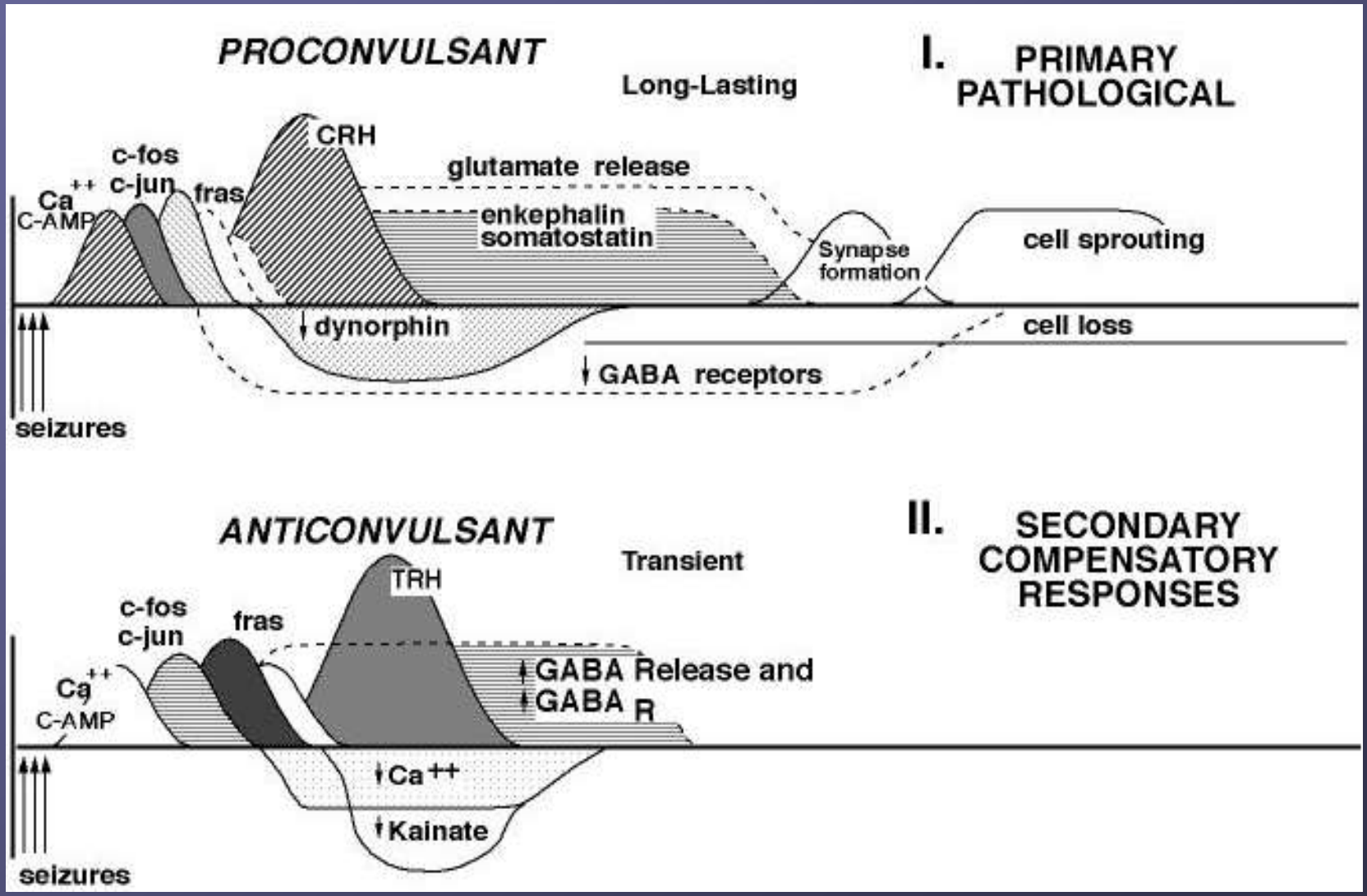
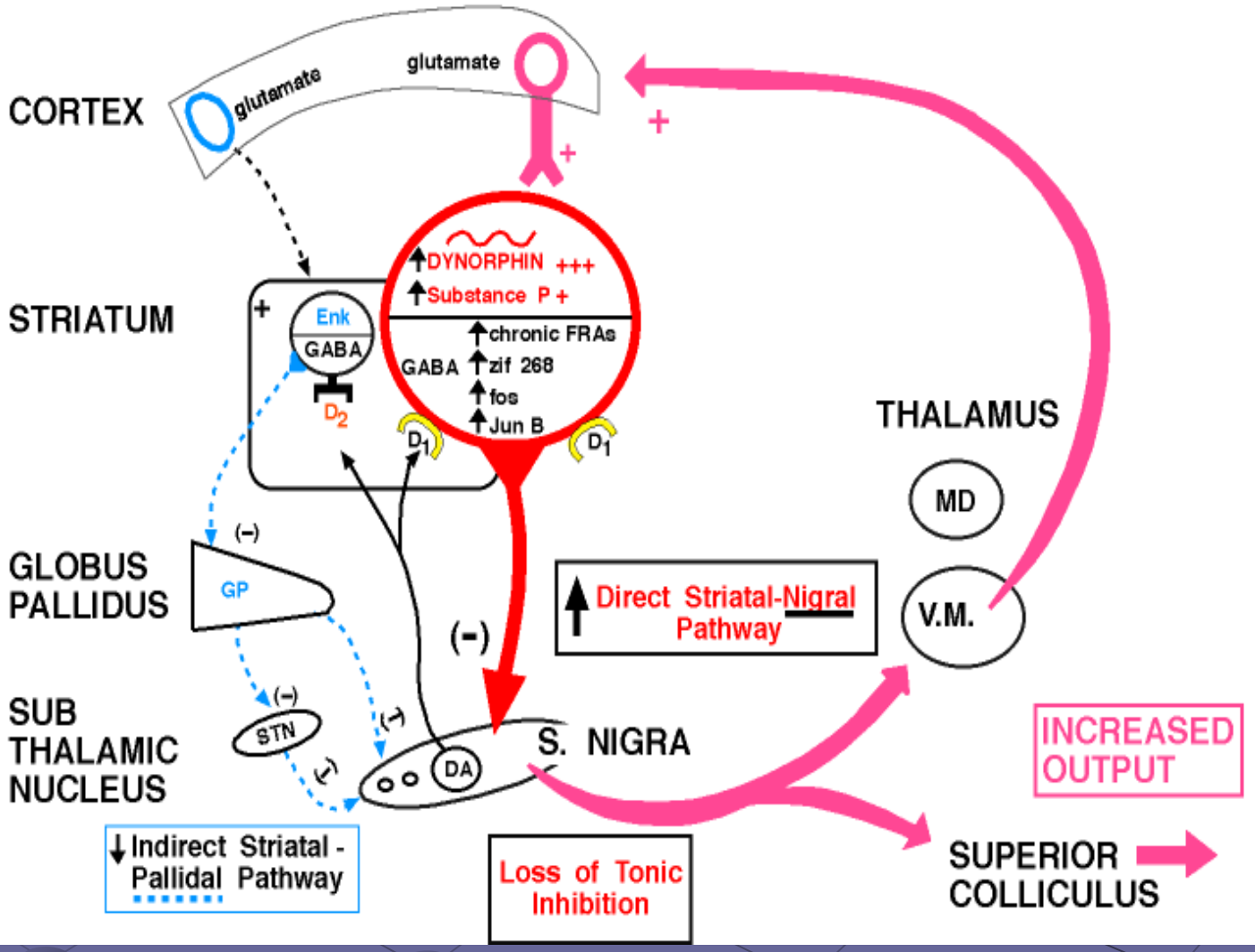
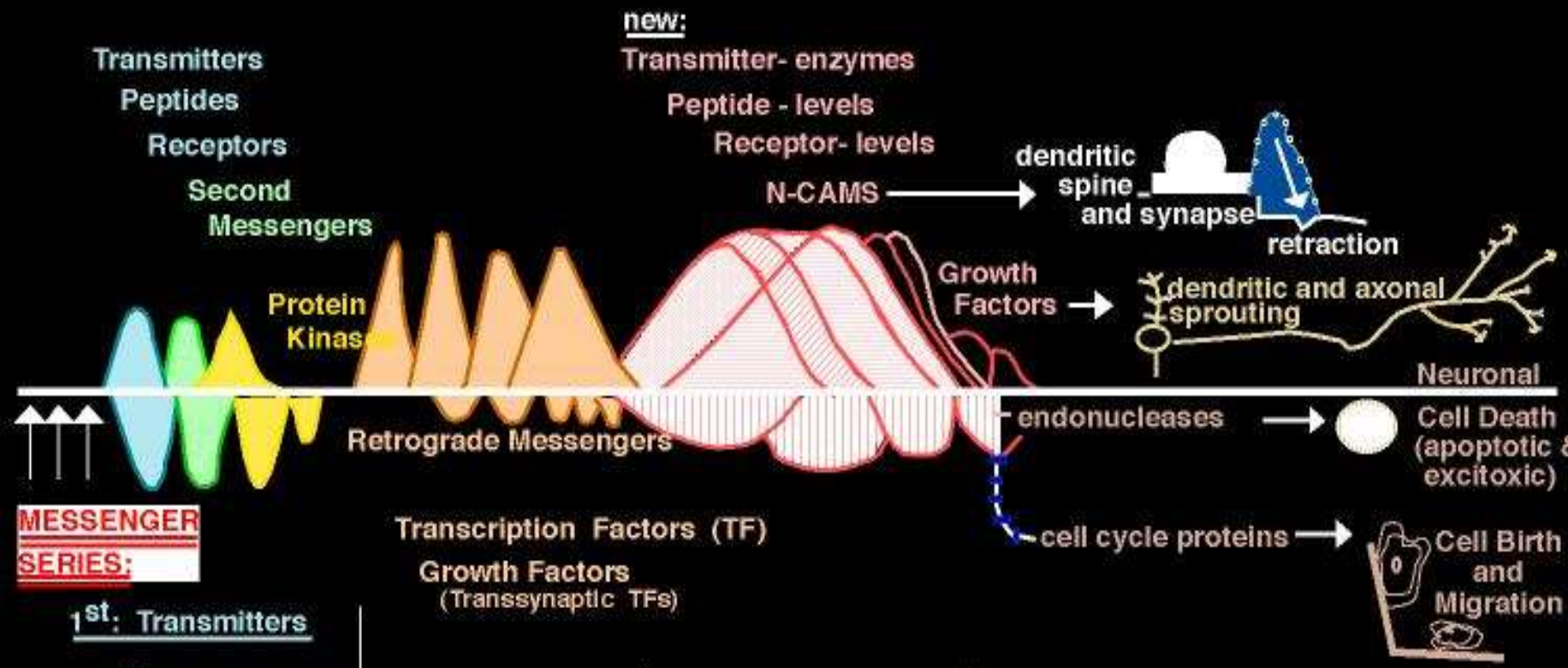
Competing pathological and adaptive endogenous responses to kindled seizures



COCAINE REPROGRAMS THE GENETIC MACHINERY OF THE DIRECT STRIATAL OUTPUT PATHWAY INCREASING MANIC SEVERITY & DYSPHORIA



REMODELING THE CENTRAL NERVOUS SYSTEM BASED ON EXPERIENCE



Signaling Pathways for Neurotransmitter Control of Gene Expression

Extracellular Stimuli
Neurotransmitters, Hormones, Growth Factors

Receptors

Transducers
G proteins, Ion Channels, Phospholipases
(cAMP, DAG, PIP2, NO, etc)

Signal Transduction to the Nucleus
Protein kinases

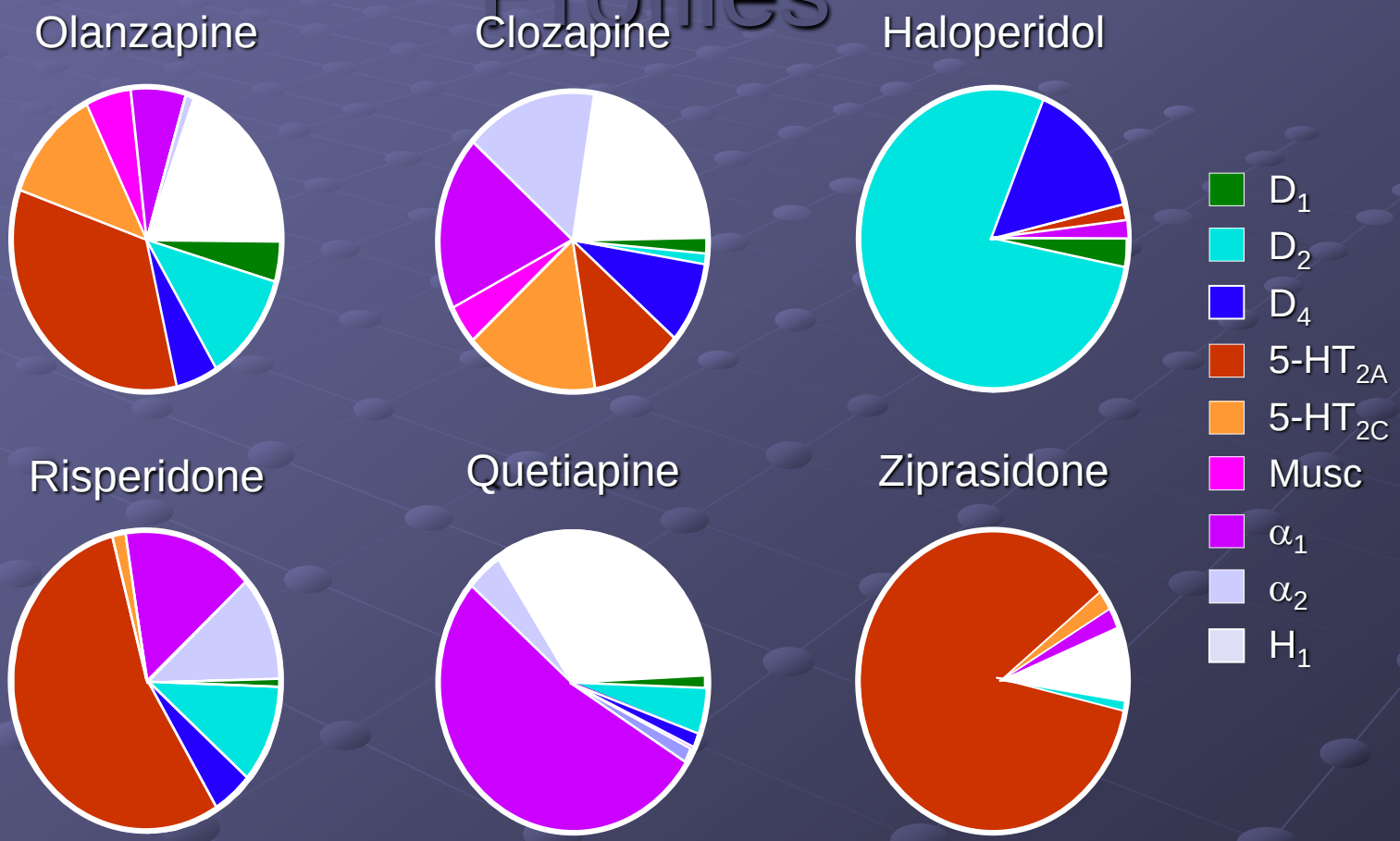
Transcription Factors
(PKA, PKC, CaMPKII, MAPK, etc)

Immediate Early Genes
Third messengers
(c-fos, fos B, etc)

Late Genes
(AP1, AP2, etc)

Protein Synthesis

Antipsychotic Profiles In Vitro Receptor-Binding Profiles



Collaborative Working Group on Clinical Evaluations. *J Clin Psychiatry.* 1998;59(suppl 12):3-9.

BIPOLAR DISORDER

Second Generation Antipsychotics: Side Effect Profile

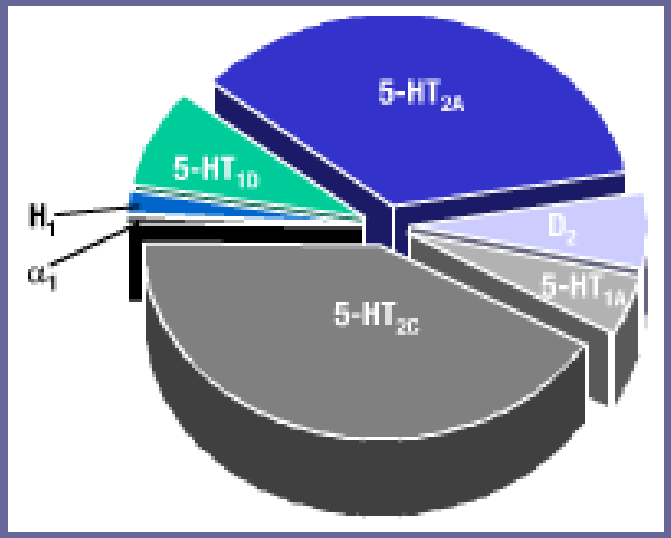
	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
EPS*	0	+	+	0	0/+
Weight gain	+++	+	+++	++	0
Anticholinergic effects	+++	0	++	0	0
Blood dyscrasia	+++	0	0	0	0
LFT elevation	+	0	+	+	0/+
Sedation	+++	+	++	++	++
QT_C	0/+	+	+	+	++

*At appropriate doses; 0 = none; + = mild; ++ = moderate; +++ = substantial

Adapted from Masand PS et al. *Handbook of Psychiatry in Primary Care*. 1998.

ZIPRASIDONE

A Distinct Receptor Profile



In vitro findings may not correlate with clinical results

Pie chart was prepared using data from human disease brain tissue, except bovine brain tissue was used for the 5-HT-$_{1D}$ receptor

Potential associations may be…

Positive symptoms

D_2 – Antagonism
Efficacy in positive symptoms

High 5-HT$_{2A}$ /D_2 – Affinity ratio
Antipsychotic efficacy, reduced EPS (compared to D_2 antagonism alone)

Negative symptoms

5-HT$_{2A}$ – Antagonism
Efficacy in negative symptoms

Overall symptoms

5-HT$_{2C}$ – Antagonism
Antipsychotic activity

Cognitive and depressive symptoms, and symptoms of social impairment

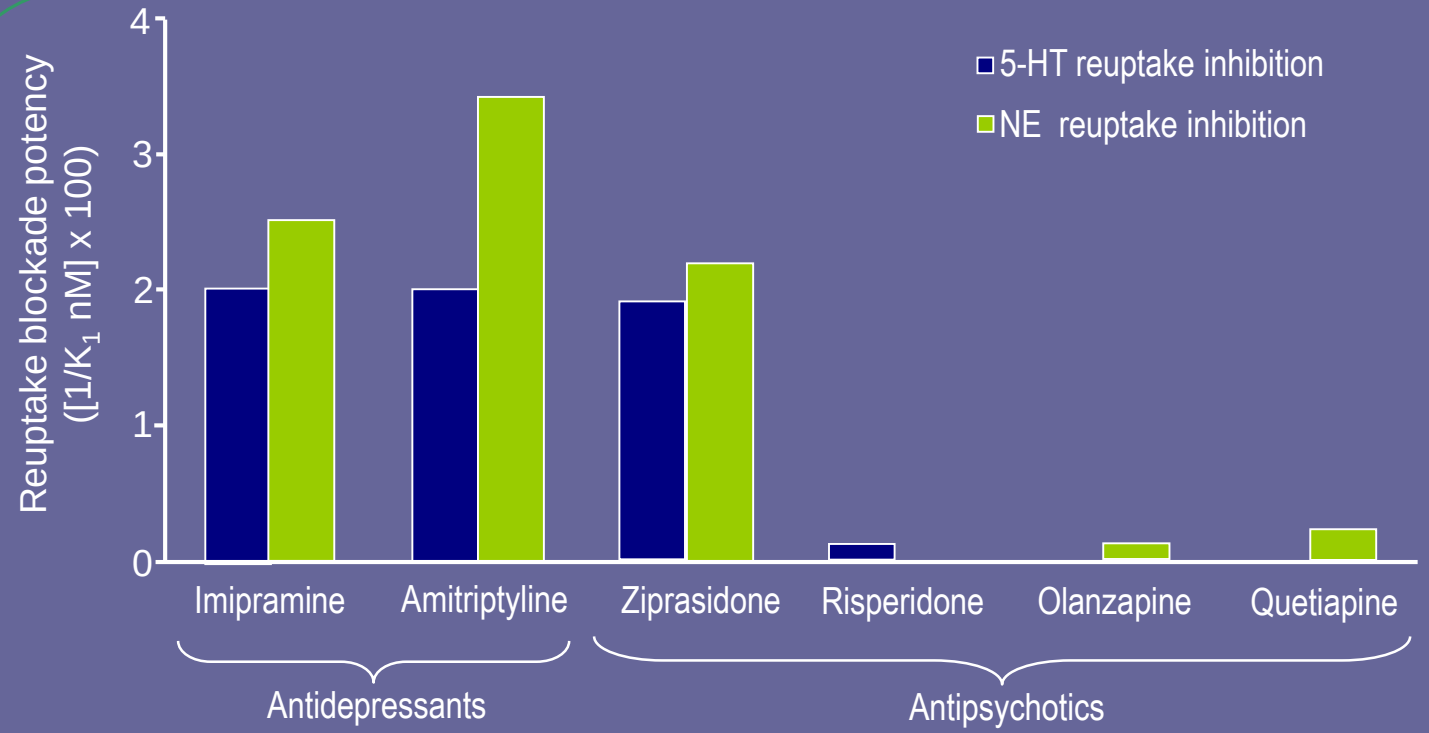
5-HT$_{1A}$ – Agonism
Antidepressant and anxiolytic activity and improved cognition

5-HT$_{1D}$ – Antagonism
Efficacy in depressive symptoms

Schmidt AW et al. *Eur J Pharmacol*. 2001;425:197-201.
Tandon R et al. *J Serotonin Res*. 1997;4:159-177.
Zorn SH et al. In: Palomo T et al, eds. *Interactive Monoaminergic Brain Disorders*. Madrid, Spain: Editorial Sintesis; 1999:377-393.

ZIPRASIDONE

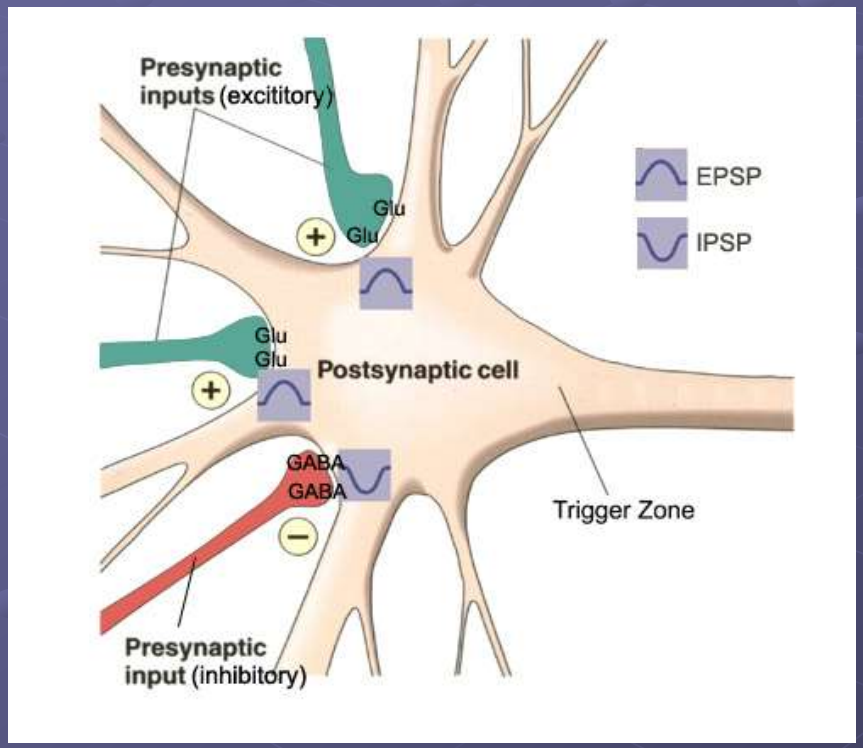
Ziprasidone Pharmacology
5-HT/NE Reuptake Inhibition



- In vitro findings may not correlate with clinical results
- Reuptake into rat brain synaptosomes

Schmidt AW et al. *Eur J Pharmacol*. 2001;425:197-201.
Zorn SH et al, In: Palomo T et al, eds. Interactive *Monoaminergic Brain Disorders*. Madrid, Spain: Editorial Sintesis;1999:377-393.

Schizophrenia and Psychosis



- Differential modulation of these pathways may help explain why some patients develop schizophrenia, while others develop psychosis. It may also help explain the balance between the positive symptoms and negative symptoms of schizophrenia.

Schizophrenic Symptoms

Deficit prefrontal DA

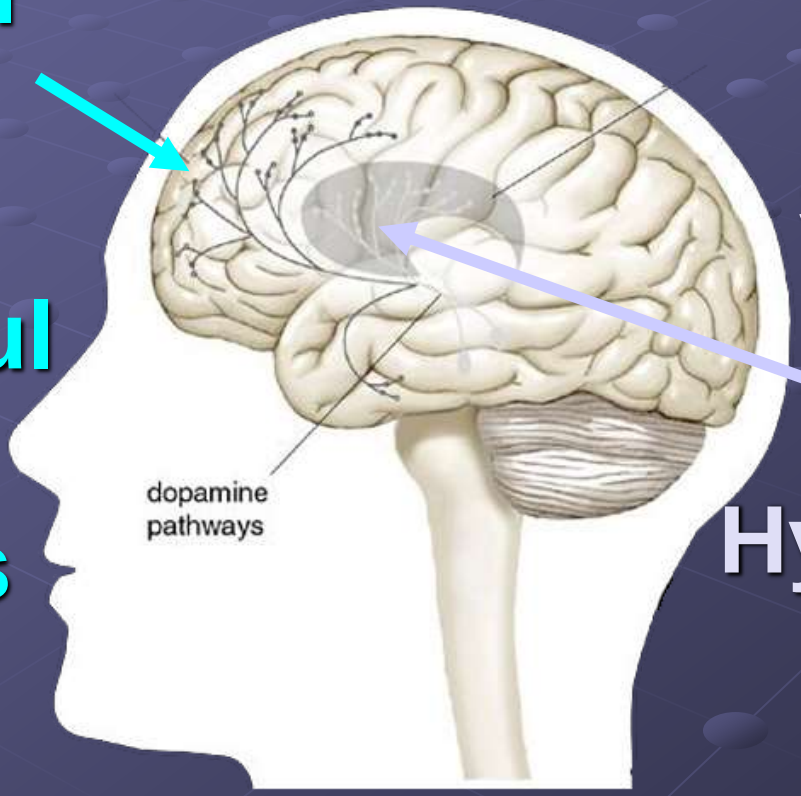
⇩

Hypostimulation D_1 receptors

⇩

Negative symptoms

← **Alterations in PFC synaptic connectivity (NMDA hypofunction)**



Excess subcortical DA

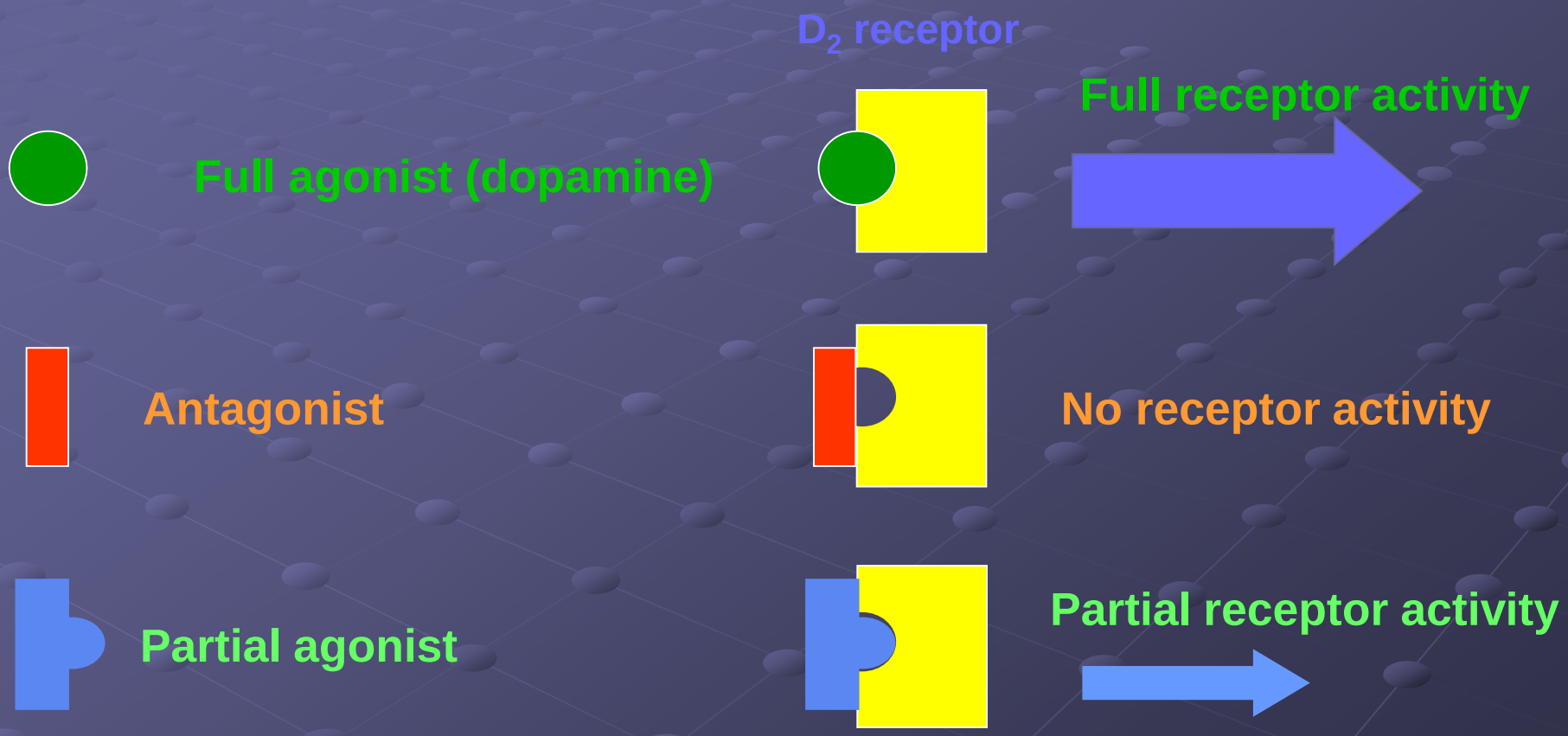
⇩

Hyperstimulation D_2 receptors

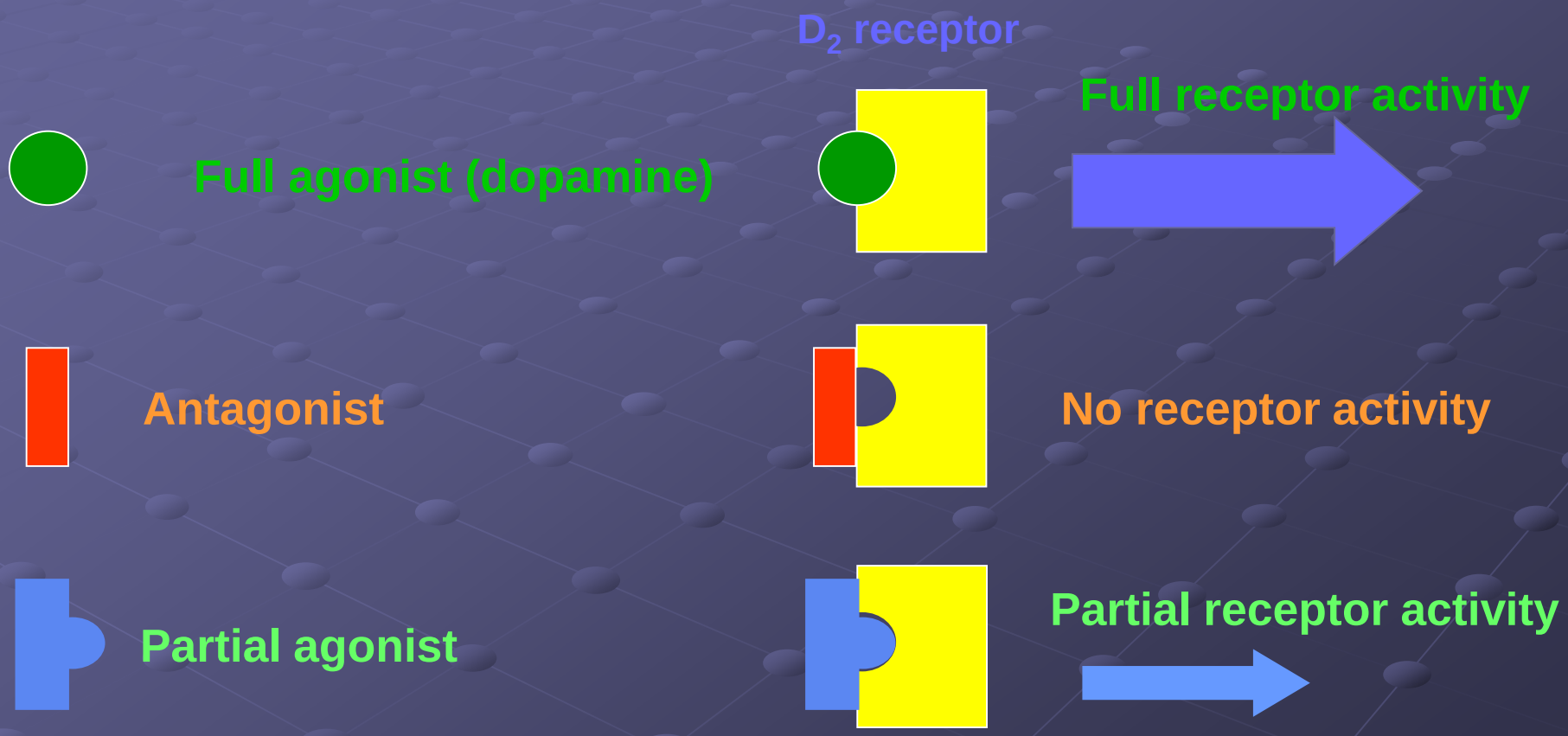
⇩

DA=dopamine; PFC=prefrontal cortex; NMDA=n-methyl-D-aspartate.

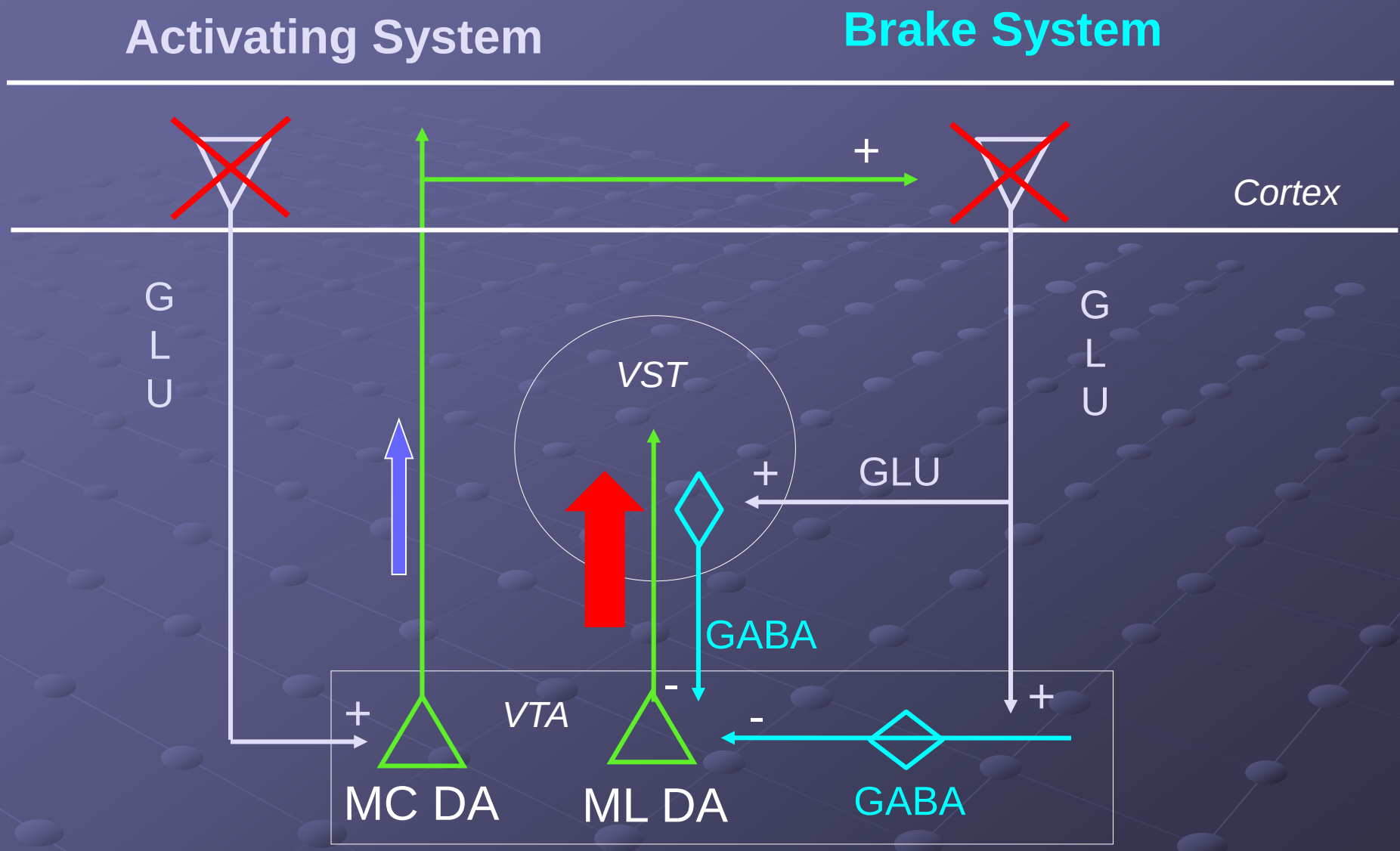
Intrinsic Activity



Intrinsic Activity

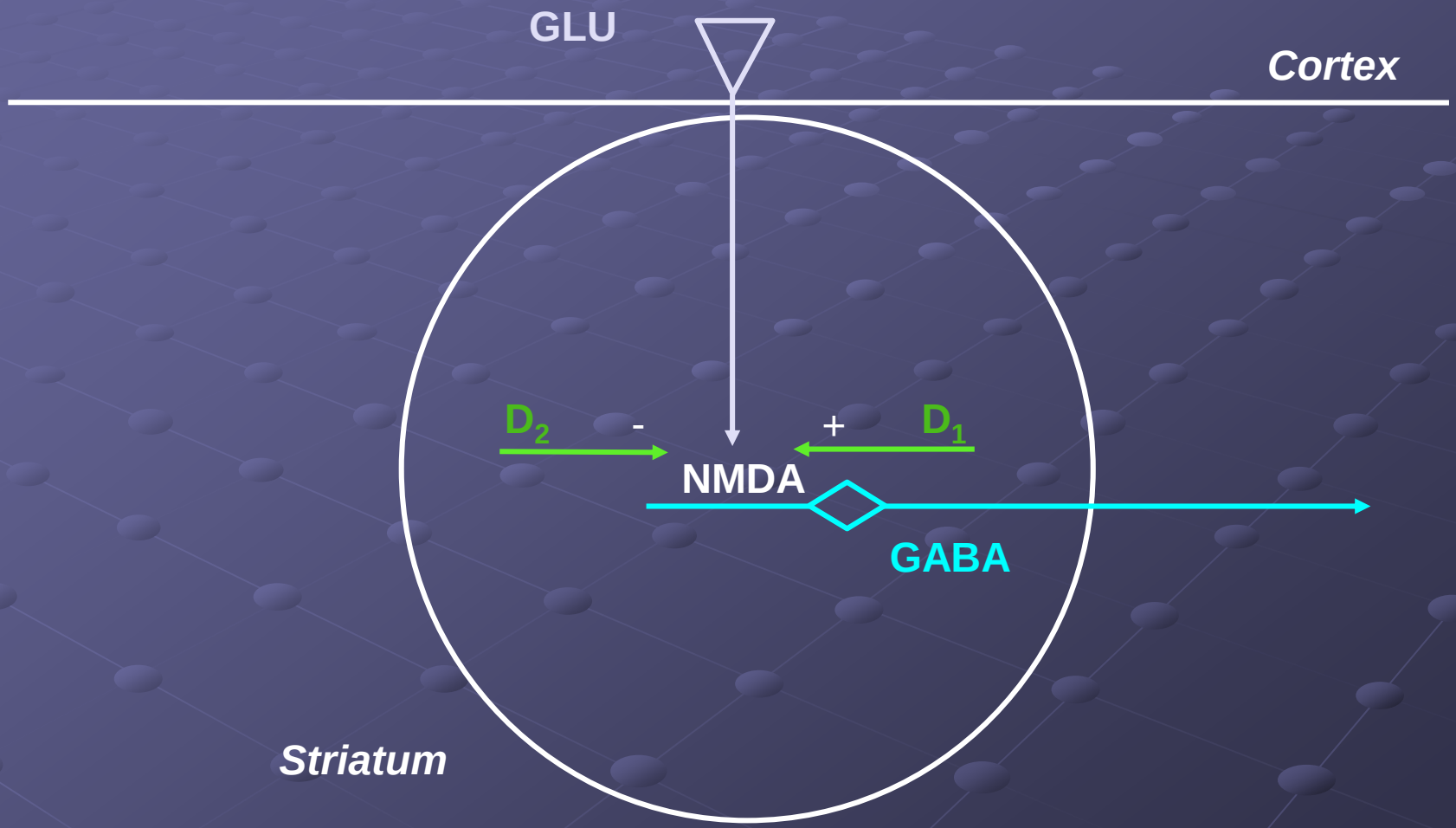


Glutamate

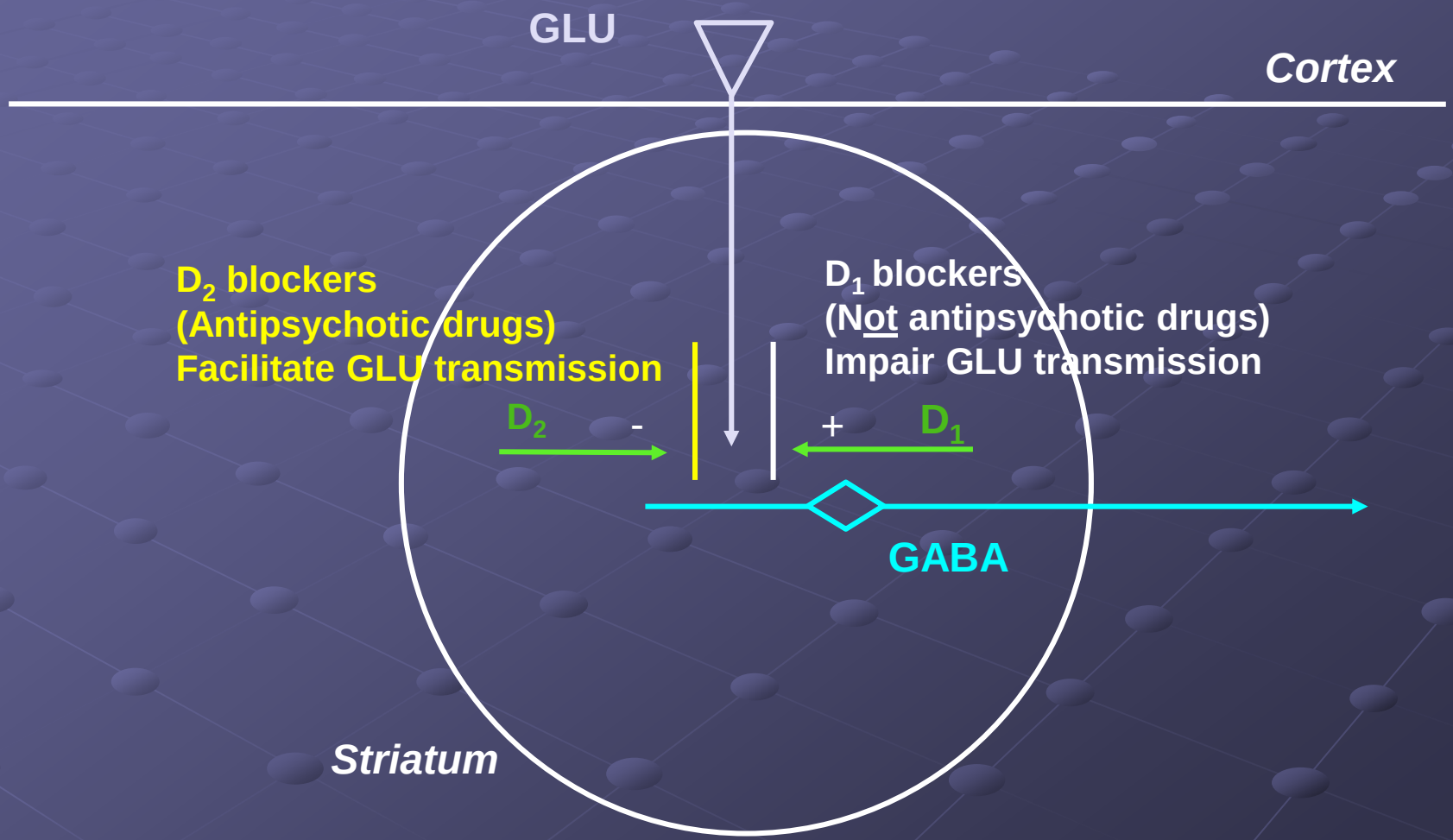


Carlsson A, et al. *Biol Psychiatry.* 1999;46:1388. Carlsson A, et al. *Brain Research Reviews*. 2000; 31:342. Carlsson M, Carlsson A. *Schizophrenia Bulletin*.1990;16(3):425. Weinberger DR, et al. *Biol Psychiatry*. 2001; 50:825.

Opposite Modulation of NMDA Transmission by D_1 and D_2 Receptors

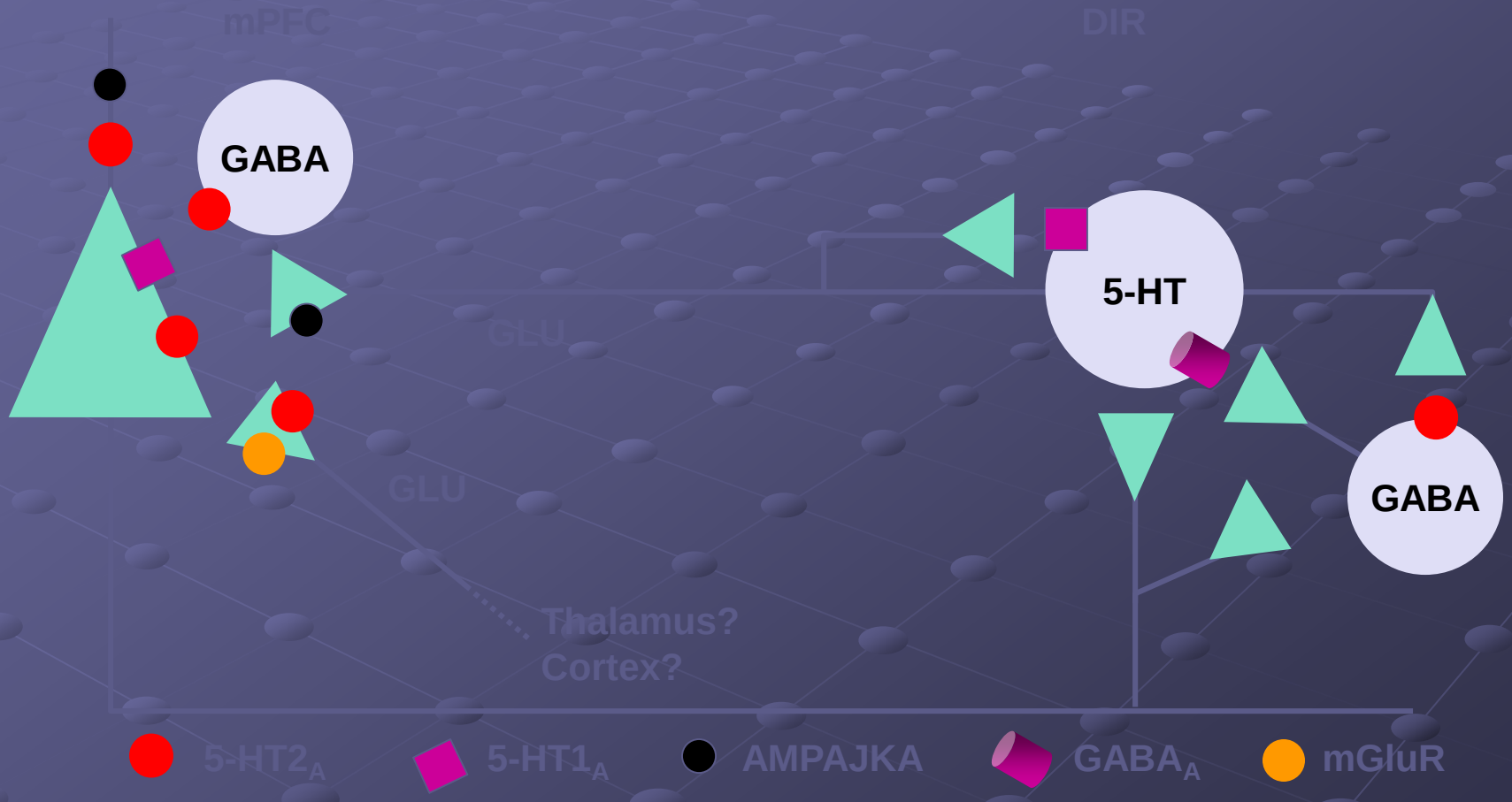


Glutamate Transmission



Laruelle M et al. *Ann NY Acad Sci*. 2003;1003:138-158.

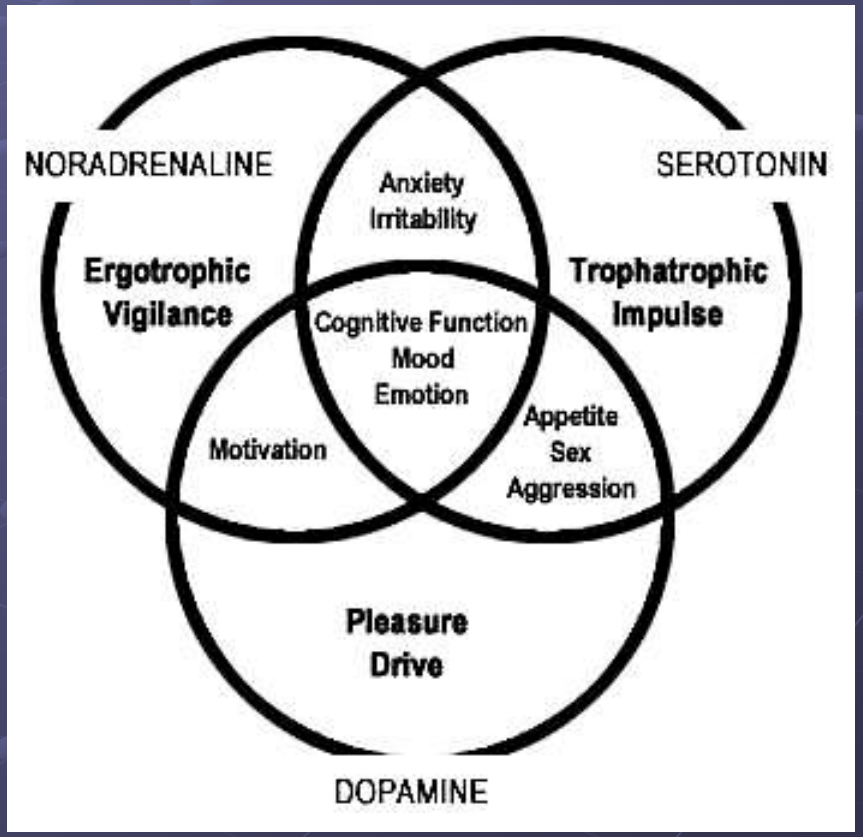
Neuronal Circuits Are Involved In Atypical Antipsychotic Drug Actions



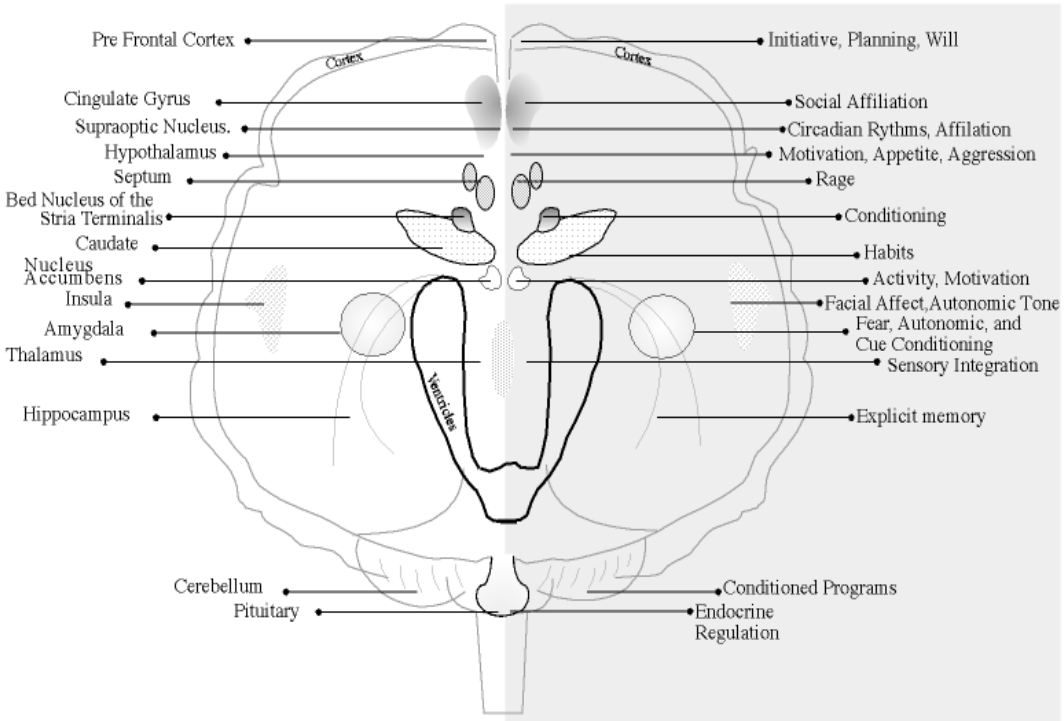
Aghajanian GK, Marek GJ. *Brain Research Reviews*. 2000; 31:302.
Martin-Ruiz R, et al. *J Neuroscience*. 2001;21(24):9856.

Clinical Application

- This is one explanation for how regulation of serotonin through SSRIs leads to changes in norepinephrine levels and pathways related to the raphe nuclei and locus ceruleus.



NEUROANATOMY OF EMOTION AND AFFILIATION

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