Antipsychotics (neuroleptics)

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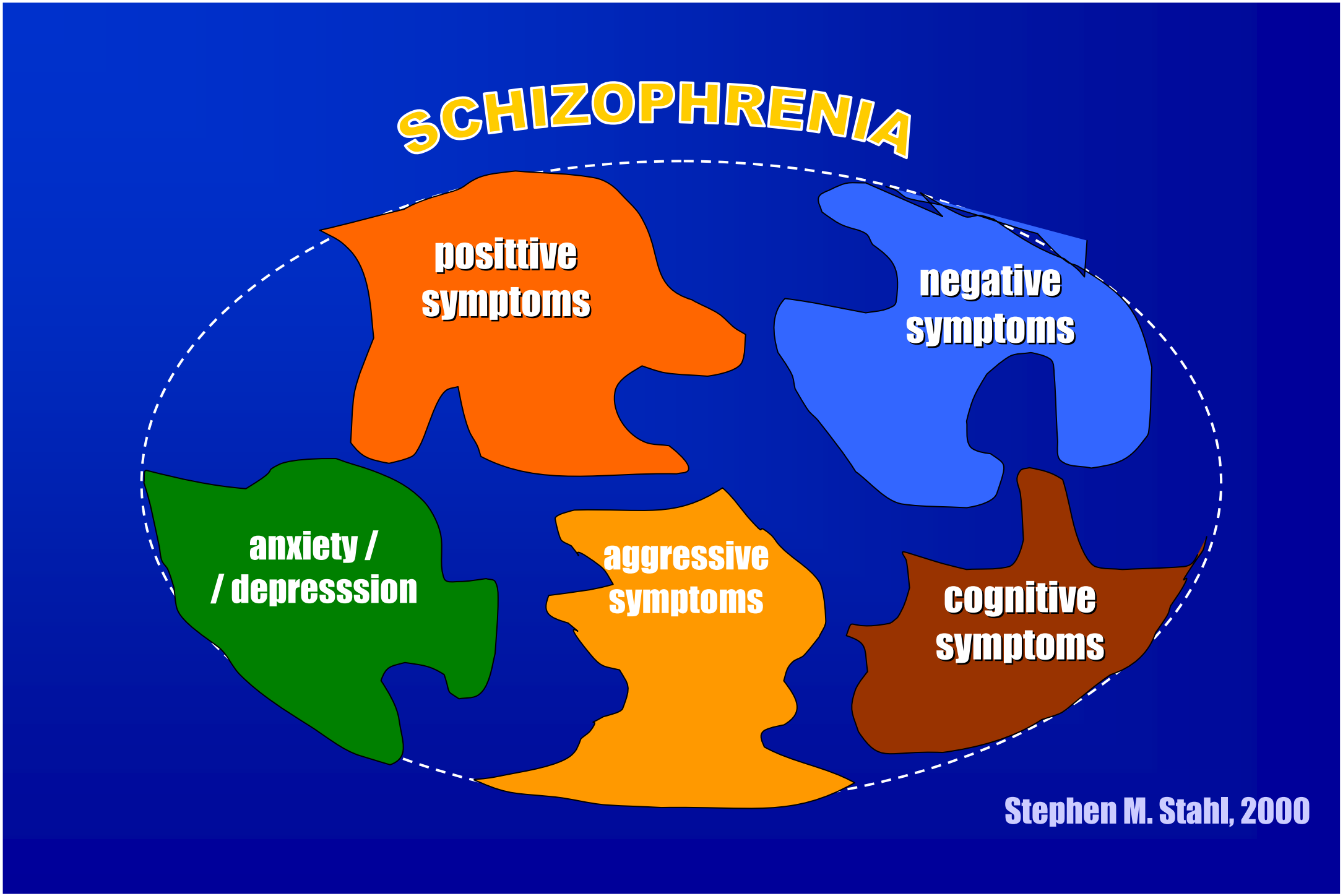
PSYCHOSIS

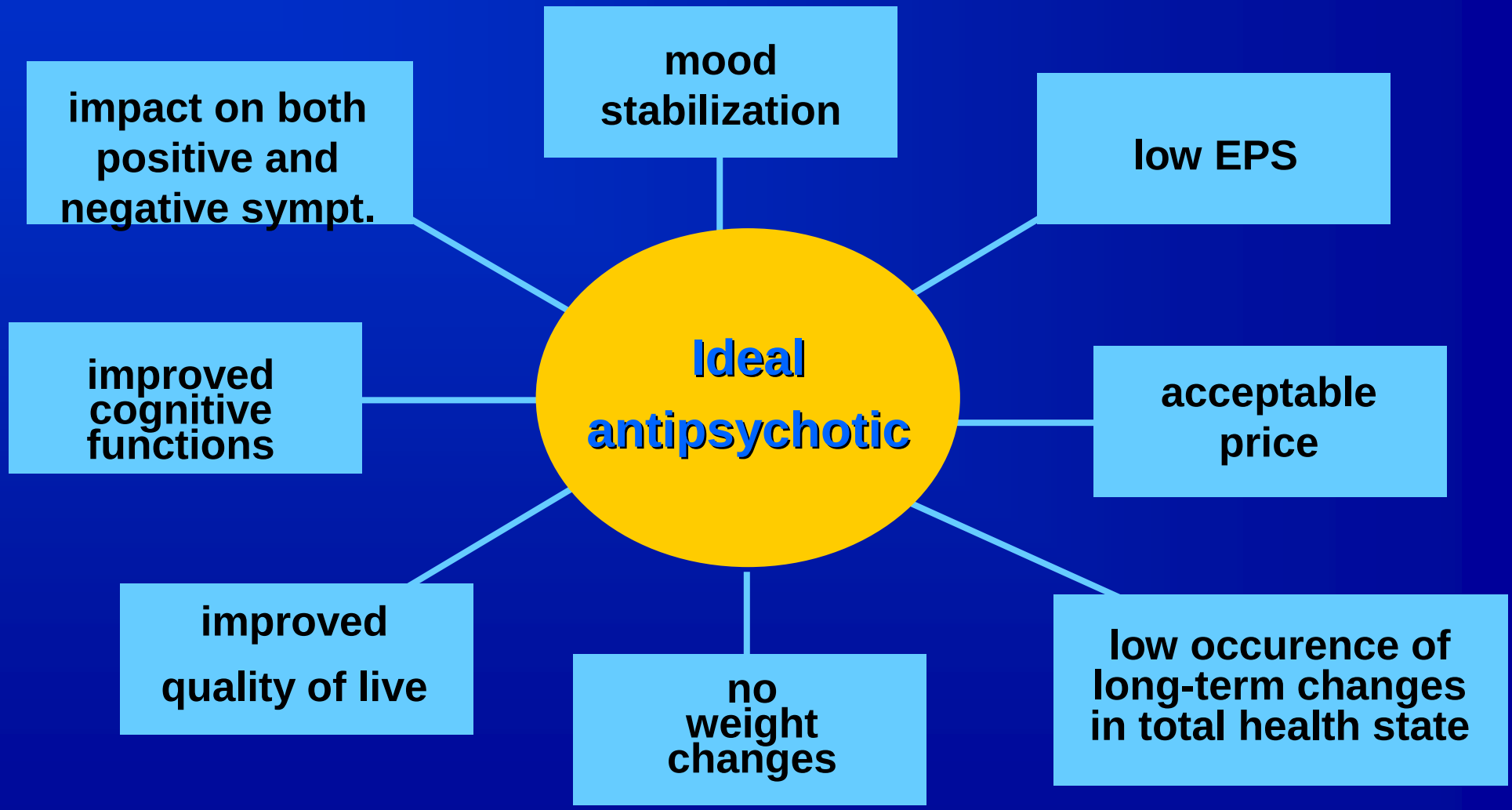
- **a person's capacity, affective response to recognize reality, communicate, and relate to others is impaired**

  - **schizophrenia,**
  - **mania,**
  - **depression,**
  - **Alzheimer's dementia**
  - **cognitive disorders**

hallucinations (auditory, visual, olfactory, gustatory, tactile**)**
delusions (misinterpretations of perceptions or experiences**)**

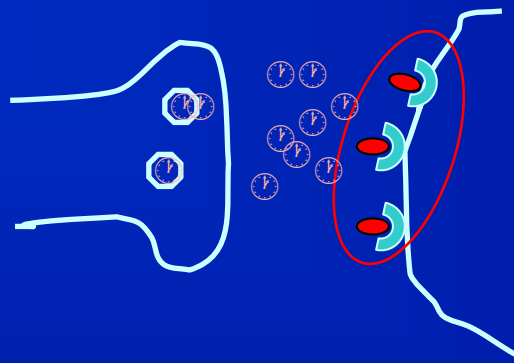

SCHIZOPHRENIA
posittive symptoms
negative symptoms
anxiety / / depresssion
aggressive symptoms
cognitive symptoms
Stephen M. Stahl, 2000

Ideal antipsychotic drug effects



Blocking of postsynaptic dopamine receptors D_2

in psychosis



- D_2 antagonist

SUPPRESSION OF POSITIVE SYMPTOMS

"Dopaminergic hypothesis of schizophrenia"

Dopamine receptor subtypes

DA r. – partly sensitive to Adrenaline and Noradrenaline, too

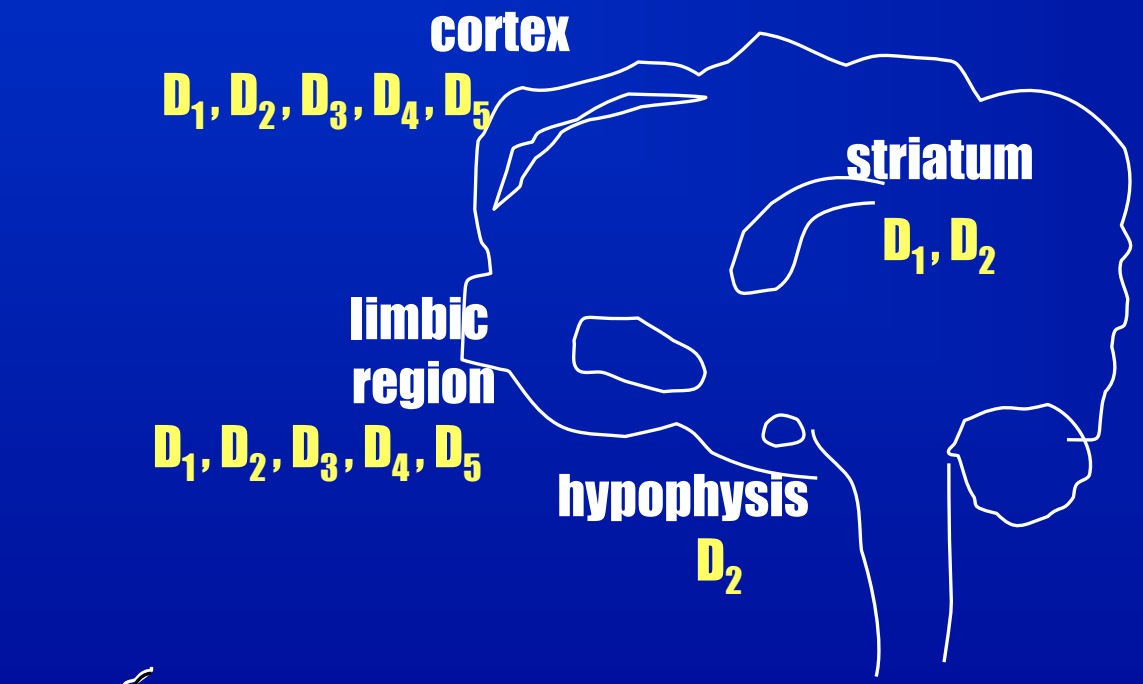
Family D1:

$D_{1, 5}$ - coupled to adenylylcyclase → ↑ cAMP – excitatory influence

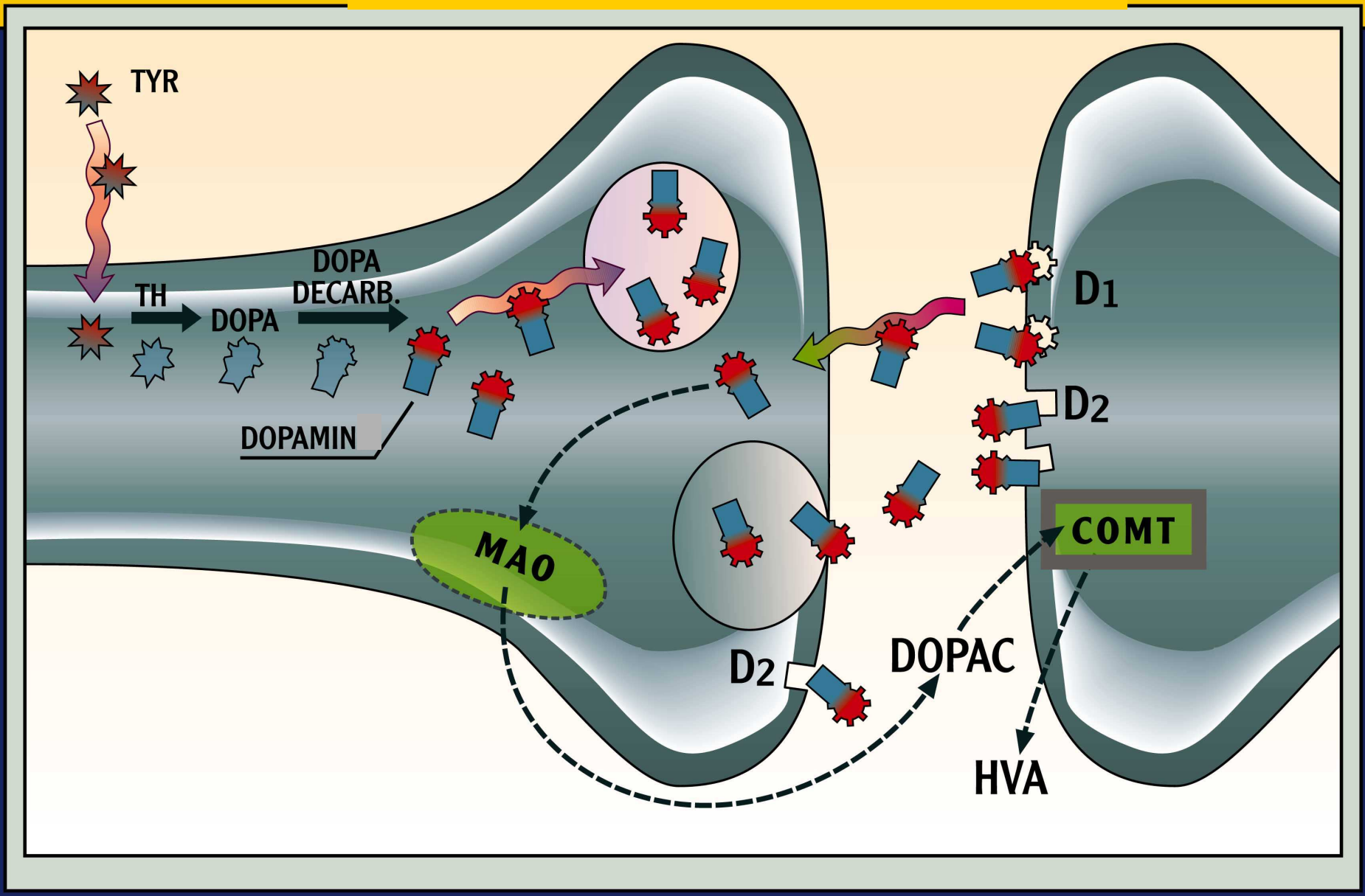
Family D2:

$D_{2, 3, 4}$ - coupled to phosphodiesterase (cAMP degradation)
→ ↓ cAMP - inhibitory influence

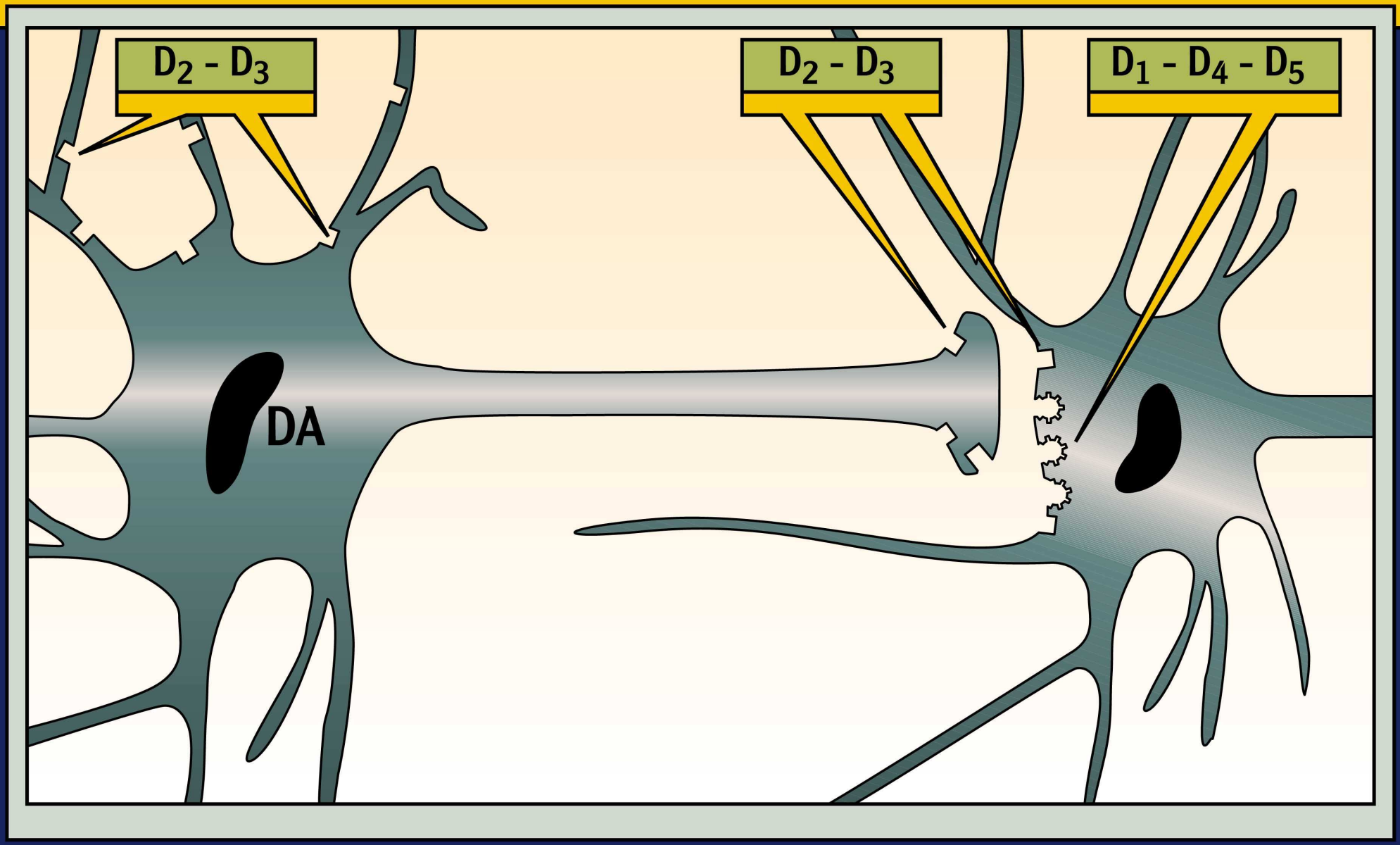
Distribution of dopamine receptors



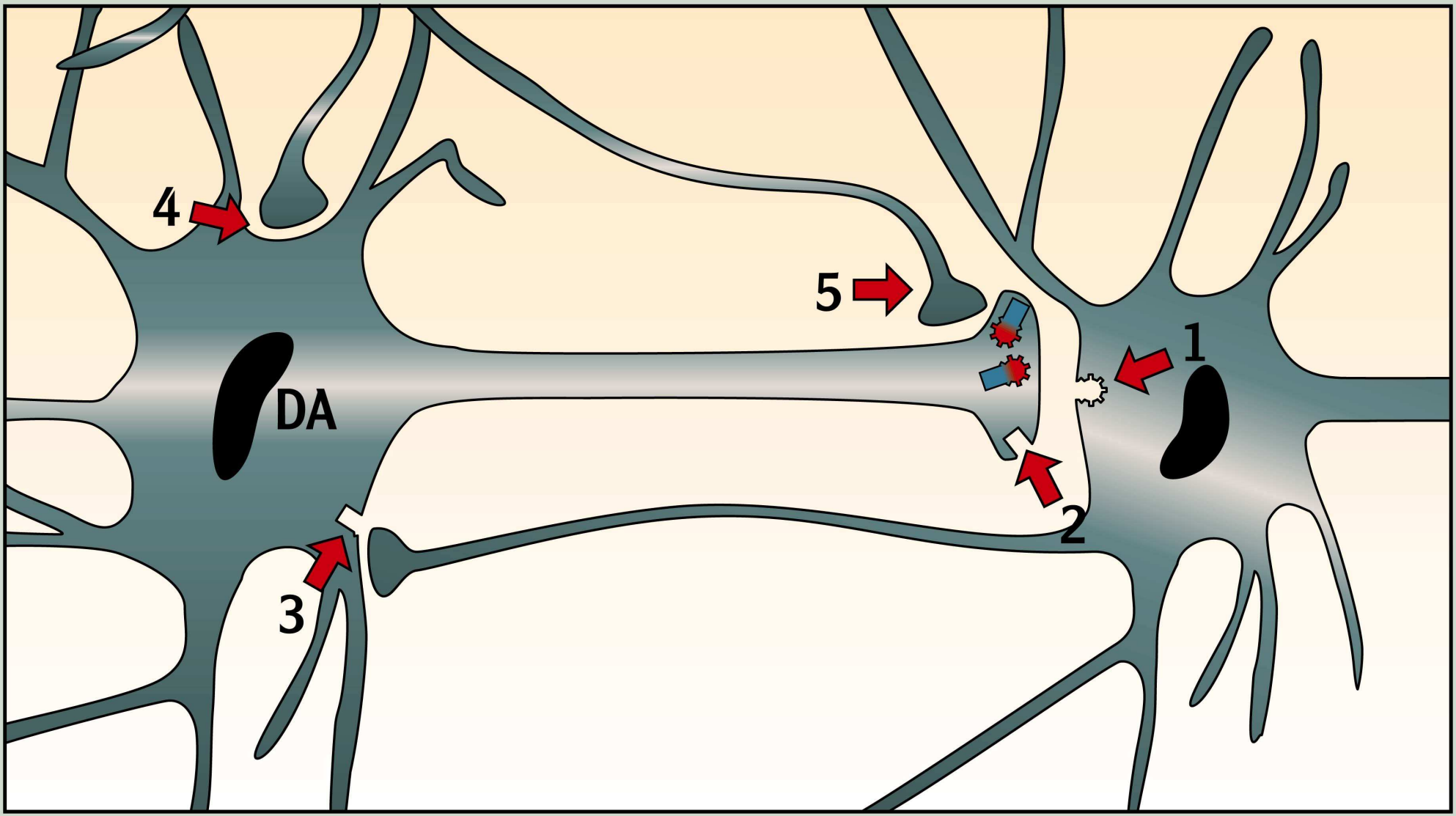
Dopaminergic neurotransmision



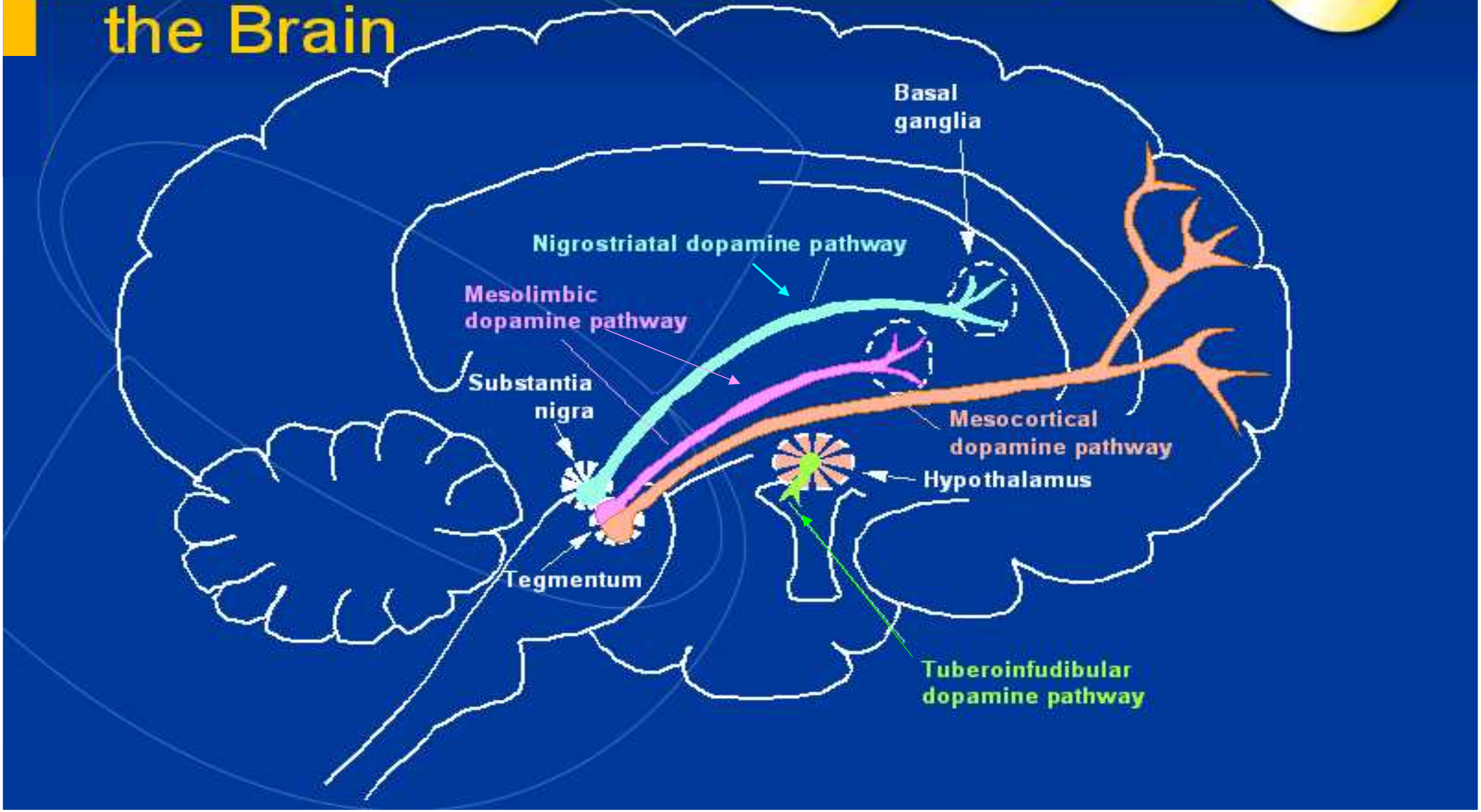
Dopamine receptors



Possible modulation of dopaminergic transmistter functions



The 4 Dopaminergic Pathways of the Brain



4 DAergic brain pathways

NIGROSTRIATAL (subt. nigra – basal ganglia)
control of movements

MESOLIMBIC (midbrain VTA – ncl. accumbens)
positive symptoms, euphoria

MESOCORTICAL (midbrain – limbic cortex)
negative symptoms,
cognitive side effects

TUBEROINFUNDIBULAR
(hypothalamus – anterior pituitary gland)
control of prolactine secretion

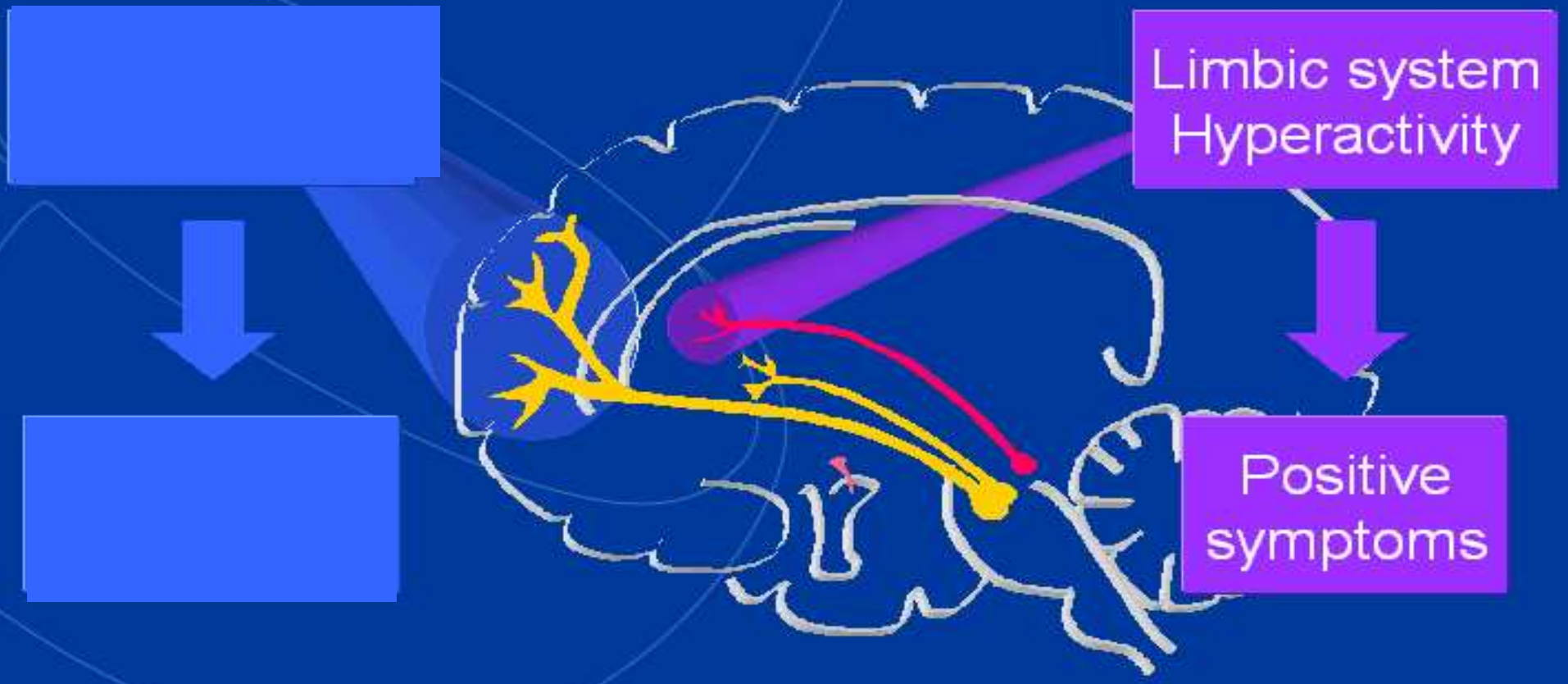
MAIN SYMPTOMS OF SCHIZOPHRENIA

POSITIVE SYMPTOMS

delusions
hallucinations
disorganised speech
disorganized behaviour
catatonic behaviour

The Dopamine Hypothesis of Schizophrenia

Mesofrontal and Mesolimbic Dopamine Pathways



MAIN SYMPTOMS OF SCHIZOPHRENIA

POSITIVE SYMPTOMS

delusions
hallucinations
disorganised speech
disorganized behaviour
catatonic behaviour

NEGATIVE SYMPTOMS

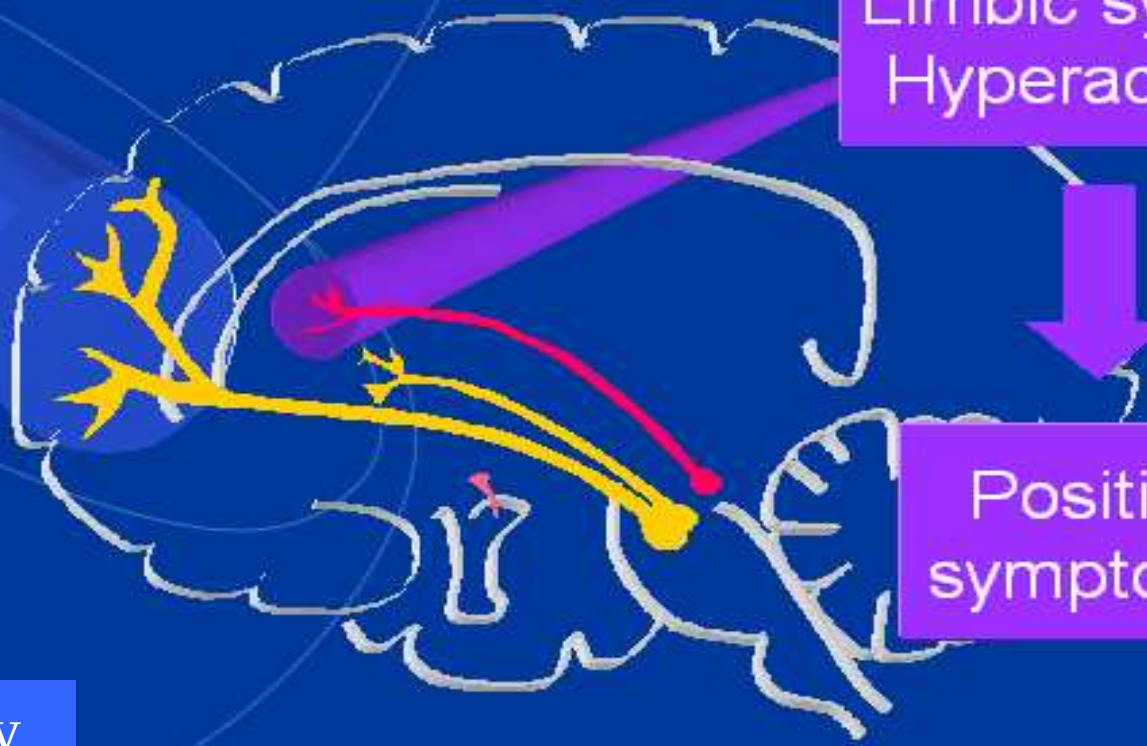
affective flattening (restriction of emotional expression)
alogia
avolition (general lack of desire, motivation, difficulty, or inability to initiate and persist in goal-directed behaviour)
anhedonia (lack of pleasure)
attention impairment

The Dopamine Hypothesis of Schizophrenia

Mesofrontal and Mesolimbic Dopamine Pathways

Frontal cortex Hypoactivity

Limbic system Hyperactivity

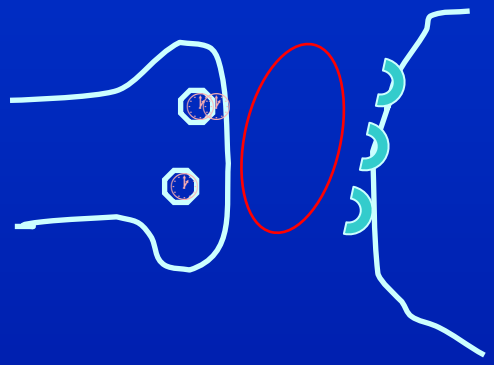


Negative symptoms

Positive symptoms

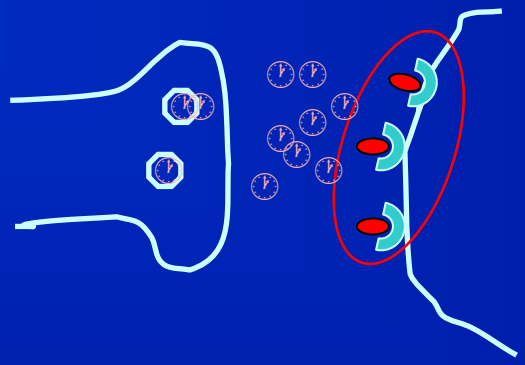
mesocortical pathway

? ? Couses of hypoactivity of mesocortical DAergic pathway ??



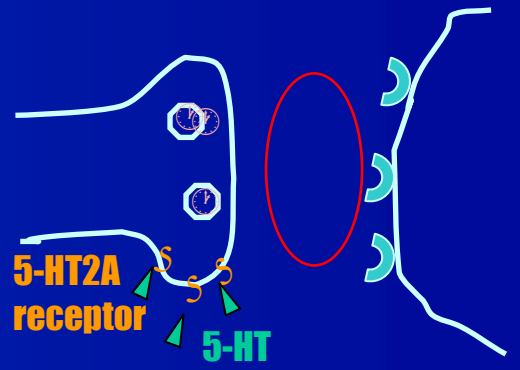
dopamine

Primary defficit
of dopamine



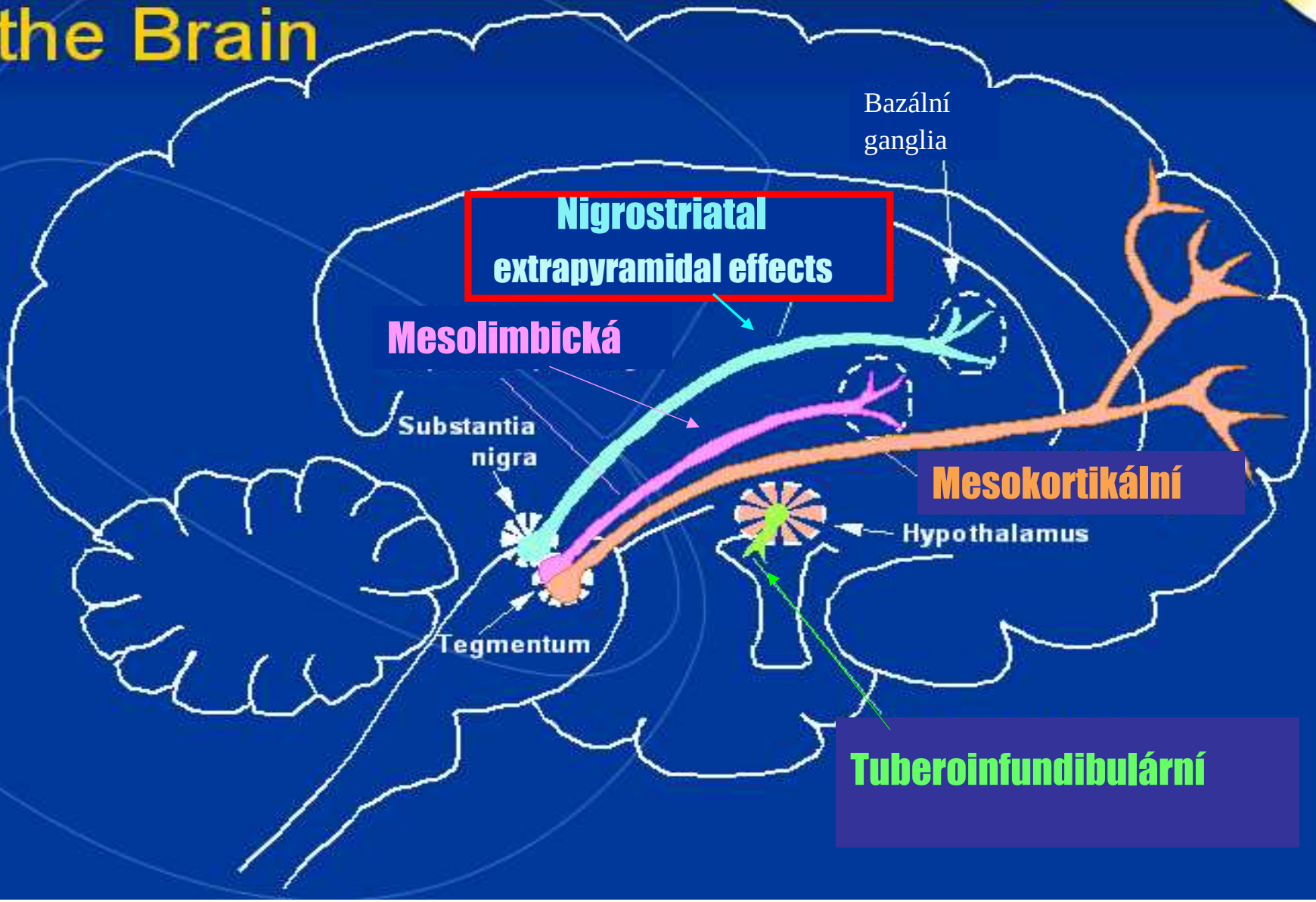
D2 antagonist

Blockade
of D2 receptors

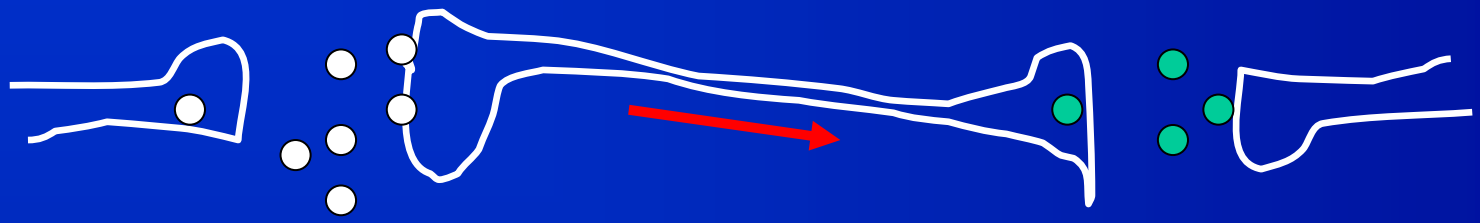


Secondary deficit
of dopamine

The 4 Dopaminergic Pathways of the Brain



nigrostriatal pathway → DA inhibits Ach activity



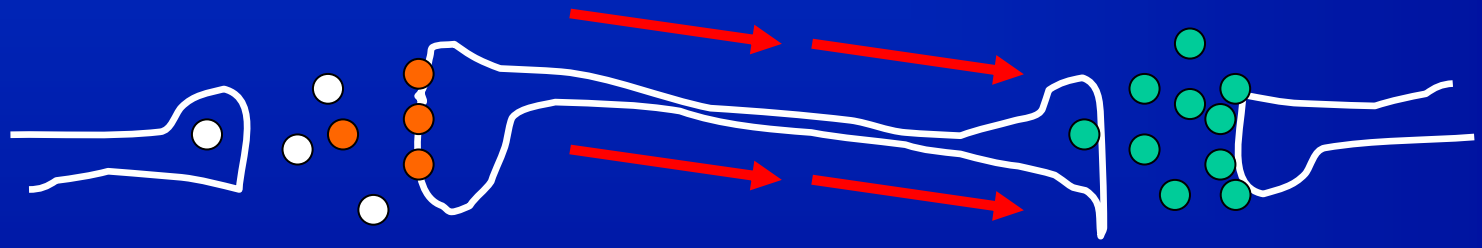
DA

Ach

antipsych.

anti-Ach

blockade of DA function → Ach hyperactive

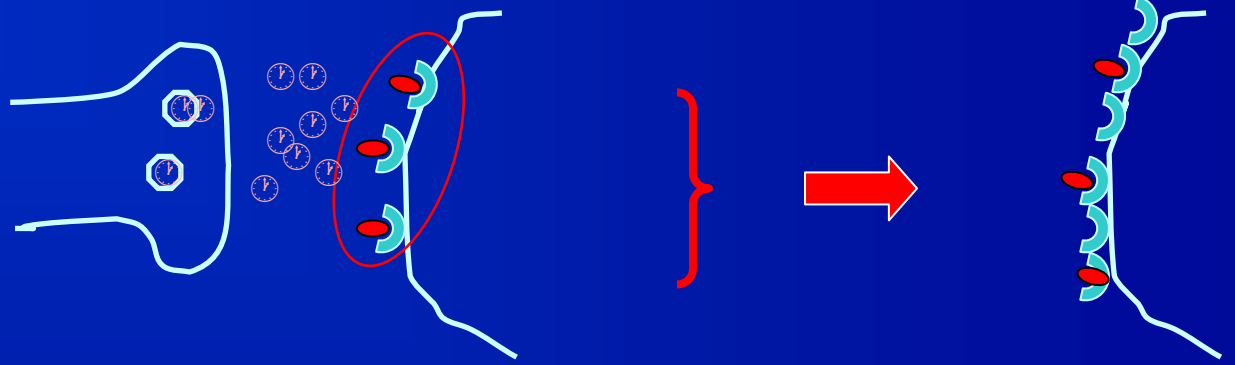


consolidation of Ach hyperactivity

Nigrostriatal dopaminergic pathway

EPS

Tardive dyskinesia



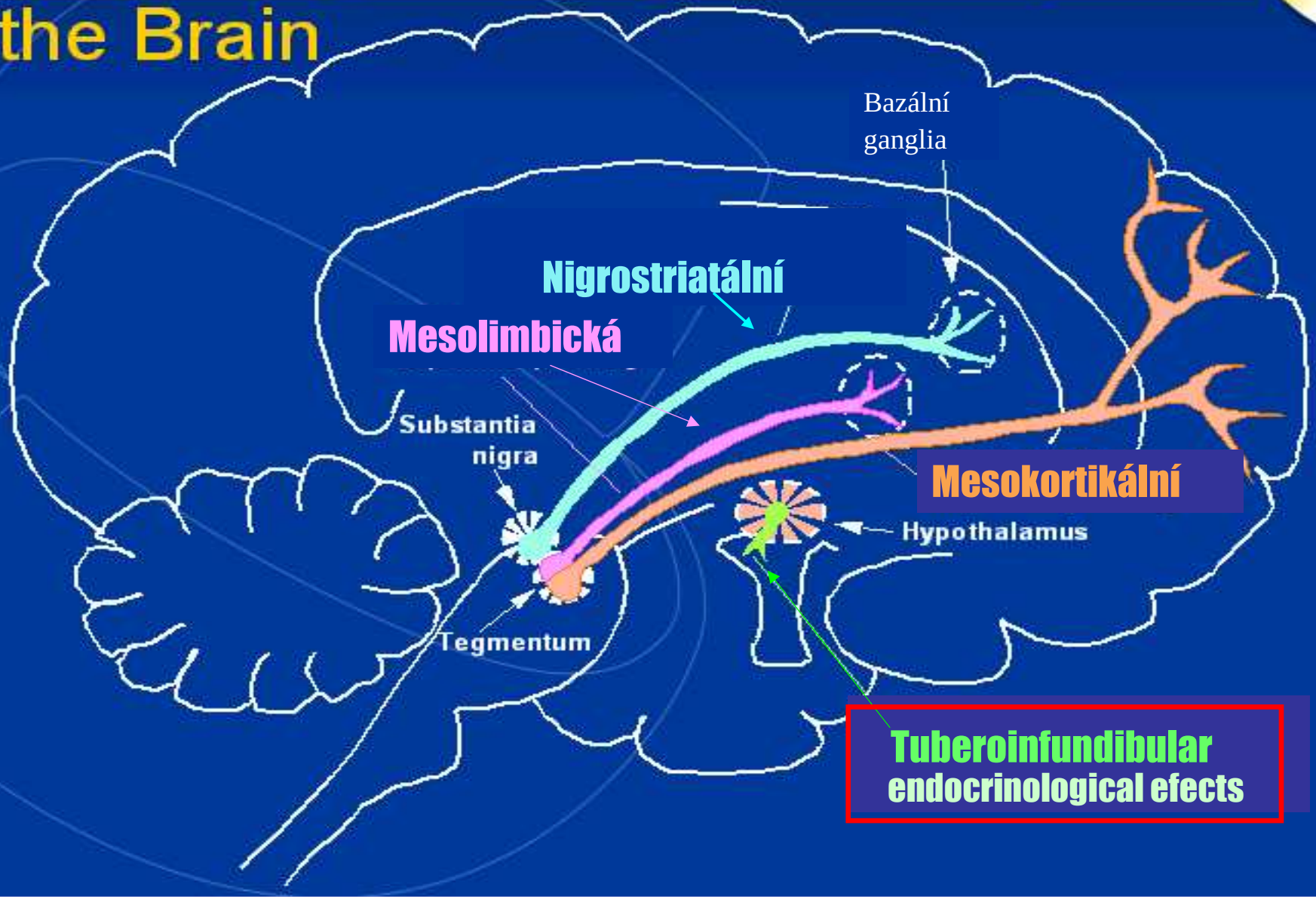
D2 antagonist

Blockade of D2 recept. in nigrostriatal pathway

D2 receptor up-regulation

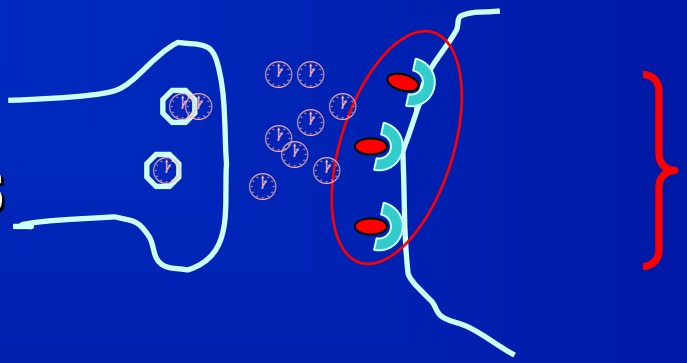
Stephen M. Stahl, 2000

The 4 Dopaminergic Pathways of the Brain



Tuberoinfundibular dopaminergic pathway

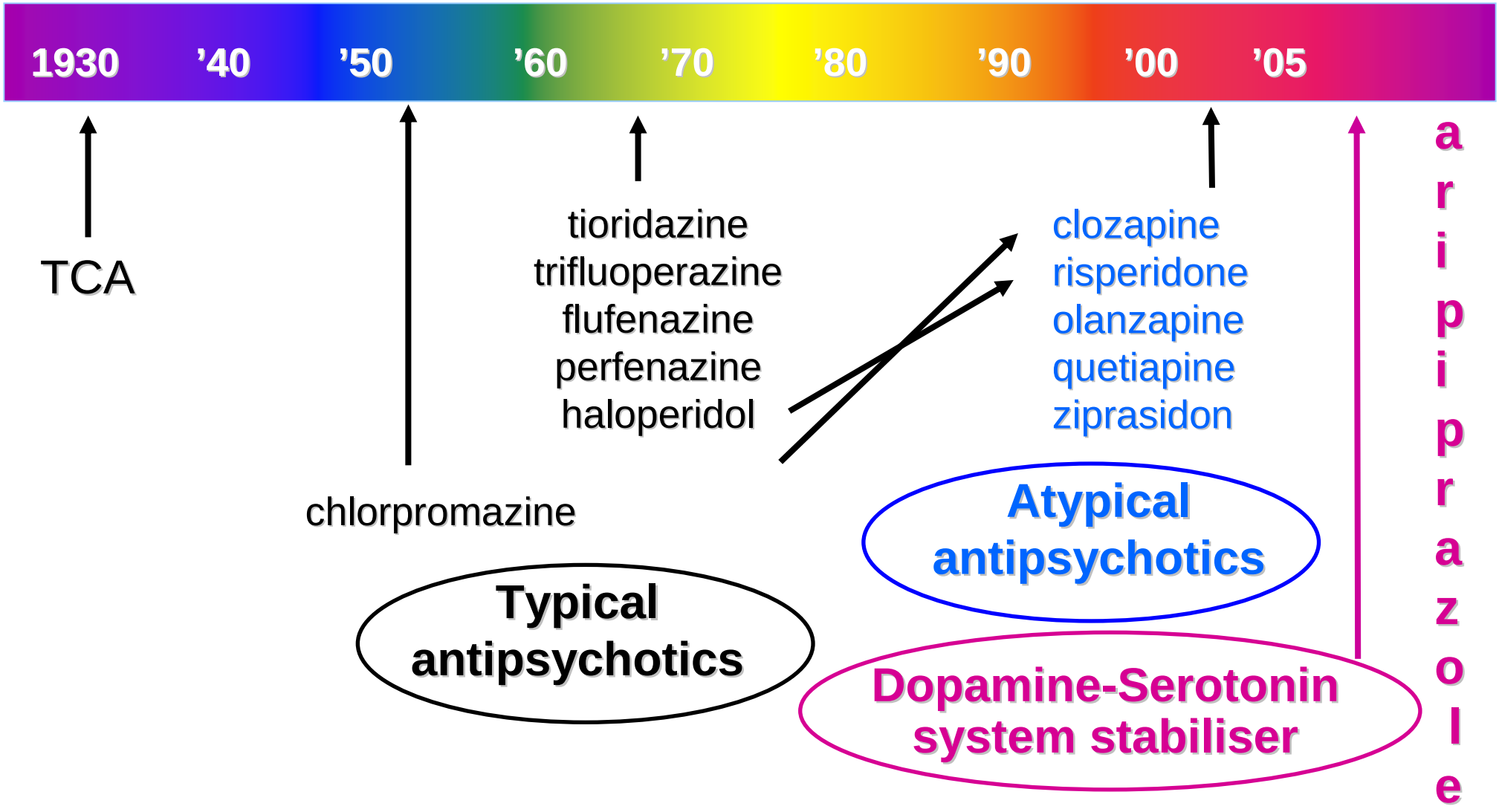
Blockade of D2 receptors



D2 antagonist

Hyperprolactinemia

Development of antipsychotics



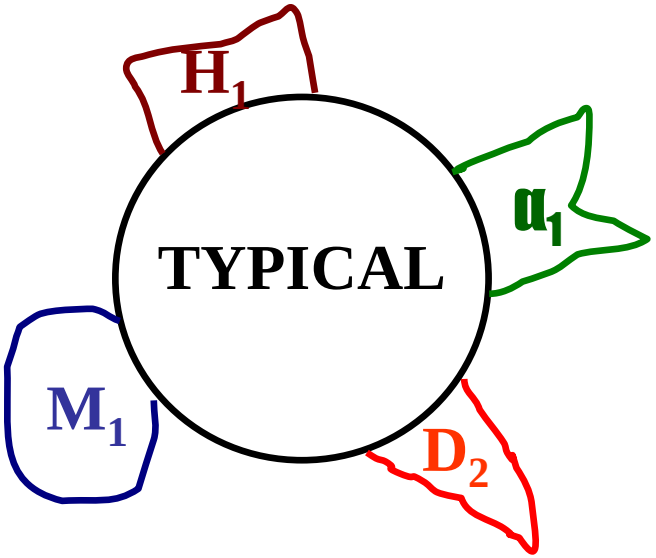
ANTIPSYCHOTICS (neuroleptics)

Typical (I. generation)

Basic (sedative): (*lower efficacy - doses in hundreds of mg*)
chlorpromazine, levomepromazine, chlorprothixen, thioridazine, clopenthixol

Incisive: (*higher efficacy - doses in mg or tens of mg*)
prochloperazine, phluphenazine, perphenazine, pimozide, haloperidol, flupenthixole
DEPOT (1x /1 – 3 weeks) – penfluridole, fluphenazine

ANTIPSYCHOTICS



D_2 blockade = antipsychotic effects
M_1 blockade = dry mouth, diplopia, constipation
α_1 blockade = ↓ BP, dizziness
H_1 blockade = drowsiness, weight gain

Stephen M. Stahl, 2000

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Adverse effects: *EPS, tardive dyskinesia, prolactinemia, malignant neuroleptic syndrom*

Neuroleptic Malignant Syndrom

idiosyncratic response (20-30% mortality; in 1-2% treated patients)
5-10 day persistence after the withdrawal of p.o. treatment,
(3-30 days after injections)

HYPERTERMIA; EPS (rigidity, dysartria, dysforia, tremor),

VEGETATIVE SY. (tachycardia, ↑ BP, tachypnoe, urinary incontinence);

DISORDERS OF BEHAVIOUR & CONSCIOUSNESS (delirium, somnolence, comma, epileptic paroxysms);

leukocytosis, homeostatic disturbance, ↑hemocoagulation ….

ANTIPSYCHOTICS (neuroleptics) ... cont.

Atypical (II. generation)

(*without EPS, tardive dyskinesia, prolactinemia, malignant neuroleptic syndrom*)

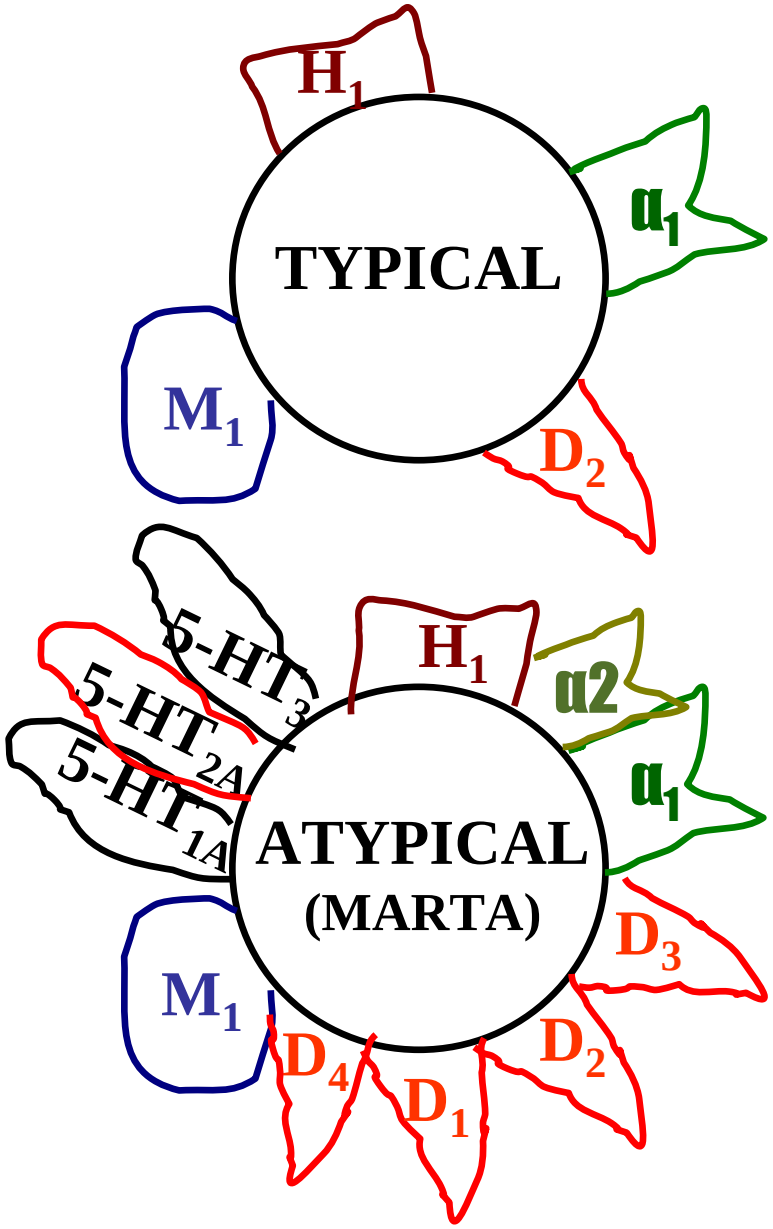
- **MARTA** *(Multi-Acting Receptor Targeted Agents)*
  clozapine, olanzapine, quetiapine

- **SDA** *(Serotonin-Dopamine Antagonist)*
  risperidone, ziprasidone, sertindole

- **D2/D3 antagonists**
  sulpiride, amisulpride

- **DSSS** *(Dopamine-Serotonin System Stabilizers)*
  aripiprazole

ANTIPSYCHOTICS



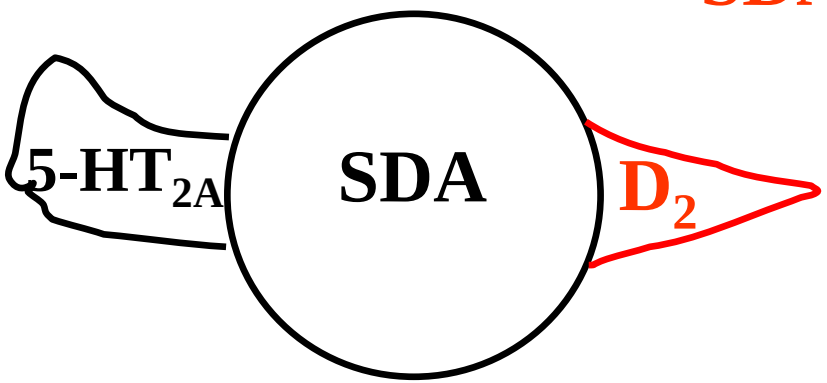
D_2 blockade = antipsychotic effects
M_1 blockade = dry mouth, diplopia, constipation
α_1 blockade = ↓ BP, dizziness
H_1 blockade = drowsiness, weight gain

More selective for mesolimbic pathways
↓
less EPS

<u>therapeutic efects</u>	<u>side effects</u>
$D_{1,2,3,4}$	α_1, α_2, M_1, H_1
$5\text{-}HT_{2A}$	

Stephen M. Stahl, 2000

SDA (Serotonin-Dopamin Antagonist)



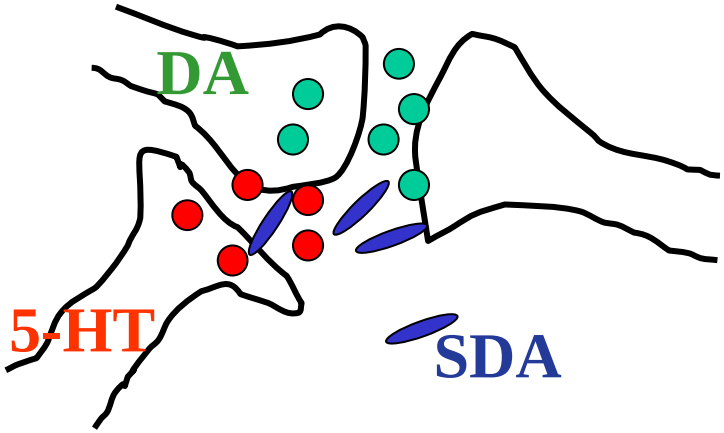
risperidone, olanzapine, sertindol, seroquel

↓

better effect on negative symptoms,

less of EPS (especially at lower dosage)

5-HT → inhibition of DA realease



5-HT r. blockade → ↑ release of DA

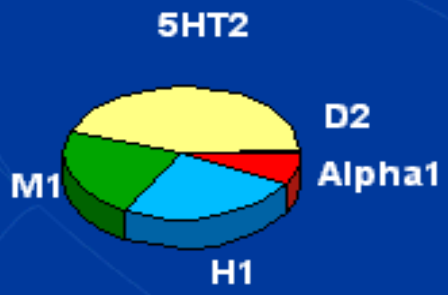
= suppression of

impact of D_2 blockade

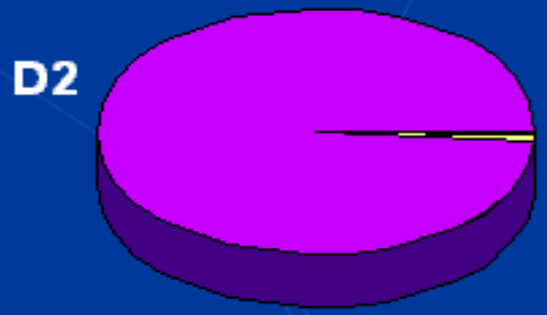
Stephen M. Stahl, 2000

ANTIPSYCHOTIC RECEPTOR BINDING

clozapine

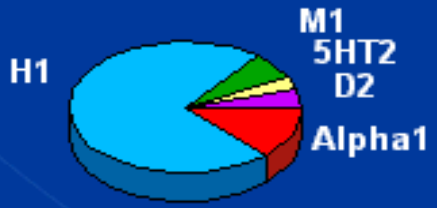


amisulpride

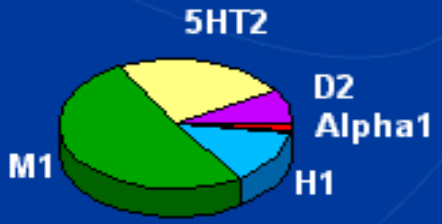


risperidone

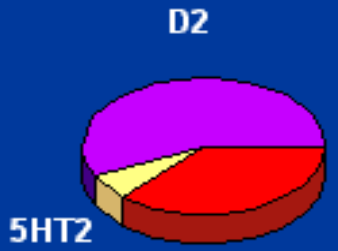
quetiapine



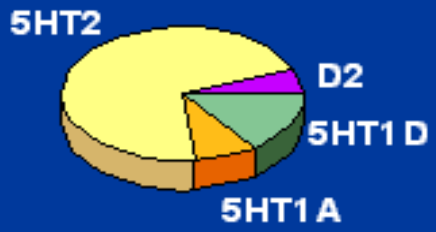
olanzapine



haloperidol



ziprasidone



From Richelson 1996; Schoemaker et al 1997; Seeger et al 1995

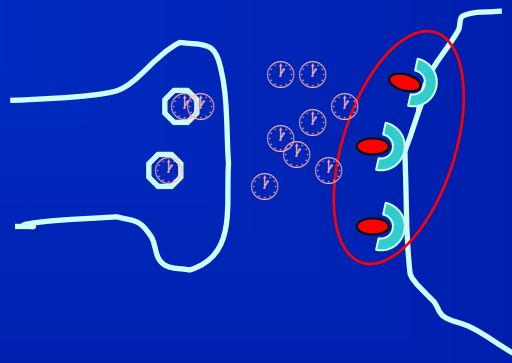
Comparative Side Effect Profiles of the New Antipsychotics

	clozapine	risperidone	olanzapine	amisulpride	quetiapine	ziprasidone
Sedation	++	+	++	+/-	+	+
EPS	-	+	+	+	(+)	+
Orthostatic hypotension	++	+	(+)	-	+	+
Weight gain	++	+ (+)	+ +	+	+ (+)	(+)
Prolactin increase	(+)	++	(+)	++	(+)	+
Salivation/dry mouth	+	(+)	+	-	(+)	(+)
Haematological effects	++	(+)	+	(+)	(+)	(+)

+ mild ++ moderate

D2/D3 antagonists

in psychosis

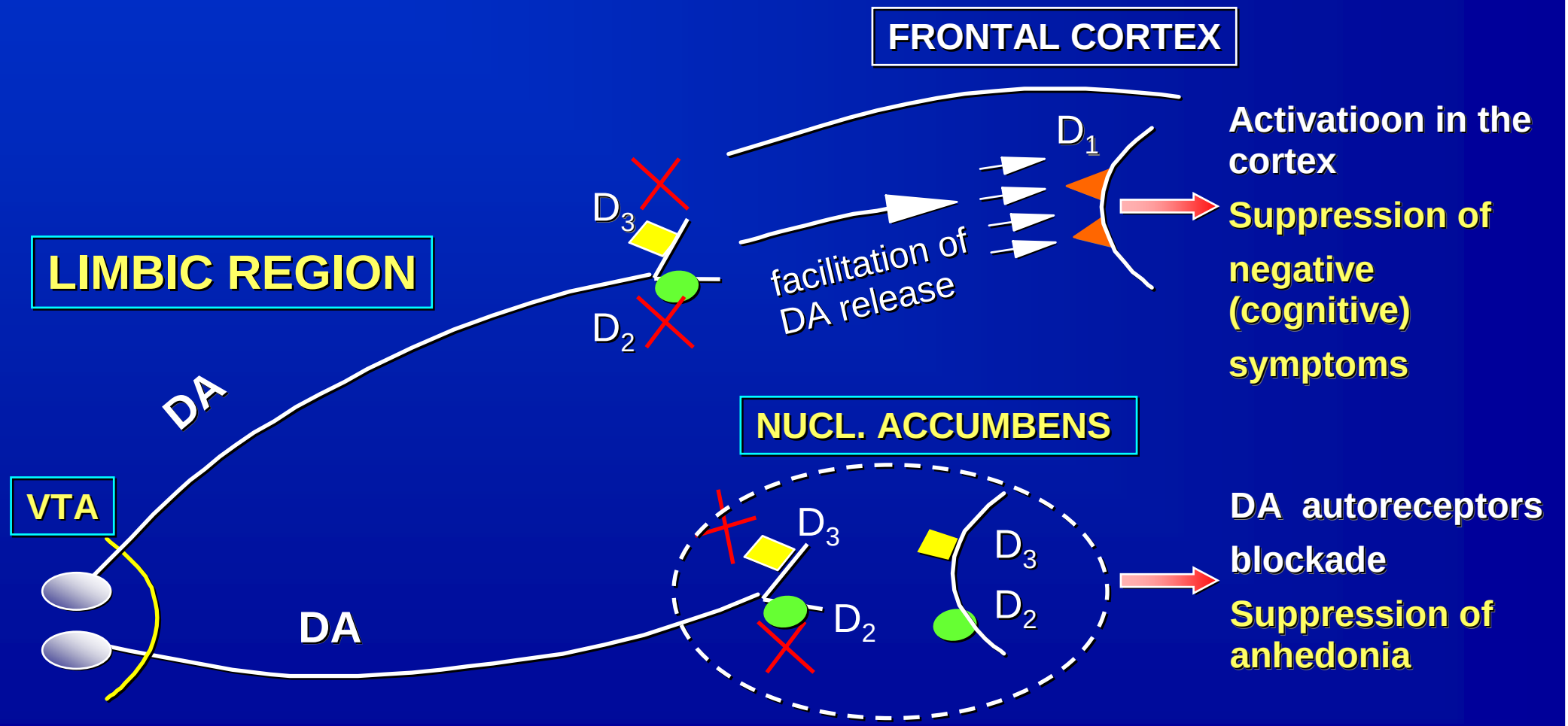


SUPPRESSION OF POSITIVE SYMPTOMS

blockade of $D_{2,3}$ postsynaptic receptors

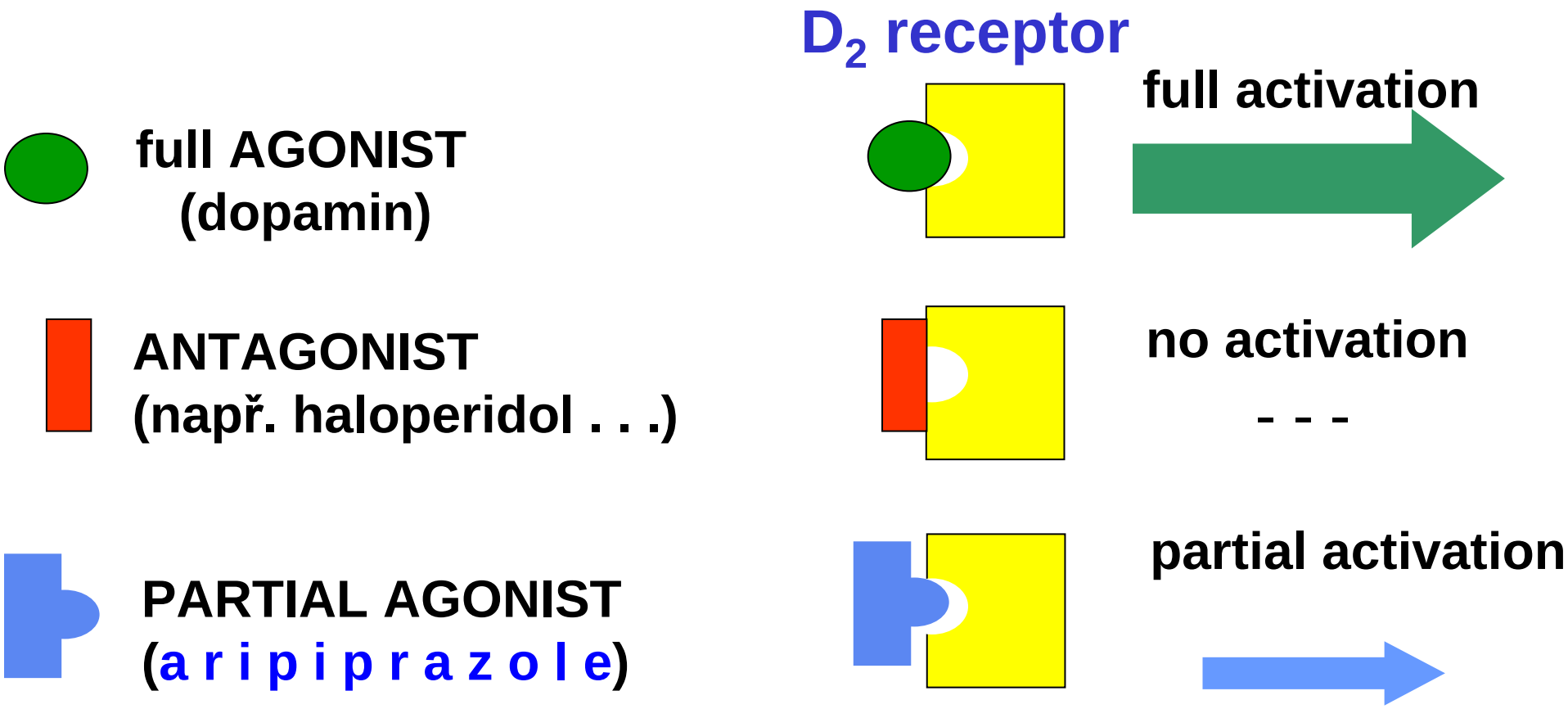
D2/D3 antagonists

Selective blockade of D_3/D_2 autoreceptors in the limbic region



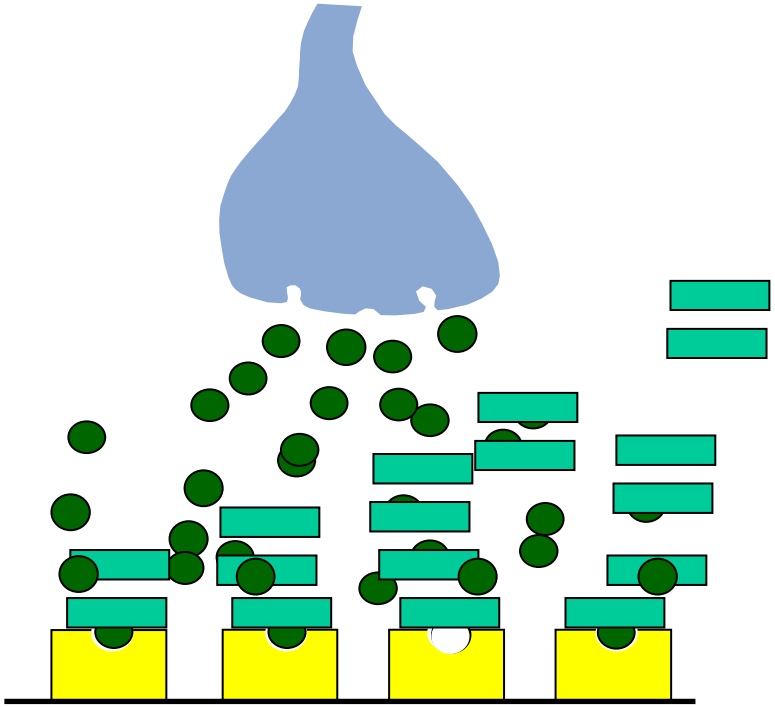
Dopaminergic D_2 receptor ligands

"INTRINSIC ACTIVITY"
ability of ligand to activate receptor

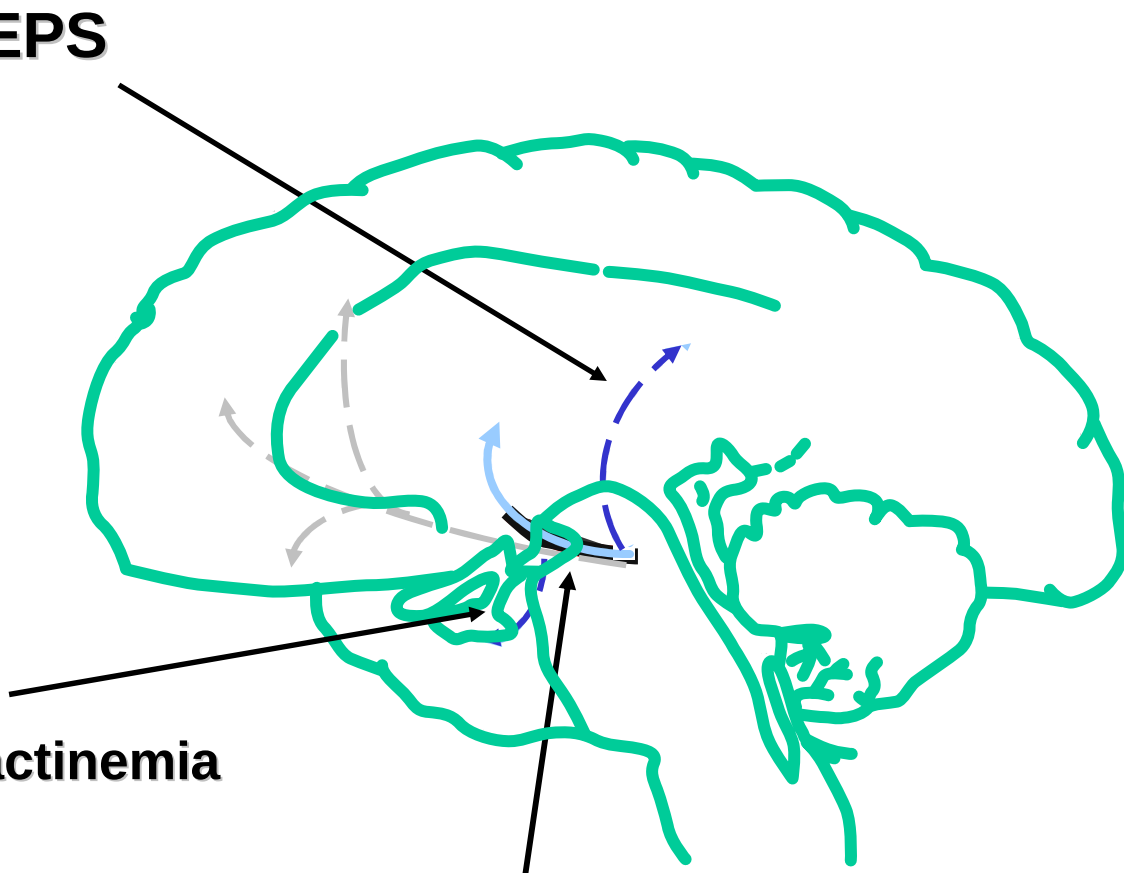


*

Influence of dopamine antagonist on: positive symptoms and EPS



DA inhibition



Pharmacological mechanisms of antipsychotics

There is need to suppress positive symptoms
65 – 70%
occupation of D2 receptors by antipsychotic.

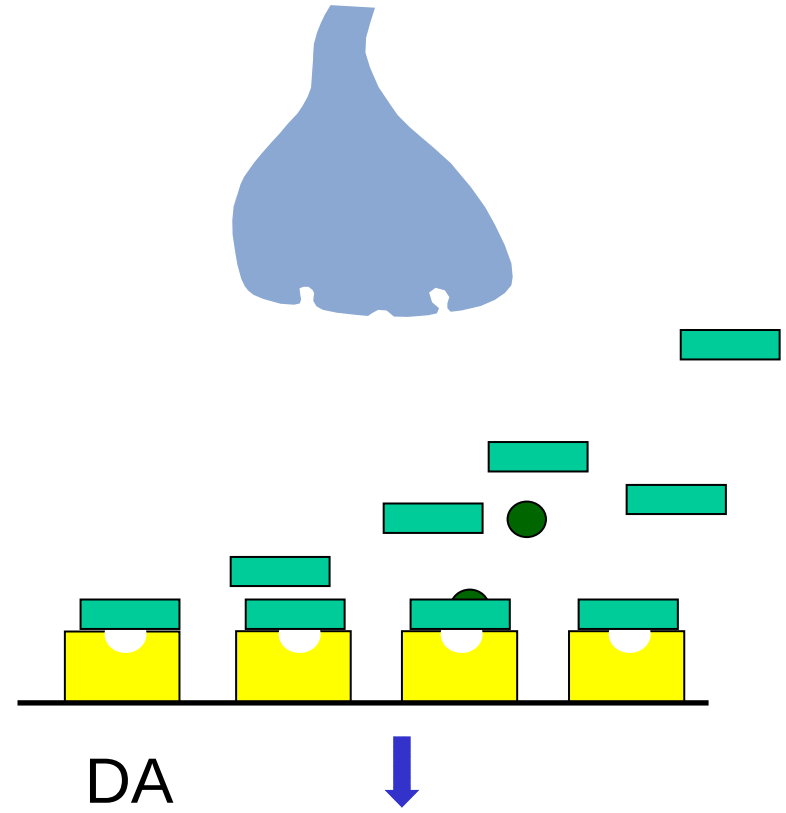
EPS occurs
up to 80%
occupation of D2 receptors by antipsychotic.

Farde L, et al.: Arch Gen Psychiatry 1992; 49:538-544

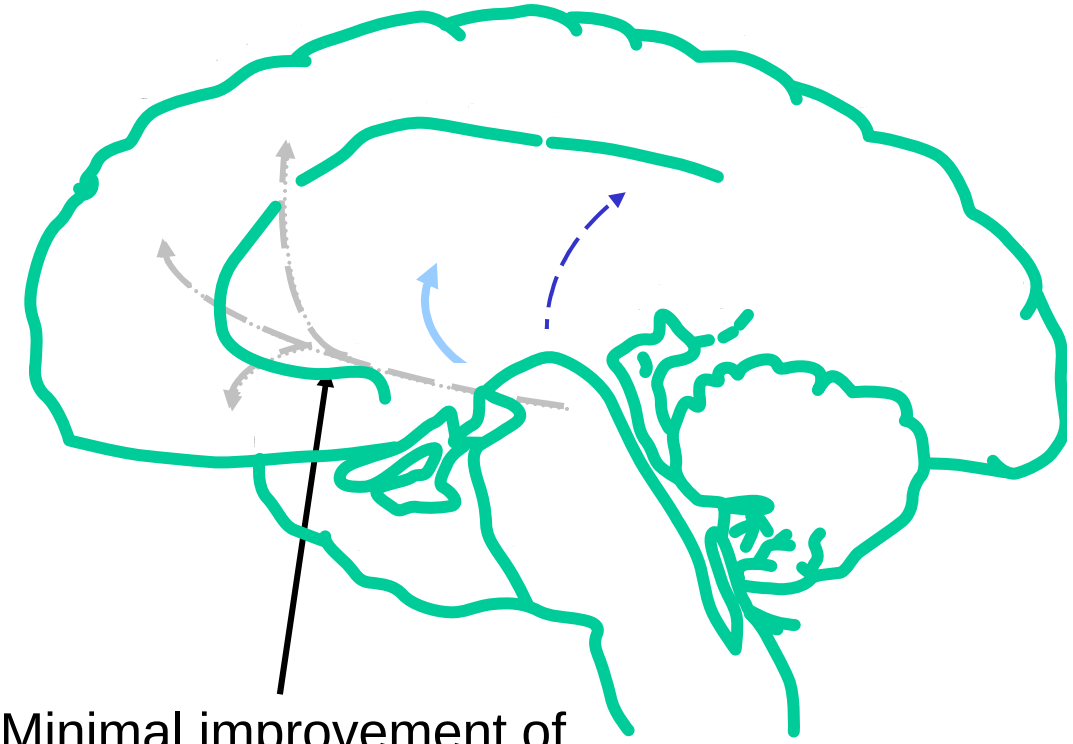
Increase in prolactine release is dose dependent
(occupation of D2-receptors).

Schlegel S, et al.: Psychopharmacology (Berl) 1996; 124:285-287

Influence of dopamine antagonist on: negative symptoms



DA inhibition



Minimal improvement of negative symptoms

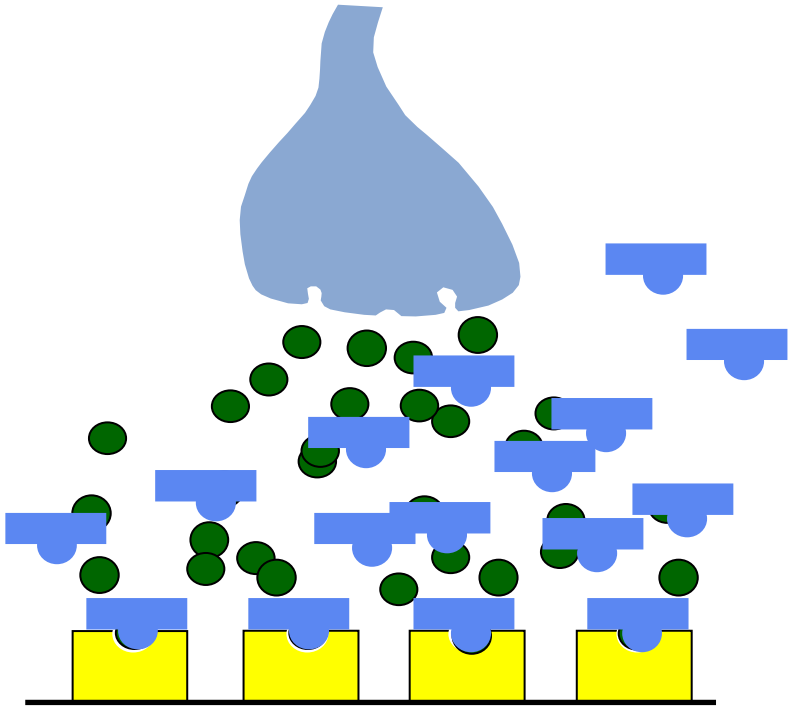
Pharmacological mechanisms of antipsychotics

Negative symptoms and affectivity are influenced by antipsychotics with antagonistic activity at 5-HT2A receptors.

Blockade of other receptors is source of adverse effects.

Farde L, et al.: Arch Gen Psychiatry 1992; 49:538-544

Influence of DAergic partial antagonism on: positive symptoms and EPS



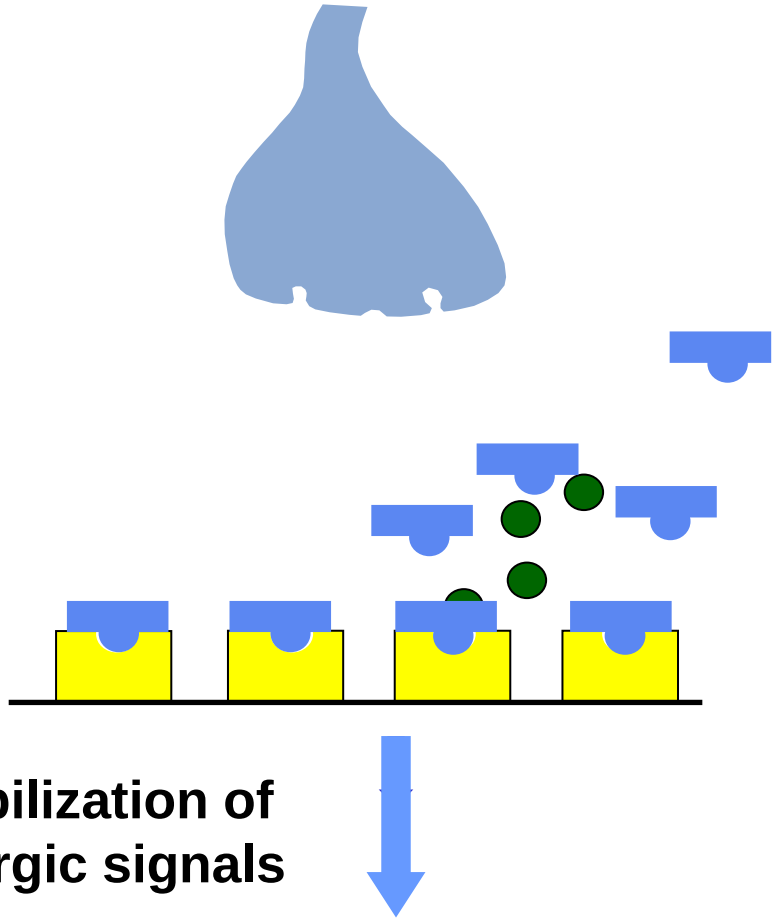
DA stabilization

without EPS

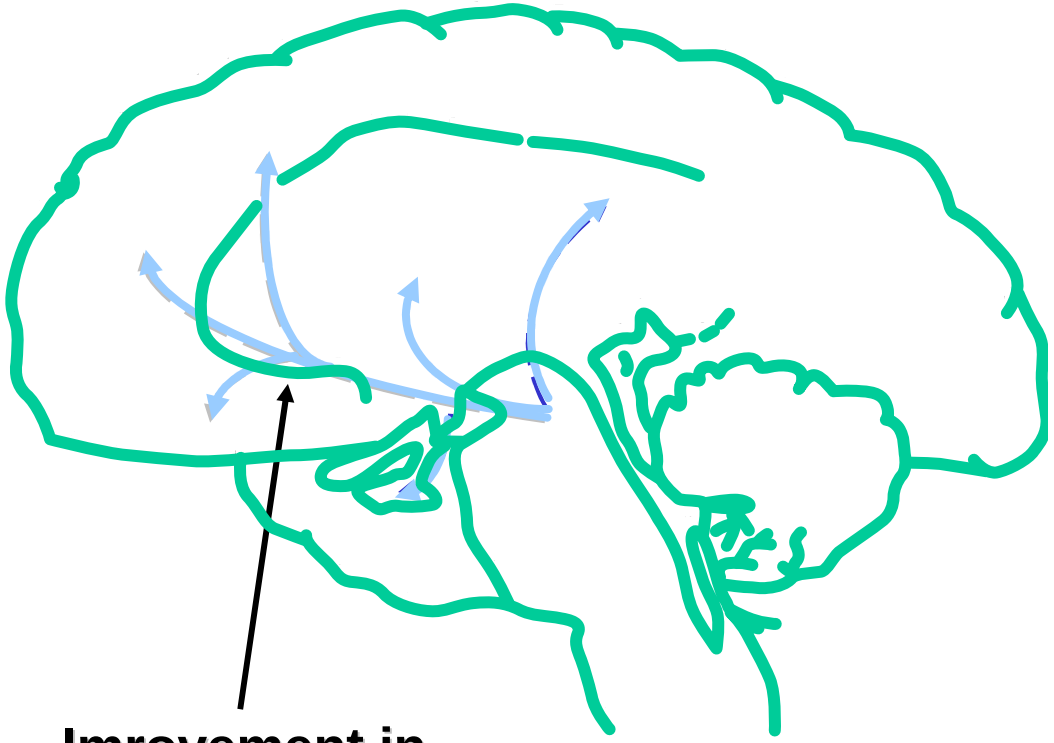
without hyperprolactinemia

suppression of positive symptoms

Influence of DA partial antagonism on: negative symptoms



Stabilization of
DAergic signals



Imrovement in
negative symptoms, cognition, motivation

Impact of receptor activities on effects of antipsychotics

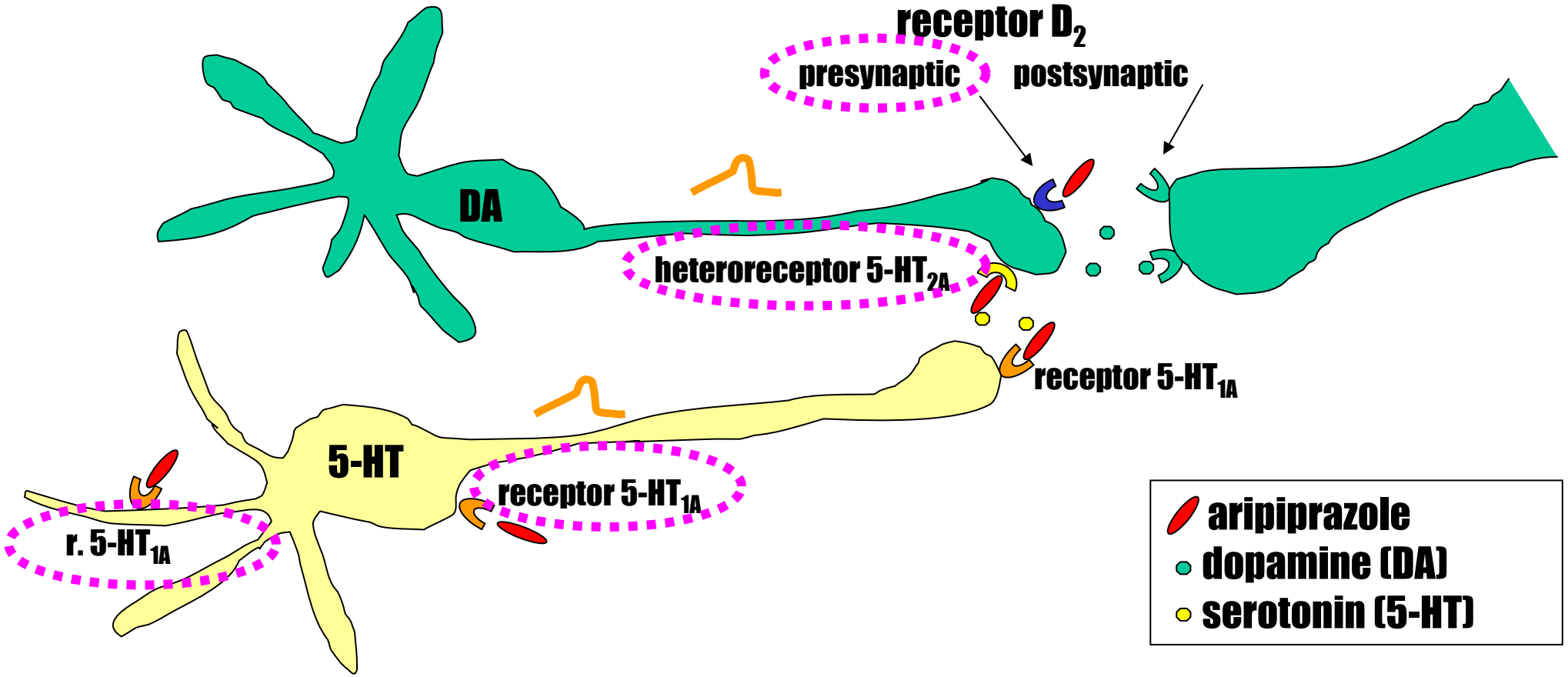
Receptor	Therapeutic effects	Adverse effects
D2	positive symptoms	EPS, endocrinological effects
5-HT2A	negative symptoms	??
5-HT1A	negative symptoms cognitive symptoms anxiety/depresssion	?
α_1	??	hypotension
α_2	??	antihypertensive effects
H_1	sedation	sedation, weight increase
M_1	suppression of EPS	anticholinergic effects

DSSS *(Dopamine-Serotonin System Stabilizers)*

ARIPIPRAZOLE suggested mechanisms of action:

- partial agonist at D_2 autoreceptors and $5\text{-}HT_{1A}$ somatodendritic receptors
- antagonist at $5\text{-}HT_{2A}$ heteroreceptors of dopaminergic neurons

(Burris at al., 2002; Jordan et al., 2002)



DSSS *(Dopamine-Serotonin System Stabilizers)*

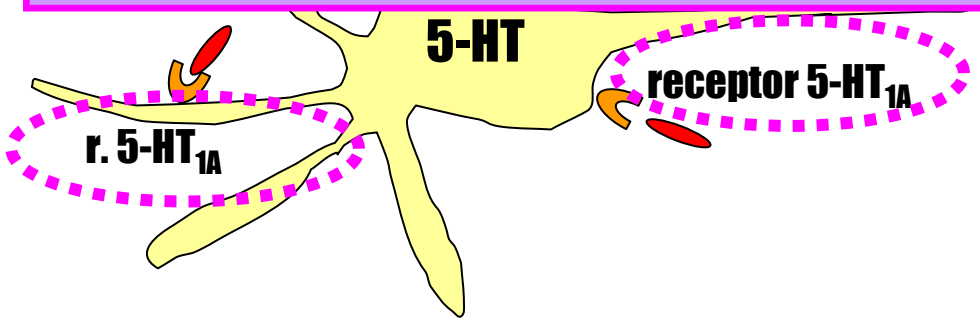
ARIPIPRAZOLE suggested mechanisms of action:

- partial agonist at D_2 autoreceptors and $5\text{-}HT_{1A}$ somatodendritic receptors
- antagonist at $5\text{-}HT_{2A}$ heteroreceptors of dopaminergic neurons

(Burris at al., 2002; Jordan et al., 2002)

- partial agonist at D2 autoreceptors → inhibition of DA release

- antagonist at 5-HT2A heteroreceptors of dopaminergic neurons
  → desinhibition of DA neurons (nigrostriatum, mesocortical region)
  → suppression of negative symptoms of schizophrenia



aripiprazole
dopamine (DA)
serotonin (5-HT)

ARIPIPRAZOL - main indications:

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1. **Schizophrenia in adults and adolescents (age 13-17)**

2. **Acute manic or mixed episodes of bipolar disorder I. (as monotherapy or with valproate in adults or adolescents of age 10-17)**

3. **Adjunctive therapy in major depression**

4. **Irritability associated with autistic disorder in pediatric patients (age 6-17)**

5. **Acute agitation associated with schizophrenia or bipolar disorder (intramuscularly)**

Kantrowitz J.T., Citrome L. From MedscapeCME Psychiatry & Mental Health Antipsychotics A-Z, 2010, www.medscape.org/viewarticle/718207

Aripiprazole

its high affinity for D2 receptor can displace from that binding other antipsychotic with lower affinity

its partial agonistic actvity can produce at least some of DAergic effects

this can explain exacerbation of psychosis in some patients on exchange of other antipsychotic pharmacotherapy to aripiprazole

Ramaswamy S, et al. Int Clin Psychopharmacol. 2004;19:45-48.

INDICATIONS FOR ANTIPSYCHOTICS

- psychoses

- sleeping disorders
- anxiety
- Huntington disease
- Tourett's syndrome
- anesthesiology / neuroleptanalgesia
- nausea, vomitus