Neurochemical basis of behavior

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Drug therapy of schizophrenia

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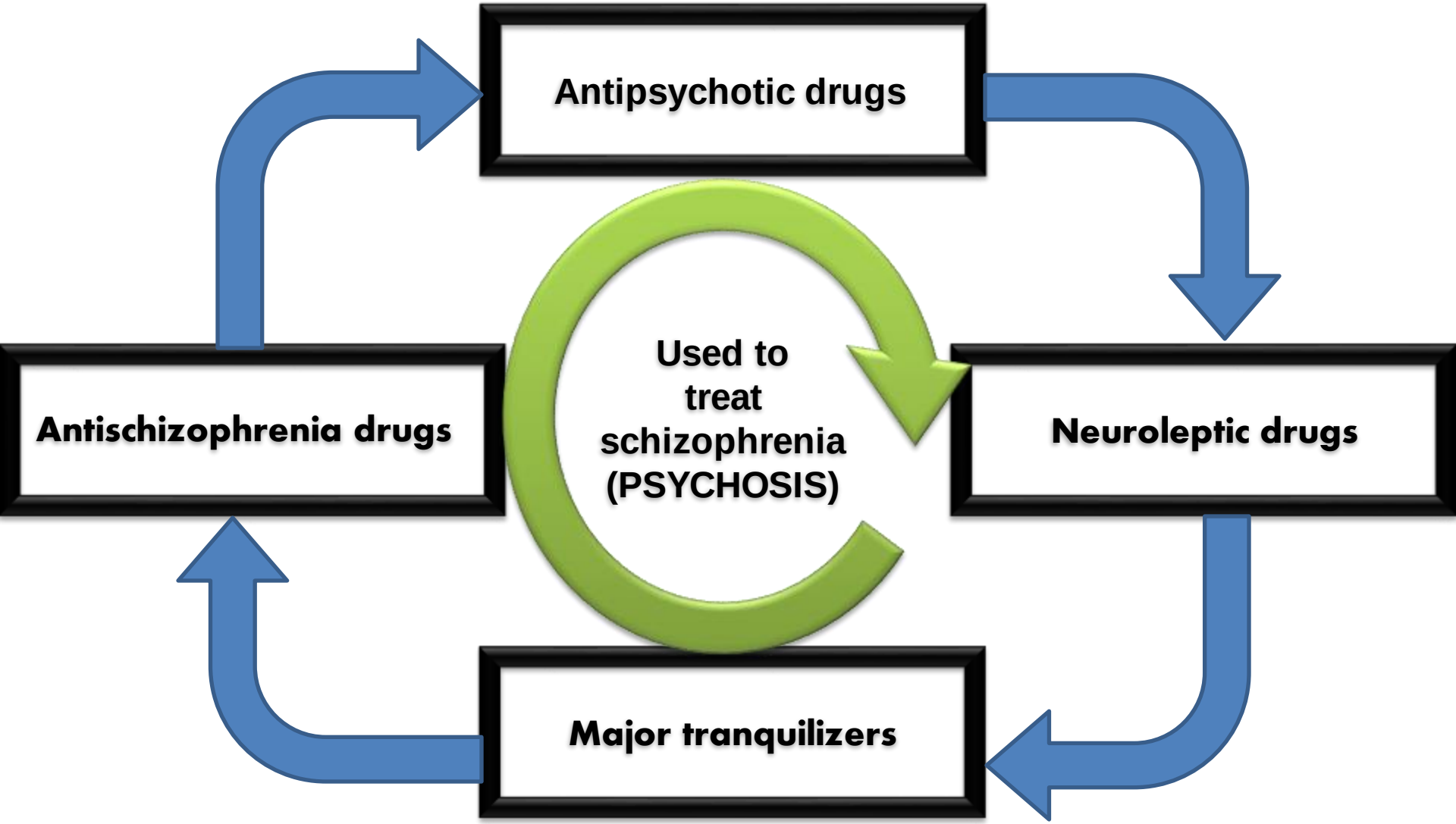
Objectives

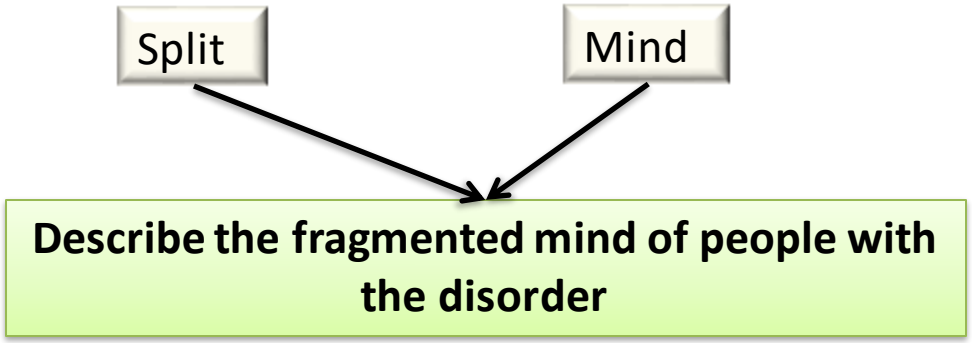
- 1- What is schizophrenia?
- 2- Diagnosis of shizophrenia
- 3- Other psychotic disorders
- 4- Epidemiology of schizophrenia
- 5- Etiology of schizophrenia
- 6- Pharmacological treatment of shizophrenia
- 7- Non-pharmacological treatment
- 8- Mechanism of action of antipsychotic drugs
- 9- Side effects of antipsychotic drugs


Antipsychotic drugs
Neuroleptic drugs
Major tranquilizers
Antischizophrenia drugs
Used to treat schizophrenia (PSYCHOSIS)

Schizophrenia

- The most debilitating mental illnesses
- Patients do not have more than one distinct personality
- 1% of the population suffer (in 12 m period)

Schizophrenia



Is a serious brain illness which are characterized by severe problems with a person's

- **thoughts,**
- **feelings,**
- **behavior,**
- **and use of words and language.**

Schizophrenia

- Major disturbances in thought, feelings, and behavior:

- Can disrupt interpersonal relationships, diminish capacity to work or live independently
- Significantly increased rates of suicide and death

Schizophrenia

- Lifetime prevalence ~1%
- Affects males slightly more often than females
- Onset typically late adolescence or early adulthood
  - Males diagnosed at a slightly earlier age
- Diagnosed more frequently in African Americans

Diagnostic Criteria for Schizophrenia

- **Two or more** of the following symptoms **for at least 1 month**; **one symptom should be either 1, 2, or 3:**
  - (1) delusions
  - (2) hallucinations
  - (3) disorganized speech
  - (4) disorganized (catatonic) behavior
  - (5) negative symptoms (diminished motivation or emotional expression)
- Functioning in work, relationships, or self-care has declined since onset
- D.D.: s addiction, bipolar disorder and depression

Clinical Picture of Schizophrenia

- Three major clusters of symptoms:
  - Positive
  - Negative
  - Disorganized

Table 9.1 Summary of the Major Symptom Domains in Schizophrenia

Positive Symptoms	Negative Symptoms	Disorganized Symptoms
Delusions, hallucinations	Avolition, alogia, anhedonia, blunted affect, asociality	Disorganized behavior, disorganized speech

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Positive Symptoms: Behavioral Excesses and Distortions

- **Delusions**
  - –Firmly held beliefs
  - –Contrary to reality
  - –Resistant to disconfirming evidence
- •Types of delusions:
  - –Persecutory delusions
- •"The CIA planted a listening device in my head"
- •65% have these

- **Hallucinations**
  - –Sensory experiences in the absence of sensory stimulation

- •Types of hallucinations:
  - –Auditory: Hearing voices
- •74% have this symptom
  - –Visual
- •Increased levels of activity in Broca's area during hallucinations

Negative Symptoms: Behavioral Deficits

- **Avolition**
  - Lack of interest; apathy
- **Asociality**
  - Inability to form close personal relationships
- **Anhendonia**
  - Inability to experience pleasure
- **Blunted affect**
  - Exhibits little or no affect in face or voice
- **Alogia**
  - Reduction in speech

Disorganized Symptoms

- **Disorganized speech (*thought disorder)***
  - Incoherence
- Inability to organize ideas
  - Loose associations
- difficulty sticking to one topic
- **Disorganized behavior**
  - Odd behavior
- Silliness, agitation, unusual dress
  - e.g., wearing several heavy coats in hot weather

Movement Symptoms

- **Catatonia**
  - Motor abnormalities
  - Repetitive, complex gestures
    - Usually of the fingers or hands
  - Excitable limbs
- **Catatonic immobility**
  - Maintain unusual posture for long periods of time
    - e.g., stand on one leg
- **Waxy flexibility**
  - Limbs can be manipulated and posed by another person

Other Psychotic Disorders

- **Schizophreniform Disorder**
  - –Same symptoms as schizophrenia
  - –Symptom duration greater than 1 month but less than 6 months
  - –Symptoms must include either hallucinations, delusions, or disorganized speech
- **Brief Psychotic Disorder**
  - –Symptom duration of 1 day to 1 month
  - –Often triggered by extreme stress, such as bereavement
  - –Symptoms must include either hallucinations, delusions, or disorganized speech
- **Schizoaffective Disorder**
  - –Symptoms of both schizophrenia and either a depressive or manic episode
  - –Symptoms of a major mood episode are present for a majority of the duration the illness

Other Psychotic Disorders

- **Delusional Disorder**

– Delusions may include:

- Persecution
- Jealousy
- Erotomania

– Loved by a famous person

- Somatic delusions
- Grandiose
- Mixed

– No other symptoms of schizophrenia

Epidemiology

- 95% of sufferers – lasts a lifetime
- 1/3 of homeless suffer from Schiz.
- 15% no respond to med
- 75% partial effective
- 20-50% attempt suicide
- 10% kill themselves
- 20% shorter life expectancy
- 25% experience secondary depression

Causes of Schizophrenia

- Genetic factors
- Chemical imbalance & physical abnormalities – neurotransmitters, brain structures
- Biological factors – age, virus, …
- Environmental factors – chronic Life stressors, changes, …

Causes - genetic influences

- Identical twin affected 50%
- Fraternal twin affected 15%
- Both parent affected 35%
- One parent affected 15%
- Brother or sister affected 10%
- No affected relative 1%

Etiology of Schizophrenia: Neurotransmitters

- **Dopamine Theory**

–Disorder due to excess levels of dopamine

- Drugs that alleviate symptoms reduce dopamine activity
- Amphetamines, which increase dopamine levels, can induce a psychosis

- Theory explanation:

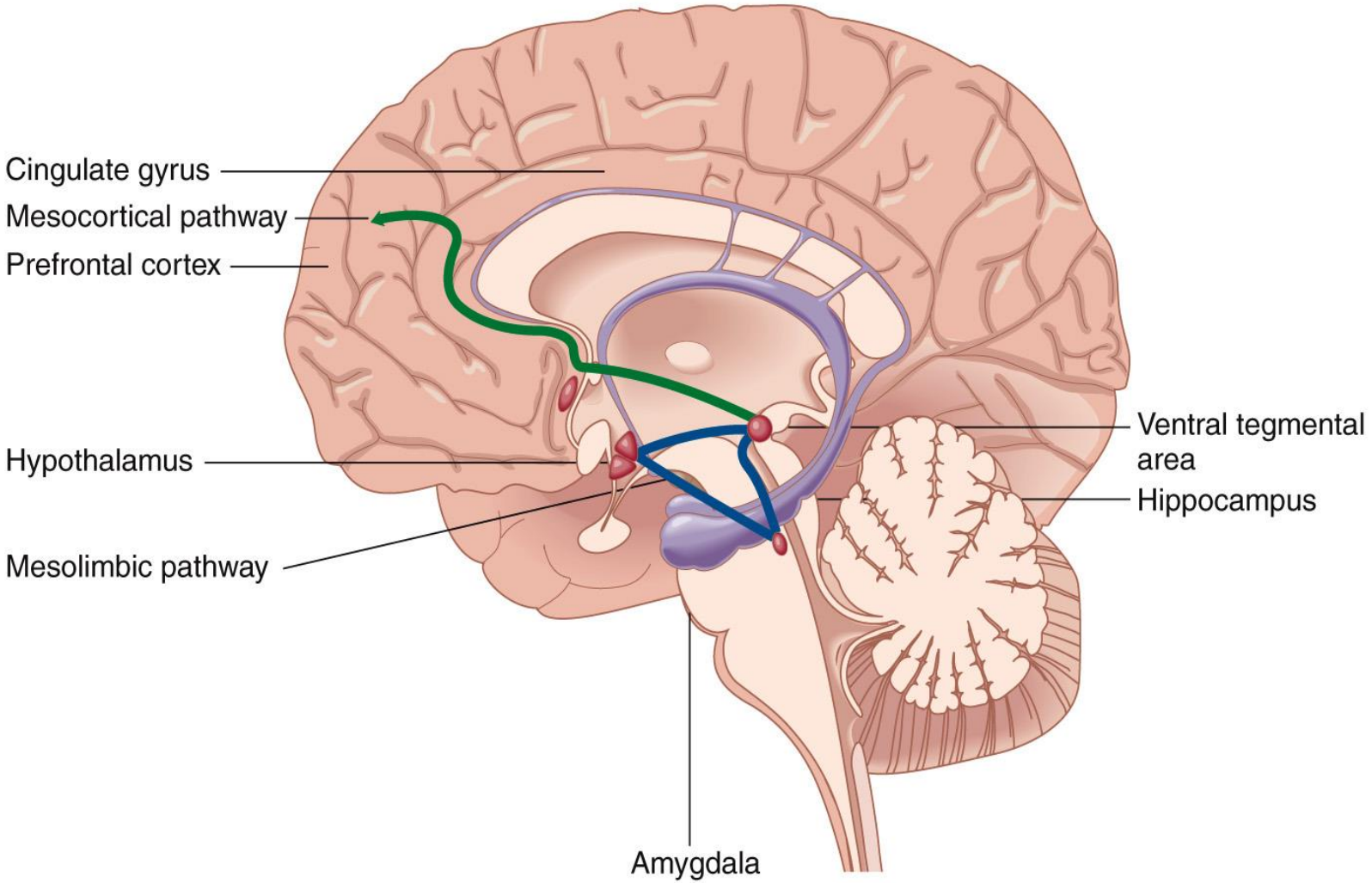
–Excess numbers of dopamine receptors or oversensitive dopamine receptors

–Localized mainly in the mesolimbic pathway

- Mesolimbic dopamine abnormalities mainly related to positive symptoms

–Decreased dopamine activity in the mesocortical pathway mainly related to negative symptoms

The Brain and Schizophrenia



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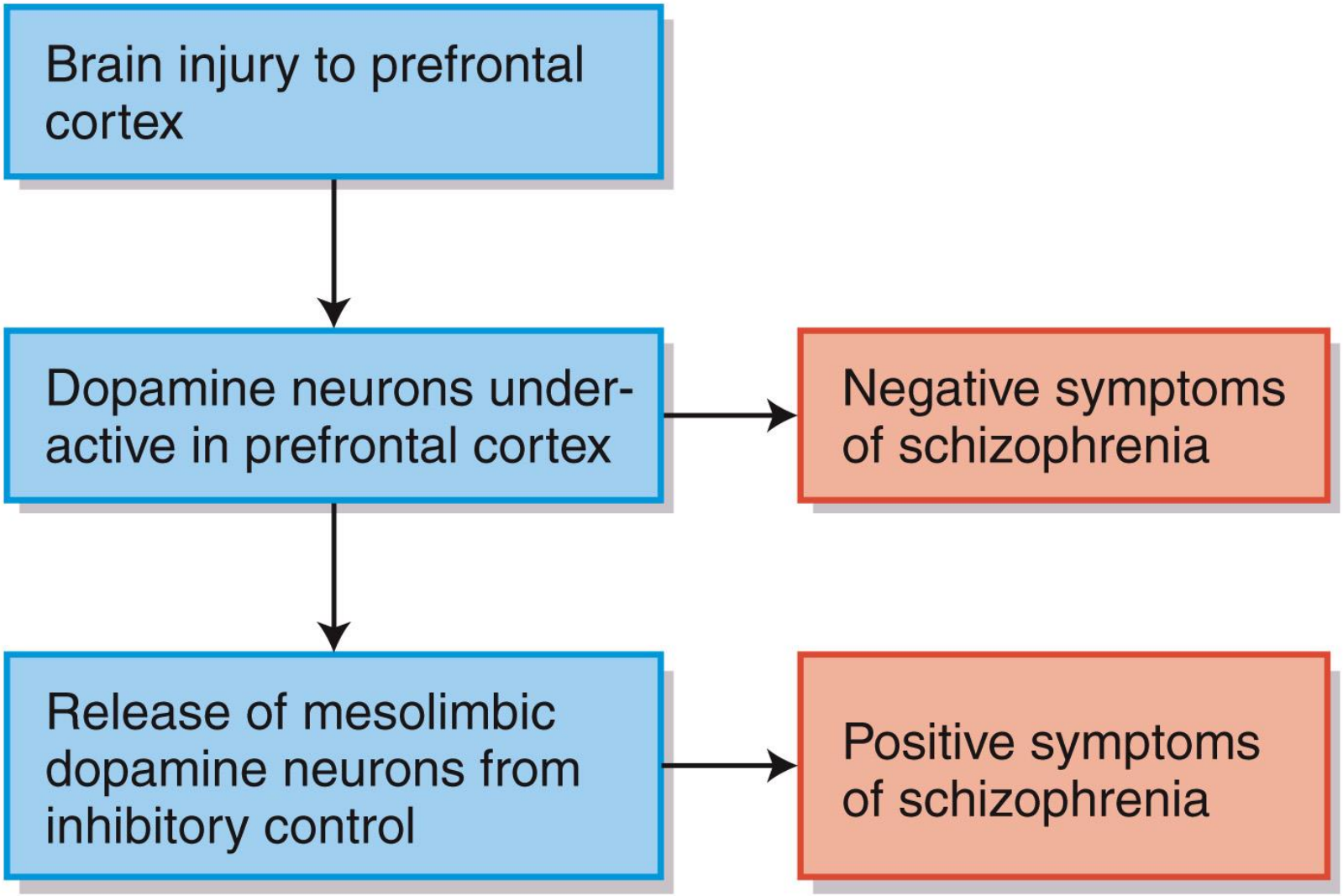
Dopamine Theory of Schizophrenia



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Etiology of Schizophrenia: Evaluation of Dopamine Theory

- Dopamine theory doesn't completely explain disorder
  - Antipsychotics block dopamine rapidly but symptom relief takes several weeks
  - To be effective, antipsychotics must reduce dopamine activity to below normal levels
- Other neurotransmitters involved:
  - Serotonin
  - GABA
  - Glutamate
    - Medication that targets glutamate shows promise

Etiology of Schizophrenia: Brain Structure and Function

- Enlarged ventricles
  - loss of brain cells
  - Correlate with
    - Poor performance on cognitive tests
    - Poor response to treatment

Etiology of Schizophrenia: Brain Structure and Function

- Structural and functional abnormalities in temporal cortex
- Reduced gray matter

Etiology of Schizophrenia: Brain Structure and Function

- **Environmental Factors**

–Damage during gestation or birth

- Obstetrical complications rates high in patients with schizophrenia

–Reduced supply of oxygen during delivery may result in loss of cortical matter

–Viral damage to fetal brain

- Presence of parasite, toxoplasma gondii, associated with 2.5x greater risk of developing schizophrenia
- In Finnish study, schizophrenia rates higher when mother had flu in second trimester of pregnancy

Etiology of Schizophrenia: Brain Structure and Function

- Developmental factors
  - –Prefrontal cortex matures in adolescence or early adulthood
  - –Dopamine activity also peaks in adolescence
- Stress activates HPA Hypothalamic–Pituitary–adrenal system, which triggers cortisol secretion
  - Cortisol increases dopamine activity
  - –Use of cannabis during adolescence associated with increased risk
- May explain why symptoms appear in late adolescence

Etiology of Schizophrenia: Psychological Stress

- Reaction to stress
  - Individuals with schizophrenia and their first-degree relatives more reactive to stress
    - Greater decreases in positive mood and increases in negative mood
- Socioeconomic status
  - Highest rates of schizophrenia among urban poor

Etiology of Schizophrenia: Family Factors

- Schizophrenogenic mother
  - Cold, domineering, conflict-inducing
  - No support for this theory

  - Hostility and poor communication

Pharmacological Treatment of Acute Schizophrenia

- Antipsychotic medications are effective for decreasing the severity of psychotic symptoms
- Nearly all patients on antipsychotic medications will experience some burden from side effects
- Antipsychotics are relatively ineffective for negative symptoms and cognitive impairment
- Antipsychotic medications are effective for preventing relapse in stabilized patients

Long-term treatment of schizophrenia

- Effective **nonpharmacological** treatments include patient and family education, skills training, supported employment, cognitive behavior therapies, and psychotherapies
- For most individuals, antipsychotic medications control the symptoms while non-pharmacological treatments manage the impairments in social, vocational, and educational functioning

Clinical Challenges

- Substance use disorders are common in people with schizophrenia
- Insight can be impaired leading people with schizophrenia to refuse treatment
- Adherence to treatments can be irregular

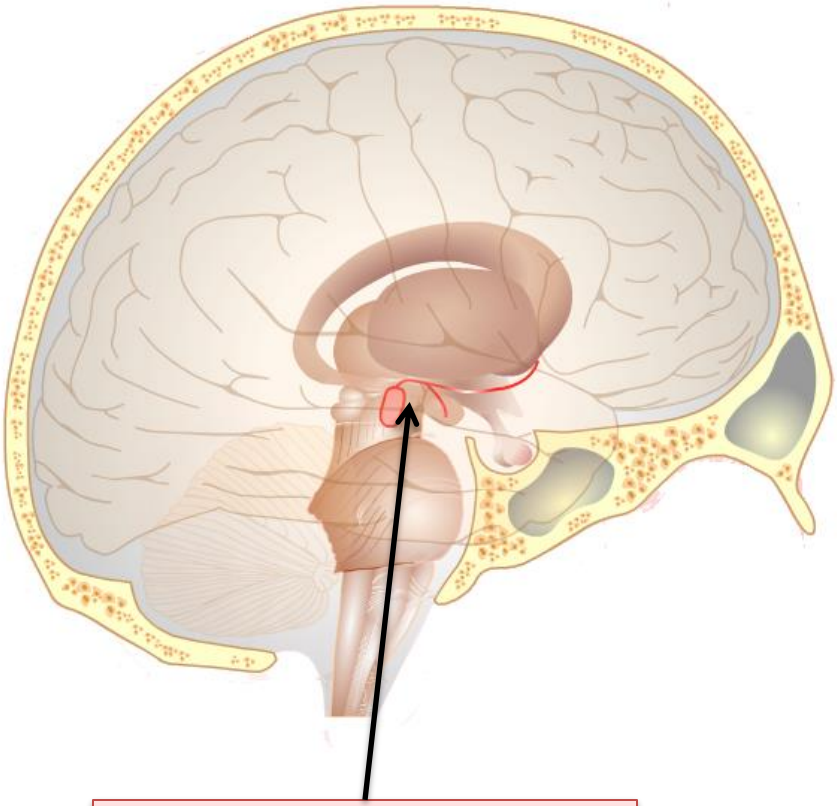
What do all antipsychotic have in common?

They reduce **dopaminergic** neurotransmission

Dopaminergic pathway in CNS

We will discuss only two pathways

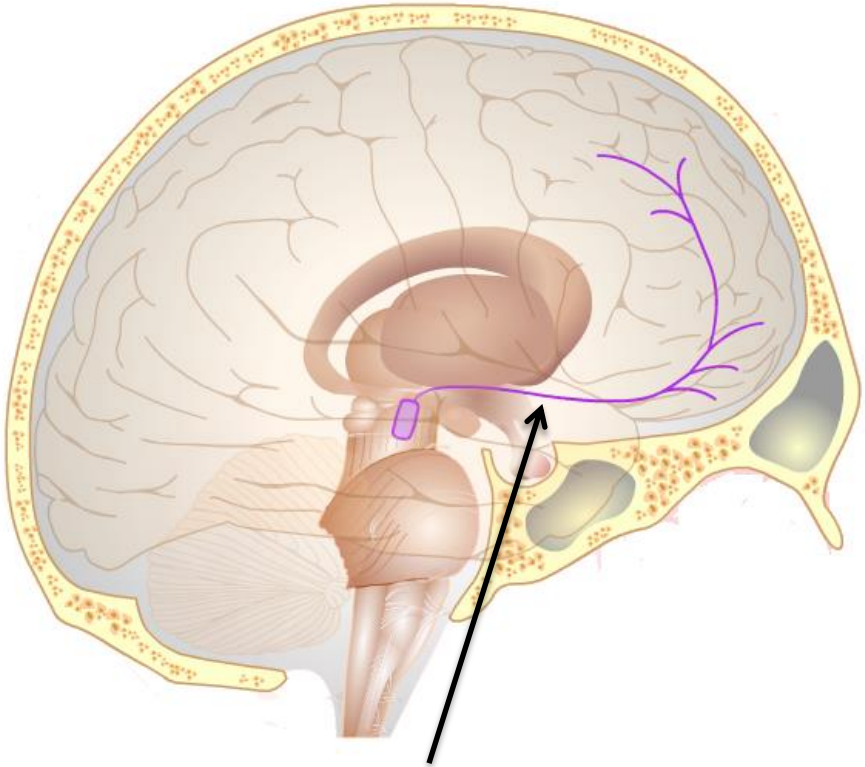
- **Mesolimbic pathway**
- **Mesocortical pathway**



Mesolimbic pathway

Excess activity implicated in:

- **Positive symptom schizophrenia e.g.**
  - **hallucinations**
  - **delusions**



Mesocortical pathway

Diminished activity implicated in :

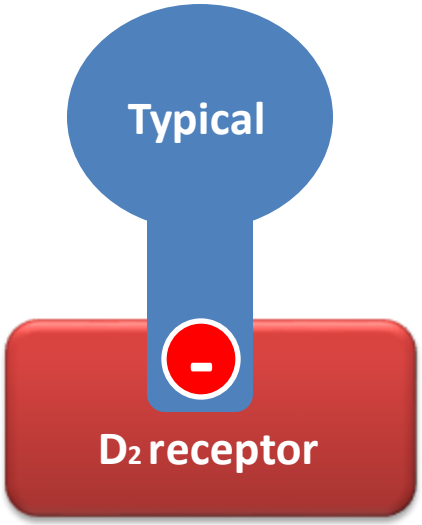
- **Negative symptoms of schizophrenia e.g.**

Restrictions in

- **emotion,**
- **thought,**
- **speech,**
- **pleasure and attention.**

Typical is D_2 antagonist

high affinity to D_2

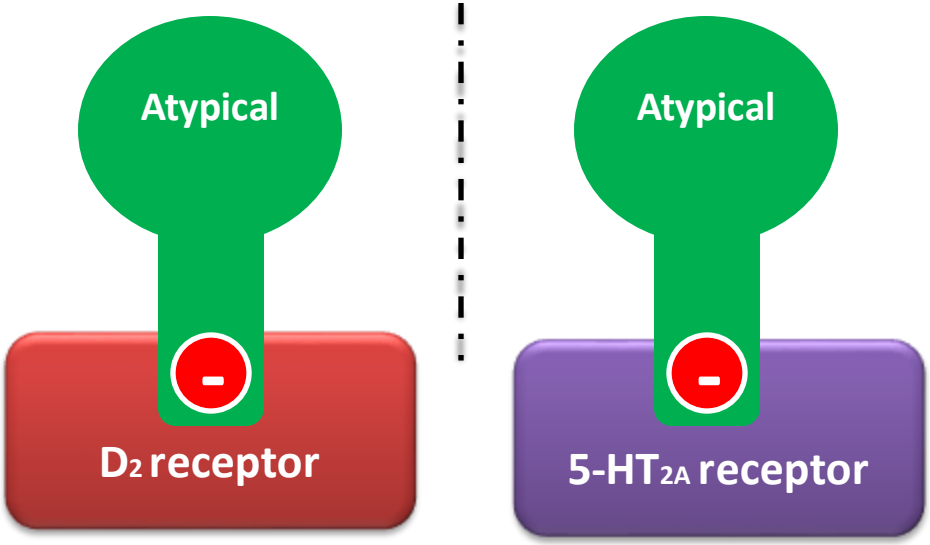


Binding to D_2 receptor
(tight)

Atypical is serotonin-dopamine antagonist

Low affinity to D_2

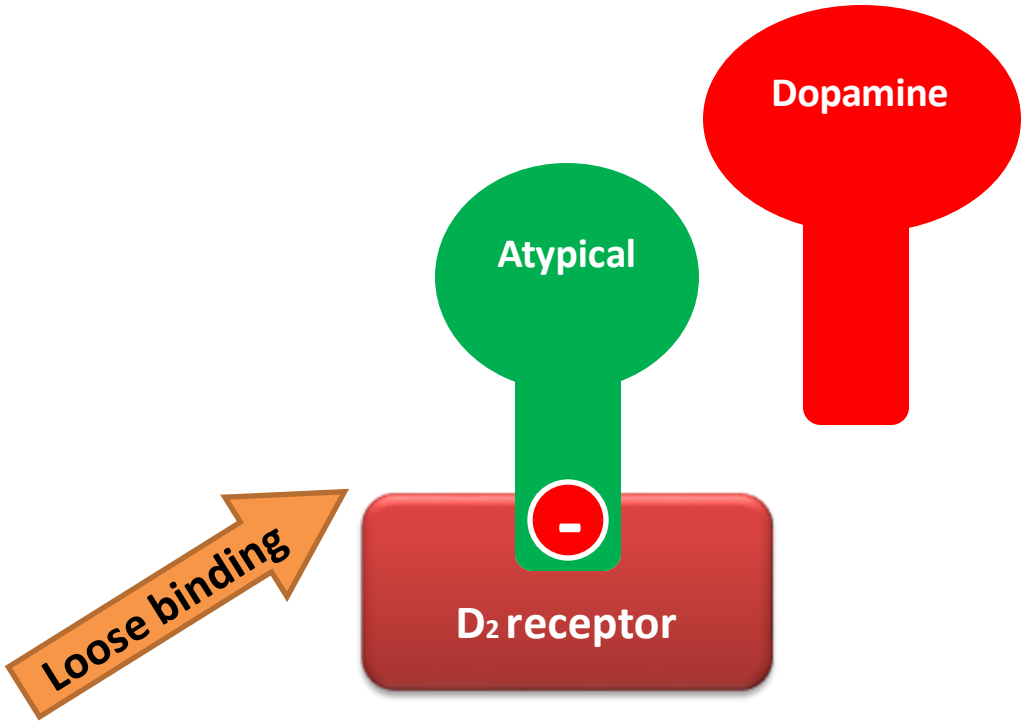
high affinity to 5-HT_{2A}



Binding to D_2 receptor
(loose)

Atypical dissociate rapidly from D_2 receptor

Atypical dissociate rapidly from **D_2 receptor**



High occupancy for D_2 → High EPS risk

Antipsychotic efficacy

D_2 occupancy

60%

75%

78%

EPS

Which has more EPS risk typical or atypical neuroleptic? And Why?

Summary

	Typical neuroleptic	Atypical neuroleptic
Mechanism of action	D_2 antagonist	• $5\text{-}HT_{2A}$ antagonist • D_2 antagonist • Rapid D_2 Dissociate
Other effect	Antagonism of H1, M1, alpha-1 receptor , among	Antagonism of H1, M1, $5\text{-}HT_{2c}$, alpha 1 receptor ,

Treatment of Schizophrenia: Medications

- **First-generation antipsychotic medications (neuroleptics; 1950s)**
  - –Phenothiazines (chlorpromazine)
  - –butyrophenones (haloperidol)
  - – thioxanthenes (Thiothixene)
  - •Reduce agitation, violent behavior
  - •Block dopamine receptors
  - •Little effect on negative symptoms
- •Extrapyramidal side effects: Tardive dyskinesia
  - –Neuroleptic malignant syndrome
- •Maintenance dosages to prevent relapse

Treatment of Schizophrenia: Medications

- **Second-generation antipsychotics**
  - Clozapine (Clozaril)
    - Impacts serotonin receptors
  - Fewer motor side effects
  - Less treatment noncompliance
  - Reduces relapse
- Side effects
  - Impairment of immune system
  - Seizures, dizziness, fatigue, drooling, weight gain
- **Newer medications may improve cognitive function:**
  - Olanzapine (Zyprexa)
  - Risperidone (Risperdal)

Side Effects of Antipsychotic Medications

- **Extrapyramidal Symptoms (EPS)**
- **Neuroleptic Malignant Syndrome (NMS)**
- Sedation
- Weight gain
- Metabolic syndrome
- Endocrinological
- Haematological
- Seizures
- Cardiovascular

Dystonic Reactions to Antipsychotic Medications

- Involuntary skeletal muscle contractions
- Often seen in young patients
- Several different possible manifestations
  - Oculogyric crisis
  - Torticollis'opisthotonos
  - Macroglossia
  - Buccolingual crisis
  - Laryngospasm

SYMPTOM	DESCRIPTION
Oculogyric crisis	Spasm of the extra orbital muscles producing a deviation of the eyes upwards and outwards. Blefarospasm
Torticollis	Head becomes persistently turned to one side, often with painful muscle spasms
Opisthotonos	Uncomfortable forced extension of the neck. When severe, the back is involved and the patient may arch off the bed
Macroglossia	The tongue does not actually swell, but it protrudes and subjectively feels swollen
Buccolingual crisis	May present as trismus, *risus sardonicus* (a grinning expression produced by spasm of the facial muscles), dysarthria, and grimacing
Laryngospasm	Spasm of the vocal cords that temporarily makes it difficult to speak or breathe. The onset is usually sudden and can be quite frightening

Treatment for Dystonic Reactions

- Anticholinergic drugs (eg benztropine 1-2mg slow IV) or Antihistaminics (eg diphenhydramine)
- Children:
  - IM or IV benztropine

Side Effects of Antipsychotic Medications

Neuroleptic Malignant Syndrome (NMS): life-threatening

- Hyperthermia, muscular rigidity, tachycardia, hyper or hypotension, autonomic instability, rhabdomyolysis, confusion
- Increased creatine phosphokinase and leukocytes
- More common in first weeks of treatment
- Increased risk with higher doses, multiple drugs, male, and young
- Can lead to loss of consciousness and death
- Misdiagnosis: catatonia, EPS, serotonin syndrome, infectious disease
- Supportive management and stop drug
- Sever cases: ICU
- Susceptible drugs: haloperidol clozapine, risperidone, olanzapine

Side Effects of Antipsychotic Medications

Sedation

- Frequent and dose dependent
- Tolerance may develop
- May be a wanted effect in agitated patients
- More sedating agents
  - Chlorpromazine
  - Clozapine
  - Quetiapine

Side Effects of Antipsychotic Medications

Preventing Weight Gain and Metabolic Syndrome:

- Goal: healthy eating, BMI<25, exercise
- Clinically Monitor
  - Weight, waist circumference, fasting glucose/lipids
- Provide dietary and exercise advice

Side Effects of Antipsychotic Medications

Hyperprolactinemia

–Amenorrhea, menstrual cycle disorders, breast enlargement, galactorrhea

–children and adolescents>adults

–esp post-pubertal girls

–Dose dependent

–Related to D2receptor affinity

–Higher in 1st generation as a class

Side Effects of Antipsychotic Medications

Haematological

- Mild leukopenia common to all
- Agranulocytosis and neutropenia infrequent
  - If occurs, stop drug
- Highest risk in clozapine
  - Especially at beginning

Antipsychotics and CVS

- Antipsychotic medications can cause various types of cardiovascular complications (e.g., **arrhythmias, hypertension, myocarditis, and orthostatic hypotension**)
- Antipsychotic drugs with increased risk included **haloperidol, olanzapine, risperidone**

Antipsychotics and Pregnancy

- Cross placenta
- Exposure during 3rd trimester→ possible EPS and/or withdrawal after delivery

- **Thank you**