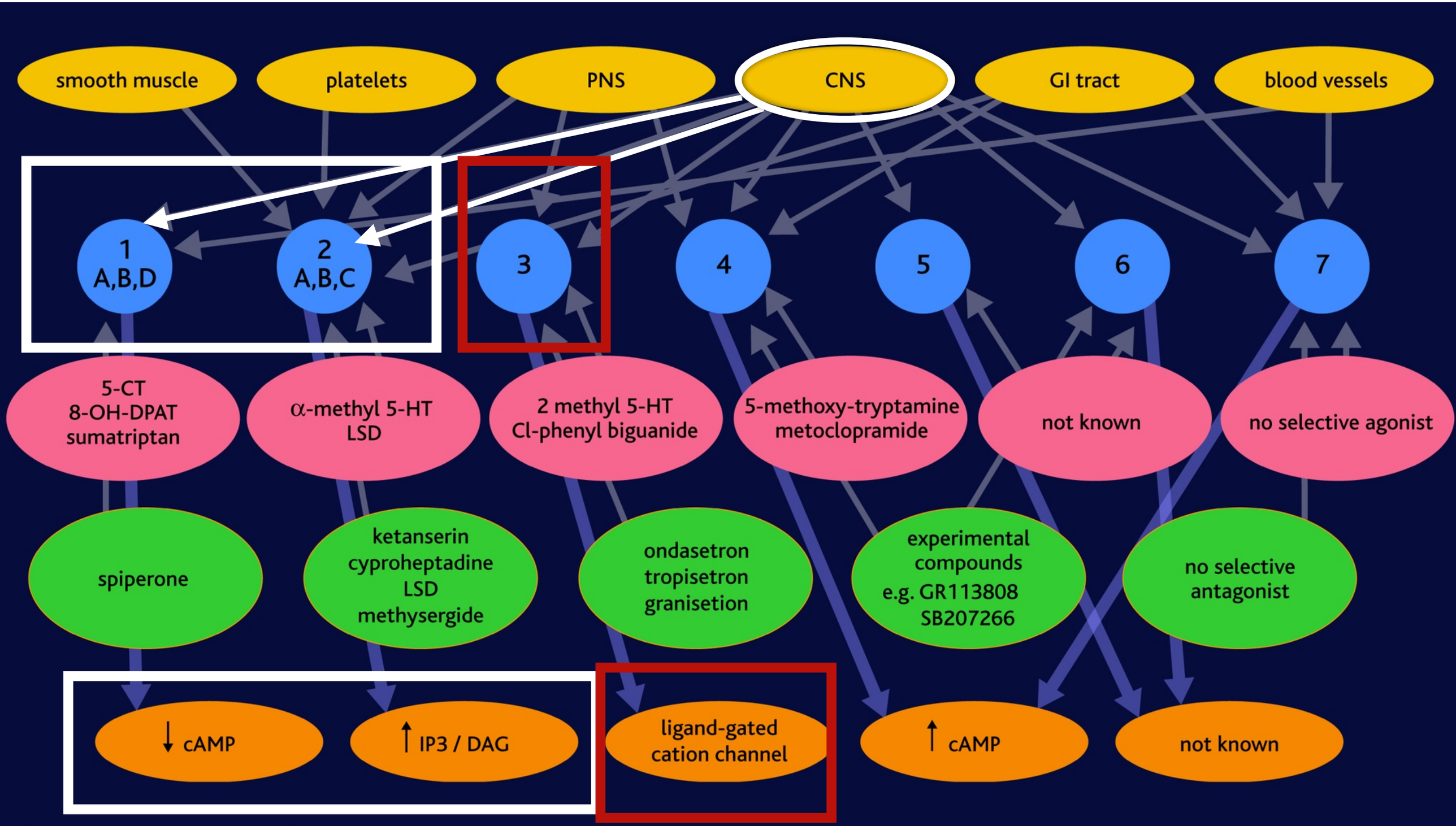
The life-cycle of major depression and its treatment



Antidepressant drugs: Main mechanisms of action

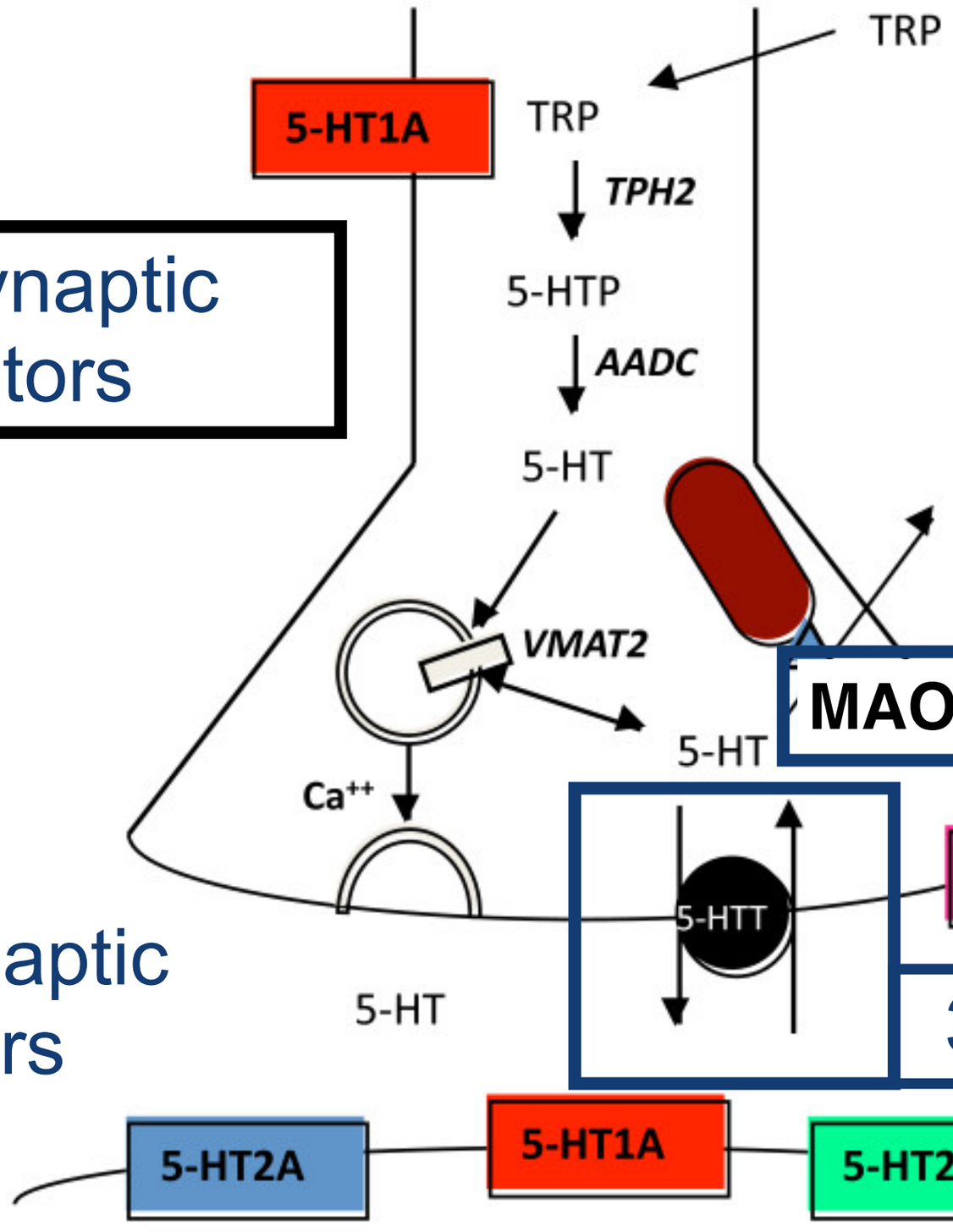
- Inhibition of 5-HT and NA re-uptake
- 5-HT_{1A} and NA pre-synaptic (Autoreceptors) blockade
- 5-HT_{1A} post-synaptic receptors activation
- 5-HT_2 post-sinaptic receptors blockade
- Inhibition of mono amino oxidases (MAO)

Serotonin receptors classification



5-HT receptors expression and the presynaptic regulation of 5-HT levels

1. Presynaptic receptors

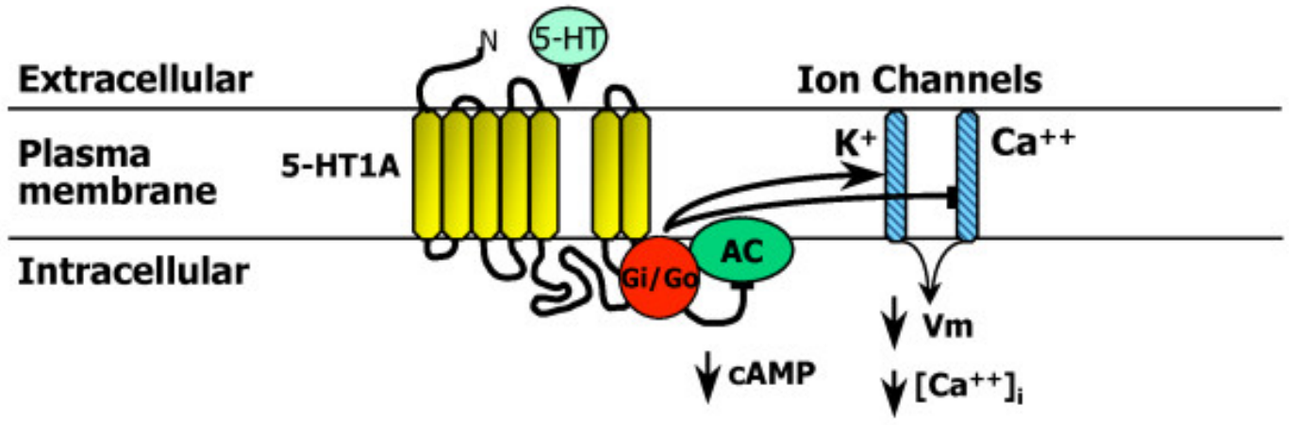


Selective Serotonin Re-uptake Inhibitors (**SSRI)**

2. Postsynaptic receptors

3. 5-HT transporters

5-HT1A receptor signalling



Coupled to inhibitory G proteins (Gi/Go)

- inhibit adenylyl cyclase (AC)
- open G-protein inward rectifying potassium channels (K+) to reduce membrane potential (Vm)
- inhibit voltage-gated calcium channels (Ca++) and reduce intracellular free calcium concentration ([Ca++]i).

Presynaptic 5-HT1A somatodendritic **autoreceptors** expressed on 5-HT neurons act as a "brake" to inhibit the activity of the entire 5-HT system

In depressed individuals:

the expression of pre-synaptic 5-HT1A autoreceptors is increased

with reduced release of 5-HT by serotoninergic neurons

the expression of post-synaptic 5-HT1A receptors is reduced

with reduced response of the post-synaptic neurons to 5-HT

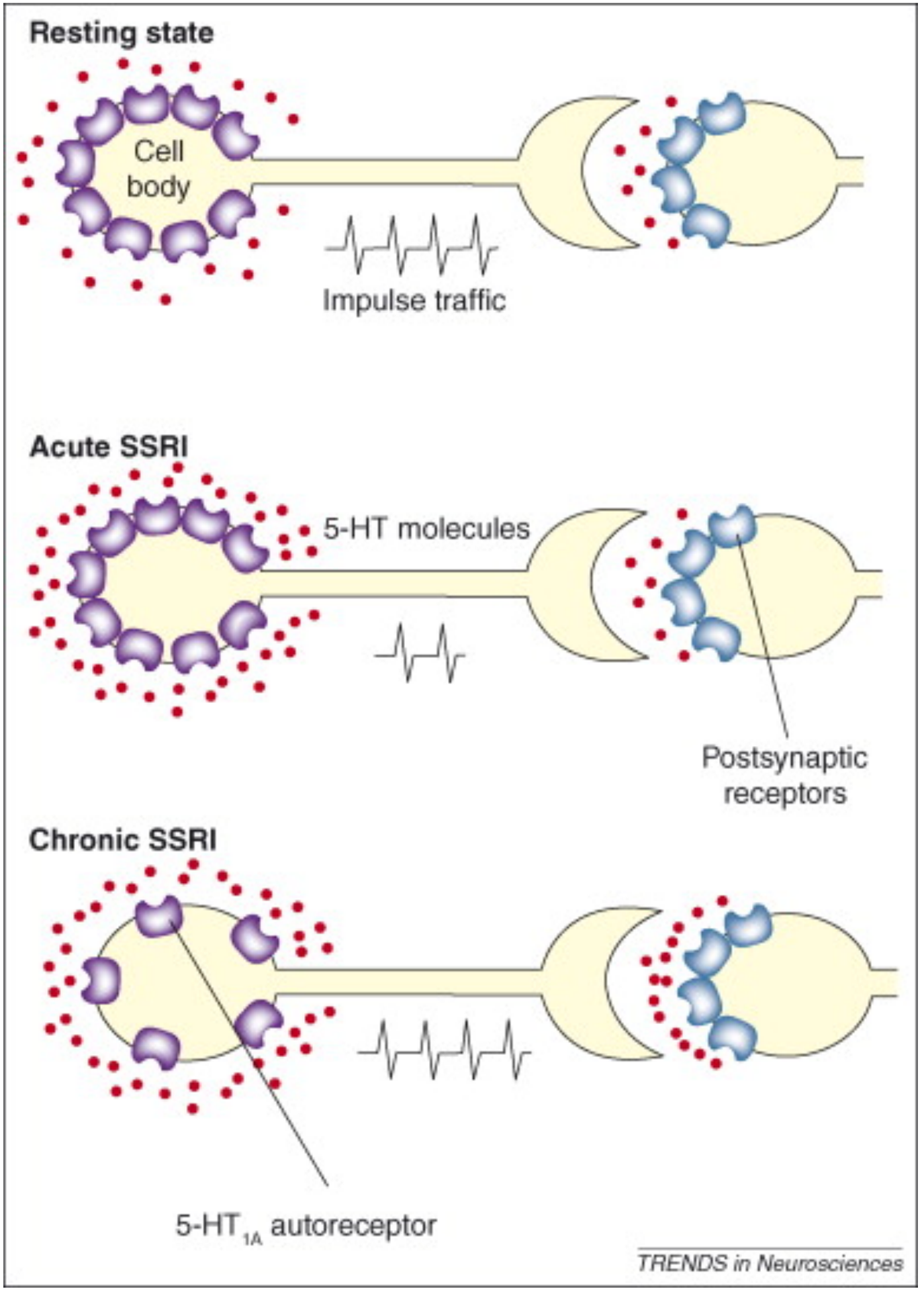
In agreement with the Monoamine Theory of Depression, a strategy for restoring the activity of the serotoninergic neurons is to block the re-uptake of 5-HT

Selective Serotonin Re-uptake Inhibitors (**SSRI)**

SSRIs mechanism of action:

Acute SSRIs:
SSRIs rapidly block 5-HT reuptake and cause an increase of 5-HT synthesis and release
5-HT1A autoreceptors on serotonin synapses detect excess serotonin and reduce serotonin release

Chronic SSRIs:
causes a gradual **downregulation** of 5-HT1A autoreceptors with gradual increase of
5-HT release



SSRI treatment

SSRIs take 3 or more weeks to take effect and this depends on two slow changes in the brain:

1. Desensitization and downregulation of 5-HT1A autoreceptors with increased release of 5-HT

2. Release of BDNF which promotes neuron growth and survival

Presynaptic 5-HT1A receptors delay antidepressant response but are also primarily responsible for the **therapeutic** effect

Postsynaptic 5-HT2 receptors are primarily responsible for the **adverse** effects due to the increased intrasynaptic serotonin levels

Antidepressant drugs

Five Categories

1. Tricyclics (Serotonin and Noradrenaline reuptake inhibitors, SNRI)
2. Monoamine oxidase inhibitors (MAOI)
3. Selective serotonin reuptake inhibitors (SSRI)
4. Atypical – DARIs (dopamine reuptake inhibitors)
5. Newest

Newest antidepressants

1. **2 nd generation SNRIs** (serotonin and noradrenaline reuptake inhibitors) e.g. Venflaxine

2. **SARIs (**serotonin reuptake inhibitors and receptor antagonists) e.g. Nefazodone

3. **NaSSAs** (noradrenaline reuptake inhibitors and specific serotonergic antidepressants) e.g. Mirtazapine

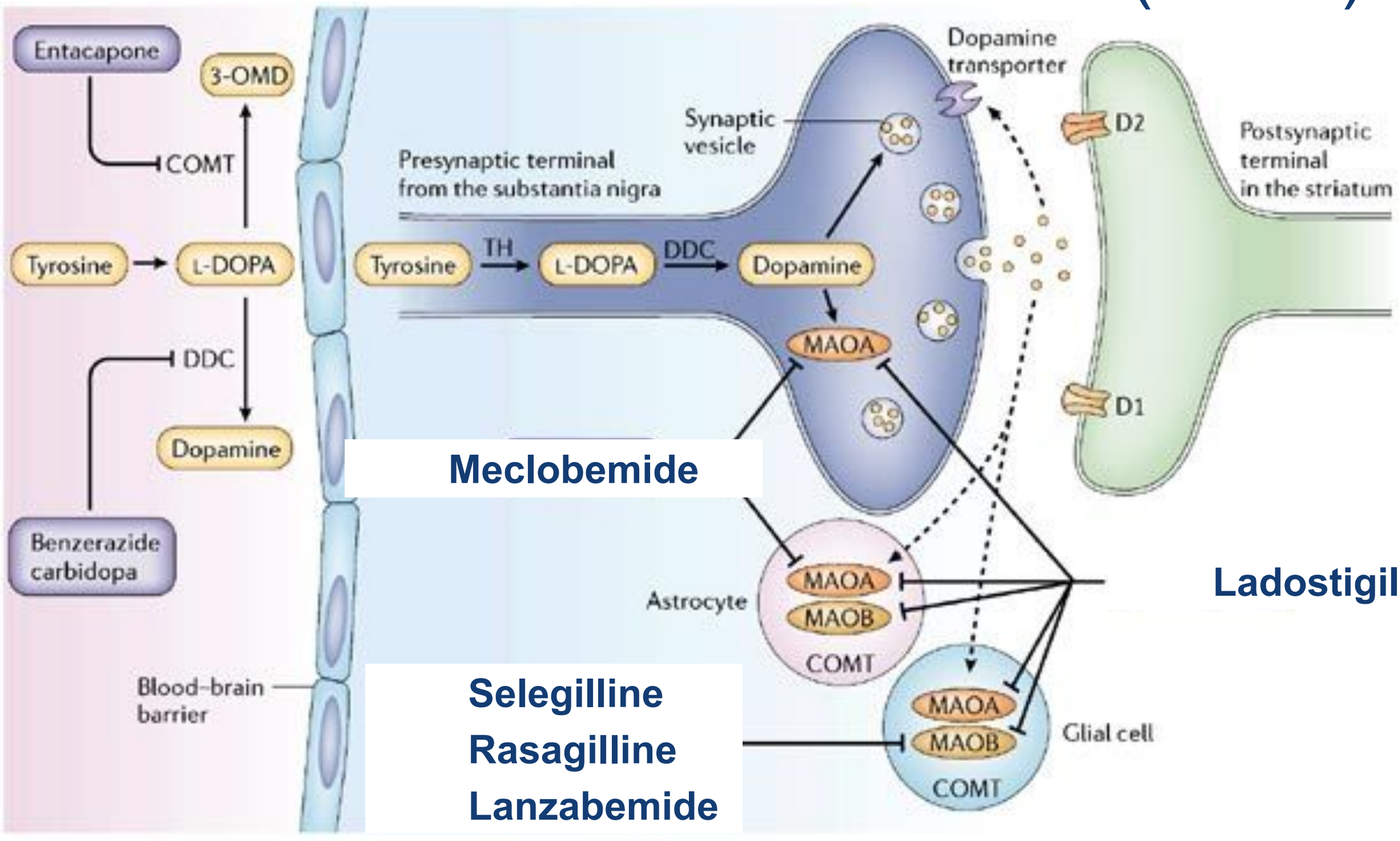
4. **NaRIs** (selective noradrenaline reuptake inhibitors) e.g. Reboxetine

TRICYCLICS (TCAs): 1st generation of SNRI's (Serotonin/Norepinephrine Reuptake Inhibitors)

Mechanisms	Drugs
5-HT and NA reuptake inhibition 'SARI' (5-HT_2 antagonism) Histamine and muscarinic receptors antagonists	Amitriptyline Amoxapine Desipramine Doxepine **Imipramine** Nortriptyline

Advantages	Disadvantages
Low cost Long clinical history Subset efficacy: Chronic pain (amitriptyline) Dyspepsia (doxepine)	Lethal in overdose (↑QT_c) Sexual dysfunction Weight gain Anticholinergic (sedation, constipation, dry mouth)

MonoAmino Oxidase Inhibitors (MAOI)



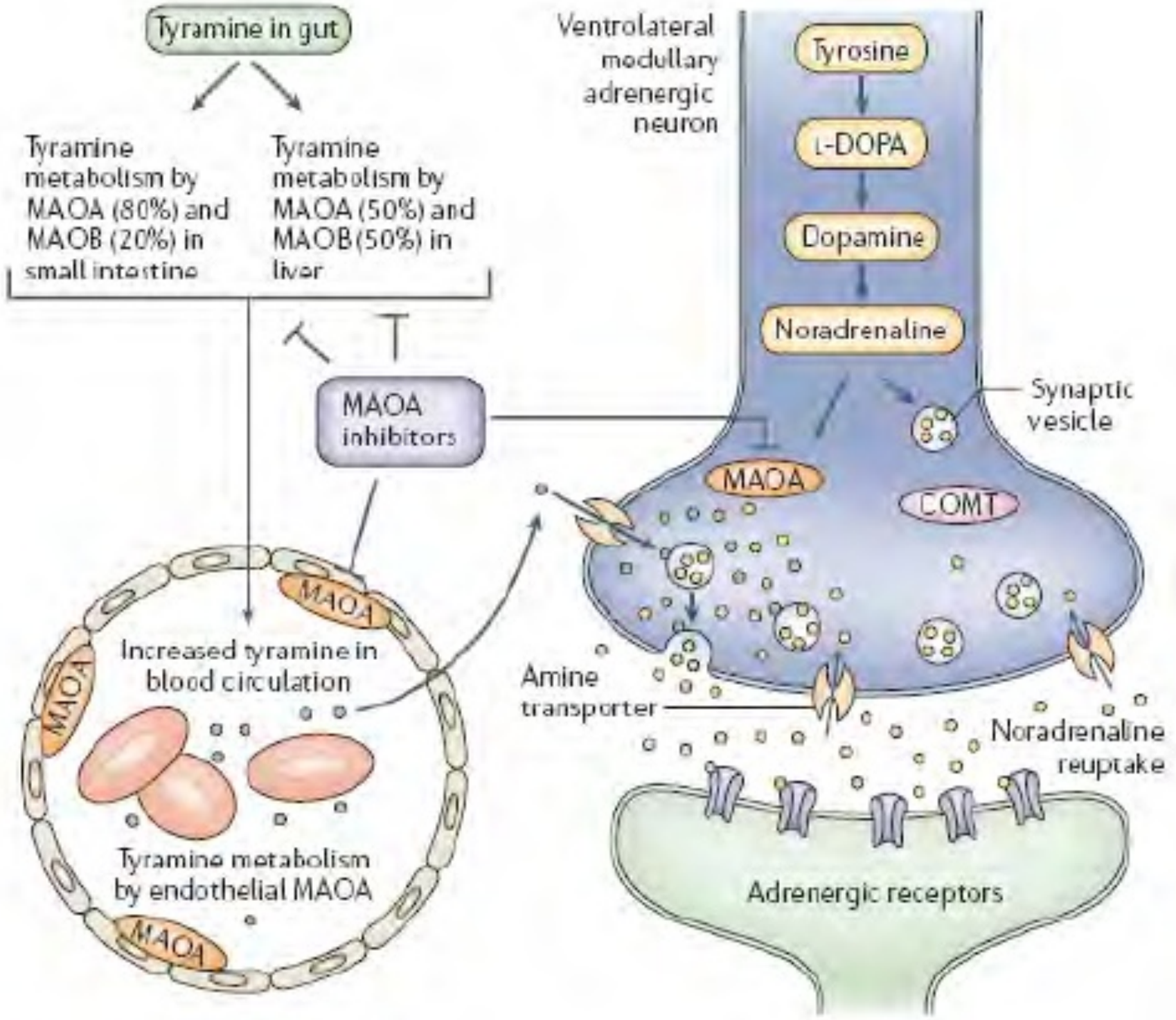
Selectivity	Clinical use
MAO-A: 5-HT > NA >> DA	Depression
MAO-B: DA>> 5-HT = NA	Parkinson's disease

MAO-A Inhibitors (MAOI)

Mechanisms	Drugs
Inhibit monoamine oxidase Results in ↑ NE and 5-HT	Irreversible Phenelzine Tranycypromine Isocarboxazid Reversible (RIMA's) **Meclobemide**

Advantages	Disadvantages
Subset efficacy: Panic disorder Social phobia	Dietary restrictions (cheese, red wine): tyramine and consequent hypertension

The mechanism of potentiation of cardiovascular effects of tyramine: the cheese effect



 Nature Reviews Neuroscience, 7:295, 2006

ATYPICAL - DARIs

Mechanisms	Drugs
Dopamine (and NA) but not serotonin uptake inhibition Presynaptic release of DA and NA	bupropion

Advantages	Disadvantages
Subset efficacy: Smoking cessation	Convulsions Nervousness

Selective Serotonin Reuptake Inhibitors "SSRI's"

Mechanisms	Drugs
5-HT reuptake inhibition Stimulation of neurosteroids synthesis?	Citalopram **Fluoxetine** (Prozac®) Fluvoxamine Paroxetine Sertraline

Advantages	Disadvantages
Safety **Anxiolysis** Side effect profile favorable: Low incidence of weight gain ↓ Anticholinergic effects	nausea, headache sexual dysfunction

Symptoms and CNS Disorders Frequently associated with Major Depression

	Depressed Mood	Anxiety	Cognitive Perturbation	Reduced Sleep Quality	Sexual Dysfunction	Pain
Depression	+++	++	++	++	+	+
Anxiety	++	+++	++	++	+	+
Schizophrenia	+	+	++	+	+	+
Parkinson's	++	+	++	++	++	++
Alzheimer's	+	+	+++	++	-	-
Epilepsy	+	+	++	++	+	+
Chronic pain	++	++	+	++	++	+++
Stroke	++	+	+++	+	+	++

2nd gen. SNRI's
(Serotonin and Norepinephrine Reuptake Inhibitors)

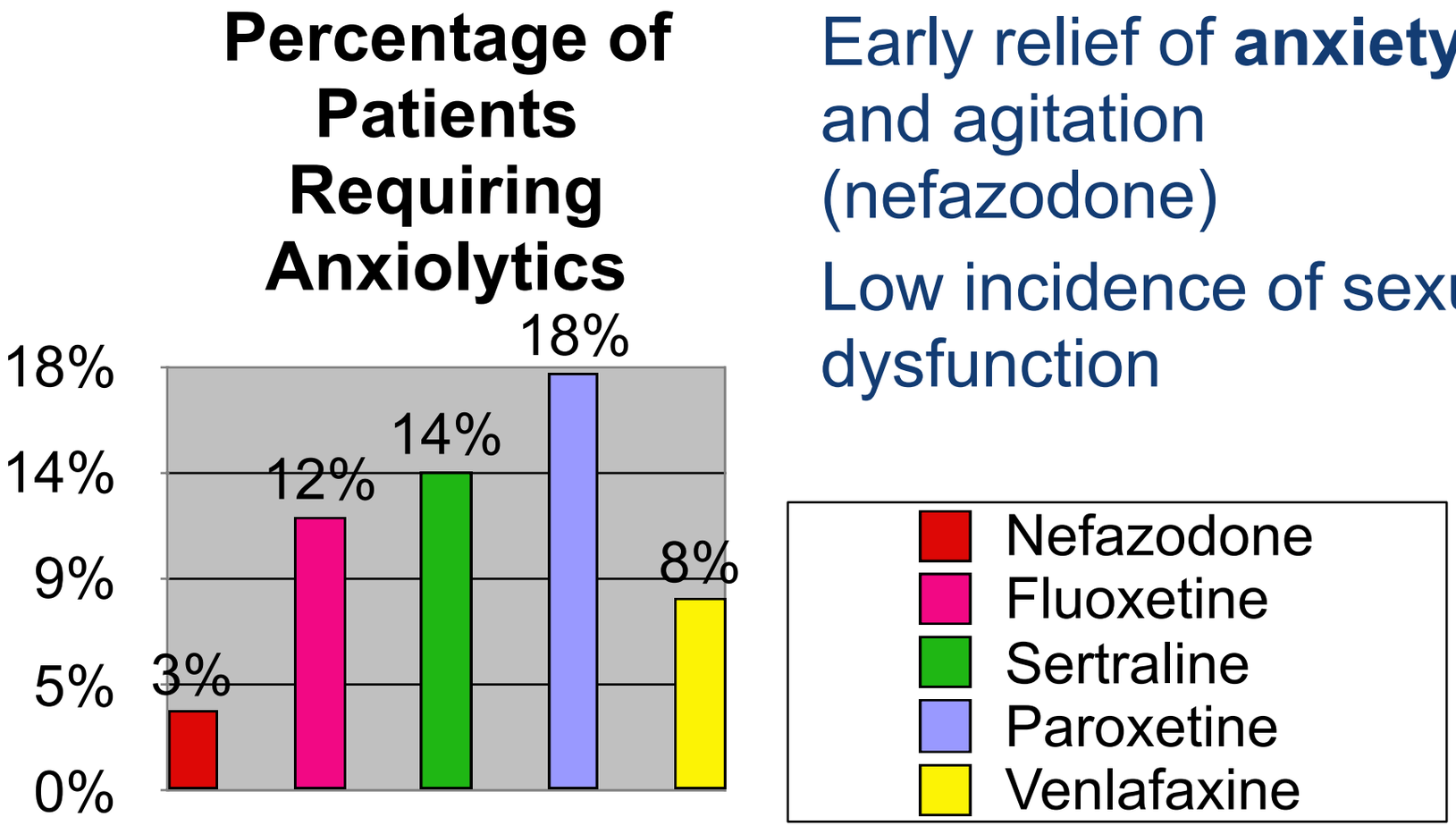
Mechanisms	**Drugs**
Serotonin and NA uptake inhibition	Venlafaxine Milnacipram

Advantages	**Disadvantages**
Anxiolysis Subset efficacy: chronic pain bipolar disorders	Weight gain Sexual dysfunction NE side effects: Tachycardia Hypertension Anticholinergics: Constipation

SARI's
Serotonin Antagonist/ Reuptake Inhibitors

Mechanisms	Drugs
5-HT reuptake inhibition 5-$HT_{2a, 2c}$ antagonism	**Nefazodone** Trazodone

Advantages	Disadvantages
Early relief of **anxiety** and agitation (nefazodone) Low incidence of sexual dysfunction	Sedation



NaSSA's
(Noradrenergic Specific Serotonergic Antidepressants)

Mechanisms	Drugs
$5HT_{2a,c}$ $5HT_3$ antagonism α_2 inhibition (blocks NA 'brakes')	Mirtazapine Risperidone Olonzapine

Advantages	Disadvantages
Anxiolysis (5-HT2 blockade) Low incidence of sexual dysfunction (selective blockade) Low incidence of nausea and vomiting (5-HT3 blockade) Fast onset of action	Sedation Weight gain due to: H_1 antagonism $5HT_{2c}$ antagonism

NaRIs
Noradrenaline reuptake inhibitors

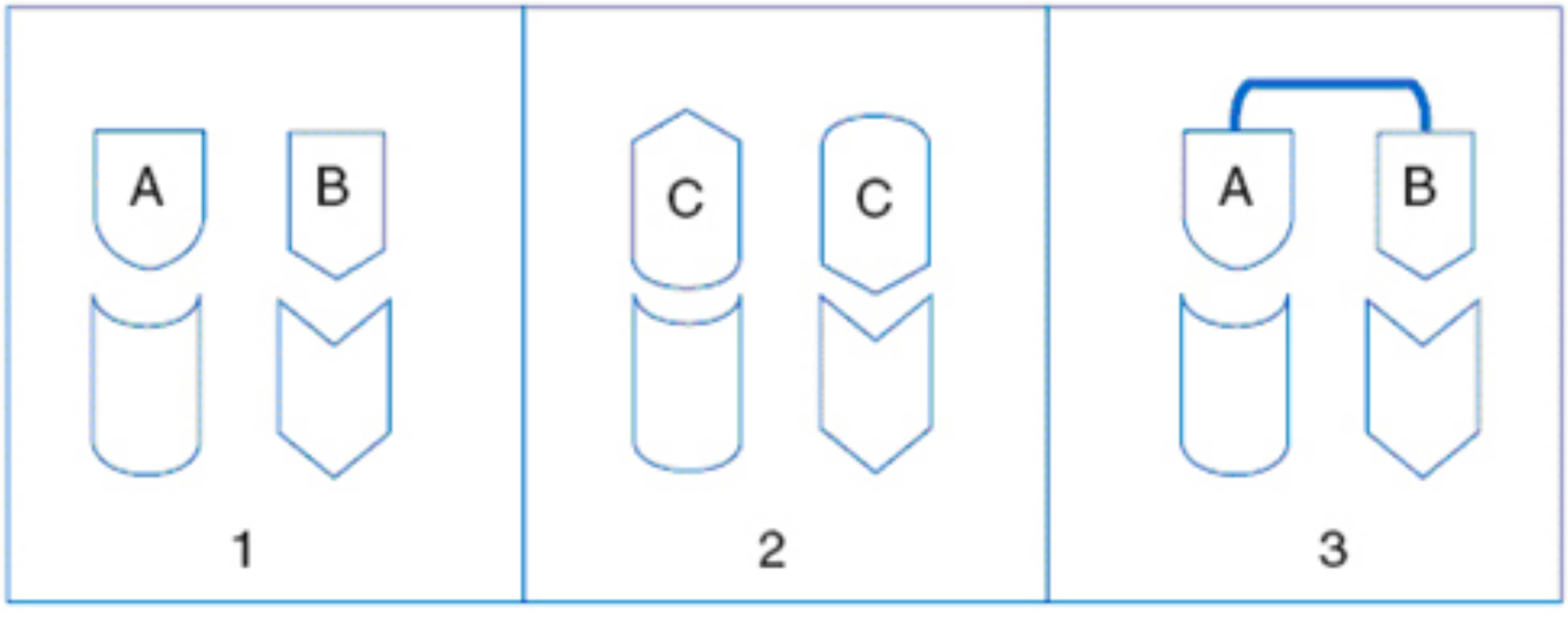
Mechanisms	Drugs
NA reuptake inhibition	Reboxetine
Advantages	**Disadvantages**
?	No more effective than NSRIs

5-HT_1 Agonists

Mechanisms	Drugs
Agonists at $5HT_1$	Buspirone Ipsapirone Gepirone
Advantages	**Disadvantages**
Anxiolysis	No proven efficacy as single agents for depression

The Multitargetig approach:
Dual- and Triple-acting antidepressants

Multitarget drugs have complementary components of action and may be more effective (synergism) and better tolerated than their highly selective counterparts

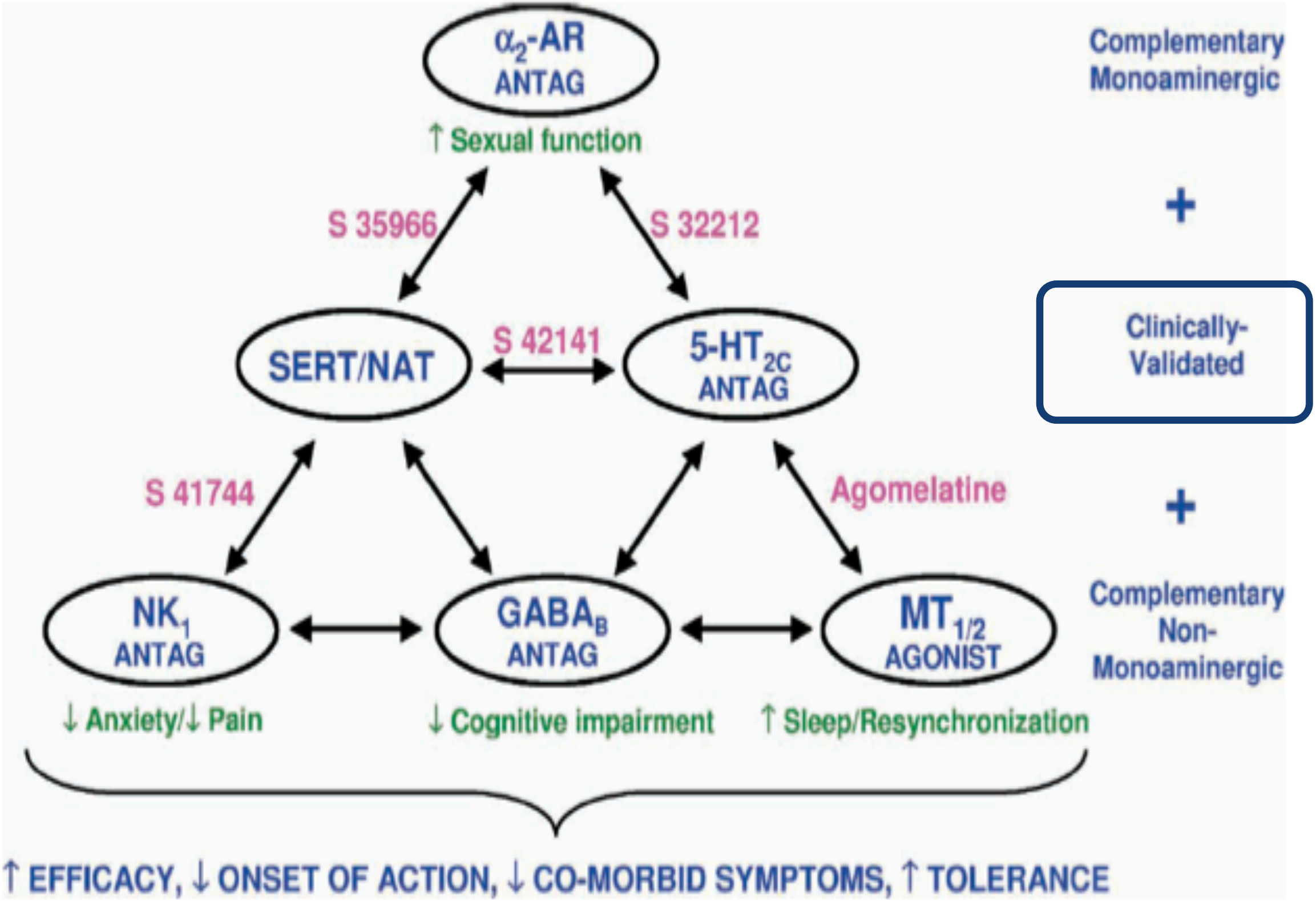


Administration of two different drugs (A and B)

Administration of a non-selective *bifunzional drug* (C)

Administration of a *bivalent drug (two drugs,* A and B, liked by a spacer)

Dual- and Triple-acting antidepressants



Nonmonoaminergic mechanisms for treatment of depression

CRF: corticotrophin releasing factor

GR: glucocorticoid receptor

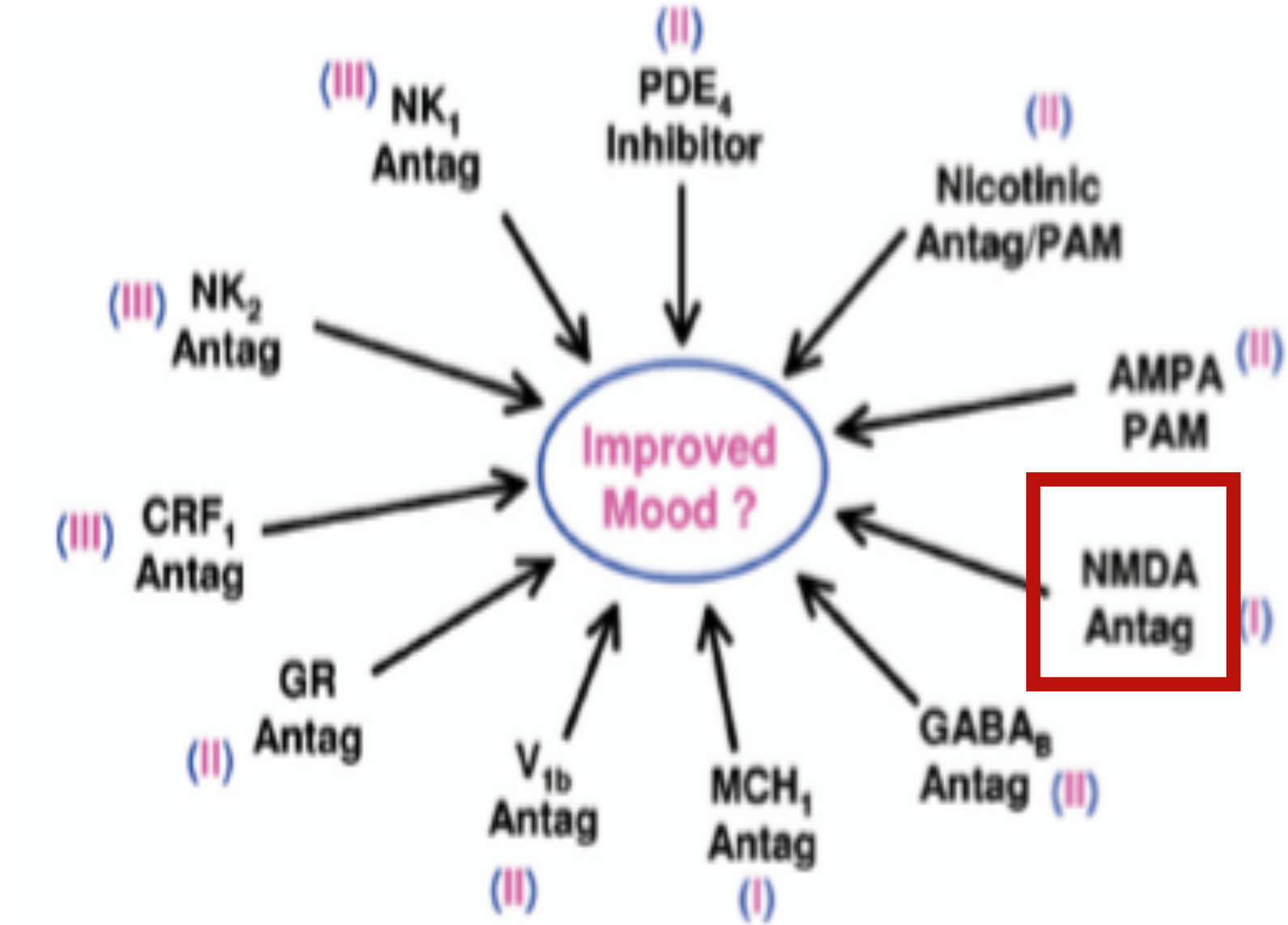
MCH: melanin concentrating hormone

NK: neurokinin

PAM: positive allosteric modulator

PDE: phosphodiesterase

V: vasopressin

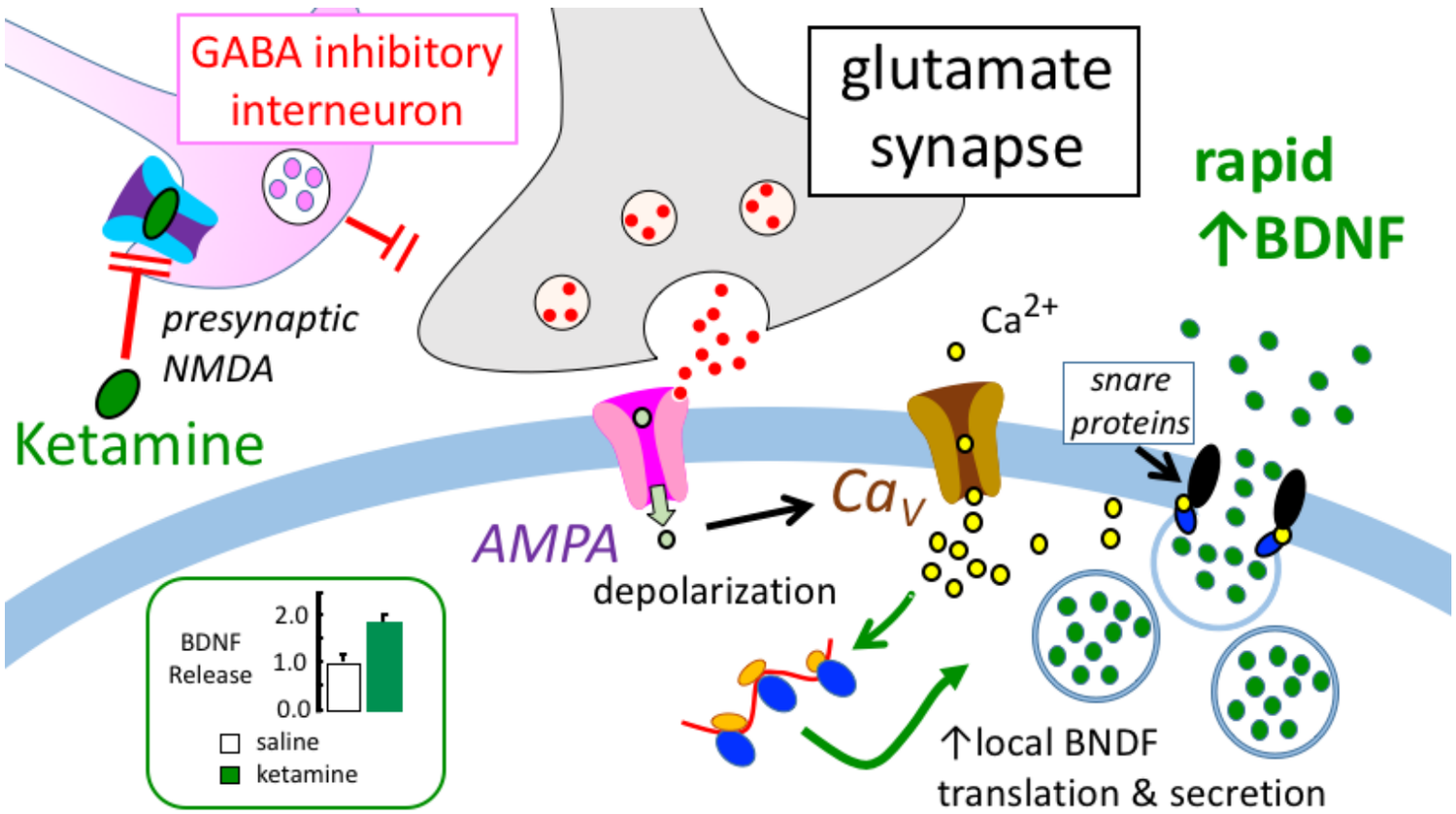


Only selective drugs to date

- No drug has reached the market
- No proof (yet) for ↑efficacy/↓delay
- Uncertain control of co-morbid symptoms

Complementary multi-target strategies

Ketamine is fast-acting antidepressant agent



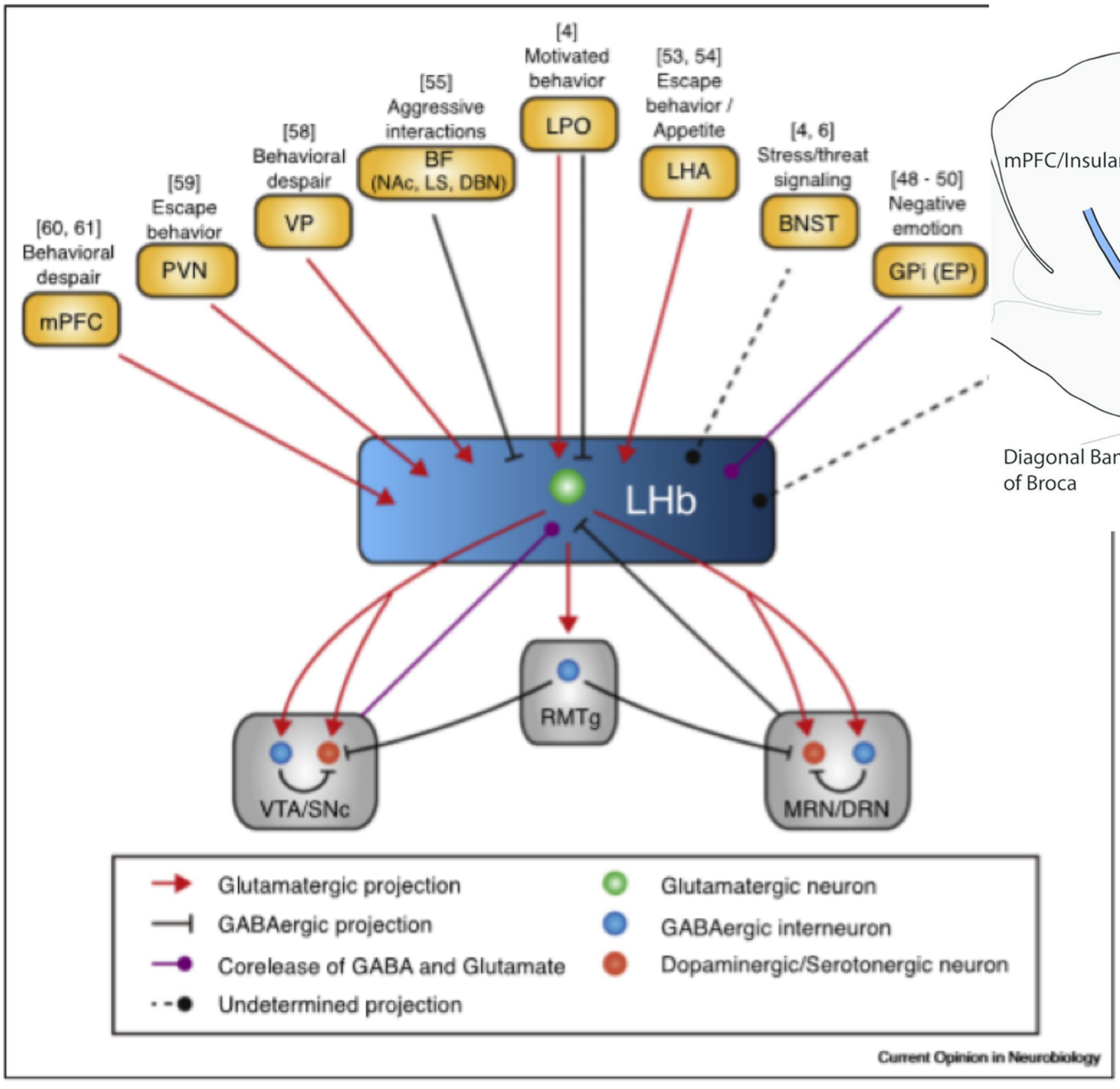
Spravato (Esketamine)

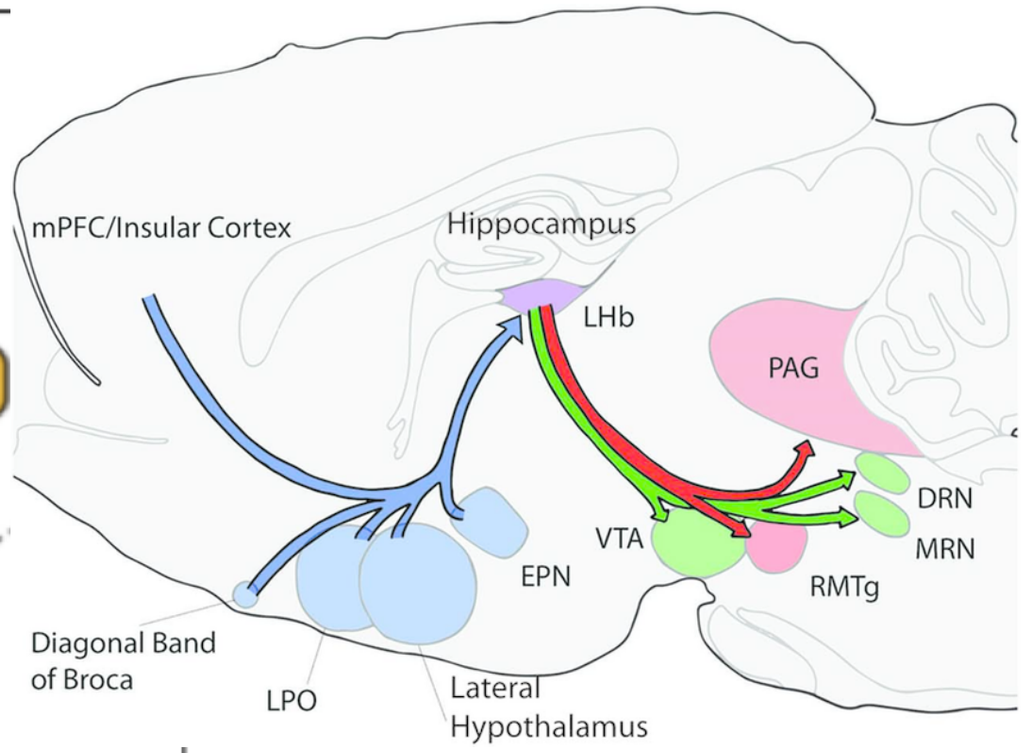
is a related form of Ketamine

It is FDA Approved for

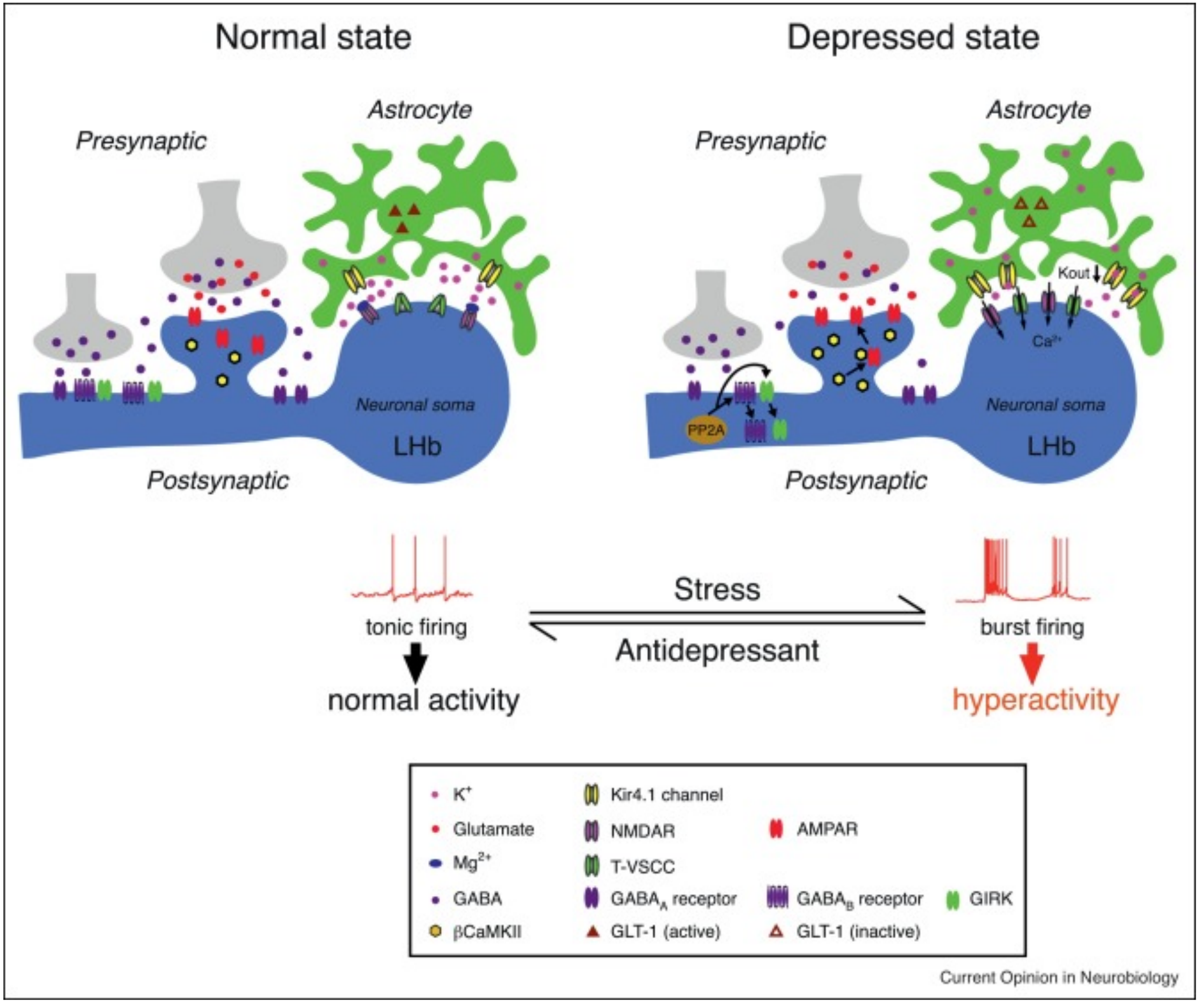
Treatment Resistant Depression

The role of Lateral Habenula in depression





The lateral habenula (LHb) is the "anti-reward" center, involved in processing aversive stimuli



Ketamine blocks NMDAR-dependent bursting activity of LHb neurons to disinhibit downstream monoaminergic reward centres and quickly elevates mood

Bipolar Disorder

Mania -

- Feeling very high on life
- Talking rapidly
- Feeling grandiose
- Racing thoughts and speech
- Erratic and impulsive actions
- Delusions and hallucinations (severe)

Hypomania -

- Like but less severe that mania
- Euphoric, energetic and productive
- No hallucinations or delusions
- Characterized by an unusually good mood

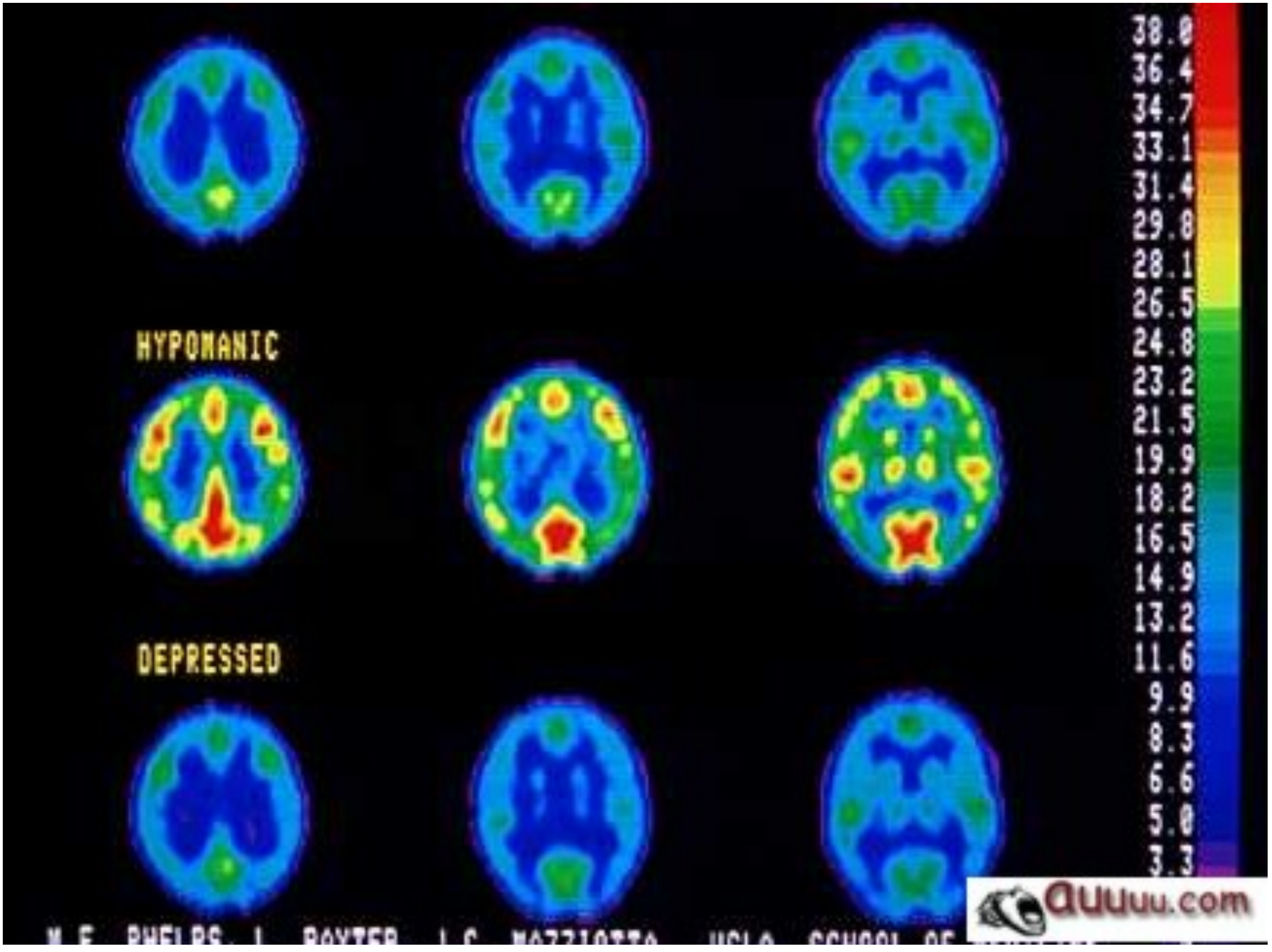
Severe Mania

Hypomania (mild to moderate)

Normal/balanced mood

Mild to moderate Depression

Severe Depression



Brain scans indicating the differences in brain activity when a patient is switching between a depressive episode and hypomanic episode

Mood Stabilizers For Bipolar Disorders

Lithium Carbonate

Anticonvulsants:

Carbamazapine

Valproic Acid

Lamotrigine

Topiramate

Proposed signaling mechanisms underlying lithium's neuroprotective effects