Psychosis

A disorder in which contact with reality is lost characterized by

1. disturbances of reality perception
2. inappropriate or diminished affect (mood)
3. impaired cognitive function

Psychosis denotes many mental disorders

Schizophrenia is a particular kind of psychosis characterized mainly by marked thinking disturbance

Schizophrenia

Schizophrenia is a chronic *remitting* and *relapsing* or progressive psychotic disorde

associated with significant impairment in social interactions and occupational functioning

and an average reduction of lifespan of 15 to 25 years

- Afflicts 1% of the population in all races and culture
- Onset of schizophrenia is in the late teens - early twenties

Symptoms

Positive Symptoms

Negative Symptoms

Cognitive impairment

Positive Symptoms

- Hallucinations (false perceptions: hearing voices others do not hear; Seeing, feeling, or smelling things other do not)
- Delusions (false beliefs: Intense suspicion; Thoughts controlled by Martians; Radios implanted in teeth)
- Disordered Thought Processes and behavior (Loose associations, Word salad, Flight of Ideas)

Negative Symptoms

Apathy, social withdrawal, anhedonia, emotional blunting, extreme inattentiveness or lack of motivation to interact with the environment (Negative symptoms are progressive and less responsive to therapy)

Cognitive impairment

Cognitive deficits and deficits in attention and executive function

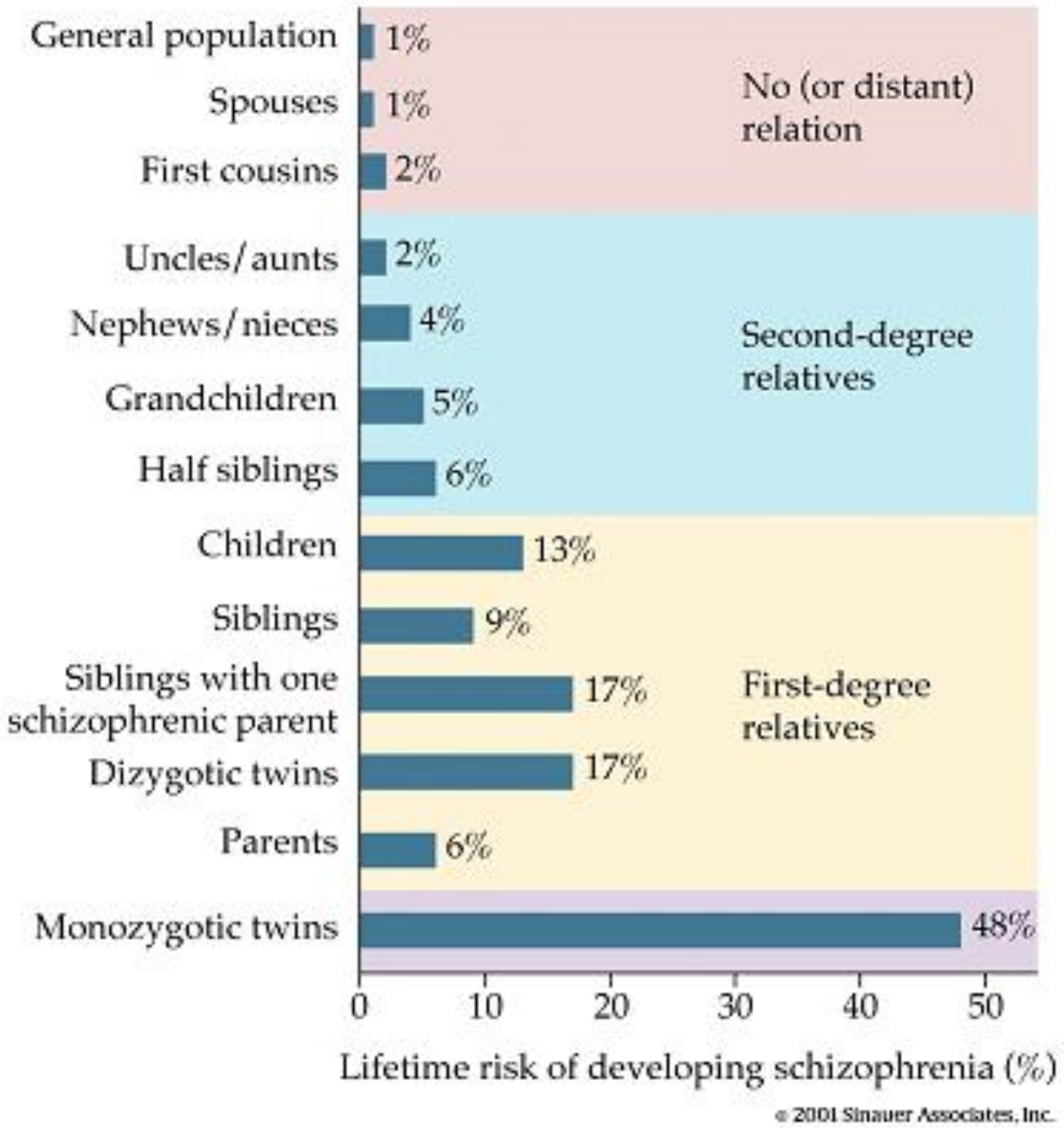
Etiology of Schizophrenia

- Etiology is unknown
- Genetic predisposition with multiple genes involved
- May or may not be present with anatomical changes

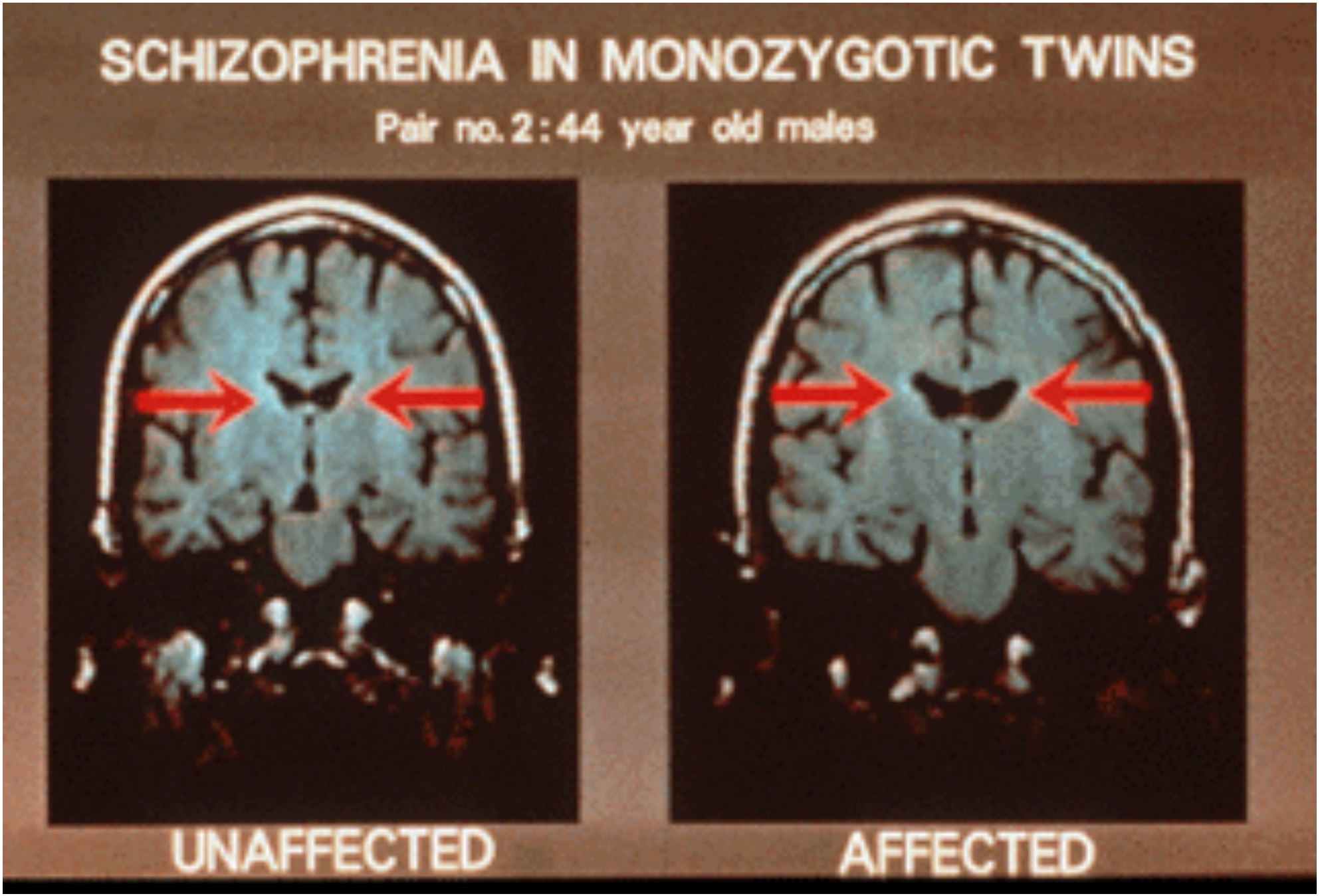
- ***Biological Correlates***

1. Heritability
2. Genetic Factors
3. Environmental stressors
4. Neurodevelopmental abnormalities

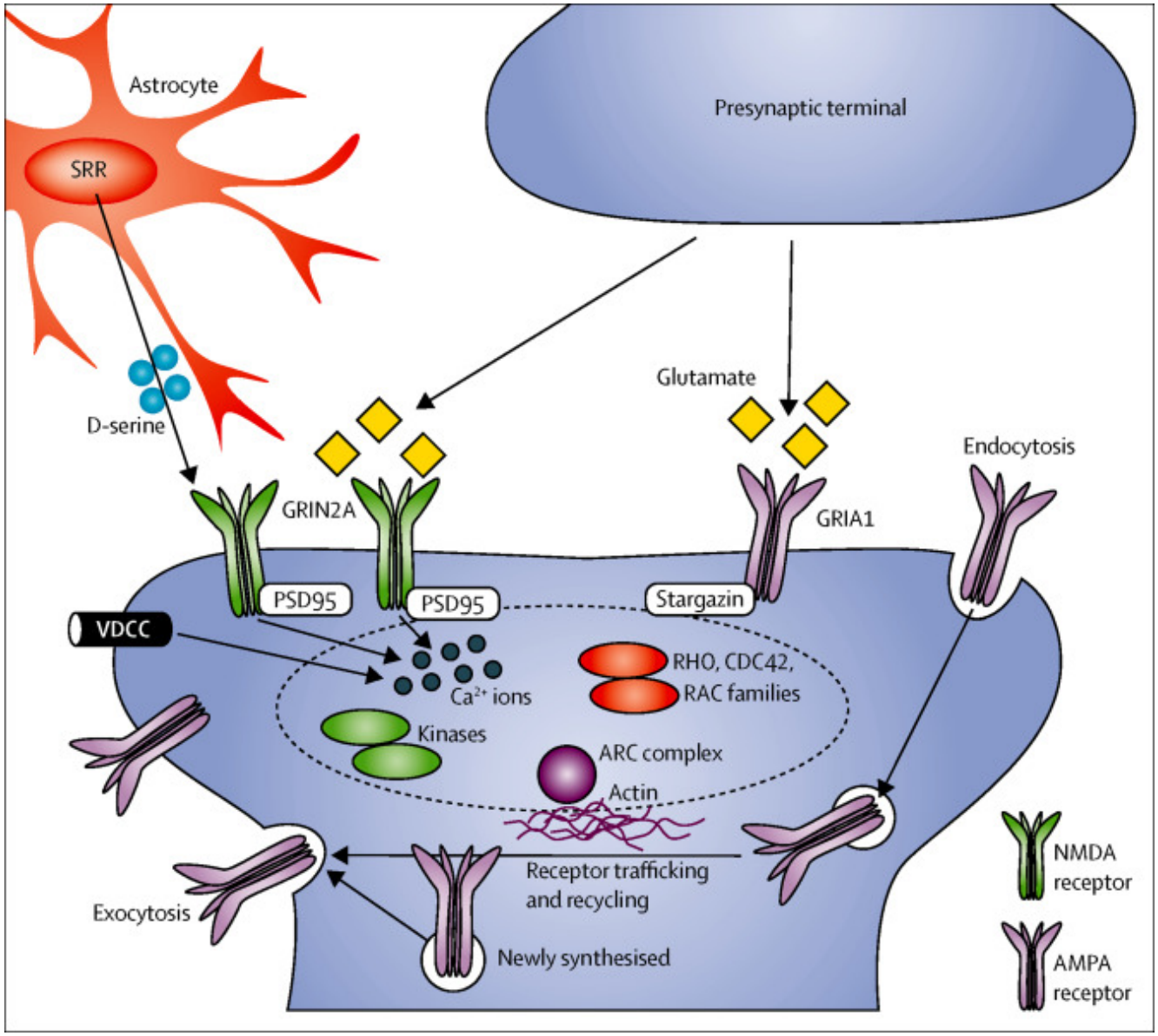
1. Heritability



1. Heritability



2. Genetic Factors



Schizophrenia is highly polygenic and the genetic risk is highly pleiotropic

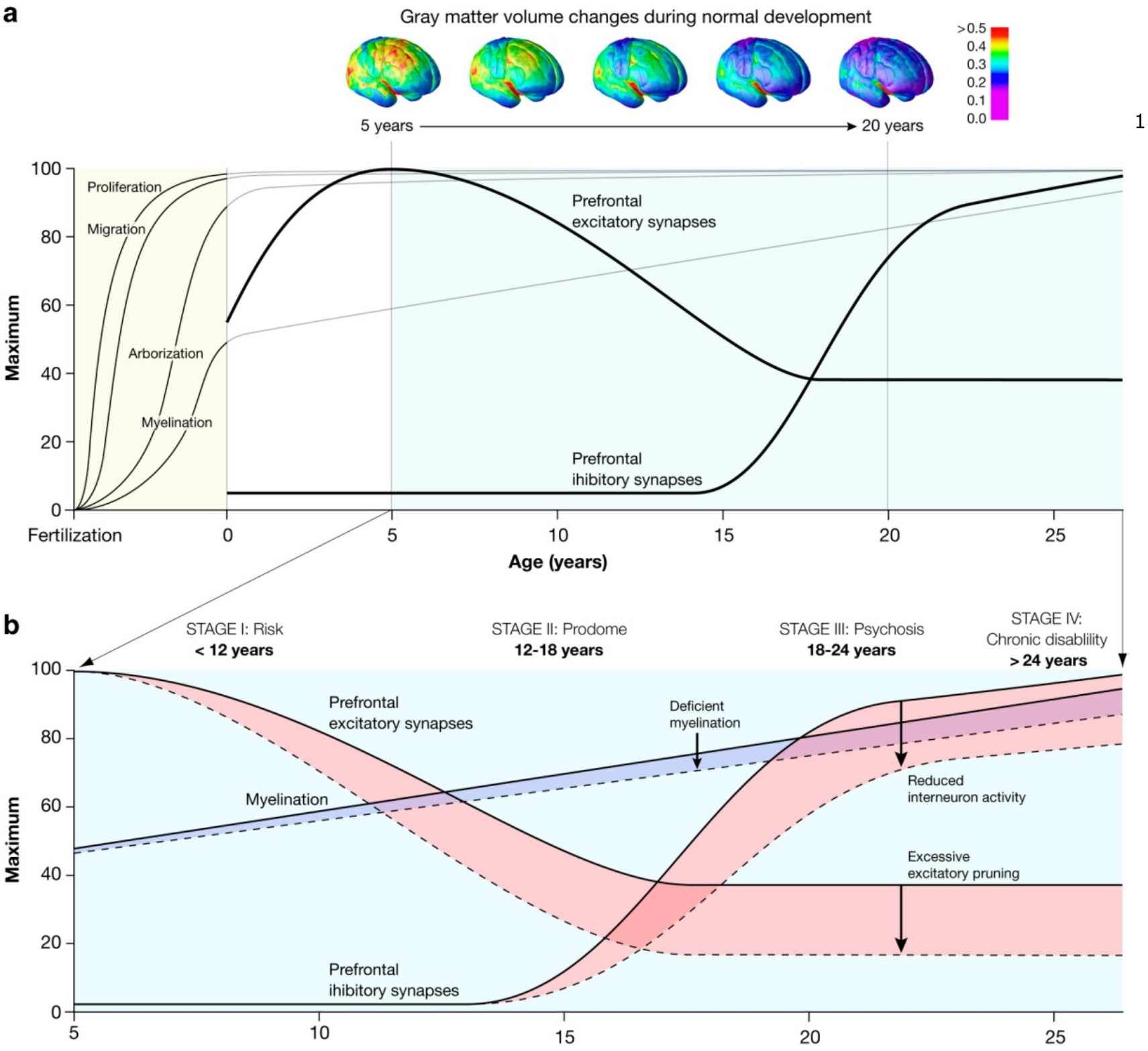
Some genes implicated:
GRIN2A (subunit of the NMDA receptor)
GRIA1 (subunit of the AMPA receptor)
CACNA1C (encoding VDCCs)
PSD95, CACNG2 (proteins associated with the post-synaptic scaffold kinases)
SRR (serine racemase)

3. Environmental stressors

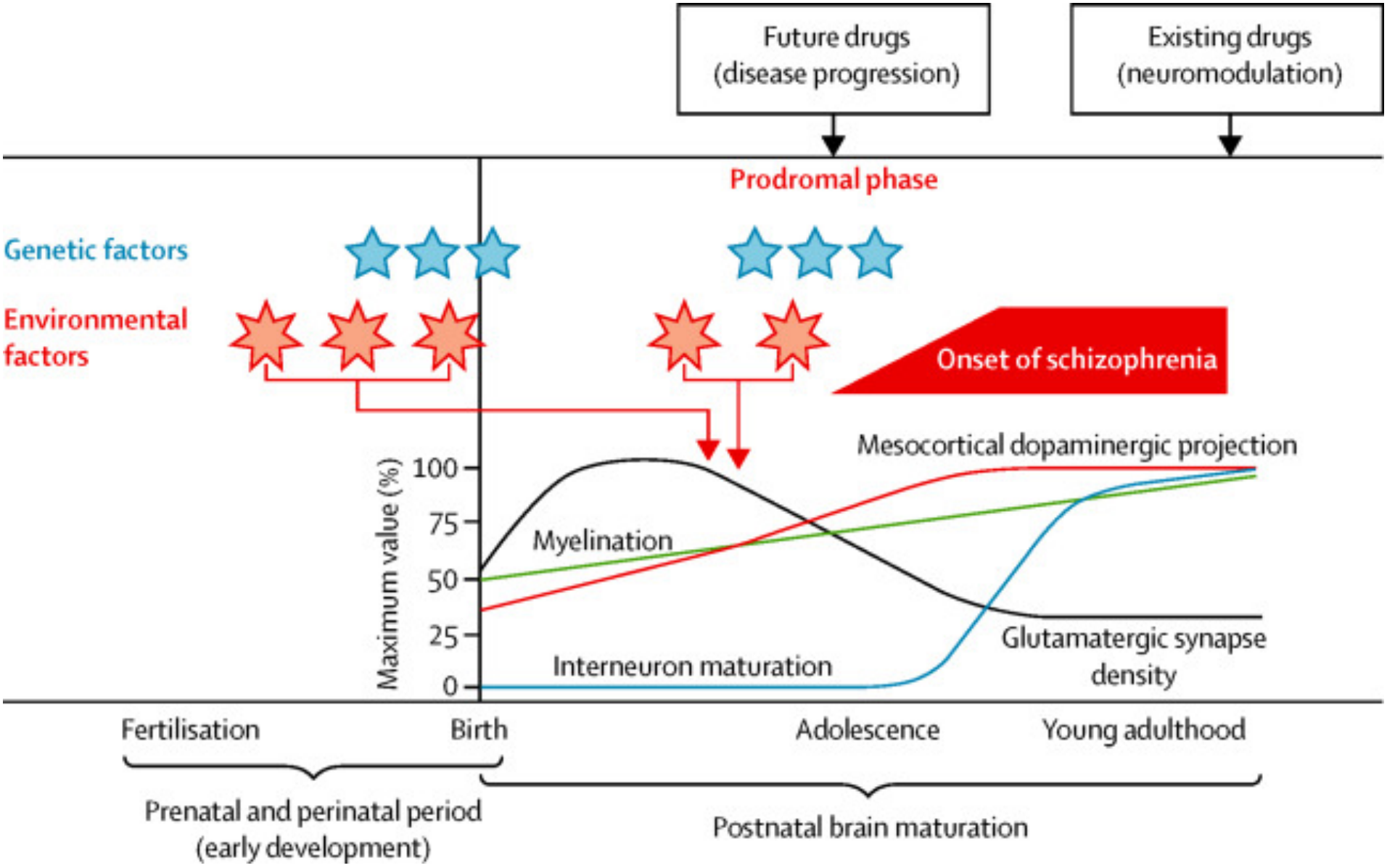
- Maternal stress, maternal infections
- Birth complications
- Nutritional deficiency; Autoimmune diseases; Head injury; Childhood adversity
- Substance of abuse

4. Neurodevelopmental Hypothesis

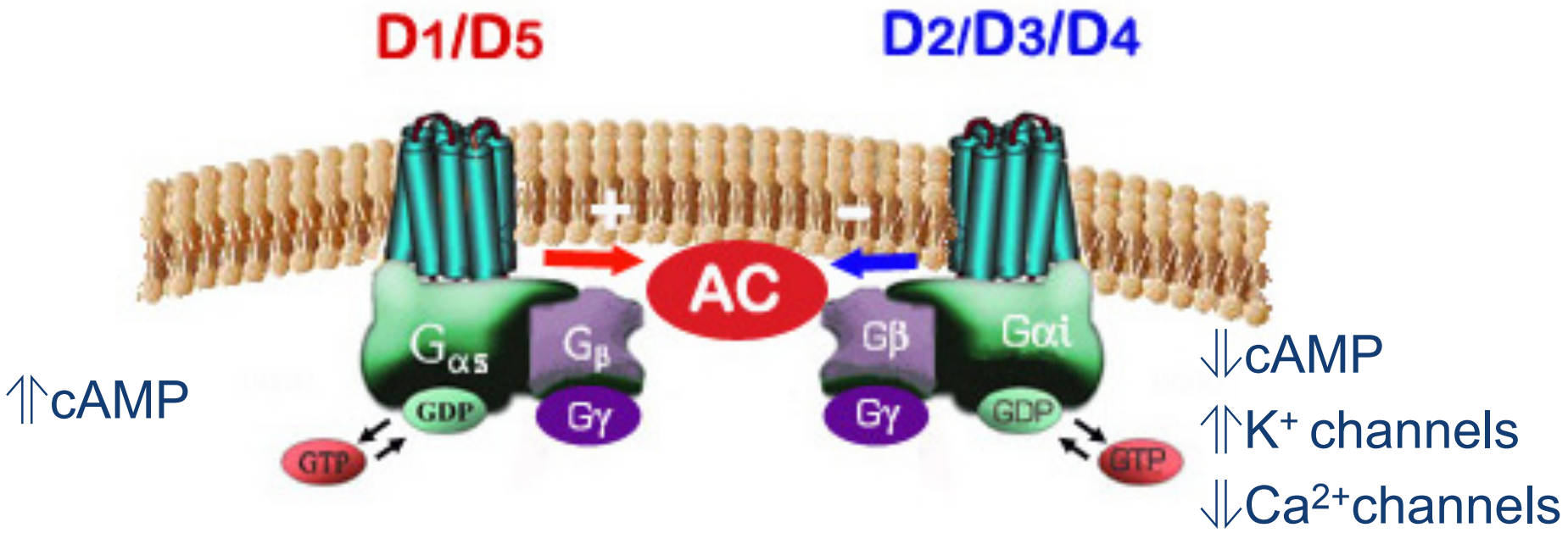
- Environmental stressors during early brain development will alter the normal program of brain maturation (*progenitor cells proliferation, neuronal migration, dendritic arborization and outgrowth*)


a
Gray matter volume changes during normal development
>0.5
0.4
0.3
0.2
0.1
0.0
5 years
20 years
Proliferation
Migration
Arborization
Myelination
Prefrontal
excitatory synapses
Prefrontal
ihibitory synapses
Maximum
100
80
60
40
20
0
Fertilization
0
5
10
15
20
25
Age (years)
b
STAGE I: Risk
< 12 years
STAGE II: Prodome
12-18 years
STAGE III: Psychosis
18-24 years
STAGE IV:
Chronic disablility
> 24 years
Prefrontal
excitatory synapses
Deficient
myelination
Myelination
Reduced
interneuron activity
Excessive
excitatory pruning
Prefrontal
ihibitory synapses
Maximum
100
80
60
40
20
0
5
10
15
20
25

4. Neurodevelopmental abnormalities



Dopamine Receptors family



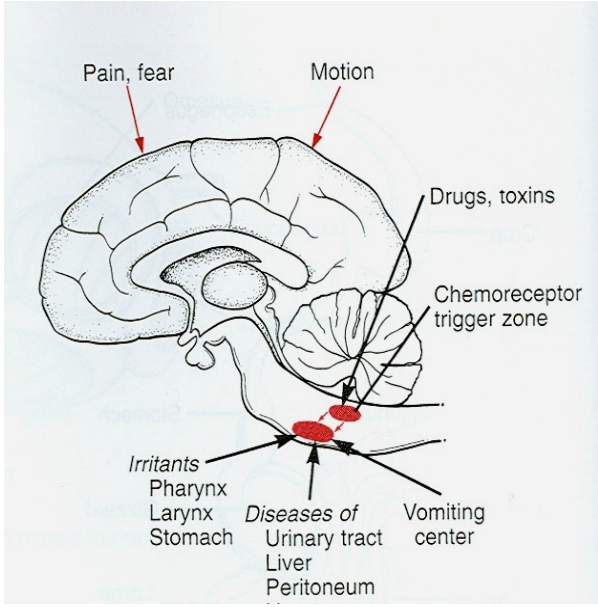
Dopamine Receptor Distribution

	D1	D5		D2	D3-4
Striatum	++			++	
Prefrontal Cortex	++				+
Limbic system	++	+		++	+
Hypothalamus	++				
Pituitary gland				++	

Dopamine System

Four major pathways for the dopaminergic system in the brain:

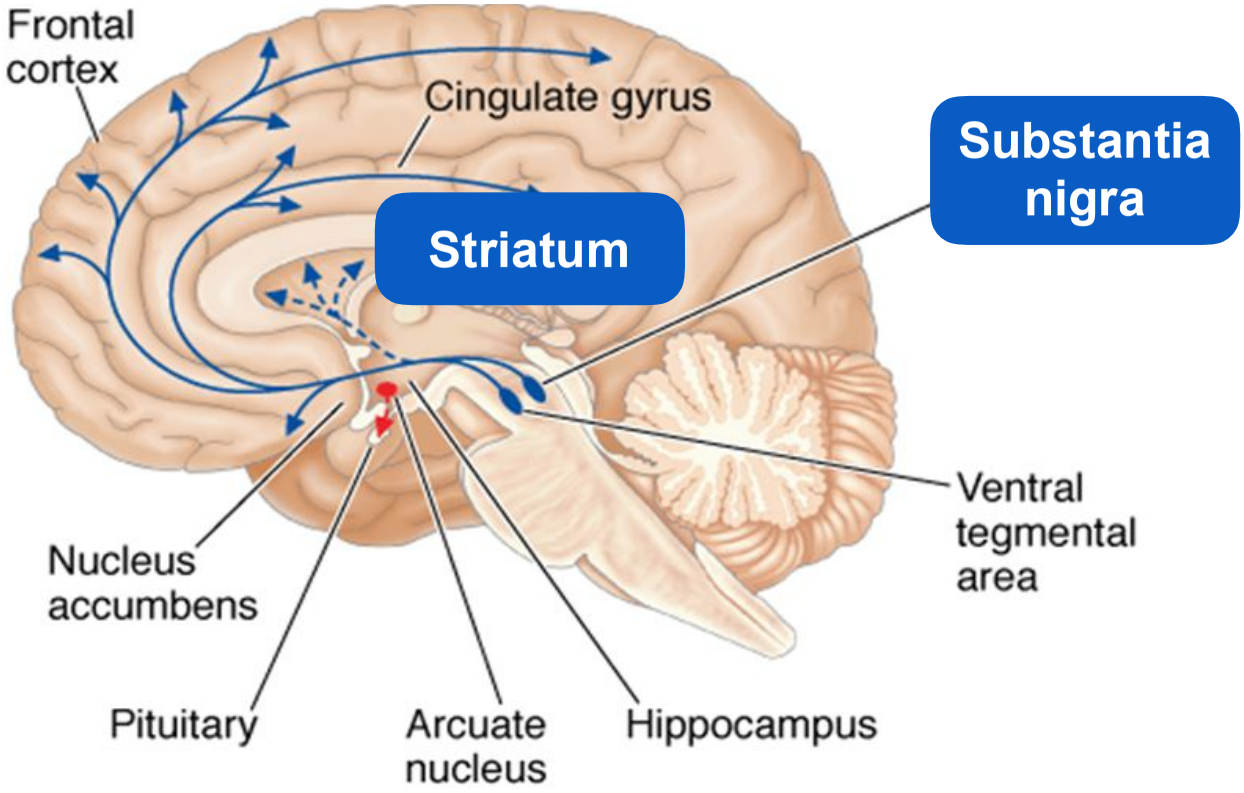
I. The Nigro-Striatal Pathway
II. The Mesolimbic Pathway
III. The Mesocortical Pathway
IV. The Tuberoinfundibular Pathway



Chemoreceptor trigger zone (Emesis)

I. The Nigrostriatal Pathway

- Projects from the substantia nigra to the basal ganglia
- A part of the extrapyramidal system, is involved in the control of motility

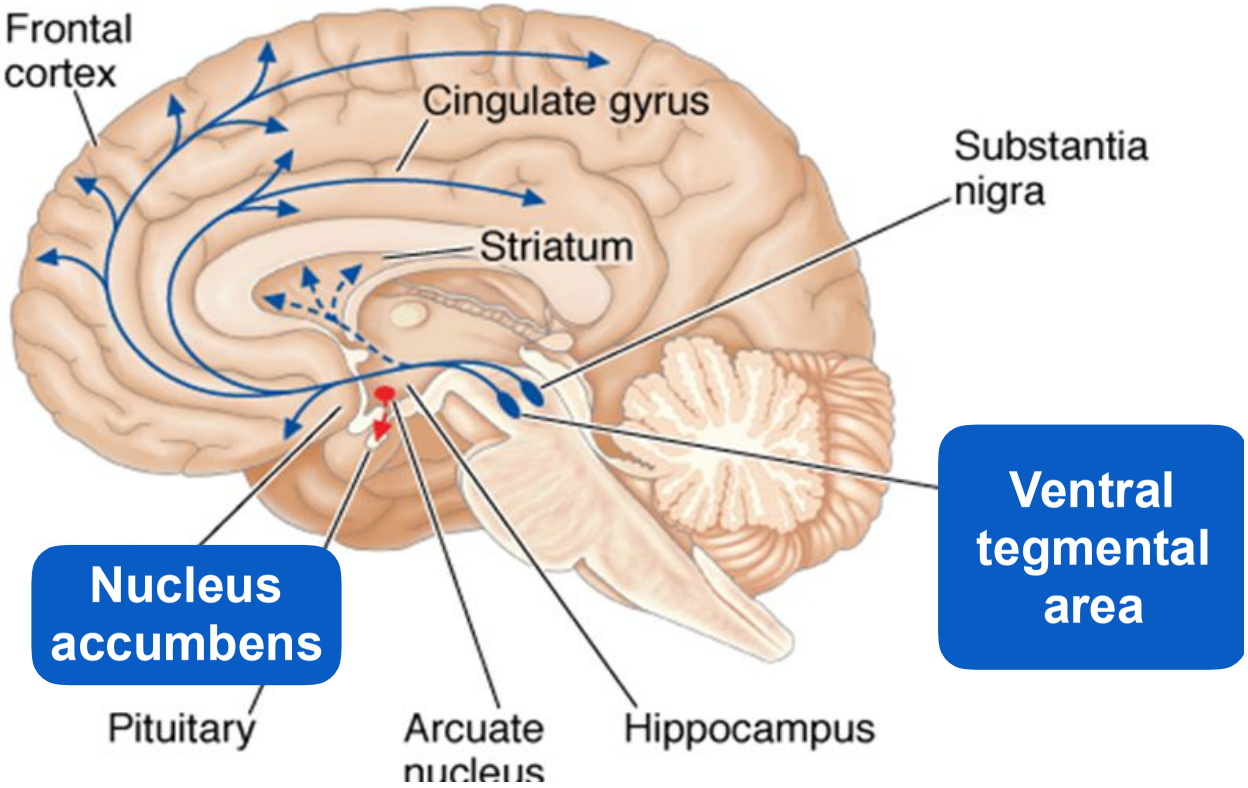


Ipoactivity results in rigidity, tremor and difficulty initiating movement (bradykinesia)

Parkinsonism

II. The Mesolimbic Pathway

Projects from the VTA to limbic system via Nucleus Accumbens, amygdala and hippocampus



Involved in modulating behavioral responses to stimuli that activate feelings of reward (motivation) and reinforcement

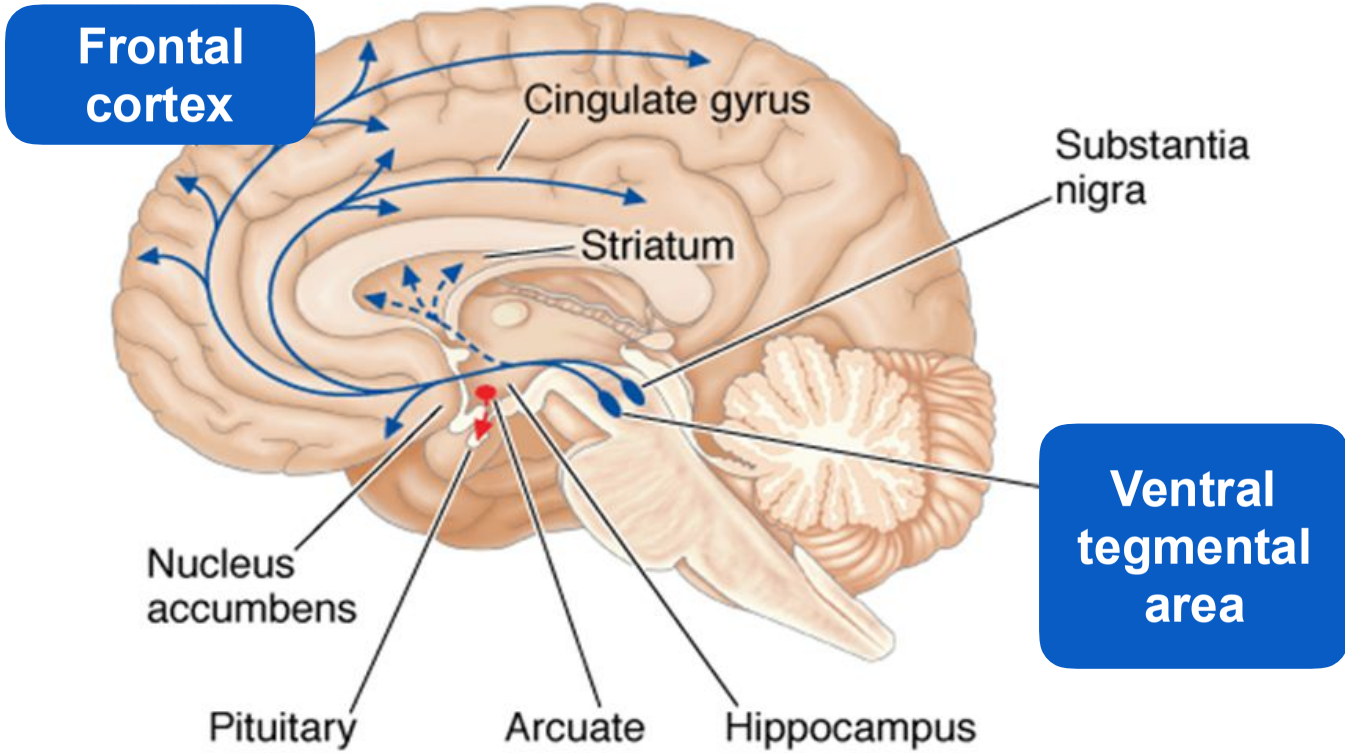
Overactivity produces delusions and hallucinations (positive symptoms of schizophrenia)

III. The Mesocortical Pathway

Projects from the VTA to frontal cortex

Involved in motivation and emotional responses

Can be associated with both positive and negative symptoms (mood)

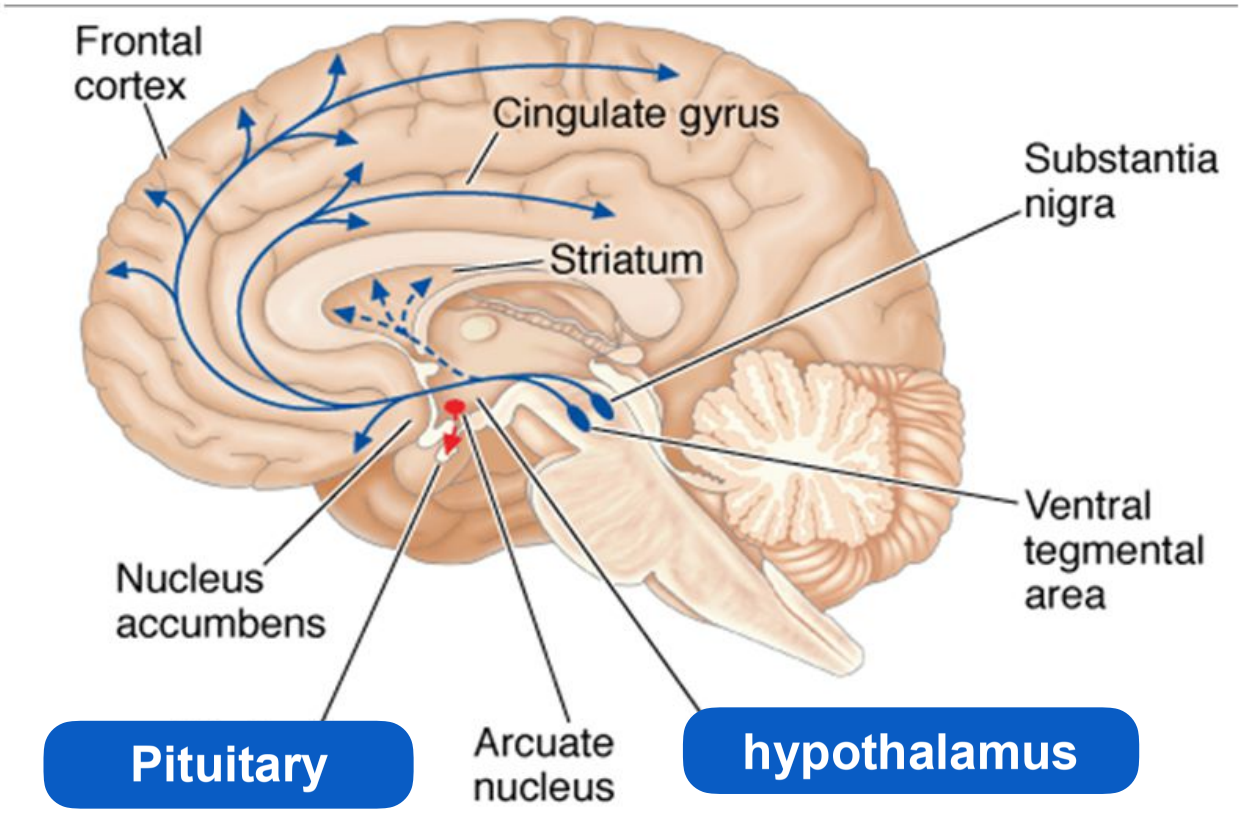


Blockade may help reduce negative symptoms of schizophrenia

IV. The tubero-infundibular pathway

Projects from hypothalamus to median eminence and pituitary gland

Involved in control of prolactine release (suppressed by dopamine)



Blockade of this pathway produces galactorrhea

Dopamine Theory of Schizophrenia

Schizophrenia could be caused by an aberrant activity of the dopaminergic system

Drugs that ***increase*** DA in the limbic system cause psychosis:

- L-DOPA (dopamine precursor) can produce hallucinations
- Apomorphine and bromocriptine (D_2 receptor agonists) produce behavioral abnormalities in animals (stereotyped behavior)
- Amphetamine and cocaine produce a psychotic behavior similar to the 'positive' features of schizophrenia

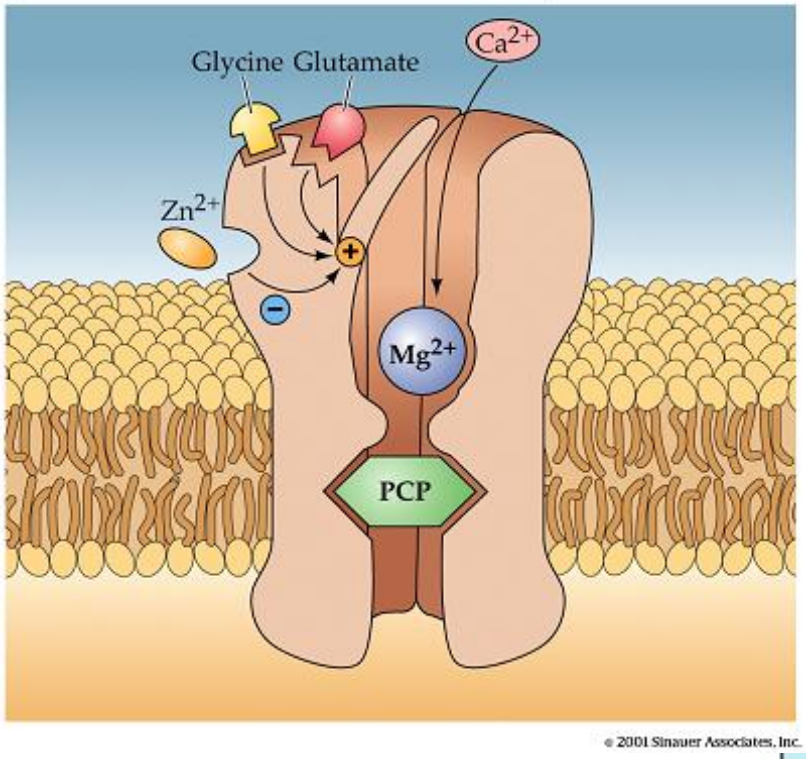
- Drugs that ***reduce*** DA activity in the limbic system (postsynaptic D_2 receptor antagonists) reduce psychosis and are effective in controlling the positive symptoms
- Many antipsychotics block the D_2 receptor

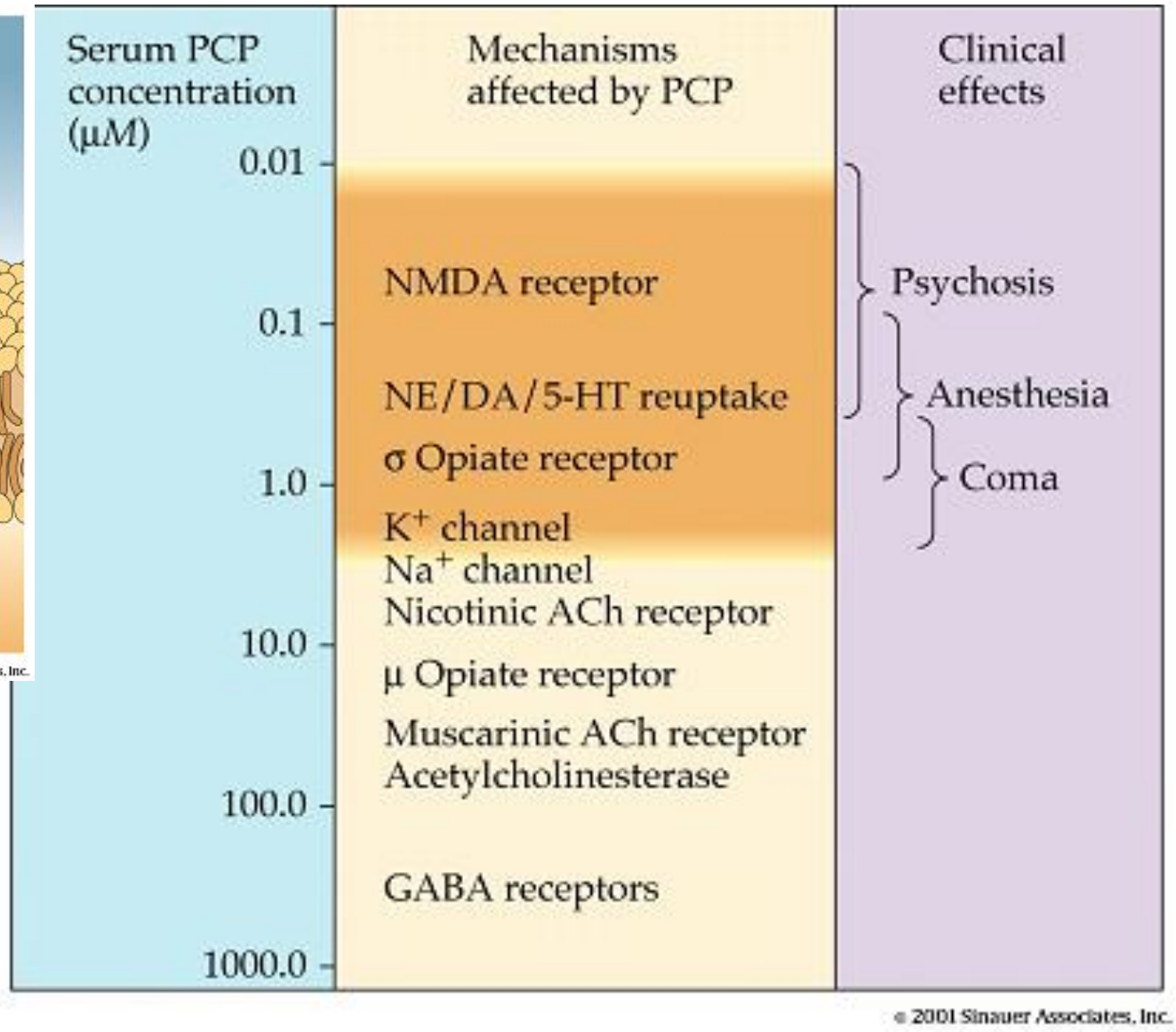
Criticisms of the DA hypothesis

- Normal levels of DA metabolites are present in CSF of many schizophrenics
- D_2 receptor antagonists are only partially effective in most (70%) patients and ineffective for some
- Delayed onset of therapeutic effects, not consistent with only an antagonism toward D2 receptors (slow developing compensatory change/adaptation?)
- *Atypical* antipsychotics have low affinity for D2 receptors

- Drugs like Phencyclidine (CPC) and ketamine (NMDA receptor blocker) or LSD (5-HT partial agonist) cause psychotic behavior

Effects of PCP on various receptors





NMDA receptor hypofunction hypothesis

NMDA receptor hypofunction causes excessive glutamate release which triggers neuronal injury throughout corticolimbic regions

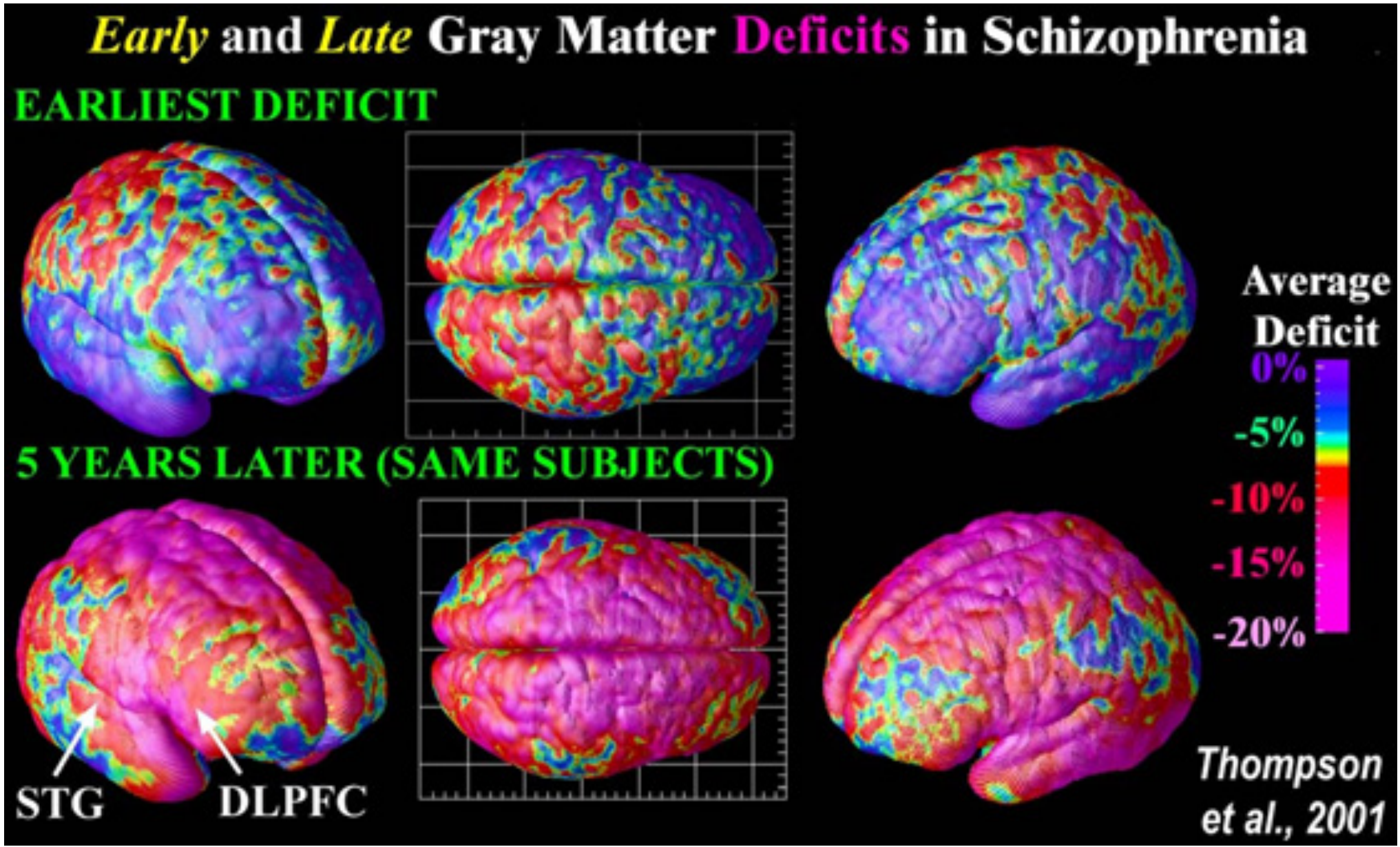
- Disruption of corticolimbic glutamatergic transmission by *acute* PCP leads to intense and disorganized hyperactivity (model for positive symptoms)

- Disruption of corticolimbic glutamatergic transmission by *chronic* PCP leads to deficits in long-term memory, attention and social interaction (model for cognitive impairment and negative symptoms)

- PCP produces hypofrontality in nonhuman primates, and this effect is reversed by antipsychotic drugs

Hypofrontality: reduced frontal lobe activity

Functional imaging techniques (fPET) reveal decreased metabolic activity in frontal cortex of schizophrenics



The role of Serotonin (5-HT)

5-HT has a modulatory effect on dopaminergic neurones

LSD, a partial 5-HT receptor agonist, produces hallucinations and behavioral disturbance

M-chlorophenylpiperazine (M-CPP), a 5-HT receptor agonist, worsens psychotic symptoms

Ritanserin, a 5-HT receptor antagonists, attenuates psychotic symptoms

Dopamine

Glutamate

Serotonin

Acetylcholine

GABA

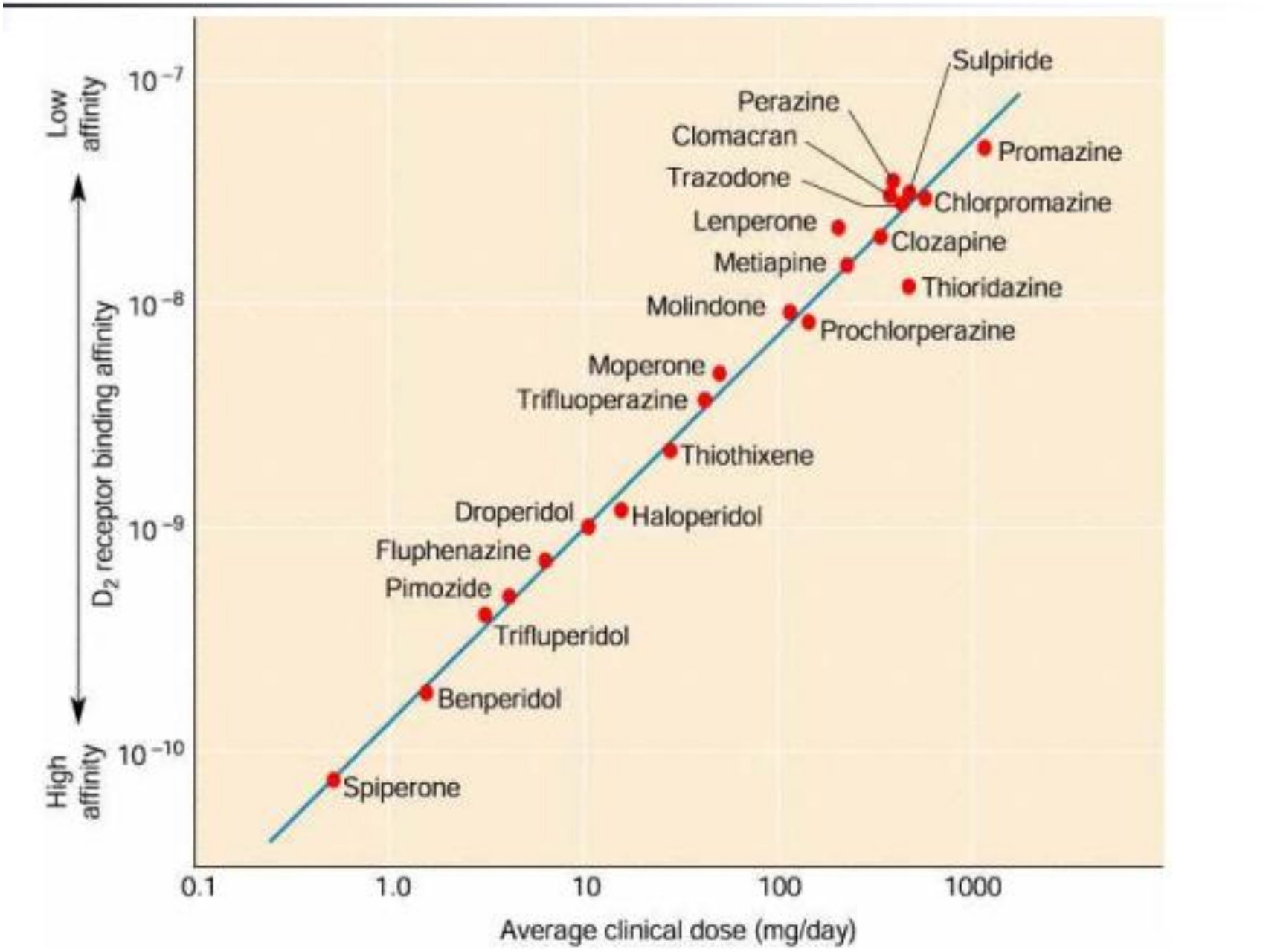
Neuropeptides

First generation TYPICAL				Second generation ATYPICAL	
1952	1960s	1970s	1980s	1990s	2000s
Chlor promazine	**Haloperidol (Serenase) Fluphenazine Thioridazine Trifluoperazine**	**Molindone Pimozide**	**Clozapine**	**Risperidone Olanzapine Quetiapine Ziprasidone**	**Aripiprazole Paliperidone Iloperidone Asenapine Lurasidone**

Have Parkinsonian side effects
Effective against positive symptoms
Not all patients respond to drug therapy

Have minimal Parkinsonian side effects
Effective against both positive and negative symptoms
Effective in "resistant" patients

1. Clinical potency of typical antipsychotic drugs correlated with their affinity for D_2 receptors



2. Antagonism of dopamine D2 receptors is the basis for both the efficacy and side effects of typical antipsychotics

EFFICACY: D2 Receptor antagonism

in the Mesolimbic pathway *decreases positive symptoms*

SIDE EFFECTS: D2 Receptor antagonism

in the Mesocortical pathway can *increase negative* symptoms

in the Nigro-Striatal pathway causes *Extra-Pyramidal Syndrome* (EPS) or Parkinsonism, Dystonia, Tardive dyskinesia, Akathisia, Neuroleptic malignant sndrome

in the pituitary gland causes endocrine changes (hyperprolactinemia, amenorrhea, galactorrhea, infertility, gynecomastia and sexual dysfunction)

3. Typical antipsychotic are also effective antagonists at ACh, 5-HT and NE receptors

Muscarinic receptor blockade

Blurred vision, Dry mouth, Sinus tachycardia, Constipation, Urinary retention, Memory dysfunction

Histamine H1 Blockade

Sedation, drowsiness, Weight gain, Hypotension

Alpha-1 receptor blockade

- NE: Arteriolar dilation→ reduction of arterial blood pressure and Dizziness
- E: Venodilation→ orthostatic hypotension - Reflex tachycardia

Typical Antipsychotic drugs

- All are equally effective but differ in their tolerability
- All show a significant delay before they become effective
- All produce significant adverse effects

Disadvantages of Typical Antipsychotics

- Limited efficacy against negative symptoms
- A substantial portion of patients (25% to 40%) respond poorly to treatment
- EPS occurs at clinically effective doses
- Drug interaction with additive effects with sedatives, anticholinergic, antihistaminergics, alfa receptor blocking agents

Advantages of Typical Antipsychotics

- Efficacious for positive symptoms
- Low-cost

Atypical antipsychotic drugs

- Are effective against positive and negative symptoms with some improvement in cognition
- Are effective in patients refractory to typical neuroleptics
- Greatly reduced or absent EPS
- Disadvantage: Expensive

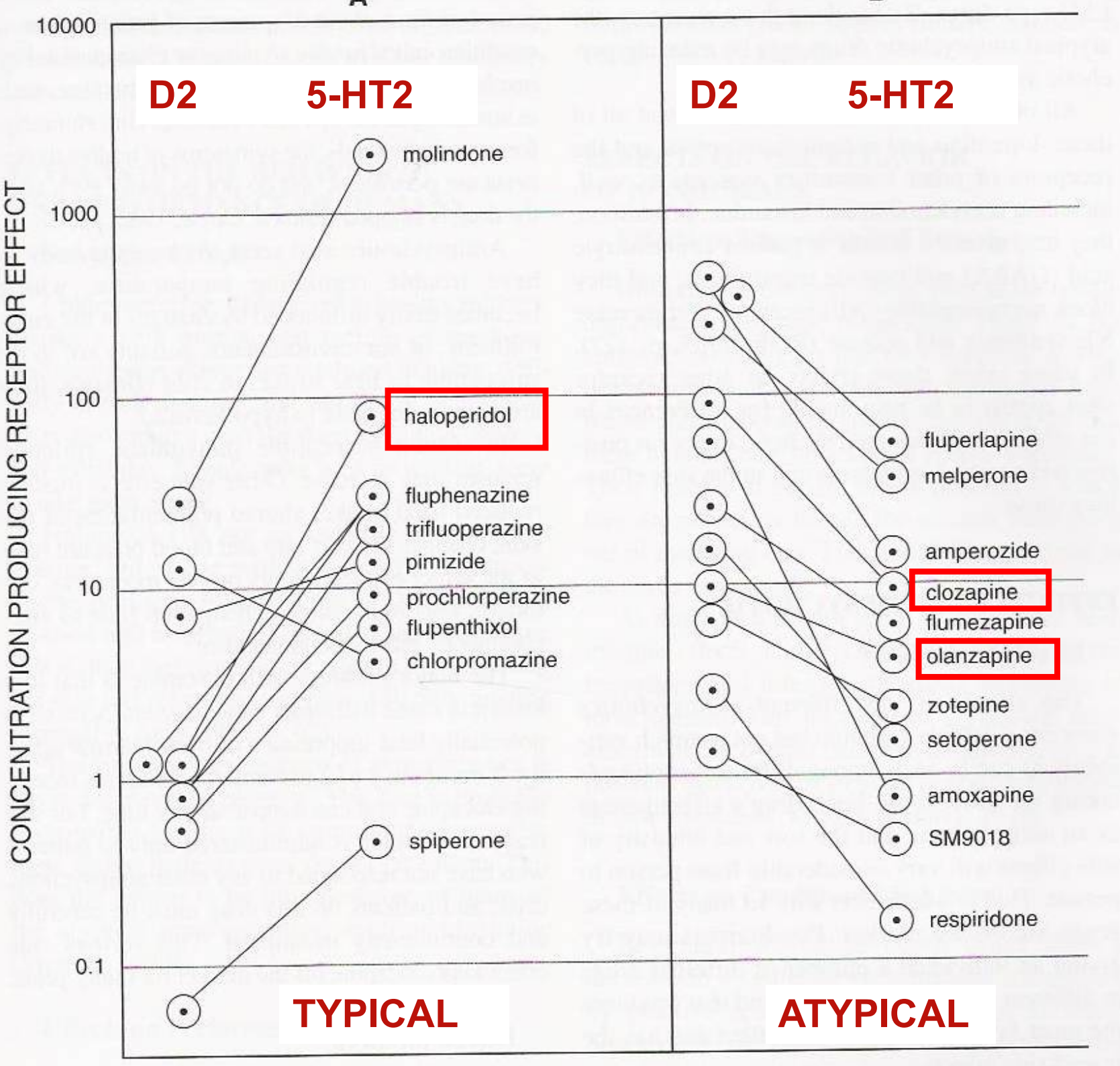
Antipsychotics: receptor order of potency

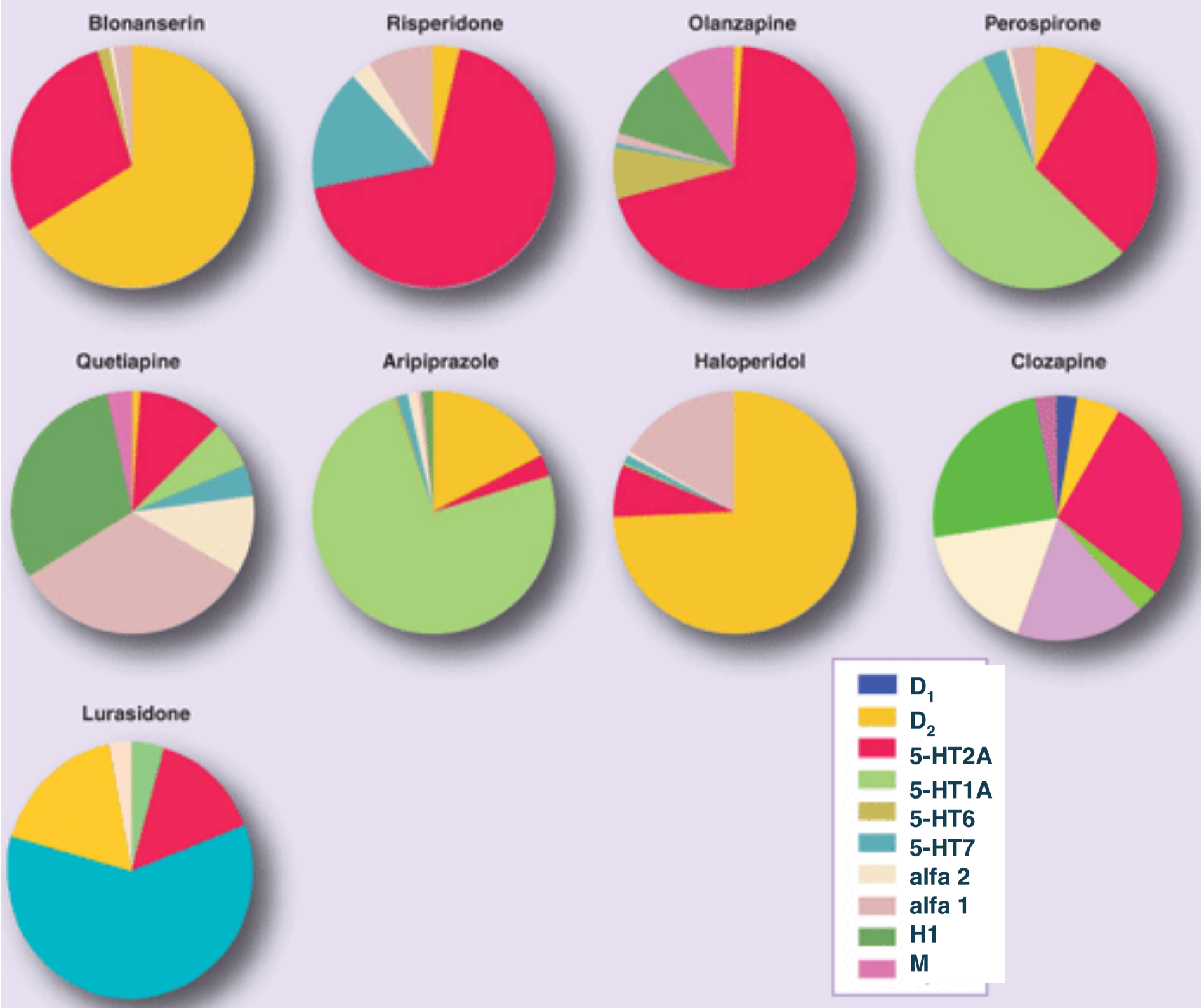
TYPICAL:

Chlorpromazine	$\alpha_1 = 5\text{-}HT_2 = D_2 > D_1 > M > \alpha_2$
Haloperidol	$D_2 > D_1 = D_4 > \alpha_1 > 5\text{-}HT_2 > H_1 > M = \alpha_2$
Clozapine	$D_4 = \alpha_1 > 5\text{-}HT_2 = M > D_2 = D_1 = \alpha_2 ; H_1$

ATYPICAL:

Quetiapine	$5\text{-}HT_2 = D_2 = \alpha_1 = \alpha_2 ; H_1$
Risperidone	$5\text{-}HT_2 >> \alpha_1 > H_1 > D_2 > \alpha_2 >> D_1$
Sertindole	$5\text{-}HT_2 > D_2 = \alpha_1$


D2
5-HT2
D2
5-HT2
CONCENTRATION PRODUCING RECEPTOR EFFECT
10000
1000
100
10
1
0.1
molindone
haloperidol
fluphenazine
trifluoperazine
pimizide
prochlorperazine
flupenthixol
chlorpromazine
spiperone
fluperlapine
melperone
amperozide
clozapine
flumezapine
olanzapine
zotepine
setoperone
amoxapine
SM9018
respiridone
TYPICAL
ATYPICAL


Blonanserin
Risperidone
Olanzapine
Perospirone
Quetiapine
Aripiprazole
Haloperidol
Clozapine
Lurasidone
D1
D2
5-HT2A
5-HT1A
5-HT6
5-HT7
alfa 2
alfa 1
H1
M

Atypical Antipsychotics: Drug/Receptor Characteristics

All atypical neuroleptics have affinities for D1, D3, D4, histamine, and α-AR receptors, display balanced D2/D1 receptors antagonism and 5-HT2 receptors antagonism

Due to the modulatory role of 5-HT on dopaminergic neurones, atypical antipsychotic drugs with 5-HT receptors contributes to:

- the low risk of producing EPS (Blockade of 5-HT2A receptors in the nigro-striatal pathway enhances dopamine release)

- the antipsychotic action (Blockade of 5-HT2A receptors in the mesocortical pathway enhances the release of both dopamine and glutamate)

- the ability to improve cognition (5-HT6 and 7 antagonists exert pro-cognitive effect

	POSITIVE SYMPTOMS	NEGATIVE SYMPTOMS	SIDE EFFECTS
CLOZAPINE	+	+/-	Seizure Agranulocytosis
RISPERIDONE	+	+/-	Weight gain EPS
OLANZAPINE	+	+/-	Weight gain Diabetes
ZIPRASIDONE	+/-	+	Weight gain
QUIETAPINE	+/-	+	Sedation Also for depression
ARIPRIPAZOLE	-	+/-	Uncontrolled movements

Modulation of neurotrophic factors by antipsychotic drugs

Expression of Brain-Derived Neurotrophic Factor (BDNF) and its high affinity receptor TrkB are reduced in the brain of schizophrenic patients

Neurotrophin (NTF) levels are reduced in the serum of schizophrenic patients

Antipsychotic drugs may be able to normalize levels of NTF or modulate their expression in order to enhance and promote neuronal plasticity

Pharmacokinetics

Absorption and Distribution

Read but incomplete and erratic absorption

Significant first-pass metabolism (F 25-65%)

High level of protein binding (92-98%)

High volumes of distribution (>7 L/Kg

Elimination half-lives are 10-24 hrs

Metabolism

Mostly completely metabolized by glucuronic acid conjugation (inactive metabolites)

Excretion

Urinary (Metabolites can be detected several months after drug discontinuation