Schizophrenia

Introduction & Definition:

Schizophrenia is **a clinical syndrome** of variable, but profoundly disruptive psychopathology that involves :

- **cognition,**
- **emotion,**
- **perception, and**
- **other aspects of behavior**

History of schizophrenia:

1-**Emil Kraepelin** (**1856 to 1926**) first delineated separate psychotic conditions. **(dementia precox)** a term that emphasized the change in cognition (dementia) and early onset (precox) of the disorder.

2- **Eugene Bleuler**

- In 1911 the term schizophrenia, as the disease is known today, was introduced by Eugen Bleuler **(1857 to 1959).**

- **He chose the term to express the presence of schisms between thought, emotion, and behavior in patients with the disorder.**

- He proposed the name to denote a **"splitting"** of psychic functions, which he considered to be the basis of the illness

2- Eugene Bleuler

- His description of the illness included primary and secondary symptoms

Primary symptoms (Four As)	Secondary symptoms
Abnormal associations	Hallucinations,
Autistic behavior and thinking,	Delusions,,
Abnormal affect,	Social withdrawal
Ambivalence	Diminished drive

3- Kurt Schneider (1887 to 1967):

- In his classification of thought disorders attempted to make the diagnosis of schizophrenia more reliable by identifying a group of symptoms of schizophrenia that were the most characteristic of the illness.
- **His so-called first rank symptoms.**

First-Rank Symptoms of Kurt Schneider

1. Audible thoughts(thought echo)	7. Made feelings
2. Voices arguing or discussing	8. Made impulses or drives
3. Voices commenting on patient's actions	9. Made volitional acts
4. Thought insertion	10. Somatic passivity (delusion of control)
5. Thought broadcasting	11. Delusional perception
6. Thought withdrawal	

3- Epidemiology of schizophrenia:

- **Lifetime prevalence:** **1 %. In the United States. DSM V(0.3 – 0.7%)**
- **Gender & age:**

- Schizophrenia is **equally prevalent in men and women**.

- The two genders differ, however, in the onset and course of illness.

- **Onset is earlier in men than in women.**

- **The peak ages of onset :**
  - ♂**:** 10 to 25 .
  - ♀**:** 25 to 35
- (women display a bimodal age distribution, with a second peak occurring in middle age).
- before 10 or after 60 : extremely rare.
- When onset occurs **after age 45, the disorder is characterized as late-onset schizophrenia.**
- In general, the outcome for female schizophrenia patients is better than that for male schizophrenia patients.

Medical illness

- Persons with schizophrenia **have a higher mortality rate** from accidents and natural causes than the general population.
- Several studies have shown that up to **80 percent** of all schizophrenia patients have significant concurrent medical illnesses and that up **to 50 percent of** these conditions may be undiagnosed.
- Persons with schizophrenia, and especially those who are homeless or injection drug users, are at increased risk for potentially life-threatening communicable diseases, such as human immunodeficiency virus/acquired immunodeficiency syndrome **(HIV/AIDS), hepatitis C, and tuberculosis.**
- Among the chronic non communicable diseases, patients with schizophrenia have significantly higher than expected rates of **epilepsy, diabetes, arteriosclerosis, and ischemic heart disease.**
- **Obesity and the concomitant metabolic syndrome involving insulin resistance DM** are becoming increasingly common problems in schizophrenic patients.

Substance Abuse

- Substance abuse is common in schizophrenia.
- especially cannabis and nicotine.

- **Nicotine & schizophrenia:**
  - **Up to 90 percent of schizophrenic patients may be dependent on nicotine. ????**
  - Nicotine administration appears **to improve some cognitive impairments** and Parkinsonism in schizophrenia, possibly because of nicotine-dependent activation of dopamine neurons.
  - Recent studies have also demonstrated that nicotine may **decrease positive symptoms such as hallucinations in schizophrenia patients** by its effect on nicotine receptors in the brain that reduce the perception of outside stimuli, especially noise.
  - In that sense, **smoking is a form of self-medication.**
  - nicotine decreases the blood concentrations of some antipsychotics.

4- Etiology :

1- Risk Factors for the Onset of Schizophrenia:

A- Genetic Risk:

- the first-degree relatives have a higher morbidity risk for schizophrenia as compared to the relatives of controls.

Prevalence of Schizophrenia in Specific Populations

Population	Prevalence (%)
General population	1
Non-twin sibling of a schizophrenia patient	8
Child with one parent with schizophrenia	12
Dizygotic twin of a schizophrenia patient	12
Child of two parents with schizophrenia	40
Monozygotic twin of a schizophrenia patient	47

B- Environmental factor:

- **Risk Factors Operating During Early Development**

1- Paternal Age

- There is a higher risk of schizophrenia (**around three to four times) in the** offspring of **fathers who are older than 50**, at the time of conception, compared to the offspring of fathers in their early 20s.

2- Season of Birth

- **Winter birth** in people who later develop schizophrenia is a robust epidemiological finding, at least in the northern hemisphere.
- It is likely to be a proxy indicator for some seasonally fluctuating environmental factor.
- The most popular hypotheses relate to seasonal variation in exposure to **intrauterine viral infections around the time of birth, or variation in light, temperature/weather, or external toxins.**

3- Pregnancy and Birth Complications

- There are a large number of published studies demonstrating some relationship between pregnancy and birth complications and the development of schizophrenia.
- The investigators found three main categories of obstetric complication to have significant estimates:
  - **abnormal fetal growth and development**: Low birth weight, congenital malformations, and small head circumference;
  - **complications of pregnancy**: Bleeding, pre-eclampsia, diabetes, and rhesus incompatibility; and
  - **complications of delivery**: Asphyxia, uterine-atony, and emergency cesarean section.
- **Taken together, they seem to implicate an increased risk of hypoxia.**

4- Urban Birth and Upbringing:

- Generally, studies show **a twofold increase in risk of schizophrenia** in urban as compared to rural settings.

- The social environment varies widely and systematically across dimensions of material deprivation,

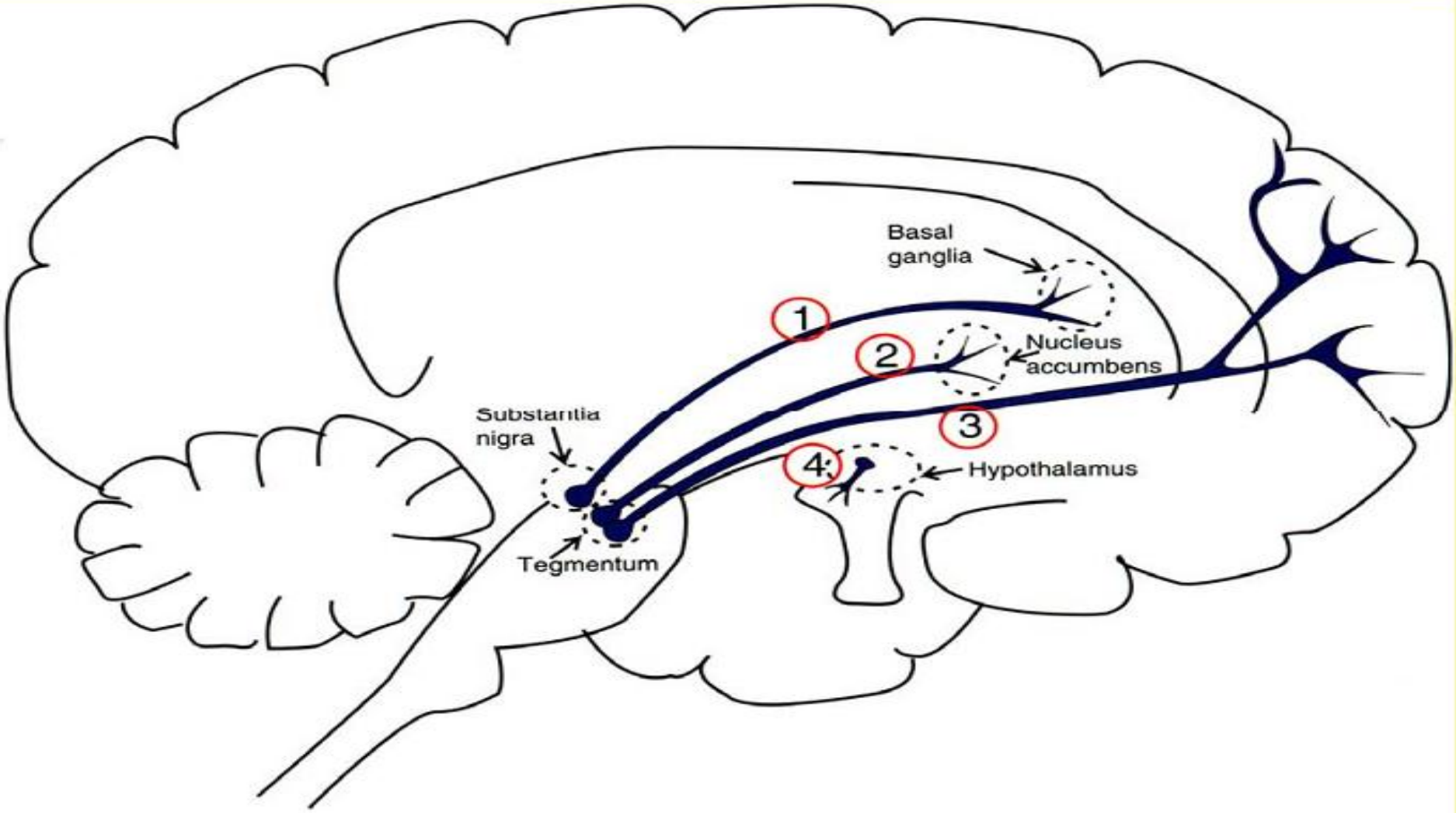
- neighborhood organization (social fragmentation), and

- ethnic composition

- Biological theories of Schiophrenia

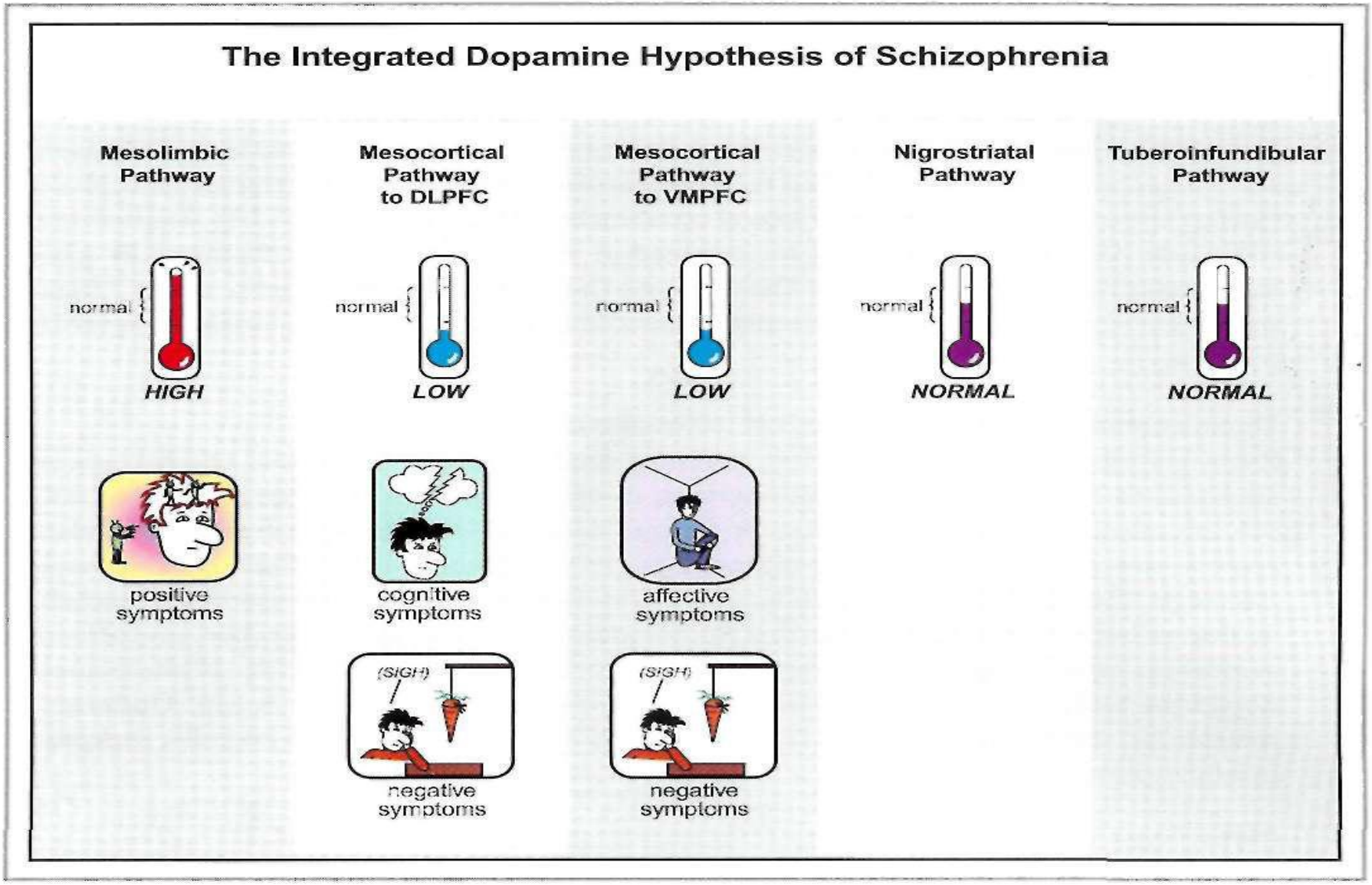
1- Dopamine Hypothesis

- **Dopamine pathways & its function**



- 1. **Nigrostriatal dopamine pathway** – projects from substanianigra to the basal ganglia or straitum (part of EP nervous system)– control Motor Function& movement.
- 2. **Mesolimbic dopamine pathway** –projects from midbrain ventral tegmental area to the nucleus Accumbens (part of limbic system) – control Emotions& is involved in many behaviors such as pleasurable sensations , the powerful euphoria of drug abuse as well as delusions & hallucinations of psychosis .
- **3. Mesocortical dopamine pathway** – projects from the midbrain ventral tegmental area but sends its axons to areas of prefrontal cortex – mediates Attention/Cognition through dorsolateral prefrontal cortex & affective symptoms through ventromedial prefrontal cortex.
- 4. **Tuberoinfandibular dopamine pathway** – projects from the hypothalamus to the anterior pituitary – control Prolactin Release.

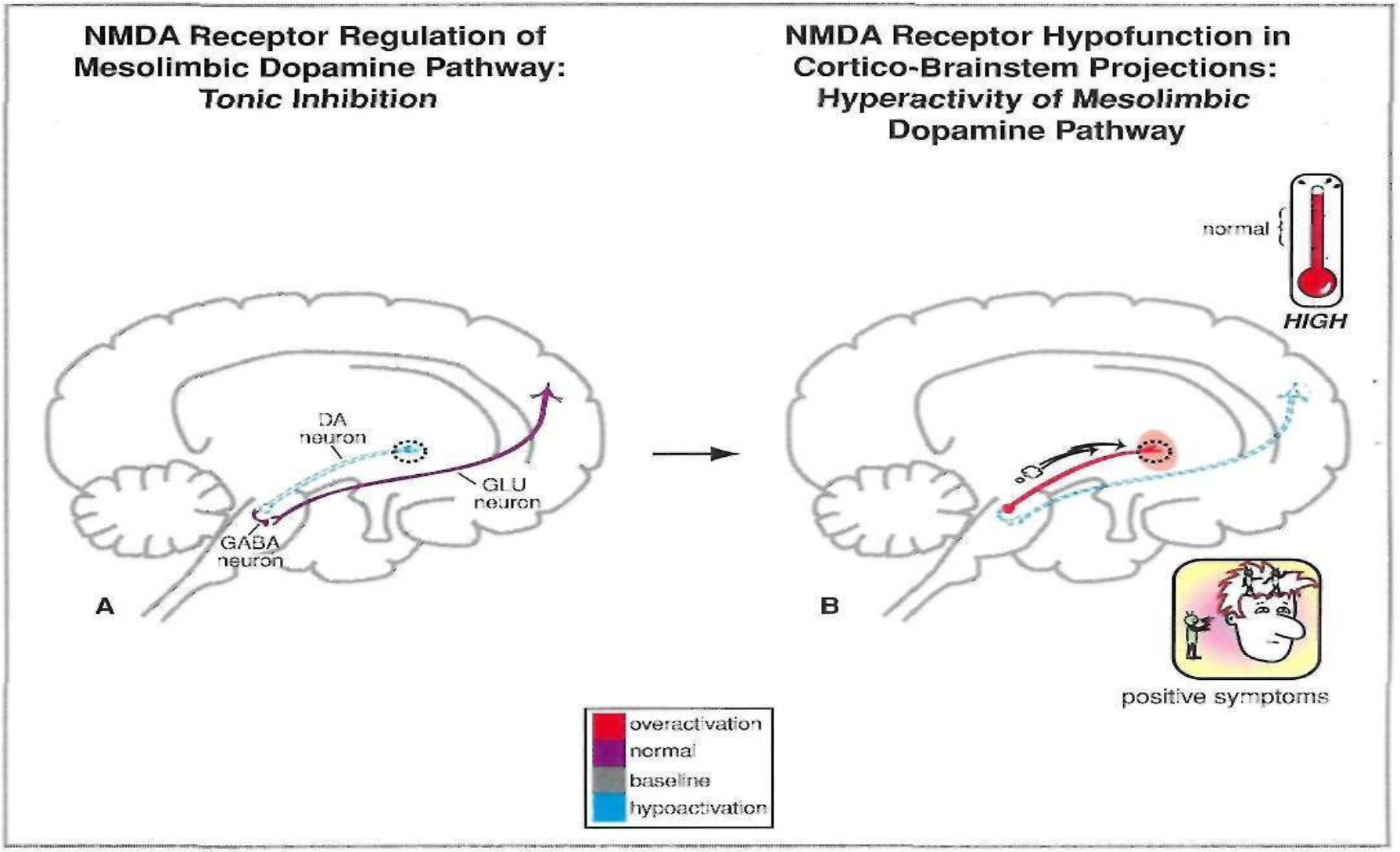
Integrated theory of schizophrenia and D2 antagonist



In untreated schizophrenia:

- Dopamine output is **high** in Mesolimbic pathway>>>>>causing +ve symptoms.
- It **is low** in Mesocortical (DLPFC>>>>>>causing cognitive & negative symptoms, **low in (**VMPFC)>>>>>> causing affective & negative symptoms.
- It is **normal** in the Nigrostriatal & tuberoinfandibular pathways.

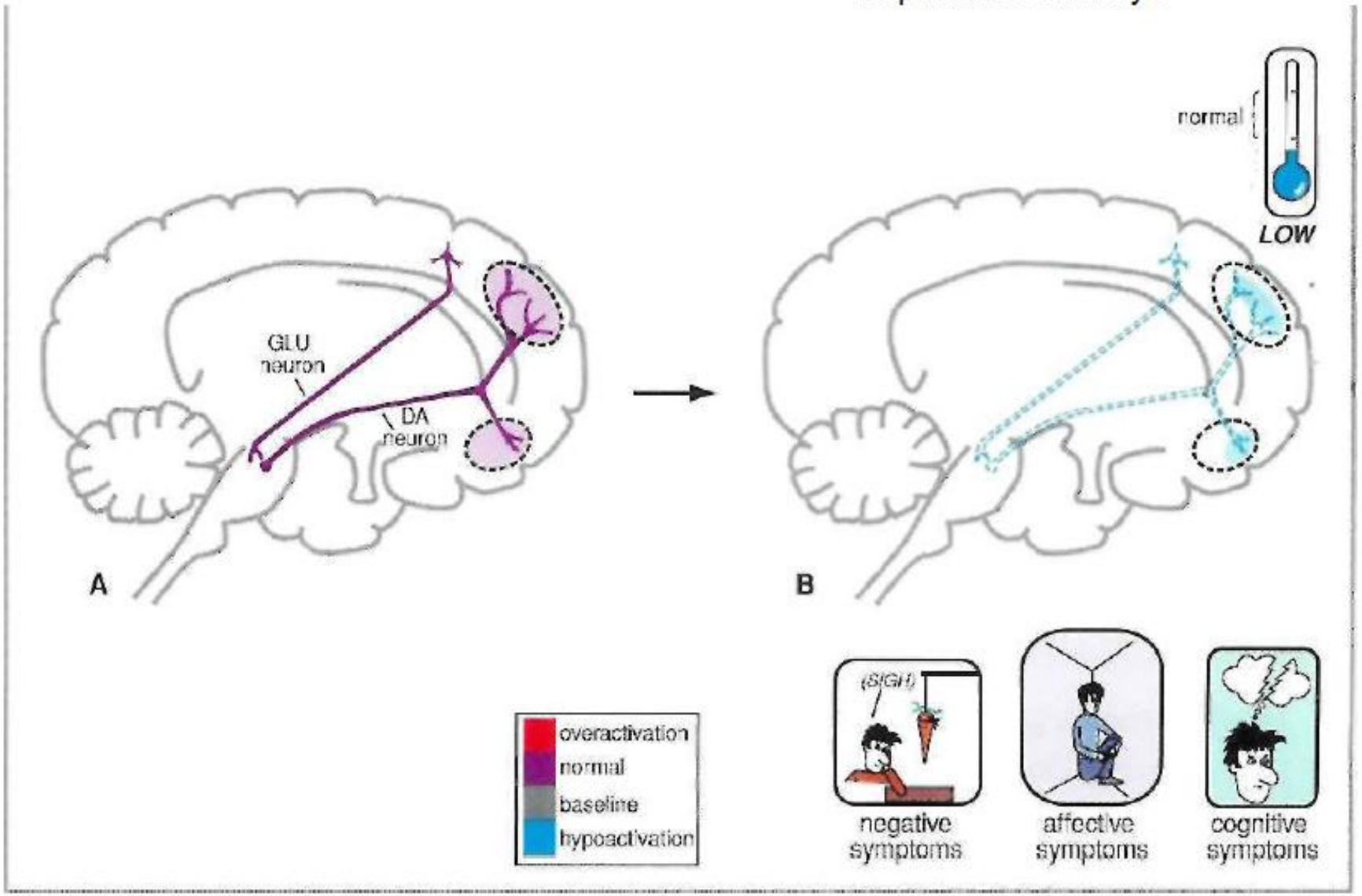
2- Corticobrainstem glutamate pathways and the NMDA receptor hypofunction hypothesis of schizophrenia



- **The cortical brainstem glutamate projection communicates with the mesolimbic dopamine pathway via a gamma aminobutyric acid (GABA) interneuron in the ventral tegmental area.**
- **Excitatory glutamate stimulates** N-methyl-d-aspartate (NMDA) receptors on the interneuron, causing GABA release, and GABA, in turn, inhibits release of dopamine from the mesolimbic dopamine pathway;
- thus the descending glutamatergic pathway **normally acts as a brake on the mesolimbic dopamine pathway.**
- If NMDA receptors in the cortical brainstem glutamate projection **are hypoactive, then the downstream effect of tonic inhibition of the mesolimbic dopamine pathway** will not occur, leading to **hyper-activity in this pathway.**
- This is the theoretical biological basis for the mesolimbic dopamine hyperactivity thought to be associated with the positive symptoms of psychosis.

NMDA Receptor Regulation of Mesocortical Dopamine Pathways: Tonic Excitation

NMDA Receptor Hypofunction in Cortico-Brainstem Projections: Hypoactivity of Mesocortical Dopamine Pathways



NMDA receptor hypofunction hypothesis and negative, cognitive, and affective

- **(A) The cortical brainstem glutamate projection communicates *directly*** with the mesocortical **dopamine** pathway in the ventral tegmental area, normally causing ***tonic excitation.***

- **(B) If N-methyl-d-aspartate (NMDA) receptors in cortical brainstem glutamate projections are hypoactive**,
- tonic excitation **here** is lost and,
- mesocortical dopamine pathways become hypoactive, potentially explaining the cognitive, negative, and affective symptoms of schizophrenia.

3- Serotonin:

- Current hypotheses posit serotonin excess as a cause of both positive and negative symptoms in schizophrenia.

- The robust serotonin antagonist activity of **clozapine** and other second-generation antipsychotics, coupled with the effectiveness of clozapine to decrease positive symptoms in chronic patients has contributed to the validity of this proposition.

4- Norepinephrine:

- **Anhedonia** the impaired capacity for emotional gratification and the decreased ability to experience pleasure has long been noted to be a prominent feature of schizophrenia.

- A selective neuronal degeneration within the norepinephrine reward neural system could account for this aspect of schizophrenic symptomatology.

5- Acetylcholine and Nicotine.

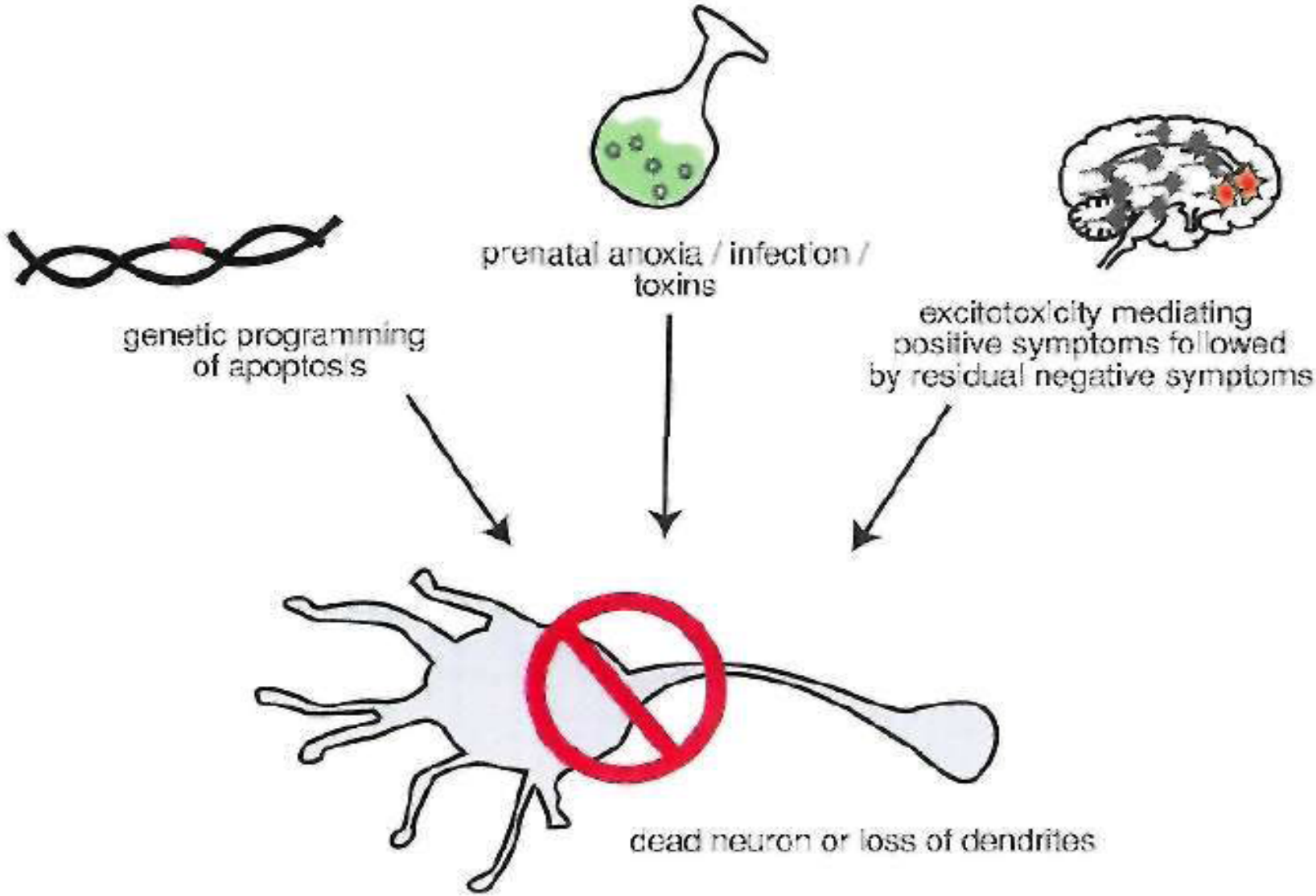
- Postmortem studies in schizophrenia have demonstrated decreased muscarinic and nicotinic receptors in the caudate-putamen, hippocampus, and selected regions of the prefrontal cortex.

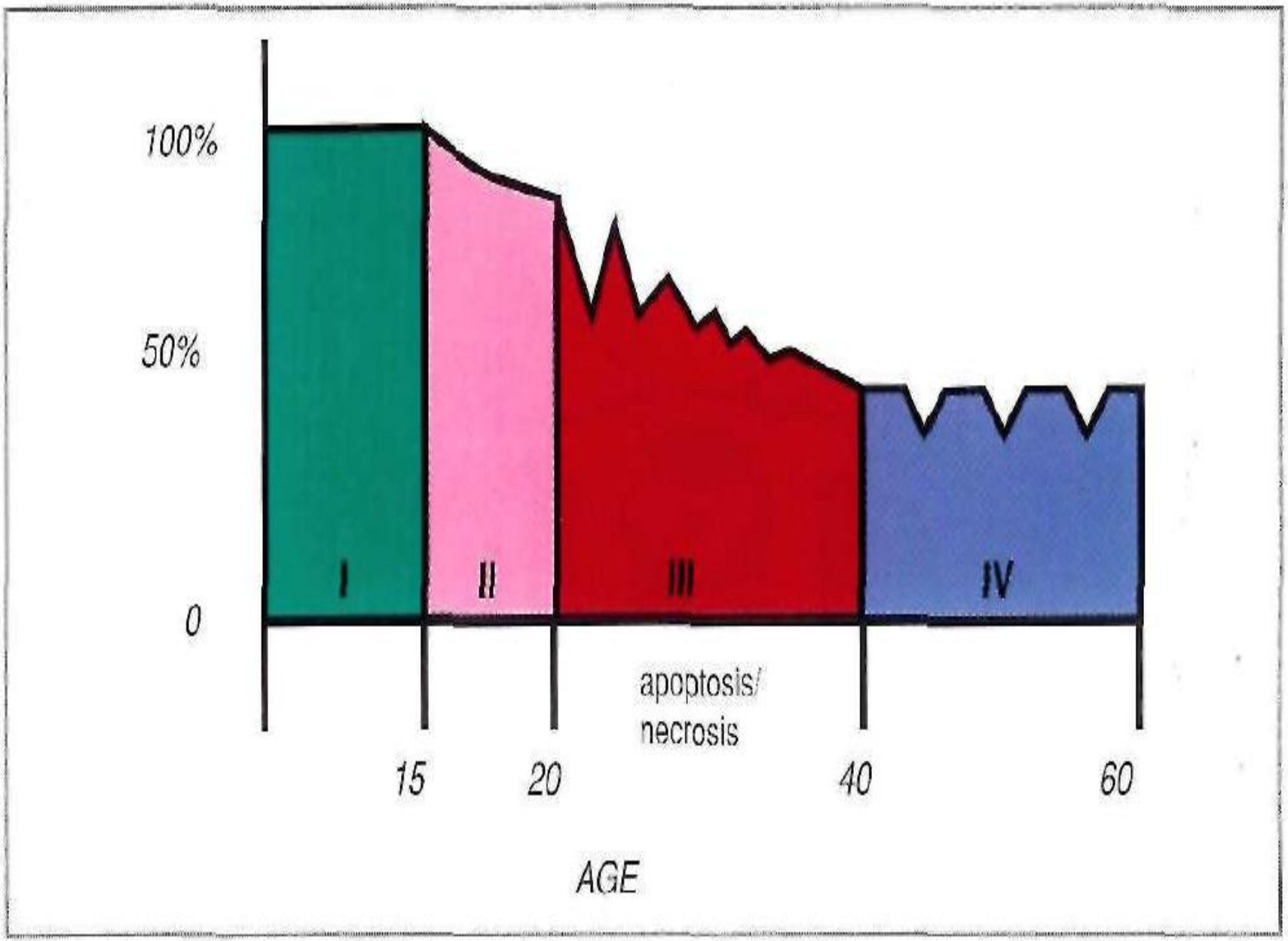
- These receptors play a role in the regulation of neurotransmitter systems involved in cognition, which is impaired in schizophrenia.
-

2- Neurodegenerative theories of schizophrenia:

- One major idea that proposes to explain the downhill course of schizophrenia and the development of treatment resistance is that neurodegenerative events in schizophrenia may be mediated by a type of excessive action of the neurotransmitter glutamate that has come to be known as **"excitotoxicity."**
- The "**excitotoxic hypothesis of schizophrenia**" proposes that neurons degenerate because of excessive excitatory neurotransmission at glutamate neurons.
- This process of excitotoxicity is not only a hypothesis to explain neurodegeneration in schizophrenia; it has also been invoked as an explanation for neurodegeneration in any number of neurologic and psychiatric conditions, including **Alzheimer's disease and other degenerative dementias, Parkinson's disease, amytrophic lateral sclerosis (ALS, or Lou Gehrig's disease), and even stroke.**
- **Explain treatment resistance to antipsychotic in schizophrenia.**

Neurodegenerative Theories of Schizophrenia




100%
50%
0
I
II
III
IV
apoptosis/
necrosis
15
20
40
60
AGE

Stages of schizophrenia. The stages of schizophrenia are shown here over a lifetime

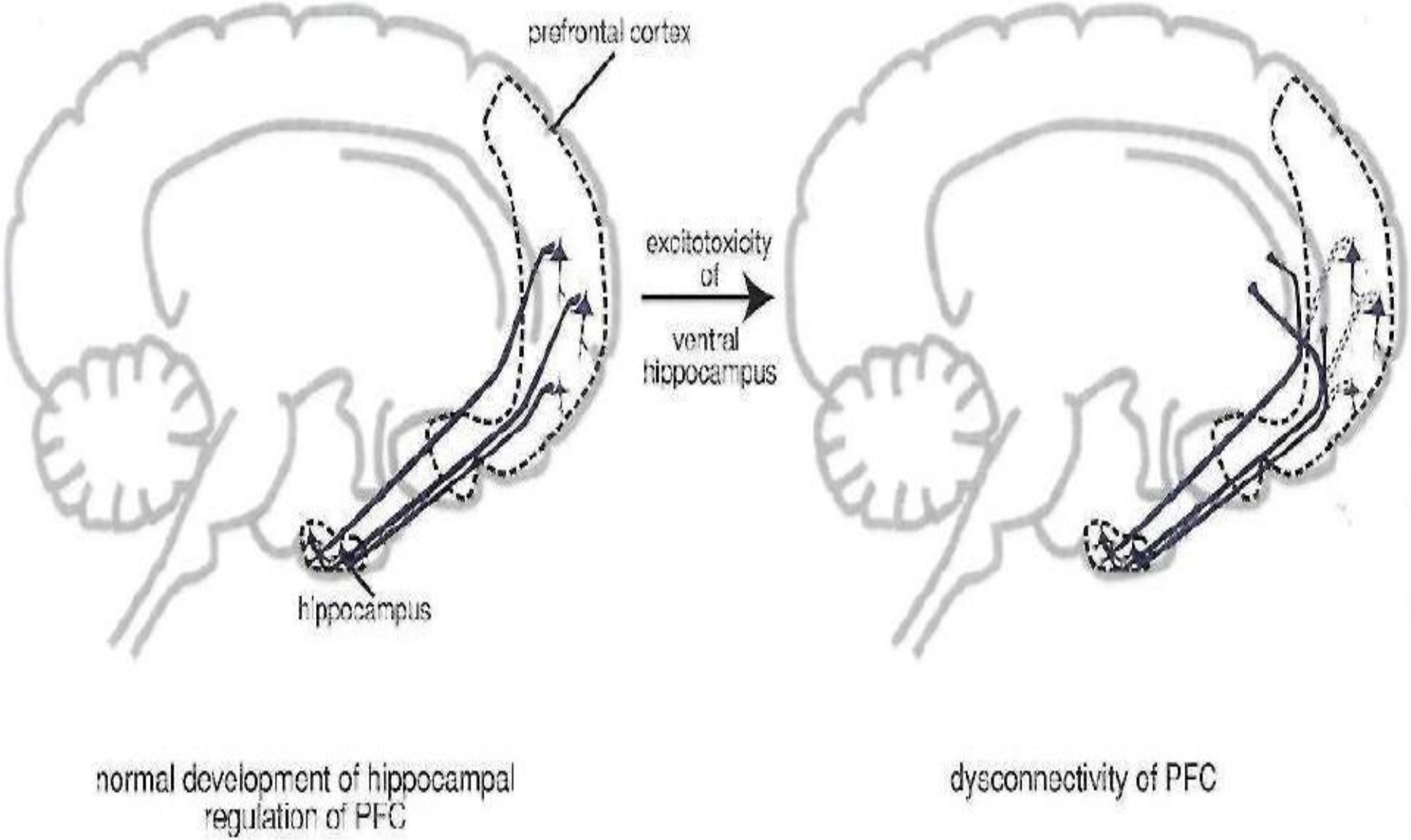
- The progressive nature of schizophrenia, illustrated here, supports a neurodegenerative basis for the disorder.
- ***The patient has full functioning (100 percent)*** early in life, and is virtually asymptomatic (Stage I).
- ***However, during a prodromal phase (Stage II) starting in the teens,*** there may be odd behaviors and subtle negative symptoms.
- ***The acute phase of the illness usually announces itself fairly dramatically in the twenties (Stage III***) with positive symptoms, remissions, and relapses but never quite getting back to previous levels of functioning.

- ***The final phase of the illness may begin in the forties or later, with prominent negative and cognitive symptoms and some waxing and waning, but often more of a "burnout" stage of continuing disability.***
- There may not necessarily be a continuing and relentless downhill course, but the patient may become progressively resistant to treatment with antipsychotic medications during this stage (Stage IV).

3- Neurodevelopmental hypothesis and genetics of schizophrenia:

- The excitotoxicity that causes such dysconnectivity could be genetically programmed or environmentally triggered.

Neurodevelopmental Hypothesis of Schizophrenia: Dysconnectivity Caused by Early Excitotoxicity



Neurodevelopmental theories of schizophrenia

- suggest that the disorder occurs as a result of abnormalities in brain development.
- Excitotoxicity that occurs early in development, before the completion of synaptic connections, could result in **dysconnectivity between brain regions and consequently symptoms of mental illness.**
- For example, with normal development the ventral hippocampus forms connections with cortical pyramidal neurons to regulate activity in the prefrontal cortex (left).
- Excitotoxicity in the ventral hippocampus prior to completion of these connections could impact development of the prefrontal cortex, causing abnormal neuronal connections that may lead to symptoms of schizophrenia (right).

Genes that affect connectivity, synaptogenesis and NMDA receptors

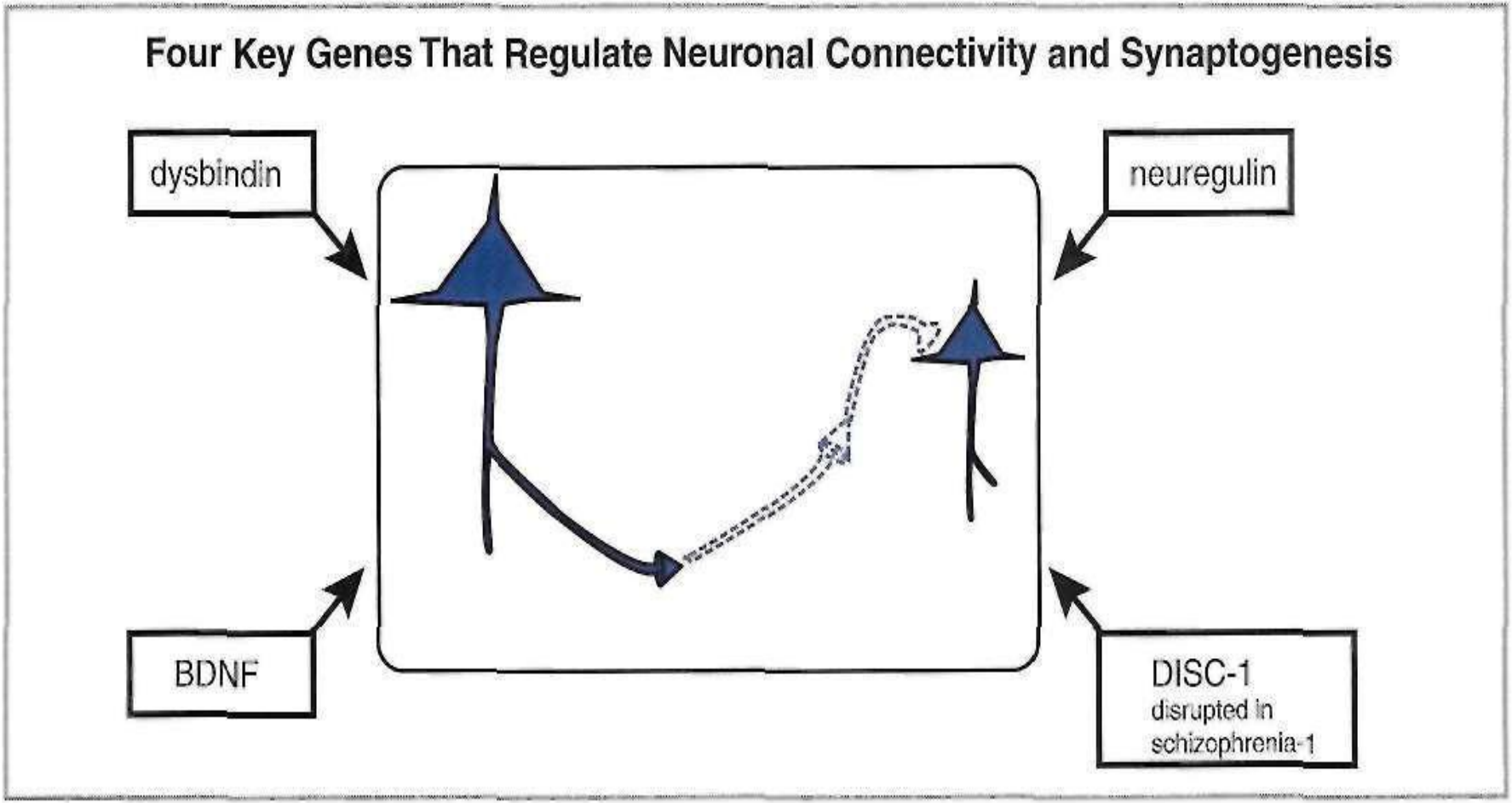
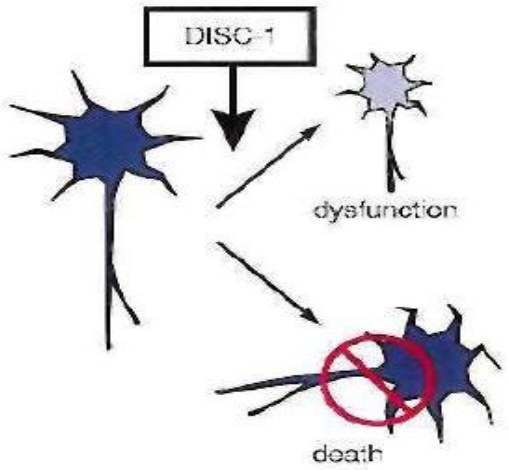


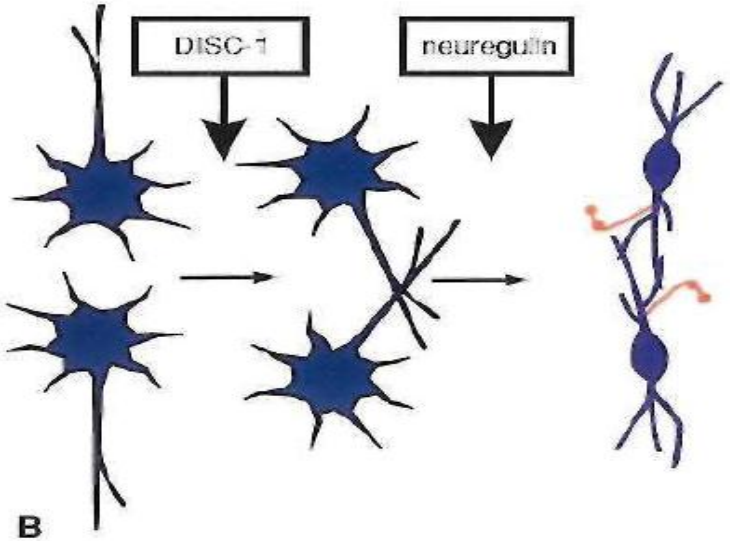
FIGURE 9-53 BDNF, dysbindin, neuregulin, and DISC-1. Four key genes that regulate neuronal connectivity and synaptogenesis in schizophrenia are the genes that code for the proteins brain derived neurotrophic factor (BDNF), dysbindin, neuregulin, and DISC-1 (disrupted in schizophrenia-1).

Neurodevelopmental Hypothesis of Schizophrenia: Subtle Genetic Abnormalities in DISC-1 or Neuregulin Causing Dysconnectivity



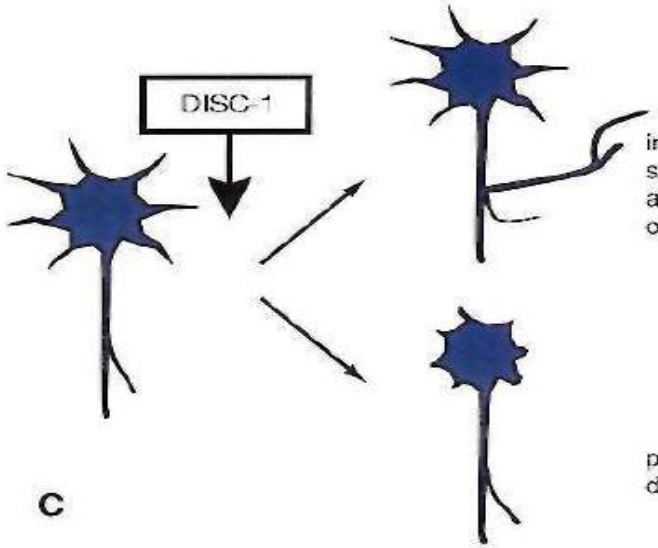
A

inadequate neurogenesis

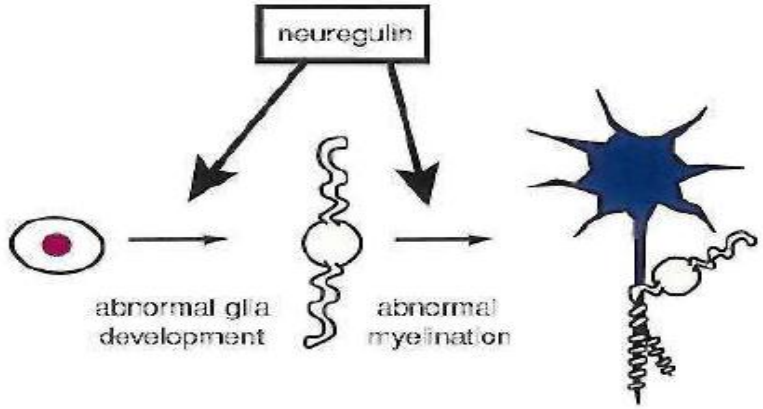


B

poor neuronal migration



C



D

Neuropathology:

1. Cerebral Ventricles

- Computed tomography (CT) scans of patients with schizophrenia have consistently shown---→ **lateral and third ventricular enlargement and some reduction in cortical volume.**

2. Reduced Symmetry

- **There is a reduced symmetry in several brain areas in schizophrenia,---→ including the temporal, frontal, and occipital lobes.**

3. Limbic System

- a **decrease in the size of the region including the amygdala, the hippocampus, and the parahippocampal gyrus**

4- Thalamus

- **volume shrinkage or neuronal loss,** in particular subnuclei.

5- Basal Ganglia and Cerebellum

- **loss or the reduction of volume of the globus pallidus and the substantia nigra**

Psychodynamic theory of schizophrenia:

1. **Psychoanalytic Theories**

- **Sigmund Freud** postulated that schizophrenia resulted from
  - **developmental fixations (oral phase)**that occurred earlier than those culminating in the development of neuroses.
  - These fixations produce defects **in ego development** and Freud postulated that such defects contributed to the symptoms of schizophrenia.

Learning Theories

According to learning theorists, children who later have **schizophrenia learn irrational reactions and ways of thinking**

by imitating parents who have their own significant emotional problems.

In learning theory, the poor interpersonal relationships of persons with schizophrenia develop

.

because of poor models for learning during childhood

Family Dynamics

1. **Double Bind.**

- The double-bind concept was formulated by Gregory Bateson and Donald Jackson to describe a hypothetical family in which **children receive conflicting parental messages about their behavior, attitudes, and feelings.**

- In Bateson's hypothesis, **children withdraw into a psychotic state to escape the unsolvable confusion of the double bind.**

2- Schisms and Skewed Families.

- In one family type, **with a prominent schism between the parents, one parent is overly close to a child of the opposite gender.**

- **In the other family type, a skewed relationship between a child and one parent involves a power struggle between the parents and the resulting dominance of one parent.**

3- Pseudomutual and Pseudohostile Families.

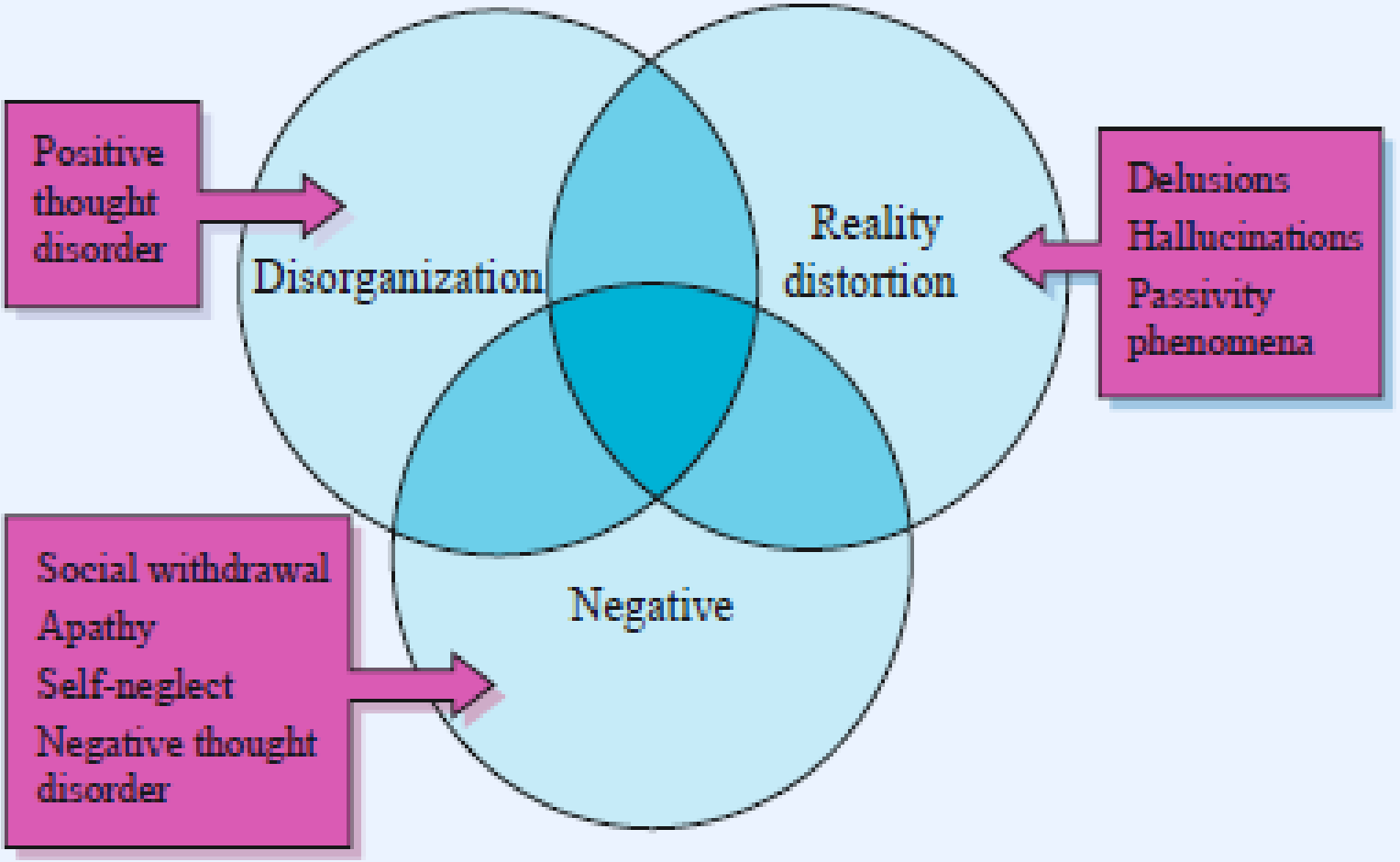
- As described by Lyman Wynne, **some families suppress emotional expression by consistently using pseudomutual or pseudohostile verbal communication.**

- **The child's verbal communication may be incomprehensible to outsiders.**

4- Expressed Emotion.(high EE)

- Parents or other caregivers may **behave with overt criticism, hostility, and overinvolvement toward a person with schizophrenia.**

SYNDROMES OF SCHIZOPHRENIA



Diagnosis

A) Characteristic symptoms:

- Two (or more) of the following.
- each present for a significant portion of time during a 1-month period (or less if successfully treated):
  - **delusions**
  - **hallucinations**
  - **disorganized speech**
  - **disorganized or catatonic behavior**
  - **negative symptoms,** i.e., affective flattening, alogia, or avolition

► **Note: Only one if :**

- delusions are bizarre
- or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B) Social/occupational dysfunction

c) *Duration*:

- Continuous disturbance persist for at least 6 months.
- at least 1 month of symptoms (or less if successfully treated) i.e., active-phase symptoms.

D) Schizoaffective and mood disorder exclusion.

E) Substance/general medical condition exclusion

F) Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

ICD-10 Diagnostic Criteria for Schizophrenia

- **General criteria for paranoid, hebephrenic, catatonic, and undifferentiated schizophrenia**
- **G1**.
- Either ***at least one*** **of** the syndromes, symptoms, and signs listed under (1) below,
- *or* **at least two** of the symptoms and signs listed under (2) should be present for most of the time during an episode of psychotic illness
- lasting for **at least 1 month (or at some time during most of the days).**

1- At least one of the following must be present:

A) thought echo,

- **thought insertion**
- **or withdrawal,**
- **or thought broadcasting;**

B) delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations;

- **delusional perception;**

C) hallucinatory voices

- giving a running commentary on the patient's behavior,
- or discussing the patient among themselves,
- or other types of hallucinatory voices coming from some part of the body;

D) persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g., being able to control the weather, or being in communication with aliens from another world).

2- *Or* at least two of the following:

- **persistent hallucinations in any modality,** when occurring every day for at least 1 month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent overvalued ideas;

- **neologisms, breaks, or interpolations in the train of thought, resulting in incoherence or irrelevant speech;**

- **catatonic behavio**r, such as excitement, posturing or waxy flexibility, negativism, mutism, and stupor;

- ***negative symptoms,*** *such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).*

G2. *Most commonly used exclusion clauses*

- If the patient also meets criteria for manic episode or depressive episode, the criteria listed under G1(1) and GI(2) above must have been met *before* the disturbance of mood developed.

- The disorder is not attributable to organic brain disease or to alcohol- or drug-related intoxication, dependence, or withdrawal

Pattern of course

- **Continuous**
  No remission of psychotic symptoms throughout the period of observation.
- **Episodic with progressive deficit**
  Progressive development of negative symptoms in the intervals between psychotic episodes.
- **Episodic with stable deficit**
  Persistent but non progressive negative symptoms in the intervals between psychotic episodes.
- **Episodic remittent**
  Complete or virtually complete remissions between psychotic episodes.
- **Incomplete remission**
- **Complete remission**
- **Other**
  Course uncertain, period of observation too short

DSM V:

A) **Two or more of the following, each present for a significant period of time during a 1 month period. At least one of these must be (1), (2), or (3):**

1. **Delusions,**
2. **Hallucinations,**
3. **Disorganized speech,**
4. **Grossly disorganized or catatonic behavior.**
5. **Negative symptoms(i.e., alogia, avolition , affective flattening)**

B) Disturbance in one or more major areas of functioning **such as work, interpersonal relations, or self care.**

C) **Duration: the disturbance persist for at least 6 months.** 6 months must include at least 1 month of active phase, and may include periods of prodromal or residual symptoms.

DSM V

D**) Exclusion of schizoaffective disorder and depressive symptoms or bipolar disorder with psychotic features**. Because either

1- no major depressive or manic episodes occurred concurrently with the active phase symptoms. Or

2- if mood episode have occurred during active phase , they have been present for a minority of total duration of active phase and residual periods of illness.

E) **Not due to the physiological effects of a substance or another medical condition.**

F)If there is a history of autism spectrum or a communication disorder of childhood onset, diagnosis of schizophrenia is made only if prominent delusions or hallucinations .

- **Specify if:**

The following course specifier are only to be used after a 1 year duration of the disorder,

1. **First episode , currently in acute episode**: first manifestation of the disorder meeting the diagnostic symptom and time criteria. An acute episode is a time period in which the symptom criteria are fulfilled.
2. **First episode, currently in partial remission:** Partial remission is a period of time during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.
3. **First episode , currently in full remission:** Full remission is a period of time after a previous episode during which no disorder specific symptoms are present.

4. **Multiple episodes , currently in acute episode:** after a minimum of two episodes.(i.e., after a first episode , a remission and a minimum one relapse)

5. **Multiple episodes , currently in partial remission :**

6. **Multiple episodes , currently in full remission :**

7. **Continuous:** Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course.
8. **Unspecified:**

- **Specify if :**

With catatonia:

- **Specify current severity**:

1) Severity is rated by a quantitative assessment of the primary symptoms of psychosis including delusions , hallucinations, disorganized speech, abnormal psychomotor behavior , and negative symptoms.
2) Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5 point scale ranging from 0 to 4.

Note:

Diagnosis of schizophrenia can be made without using this severity.

Associated features supporting the diagnosis:

1. **Inappropriate affect,(**e.g., laughing in the absence of an appropriate stimulus.)
2. **A dysphoric mood** that can take the form of depression, anxiety, or anger.
3. **A disturbed sleep pattern**,(e.g. , daytime sleeping and nighttime activity.)
4. **Lack of interest in eating or food refusal,**
5. **Depersonalization, derealization, and somatic concern.**
6. **Anxiety and phobia.**
7. **Cognitive deficits;** decrements in declarative memory, working memory , language function, and other executive functions as well as slower processing speed.

Associated features supporting the diagnosis:

8. Abnormalities in sensory processing, and inhibitory capacity,as well as reduction in attention.
9. Social cognition deficit.
10. Lack of insight.(predict---->non adherence to treatment,
    ---->high relapse rate,
    ---->increase number of involuntary treatment,
    ----->poorer psychosocial functionig,
    -----> aggression,
    -----> poor course of illness.
11. Hostility and aggression.

Neurological soft signs:

- Impairments in motor coordination,
- Sensory integration,
- And motor sequencing of complex movement; left – right confusion.
- And disinhibition of associated movement.

Development and course:

- Onset may be abrupt or insidious onset. But majority manifest as slow and gradual onset.

- Prognosis:

over the 5- to 10-year period after the first psychiatric hospitalization :

- **10 to 20 %: having a good outcome.**
- **>50 % having a poor outcome.**

	Good Prognosis	Poor Prognosis
Age of onset:	Late onset	Young onset
Gender	female	male
onset	Acute or gradual	Insidious onset
Obvious precipitating factors, presence of stressor	present	No precipitating factors
premorbid social, sexual, and work histories	Good	Poor premorbid social, sexual, and work histories
Mood disorder symptoms (especially depressive disorders)	Present	Withdrawn, autistic behavior
Marrital status	Married	Single, divorced, or widowed

Family history	**Family history of mood disorders**	**Family history of Schizophrenia**
Support systems	**Good**	**Poor support systems**
Symptoms	**Positive**	**Negative symptoms and cognitive Symptoms.**

Differential diagnosis:

1) Major depression or bipolar disorder with psychotic features.
2) Schizoaffective disorder:
3) Schizophreniform disorder and breif psychotic disorder:
4) Delusional disorder:
5) Schizotypal personality:
6) OCD and body dysmorphic disorder:
7) Post trumatic stress disorder:
8) Autism spectrum or communication disorder:
9) Other mental disorders associated with a psychotic episode:

Co morbidity:

1. Cigarette smoking,
2. With anxiety disorder,
3. OCD and panic disorder sometimes precede the onset of schizophrenia.
4. Medical disorders as weight gain, metabolic syndrome, cardiovascular disease, and pulmonary disease are more common in schizophrenia.


Thank
You