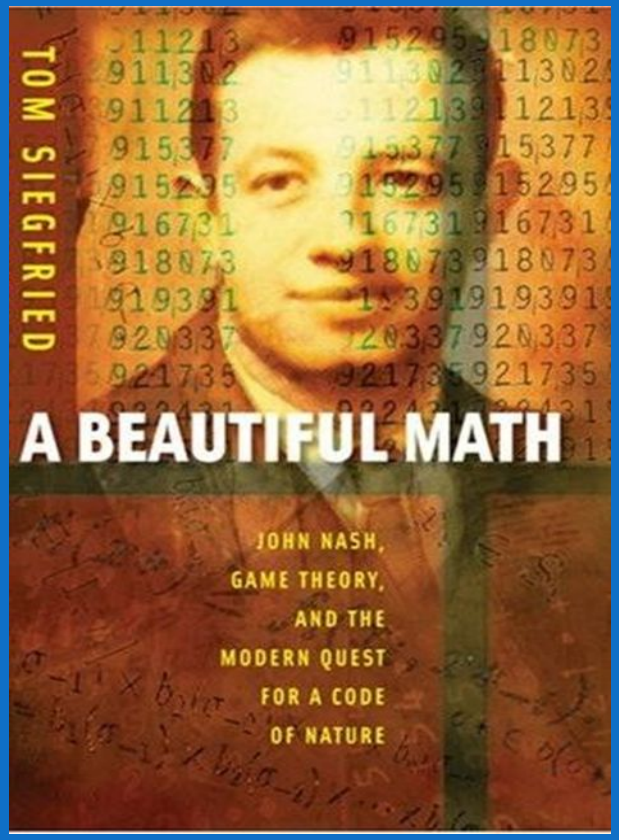
# Schizophrenia



# Schizophrenia: DSM-5 Criteria

A. Two or more of the following present for at least one month: (at least 1 must be 1,2 or 3)

1. Delusions
2. Hallucinations
3. Disorganized speech
4. Disorganized behavior
5. Negative symptoms

B. Low level of function

C. Continuous signs of the disturbance for at least 6 months

D. Not due to substance abuse or medical conditions

**Specifier**

**With Catatonia**

**Course Specifiers**

**First episode**- acute, in partial remission, in remission

**Multiple episodes**- acute, in partial remission, in remission

**Continuous**

# Schizophrenia

- Only one criteria needed if delusions bizarre or hallucinations consist of a voice keeping a running commentary or two voices talking to each other
- Must cause significant social/occupational dysfunction
- Continuous signs of disturbance for 6 months
- 
- < 6 months = schizophreniform

# Schizophrenia subtypes

- Paranoid: preoccupation with one or more delusions or frequent auditory hallucinations
- Disorganized: disorganized speech, behavior and flat or inappropriate affect are all present
- Catatonic: motoric immobility or excessive activity, extreme negativism, peculiar movements, echolalia or echopraxia

# Epidemiology

1-1.5% prevalence

M=F

Winter- born

Equal prevalence around the world

More in large cities

More among homeless

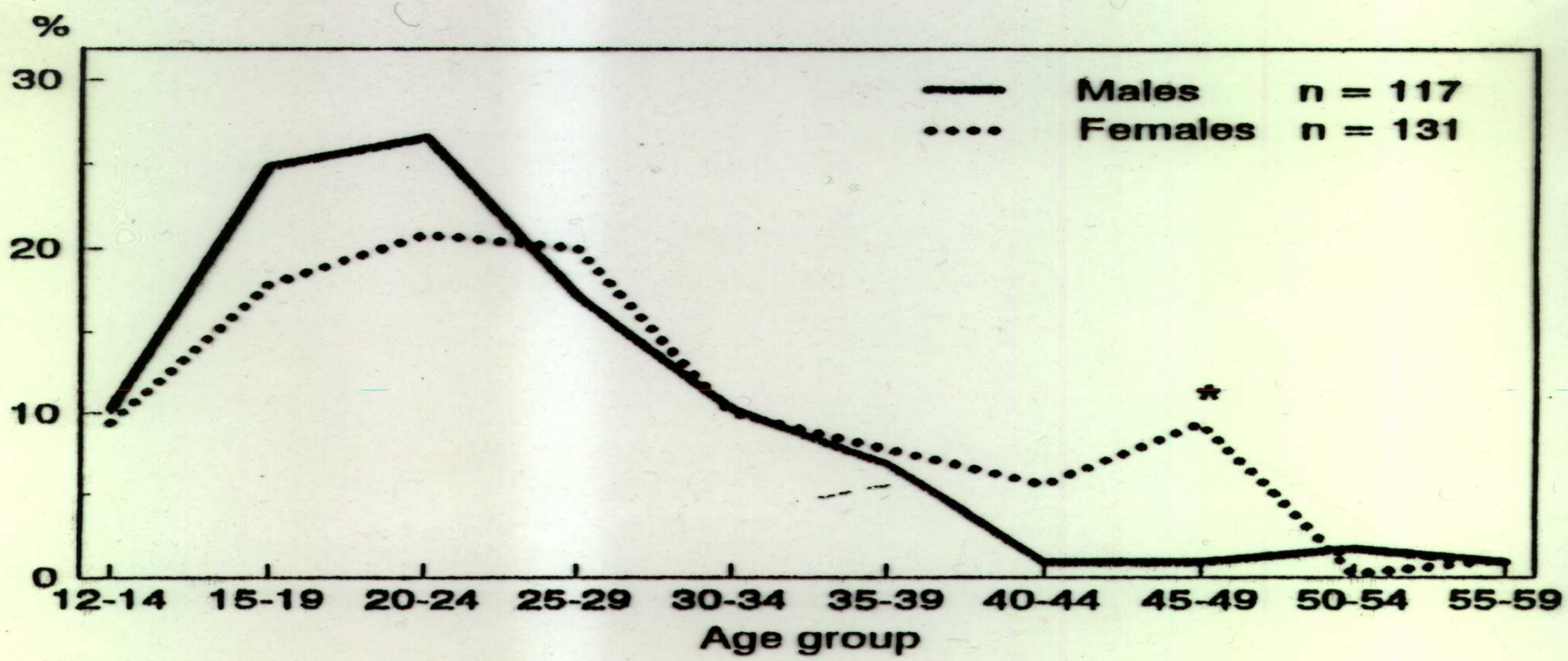
Socioeconomical deterioration

Onset symptoms in males peaks 17-27 yrs

Onset symptoms in females: 17-37 yrs

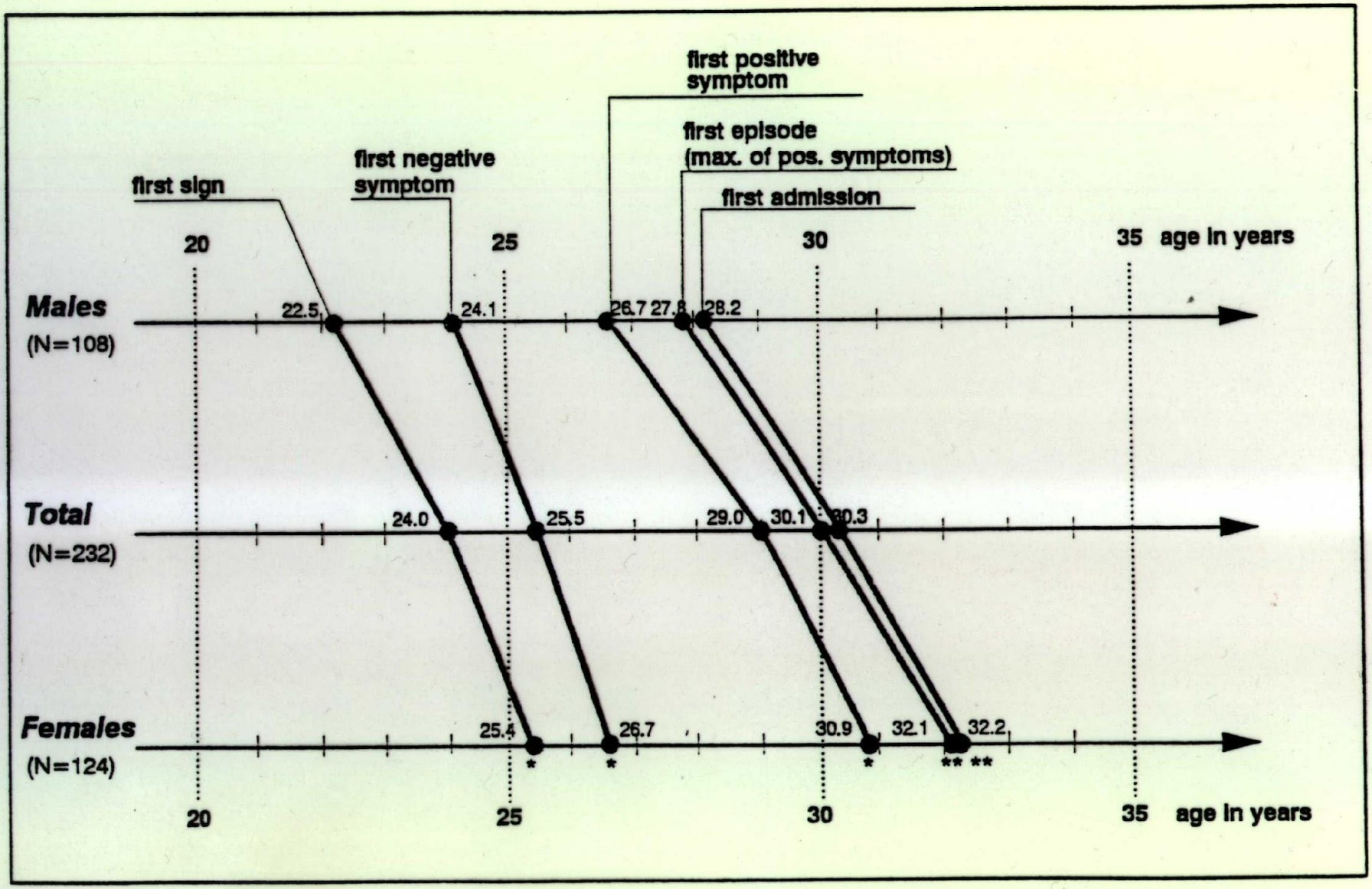
Only 10% new cases have onset after 45 years

**Figure 2. Age distribution of onset of schizophrenia (first sign of mental disorder) for men and women**




Schizophrenia diagnoses = International Classification of Diseases–9 295, 297, 298.3, 298.4 (World Health Organization 1978); subjects are from the ABC (age, beginning, course) sample—Mannheim, Heidelberg, Rhine-Neckar District, Upper Palatinate District; $^{*}p < 0.05$. Adapted from Häfner et al. 1993*b*.

**Figure 1. Mean age values at five definitions of onset until first admission**




Difference between men and women: $^{*}p \leq 0.05$; $^{**}p \leq 0.01$. (First episode sample of broad definition schizophrenia, $n = 232$.)

# Clinical characteristics

- Positive signs- excess of function
- Negative signs- deficiency of function
- Disorganization of thought process and behavior
- Cognitive dysfunction
- Affective changes

# Positive signs= psychosis

- Disorders of perception=hallucinations
- Disorders of thought=delusions

# % of Patients w Positive and Negative symptoms

| | | Mild | Severe |
|---|---|---|---|
| **Hallucinations** | | | |
| Auditory | 19 | 51 | |
| Voices commenting | | 22 | 12 |
| Voices conversing | | 27 | 12 |
| Somatic-tactile | 10 | 6 | |
| Olfactory | | 5 | 1 |
| Visual | 16 | 15 | |
| **Delusions** | | | |
| Persecutory | 19 | 47 | |
| Jealousy | 2 | 1 | |
| Guilt, sin | 16 | 2 | |
| Grandiose | 15 | 15 | |
| Religious | 12 | 11 | |
| Somatic | 11 | 11 | |
| Delusions of reference | | 13 | 21 |
| Delusions of being controlled | | 25 | 12 |
| Delusions of mind reading | 19 | 14 | |
| Thought broadcasting | | 11 | 2 |
| Thought insertion | | 15 | 4 |
| Thought withdrawal | | 11 | 6 |

**Positive**

# Domains of neurocognitive function

- Attention- WSCT
- Perceptual motor processing- Finger taping, STROOP
- Executive function tower of London, WSCT,
- Memory- WMS  CVLT
- Vigilance- CPT
- Verbal memory and  fluency- REY
- working memory-Digit span backwards
- Semantic memory
- social cognition- affect perception

# Types of cognitive disorders

**Lower than normal baseline IQ- premorbid in 25% of patients**

**Cognitive dysfunction after the emergence of the disease- 50% of patients**

**Mainly- executive function, attention, long term memory**

**Cognitively intact- 25% of patients, mostly those who commenced early pharmacological treatment**

# Negative symptoms

Restricted emotional output
Poverty of thought
Poverty of speech
Loss of ability to plan, to exhibit orderly consecutive function, to distinguish between important and unimportant, to make dicisions
Narrowing of interests and hobbies
Loss of motivation and initiative
Loss of social needs and interpersonal interactions
20% with medications, 100% without medications
The accumulation of negative symptoms="deficit"
Destruction of frontal lobe neurons
Irreversible with medications

# % of Patients w Positive and Negative symptoms

| | Mild | Severe |
|---|---|---|
| **Negative symptoms** | | |
| **Affective flattening** | | |
| Unchanging facial expression | 54 | 33 |
| Decreased spontaneous movements | 37 | 14 |
| Paucity of expressive gestures | 34 | 24 |
| Poor eye contact | 39 | 16 |
| Affective nonresponsivity | 18 | 18 |
| Inappropriate affect | 29 | 22 |
| Lack of vocal inflections | 40 | 9 |

**Negative**

# % of Patients w Positive and Negative symptoms

| | Mild | Severe |
|---|---|---|
| **Alogia** | | |
| Poverty of speech | 20 | 20 |
| Poverty of content of speech | | 33 | 6 |
| Blocking | 12 | 3 |
| Increased response latency | | 17 | 6 |
| **Avolition-apathy** | | |
| Grooming and hygiene | 33 | 41 |
| Impersistence at work or school | | 13 | 74 |
| Physical anergia | 36 | 31 |
| **Anhedonia-asociality** | | |
| Recreational interests, activities | | 38 | 41 |
| Sexual interest, activity | 11 | 23 |
| Intimacy, closeness | 24 | 35 |
| Relationship with friends, peers | | 25 | 63 |
| **Attention** | | |
| Social inattentiveness | 25 | 32 |
| Inattentiveness during testing | | 33 | 19 |

**Negative**

# % of Patients w Positive and Negative symptoms

| | Mild | Severe |
|---|---|---|
| **Bizarre behavior** | | |
| Clothing, appearance | 8 | 4 |
| Social, sexual behavior | 17 | 7 |
| Aggressive/agitated behavior | 14 | 6 |
| Repetitive/stereotyped behavior | 7 | 4 |
| **Positive formal thought disorder** | | |
| Derailment | 30 | 4 |
| Tangentiality | 28 | 4 |
| Incoherence | 9 | 1 |
| Illogicality | 10 | 1 |
| Circumstantiality | 14 | 0 |
| Pressure of speech | 14 | 0 |
| Distractible speech | 12 | 1 |
| Clanging | 1 | 0 |

# DDX of negative symptoms

Parkinsonian side effects of antipsychotic typical medications

Pharmacological sedation

Postpsychotic or comorbid depression

Active psychosis

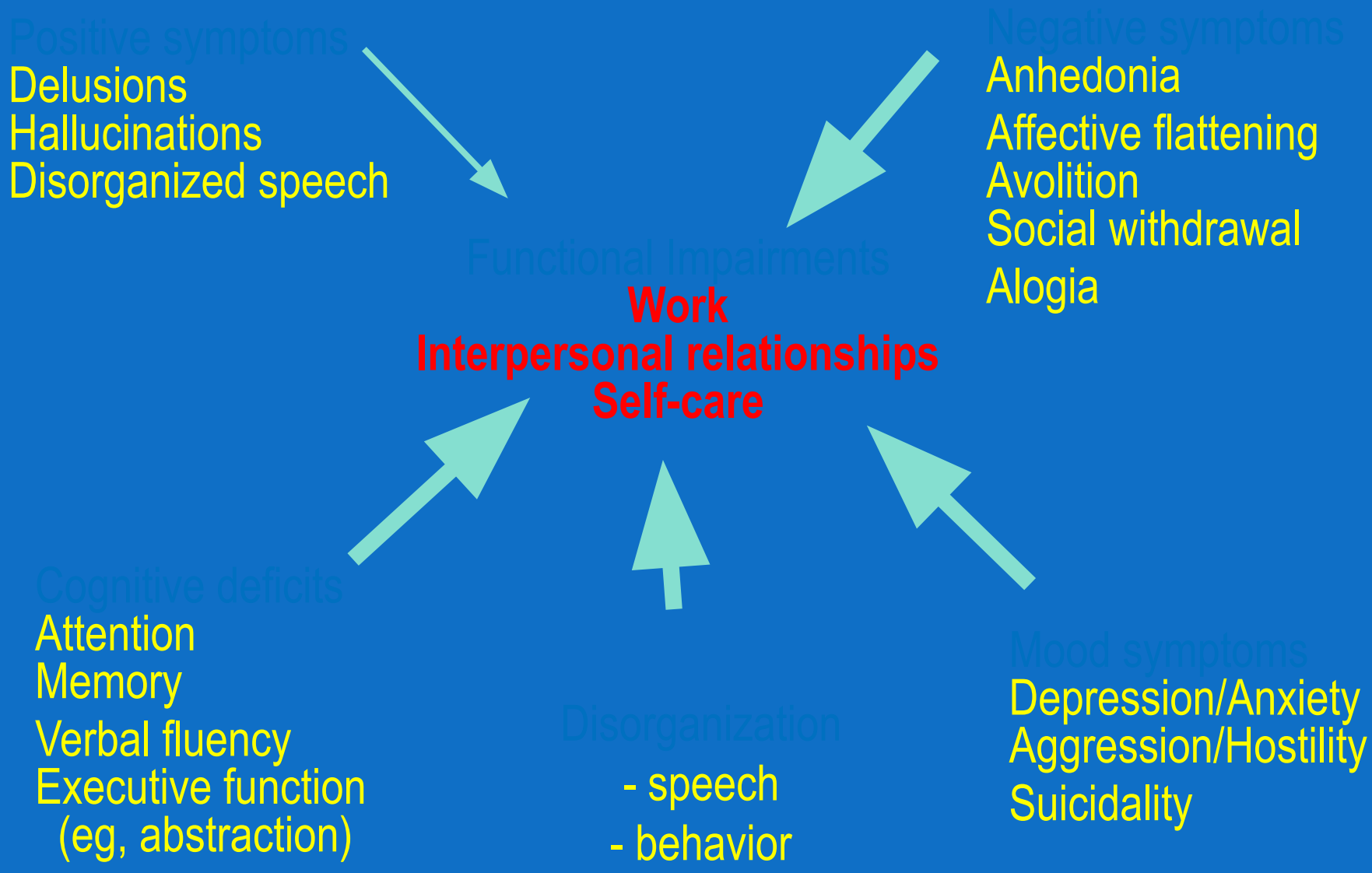
Anxiety

Adjustment reaction to the illness

# Affective symptoms

- Secondary to the disease
- Reactive to the disease and to the frightening psychotic symptoms
- Depressogenic mnedications (haloperidol)

# Features of Schizophrenia



# DDX of schizophrenia

- Schizophreniform Disorder
- Brief Psychotic Disorder
- Delusional Disorder
- Schizoaffective Disorder
- Schizoid Personality
- Schizotypal Personality Disorder
- Paranoid Personality Disorder

Mood Disorders with Psychotic Features

- Major Depression
- Bipolar Disorder

Other Disorders

- substance induced (e.g. PCP, amphetamine, cocaine, hallucinogens, cannabis, alcohol, a variety of prescribed medications
- most diseases affecting the central nervous system

# Clinical course

- Prodrome
- Psychotic episodes with or without inter- episode residual symptoms
- Chronically active course
- Residual course

# Clinical course

Generally marked by chronic course with superimposed episodes of symptom exacerbation

1/3 have severe symptoms & social/vocational impairment and repeated hospitalizations

1/3 have moderate symptoms & social/vocational impairment and occasional hospitalizations

1/3 have no further hospitalizations but typically have residual symptoms, chronic interpersonal difficulties and most cannot maintain employment

M- 18Y, F 25-30Y and another peak around menopause, but can stert at any age including children

Without treatment- progressive deterioration, negative symptoms and cognitive decline

With time- less positive and more negative symptoms

Earlier pharmacological treatment- prevents functional deterioration and cognitive deterioration, decreases suicidality. Medications are neuroprotective!!!

Possible periods of symptom remission

Possible severe and chronically deteriorating course

Rare cases of spontaneous remission and return to mormal premorbid function

A low % of patients do not improve with any medication

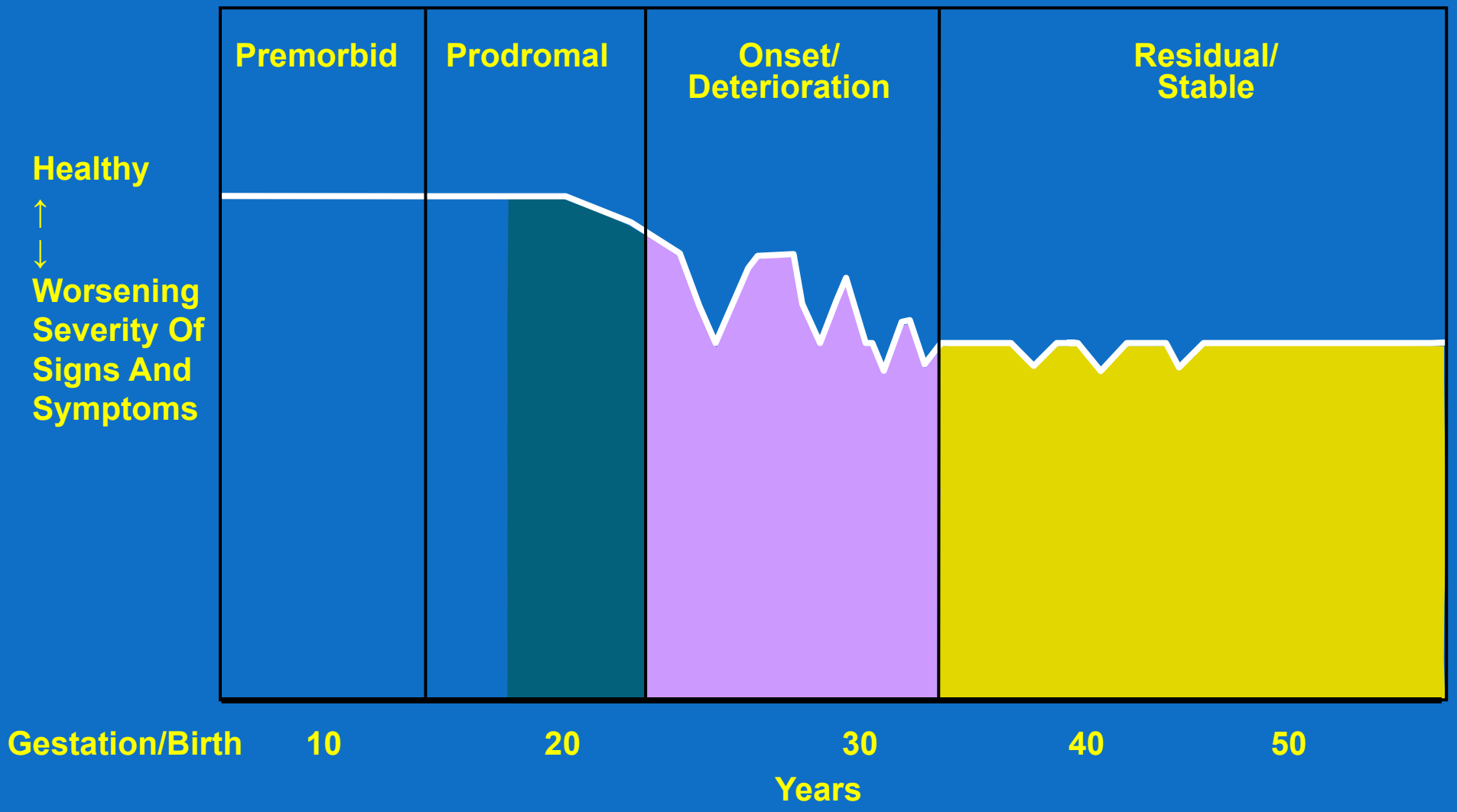
Cases of excellent reaction to medications- stop medications- recurrence- no reaction to medications

With full compliance- could become completely asymptomatic and preserve normal function and cognitive ability

A 20th-century artist, Louis Wain, who was fascinated by cats, painted these pictures over a period of time in which he developed schizophrenia. The pictures mark progressive stages in the illness and exemplify what it does to the victim's perception

# Stages Of Illness

## Natural History Of Schizophrenia



# Prognosis

- 5-10 years after the first episode:
- 10-20% stable improvement
- 10-20% partial improvement
- 50% deterioration
- 40-60%- some form of deficit

# Factors affecting course and prognosis

- Age of onset
- Sex
- Previous levels of function
- Acute vs. slow onset
- Family history
- Triggers
- Duration of symptoms prior to initiation of pharmacological treatment
- Substance use
- Number of psychotic episodes- the more- the worse is the outcome

# Etiology

- Studies of monozygotic twins -40-50% concordance
- 50% genetic risk
- Estimated: the other 50% due to as of yet unidentified environmental factors including *in utero* exposure

# Etiology

- Possibly due to aberrant neuro-developmental processes such as increase in normal age-associated pruning frontoparietal synapses that occur in adolescence and young adulthood
- Excessive activity in mesocortical and mesolimbic dopamine pathways

Genetic

Peripartum complications

Intrauterine infections (toxoplasmosis, influenza)

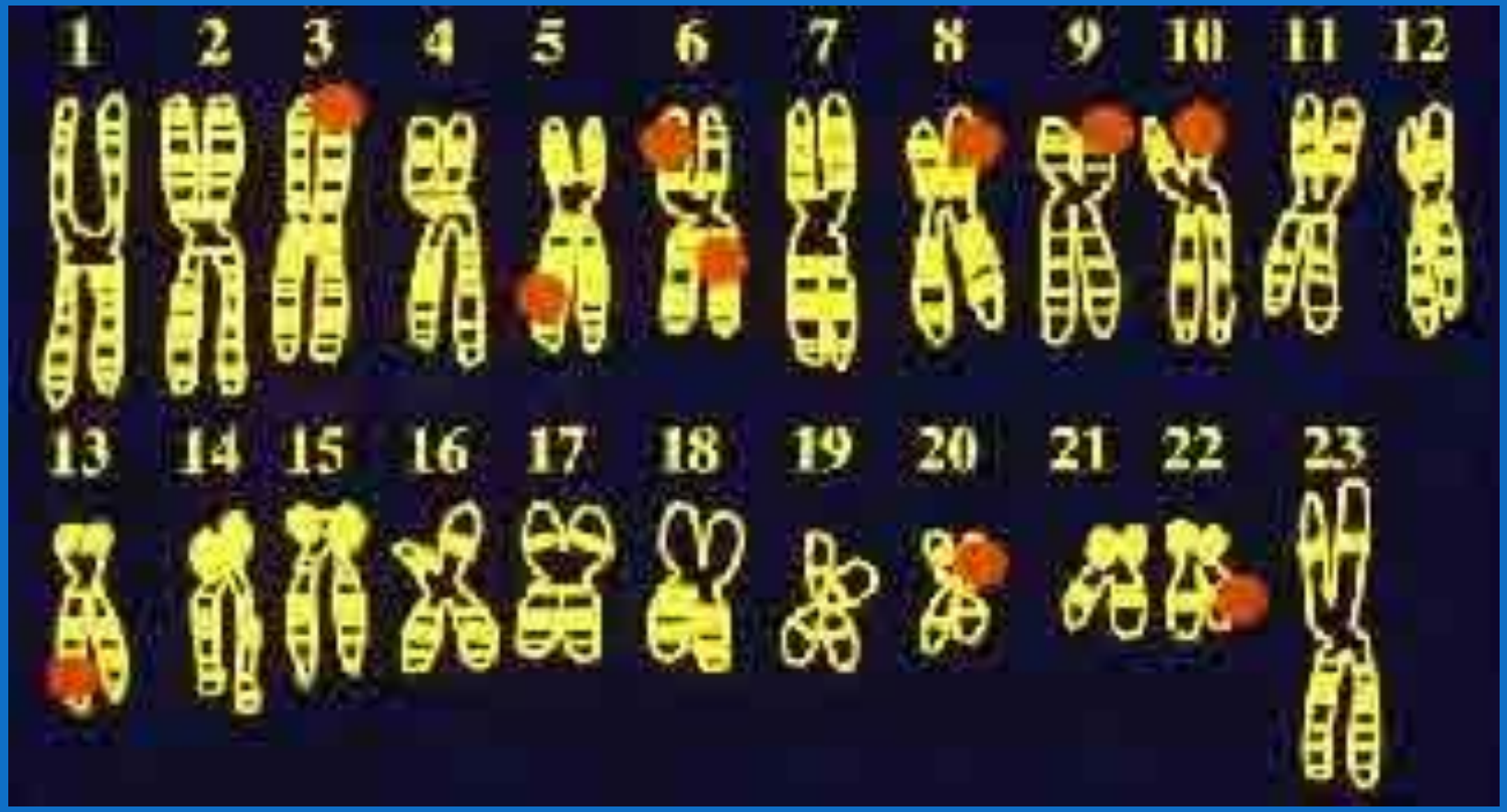
Cannabis use

Othe substances use

Possible stressor before the first episode (that is- without the stressor the episode could have appeared significantly later)

| Chance of disease(%) | |
|---|---|
| % 1 | General population |
| 5% | Grandparent ill |
| 13-20% | One parent ill |
| 46-50% | Both parents ill |
| %9 | Sibling is ill |
| % 17 | Sibling and parents ill |
| 46-48% | Monozygotic twin |
| 4-14% | Dizygotic twin |
| 2-4% | First cousin, uncle/aunt |

# Genetic Loci Linked to Schizophrenia



# Neurodevelopmental theory

**Neurodegenerative disorder**

**Progressive after each psychotic episode**

**No gliosis**

**Structural pathology prior to the first episode**

**Brain development genes**

**Ventricular enlargement**

**Gray matter loss**

**Structural deficits in the limbic system and in medial temporal lobe**

**Changes in neurone connectivity and in neurone size**

**Loss of mitochondria**

# Candidate Neurodevelopmental Molecules and Schizophrenia

| Findings in schizophrenia | Candidate molecules | Developmental events |
|---|---|---|
| | HOX (segmentation) and POU (neurogenesis) families | Early pattern formation |
| | EGF and FGF families | Cell proliferation |
| Decreased NCAM and Reelin | NCAM and Reelin | Cell migration |
| Decreased GAP-43 | LAMP and GAP-43 | Axonal outgrowth |
| Decreased in hippocampus | Wnt family and β& γ-catenins | Cell adhesion and proliferation |
| Decreased BDNF and Neuregulin | NGF family and NGF proteins BDNF and Neuregulin | Survival of connections |
| | BCL-2 family, p53, Cyclin D | Programmed cell death |
| | MBP, Myelin promoting factors | Myelination |
| | Estrogen and Androgen receptors | Pubertal changes |

HOX - homeotic genes; EGF - epidermal growth factor; FGF - fibroblast growth factor; NCAM - neural cell adhesion molecule; LAMP - limbic associated membrane protein; GAP - growth associated protein; BDNF - brain derived neurotrophic factor.

# Neuroimaging findings

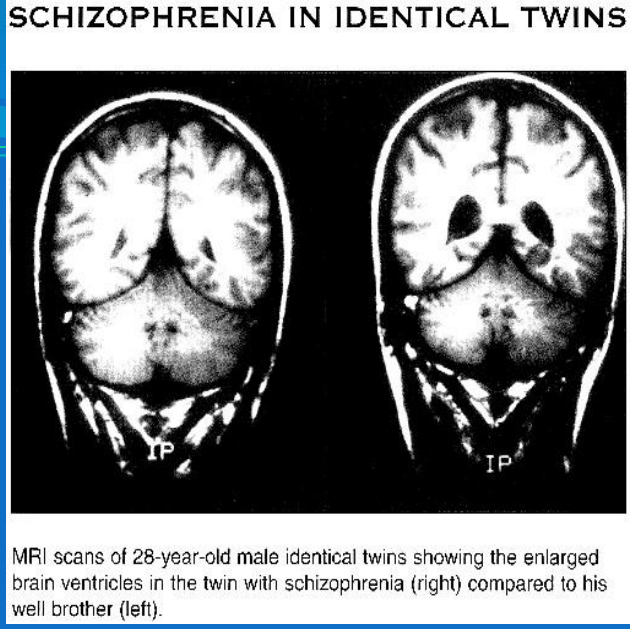
DA, 5HTP

Enlarged ventricles, decreased grey matter

Decreased frontal lobe function

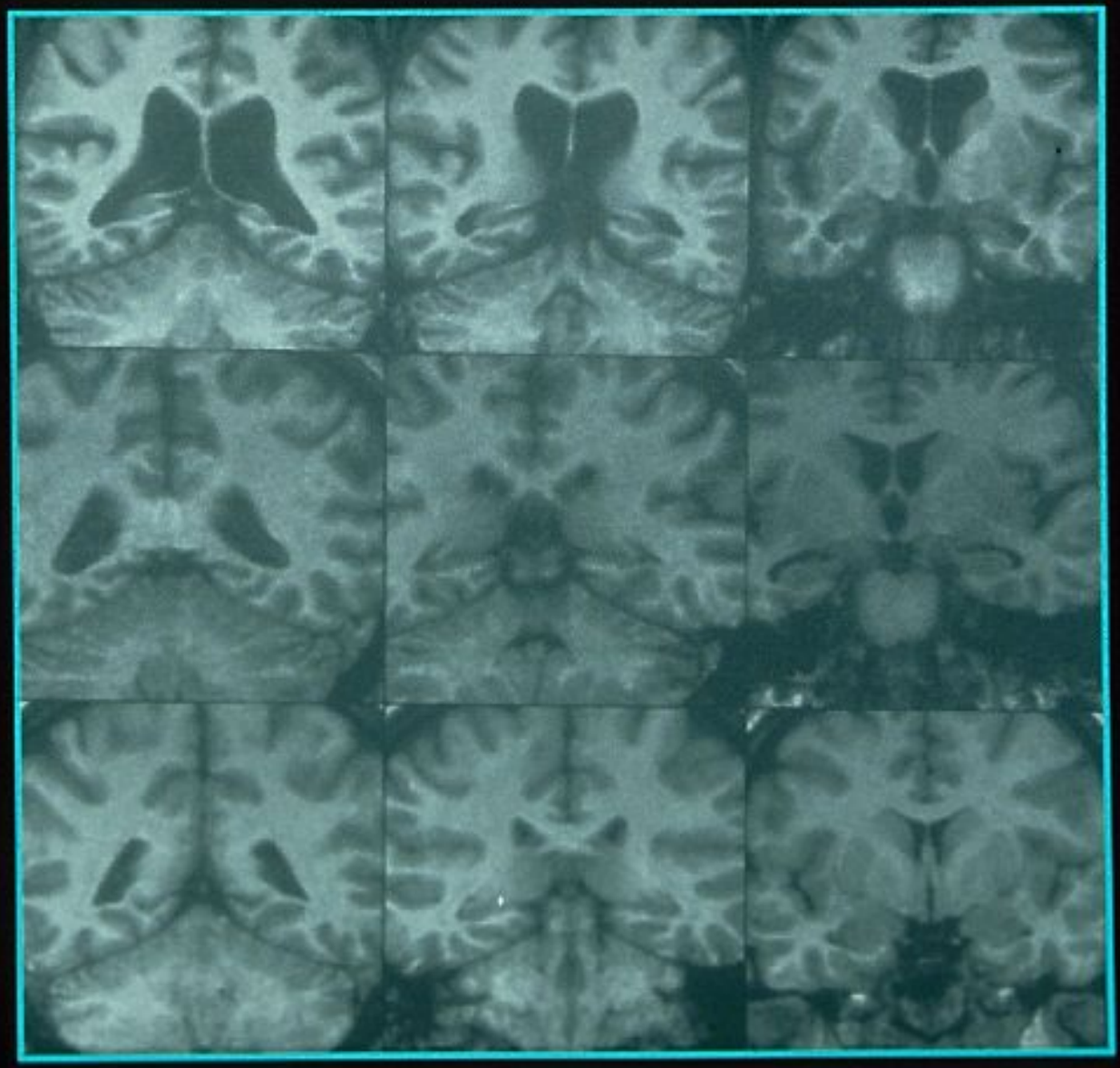
low EVOKED POTENTIAL- P300

SACADIC EYE MOVMENT

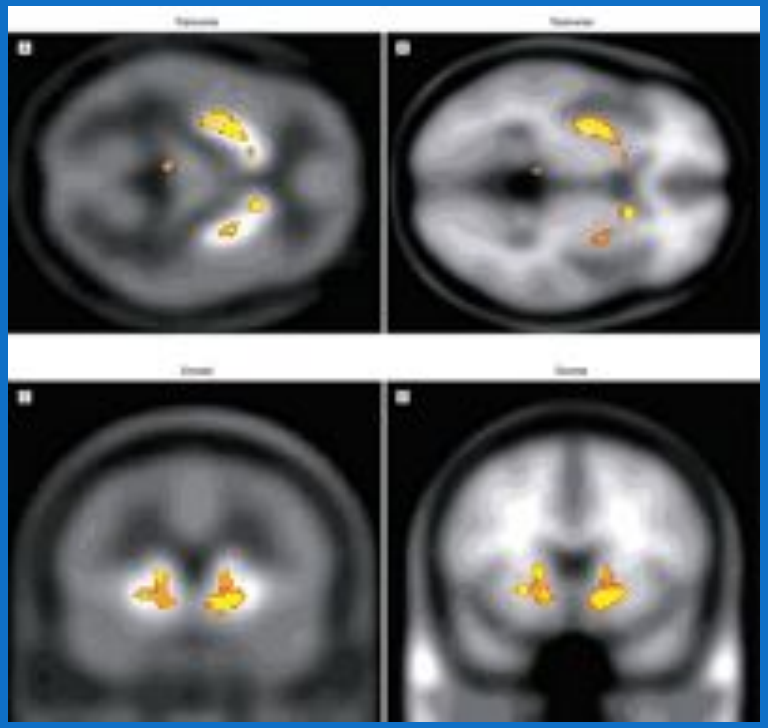


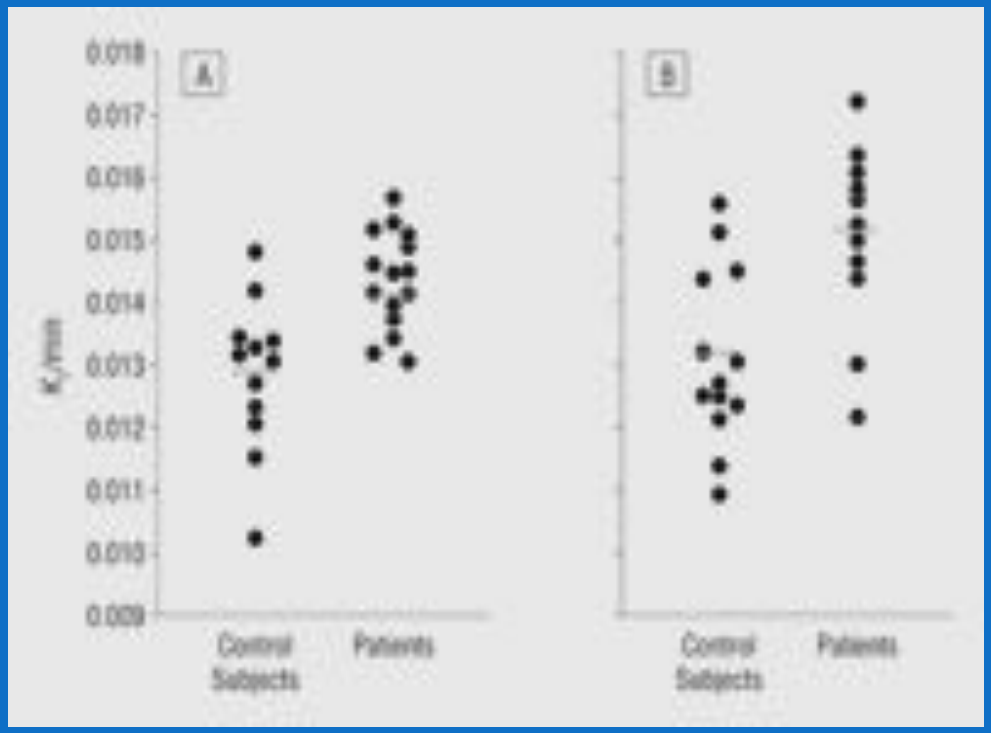
MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).

# MRI OF VENTRICULAR SYSTEM



# [$^{18}$F]fluorodopa uptake in the striatum and the vetral striatum of schizophrenics and normals






*McGowan et al. Arch Gen Psychiatry. 2004*

# The Energy Metabolism Hypothesis of Schizophrenia

- Decreased cerebral blood flow in frontal cortex and an increase in limbic regions *(Franzen & Ingvar, 1975, Cohen et al.,1988)*.
- Abnormal glucose utilization in frontal, temporolimbic and diencephalic regions *(Bauchsbaum,1990)*.
- Reduced ATP in the prefrontal cortex and the temporal lobe *(Fujimoto et al., 1992, Riehemann et al., 2000)*.

# The Involvement of Mitochondria in Schizophrenia

- Reduced oxygen uptake in brain biopsies *(Takahashi, 1954)*.
- Deformation and reduction in the number of mitochondria in anterior limbic cortex and in striatum *(Uranova & Aganova, 1989, Kung L., 1999)*.
- Dysfunction of the oxidative phosphorylation system in the frontal cortex, basal ganglia and platelets. *(Cavalier et al., 1995, Maurer & Moller, 1997, Burkhardt et al., 1993, Whateley et al., 1998, Ben-Shachar et al., 1999, Dror et al., 2002)*.
- Altered mitochondrial related gene expression including those of complex I subunits *(Mulcrone et al., 1995, Whatley et al., 1996, Dror et al., 2002, Middleton, 2002, Prabakaran et al., 2004, Altar et al., 2005)*.

# Dopamine pathways

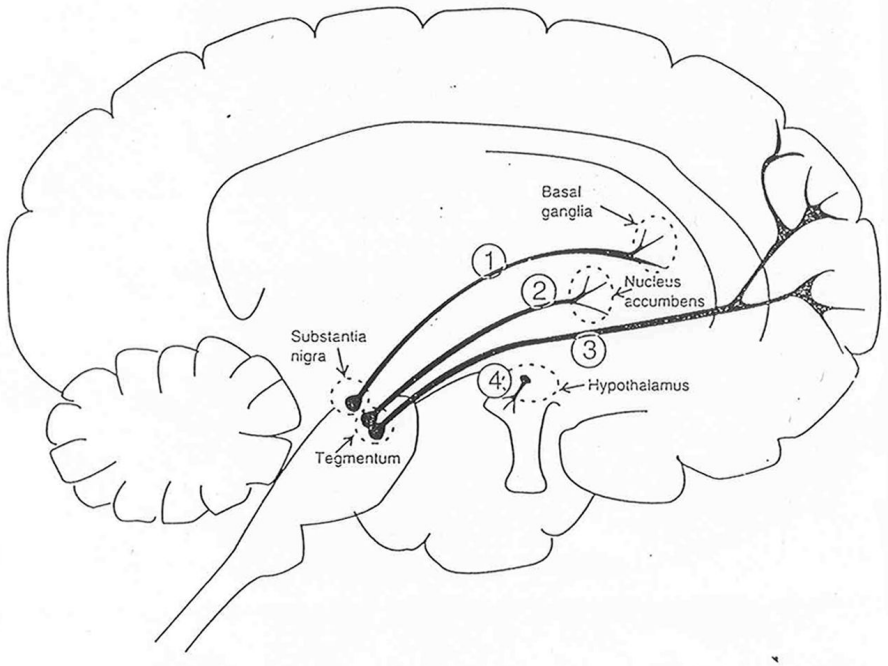



FIGURE 9–3. Four dopamine pathways in the brain. The neuroanatomy of dopamine neuronal pathways in the brain can explain both the therapeutic effects and the side effects of the known antipsychotic agents. (1) The nigrostriatal dopamine pathway projects from the substantia nigra to the basal ganglia, and is thought to control movements. (2) The mesolimbic dopamine pathway projects from the midbrain ventral tegmental area to the nucleus accumbens, a part of the limbic system of the brain thought to be involved in many behaviors, such as pleasurable sensations, the powerful euphoria of drugs of abuse, as well as delusions and hallucinations of psychosis. (3) A pathway related to the mesolimbic dopamine pathway is the mesocortical dopamine pathway. It also projects from the midbrain ventral tegmental area, but sends its axons to limbic cortex, where it may have a role in mediating positive and negative psychotic symptoms or cognitive side effects of neuroleptic antipsychotic medications. (4) The fourth dopamine pathway of interest is the one that controls prolactin secretion, called the tuberoinfundibular dopamine pathway. It projects from the hypothalamus to the anterior pituitary gland.

# Dopamine involvement

## Increased mwsolimbic DA activity

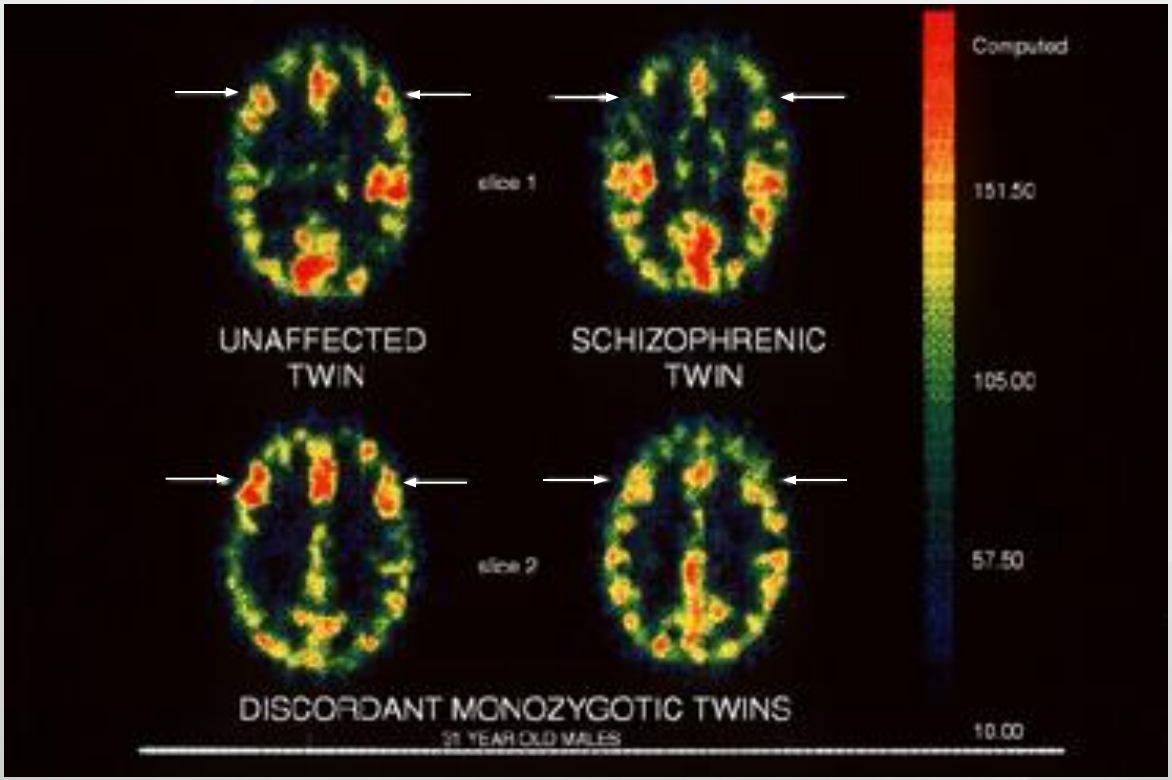
- Delusions
– Hallucinations
-Aggression

## Decreased mesocortical DA activity

Negative symptoms and functional/ cognitive deterioration

# Neuroimaging

**Healthy** **Ill**




**PET scans from a study of identical (monozygotic) twins, who are discordant for schizophrenia (only one has the disorder) demonstrate that individuals with schizophrenia have reduced brain activity in the frontal lobes (top of scan).** *D. Weinberger. E. F. Torrey, K. Berman*

# DA receptors

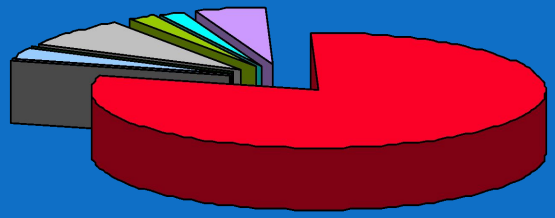
**$D_1$-like receptors- $D_1$ and $D_5$ → cAMP ↑**

**$D_2$-like receptors- $D_2$, $D_3$ and $D_4$ → cAMP ↓**

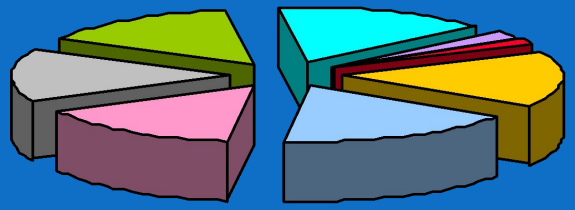
| $D_5$ | $D_4$ | $D_3$ | $D_2$ | $D_1$ | **Brain DA post synaptic receptors** |
|---|---|---|---|---|---|
| - | - | + | +++ | +++ | Caudate putamen |
| - | + | +++ | +++ | +++ | Nucleus accumbens |
| - | - | + | + | + | Spetum |
| - | - | + | +++ | +++ | Olfactory tubercle |
| - | + | + | + | +++ | Amygdala |
| ++ | + | + | + | + | Hippocampus |
| - | + | + | + | + | Cortex |
| + | + | + | + | + | Hypothalamus |
| ++ | + | + | + | + | Thalamus |
| - | - | + | + | + | Cerebellum |

# Receptor Binding Profiles of Conventional and Atypical APDs

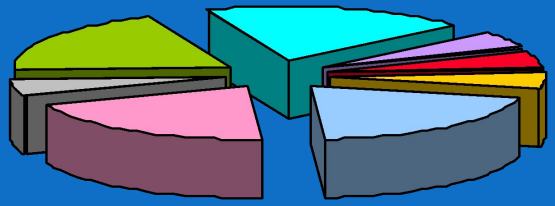
Haloperidol



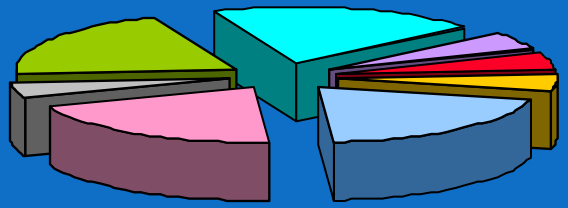
Clozapine

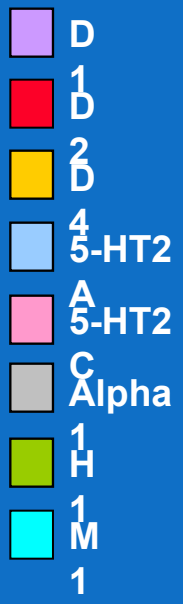


Risperidone



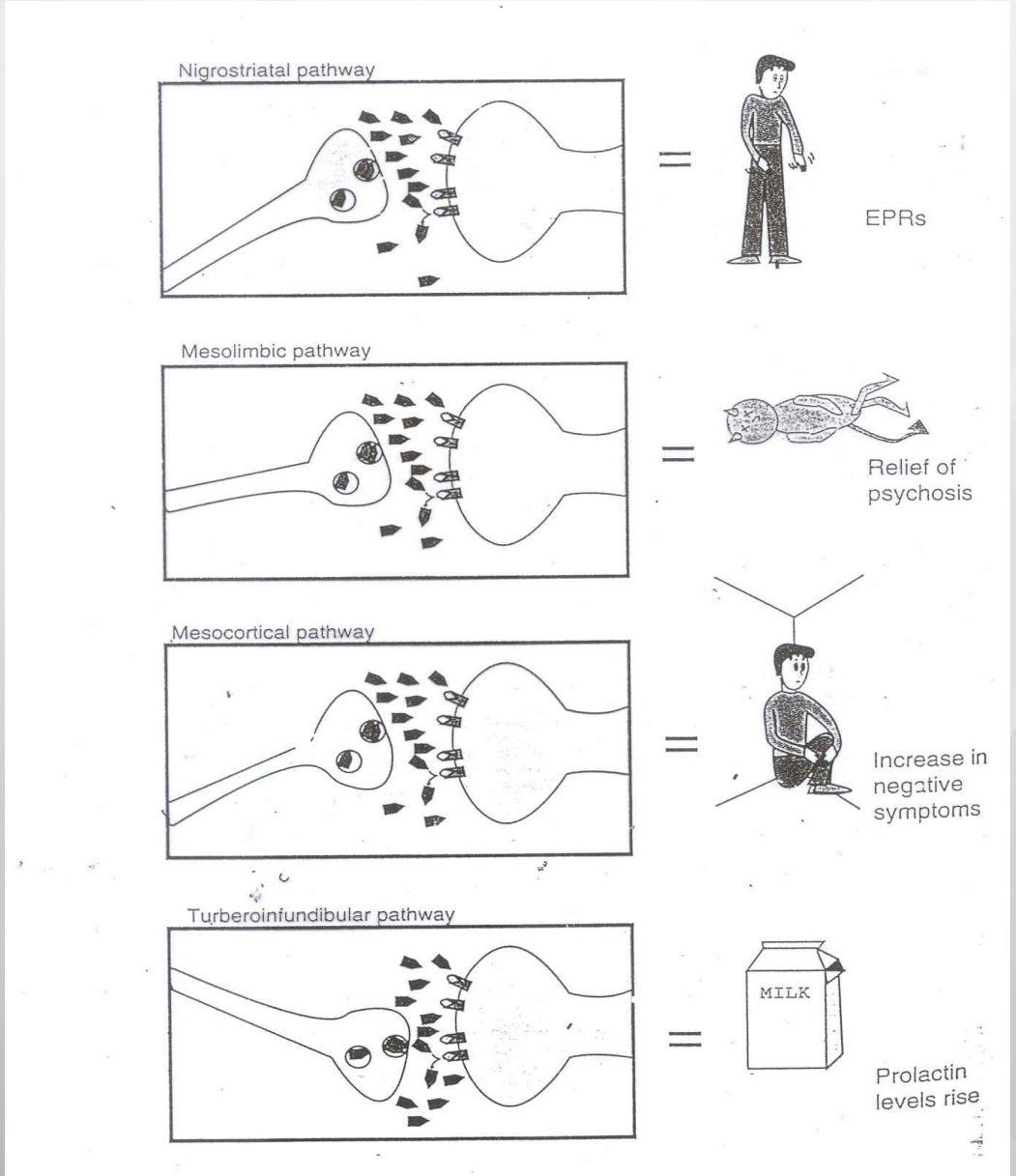
Olanzapine






*J Pharmacol Exp Ther* 1996;277:968;*J Clin Pharmacol* 1999;39:1S; *Psychopharmacology* 1993;112:S60;*Am J Psychiatry* 1997;154:782.

# DA pathways induced side effects of antipsychotics



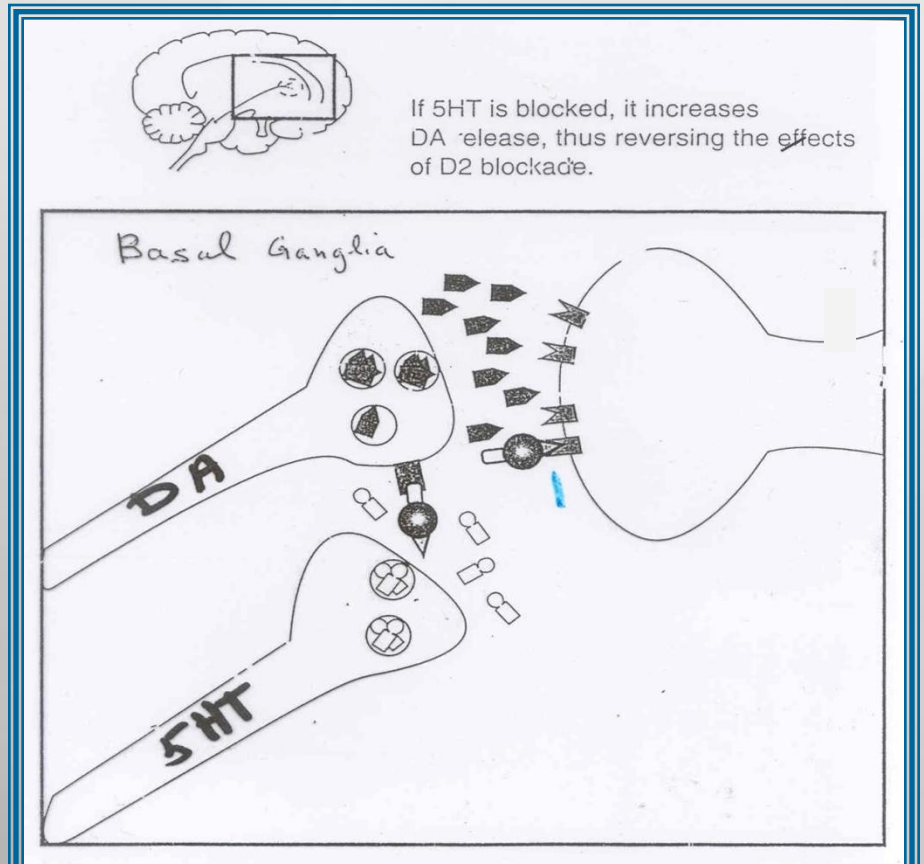
# Evidence of Serotonin Involvement in Schizophrenia Pathophysiology

- Postmortem Studies in Schizophrenics
  - Increase in 5-HT transmission and 5-HT-transporter density in subcortical regions, but no change or decrease in cortical regions.
  - Decrease or no change in 5-$HT_2$-receptor density in prefrontal cortex.
- Agonist-Challenge Studies
  - Administration of *m*-chlorophenylpiperazine (mCPP) a partial 5-HT agonist exacerbates symptoms in unmedicated schizophrenics
  - 5-HT agonist LSD produces hallucinations and other psychotic symptoms

# DA- 5HTreceptors effects of antipsychotics

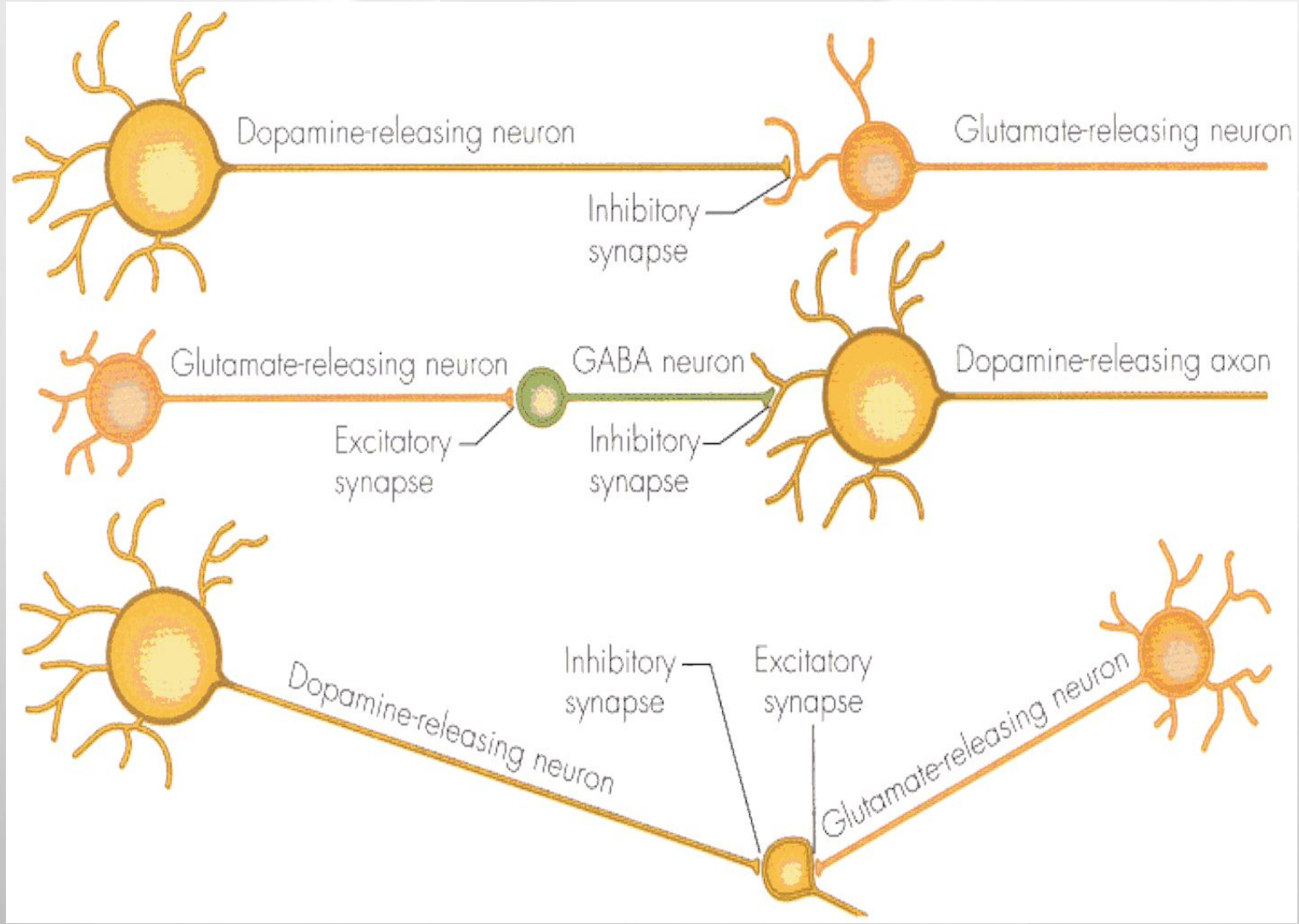
5HT inhibits DA release in the basal ganglia *(EPS)* and prefrontal cortex *(negative symptoms)* but not in the mesolimbic system.

If 5HT is blocked, it increases DA release, thus reversing the effect of D2 blockade



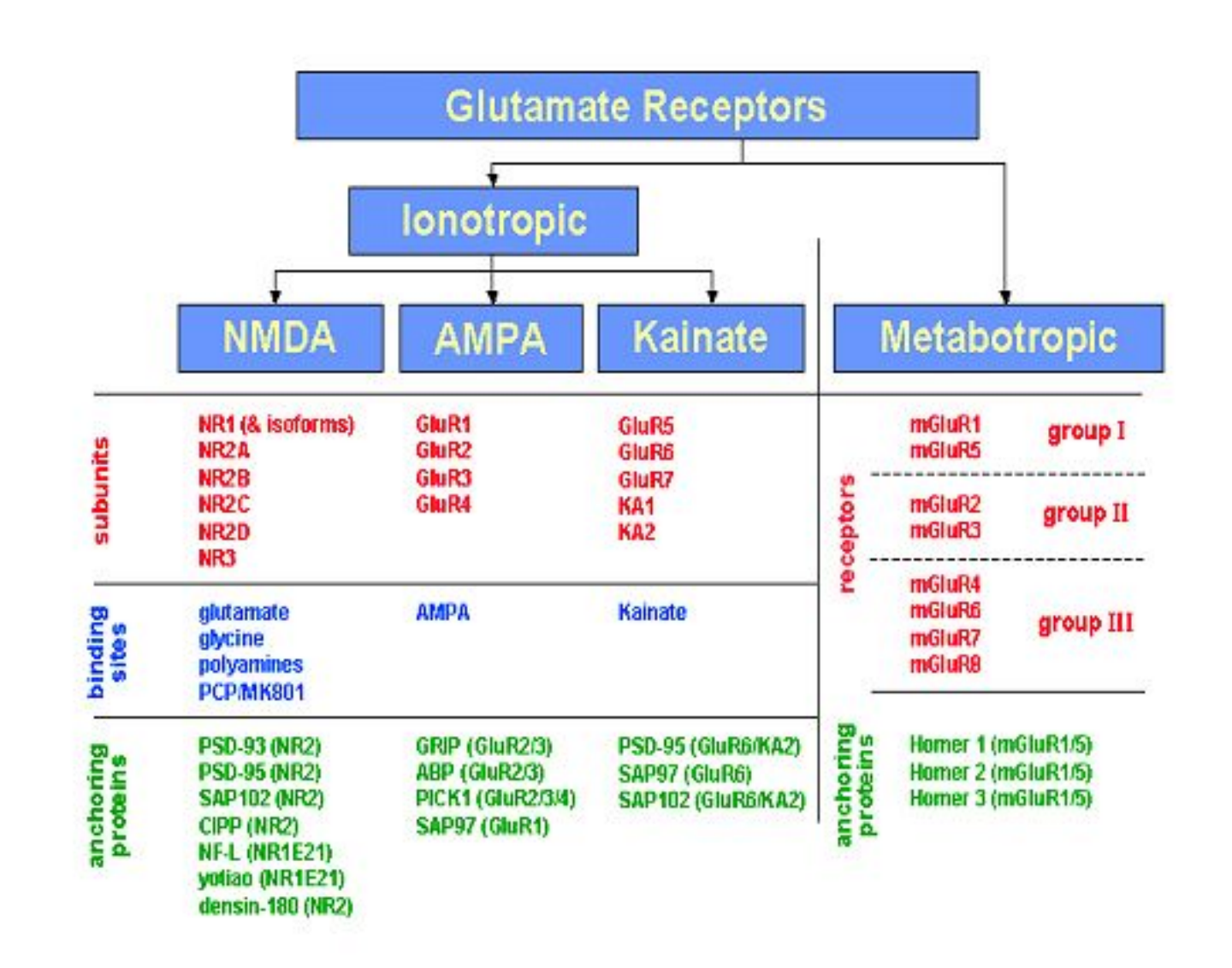

5HT inhibits DA release in the basal ganglia and prefrontal cortex but not in the mesolimbic system.

# Glutamate Dopamine interaction




1. Dopaminergic neurons have inhibitory projections to glutamatergic neurons.
2. Glutamatergic neurons directly excite GABAergic neurons, which inhibit the release of dopamine.
3. Dopaminergic neurons (IPSPs) often compete with glutamatergic neurons (EPSPs).

# Glutamate receptors subunits

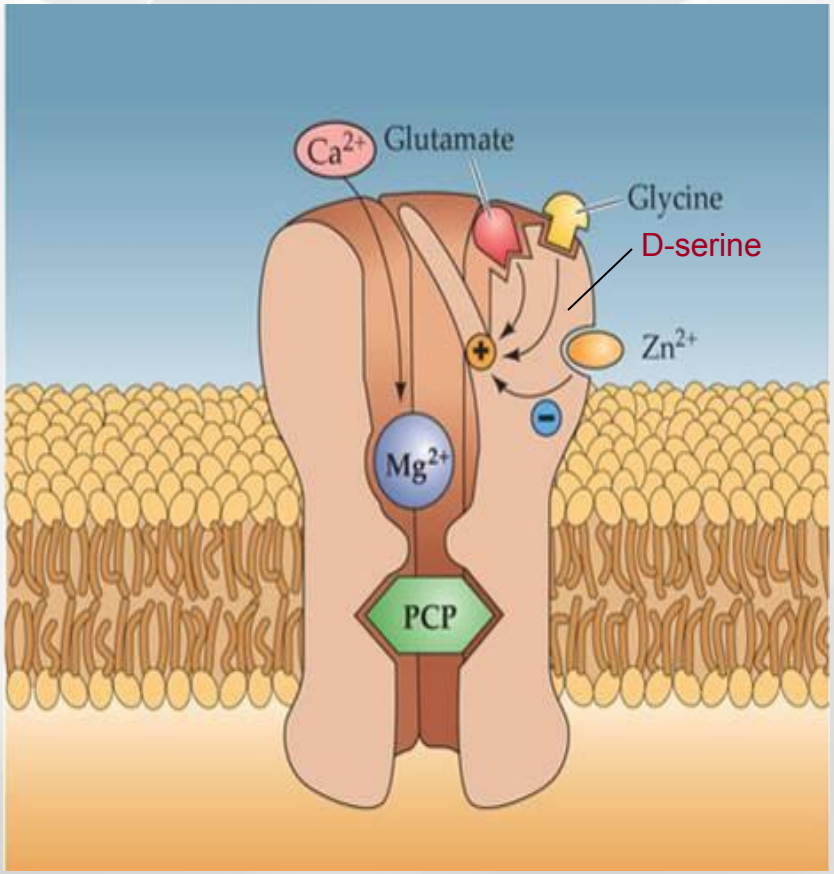


# Glutamate in schizophrenia

## Clinical Data

- Lower concentrations of glutamate in the prefrontal cortex and the hippocampus.
- Increase in KA receptors in the prefrontal cortex
- Increase in AMPA receptors in the medial temporal lobe.
- Lower levels of mRNA encoding AMPA and KA receptor subunits in the hippocampus and parahippocampus.
- NMDA abnormalities
- Correlation – amount of glutamate receptor deficiency is related to deterioration of memory and reasoning

# NMDA receptor




Glycine and D-serine increase glutamate transmission

A clinical study reports improvement in negative symptoms in an add-on strategy.

# Cortical-subcortical glutamate/ GABA/ DA cycle In schizophrenia

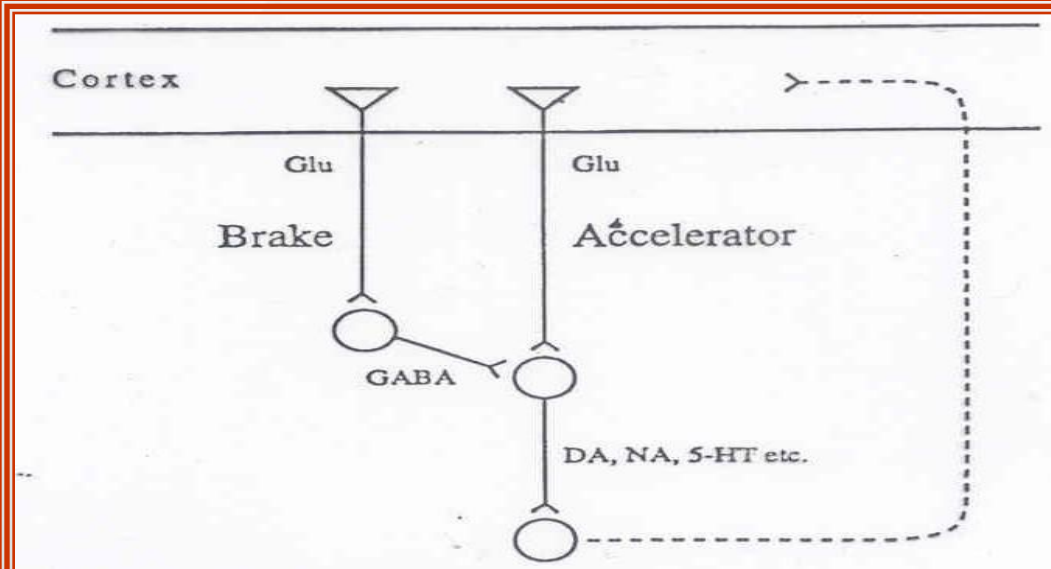
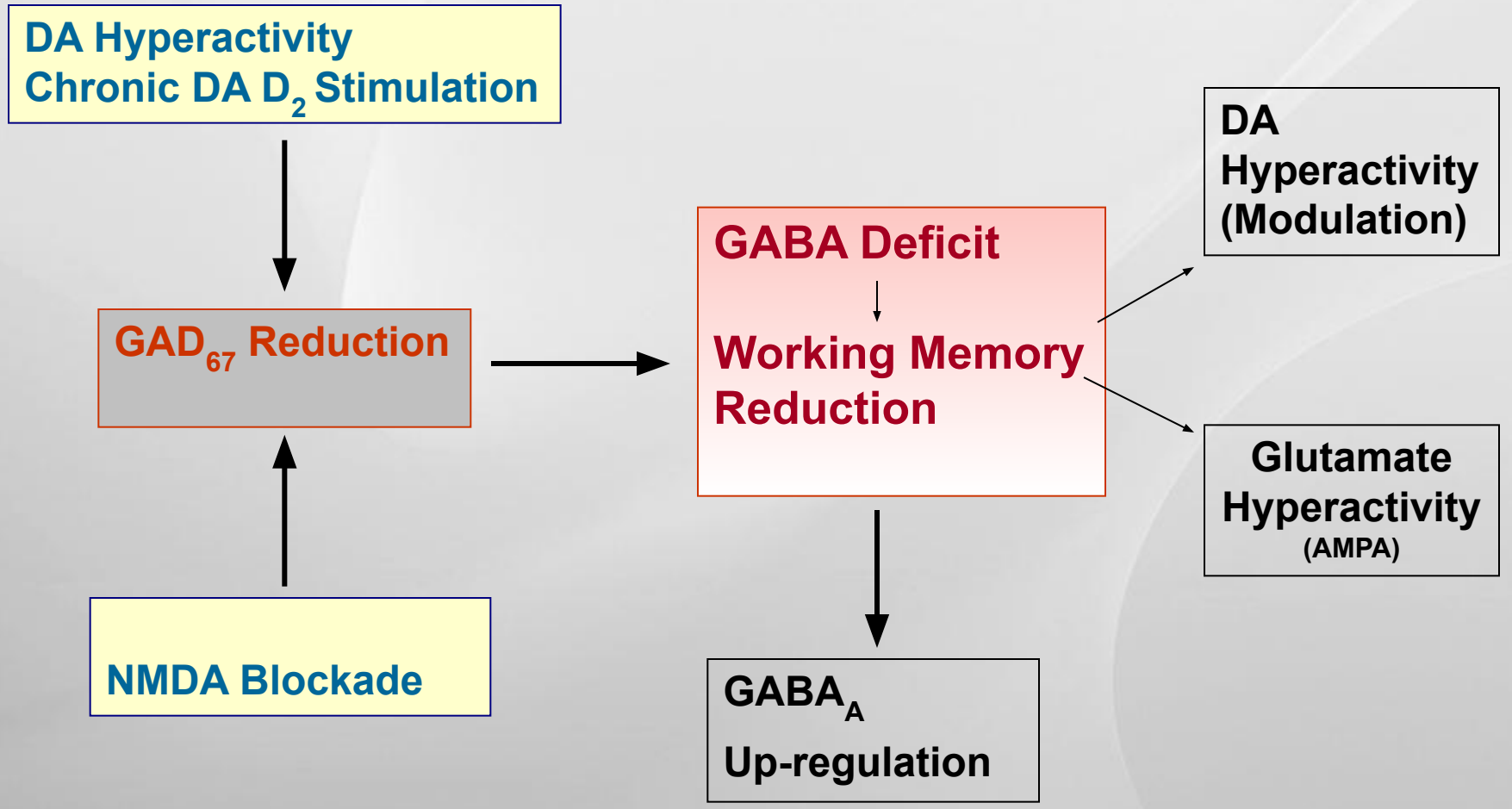



Figure 1. Cortical glutamate/GABA-mediated steering of subcortical systems. Hypothetical scheme showing the cortical regulation of the activity of the monoaminergic brainstem neurons by means of a direct glutamatergic pathway ("accelerator") and an indirect glutamatergic/gabaergic pathway ("brake"). The outcome of a glutamatergic failure will partly depend on the balance between the accelerator and the brake. If the latter predominates in the cortical regulation of a dopaminergic pathway, for example, such failure will lead to an elevated activity of this pathway. As indicated, feedback loops probably exist, at least partly mediated via the striatum and the thalamus. If, for example, the release of dopamine is enhanced by amphetamine, the feedback regulation will increase the activity of the brake, that will counteract the amphetamine-induced release. If the brake fails after treatment with an NMDA-receptor antagonist, or in the case of a hypothetic glutamatergic deficiency in schizophrenia, the amphetamine-induced release of dopamine will be enhanced.

# GABA IN SCHIZOPHRENIA



# Mortality and Cardiovascular Morbidity Among Patient With Schizophrenia

- **Death risk 3.7 to 4.6 times higher than in general population**
- **The risk of MI in 5-fold higher with Typicals**
- **Causes- asphyxion, arrhythmias, thromboembolic events, seizures, pulmonary causes, agranulocytosis**

# The metabolic syndrome
# x- syndrome

- **Obesity**
- **Hyperlipidemia**
- **Hypertension**
- **Diabetes**
- **smoking**

# Smoking

- **80 % of smoking among individuals diagnosed with schizophrenia**

- **Self treatment- nicotin decreases auditory hallucinations**

# Issues in Treating Schizophrenia

- ~30% respond poorly to treatment
- Noncompliance rate ~50% at 1 year
- High relapse rate per year
  - treated ~25%
  - untreated/poor compliance ~70%

# Suicidality

1/2 attempt suicide
10-15% commit suicide
Risk factors- postpsychotic depression and premorbid high level of functioning

# Schizophrenia and addiction

- 47 % have met criteria for some form of a drug/ETOH abuse/addiction
- The odds of having an alcohol addiction- X3 than general population
- The odds of drug assiction- X6 than general population

Regier et al. **Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study.** JAMA. 1990 Nov 21;264(19):2511-8.

# Treatment

- Positive symptoms respond better than negative to medications
- Antipsychotics are mainstay of treatment, affect sometimes also negative symptoms
- Typical APS- highly effective for positive symptoms but motor SE
- Atypical APS: highly effective for positive symptoms, can sometimes be effective for negative symptoms, (but can lead to metabolic syndrome
- Risk of TD approximately 3-5% per year for typical antipsychotics
- Highest in older women with affective disorders
- Risk of dystonic reaction highest in young males
- Clozapine- the most effective antipsychotic medication of all, effective in treatment resistant cases, improves general function, decreases suicide rate. Risk- agranulocytosis 1%
- Long acting preparations increase compliance

# Length of treatment

- 1 psychotic episode + full pharmacological remission- minimal period of treatment is 2 years
- 2 and more episodes- chronic treatment is recommended (70% relapse after 2 episodes, almost 100% relapse after 3 episodes)
- Chronic treatment is neuroprotective and prevents negative symptoms

# Adjunctive methods of treatment

- **Rehabilitation programs!**
- **Lifestyle modification**
- **Avoidance of substances of abuse**
- **Supportive psychotherapy, spiritual support for those who request it, alternative medicine for those who request it- <u>are not a substitute for treatment!</u>**
- **Remember that the mainstream of treatment is pharmacological!**

# Take home points

- Schizophrenia is a severe, genetic, neurodevelopmental disorder that negatively affects every single level of functioning and causes serious disability
- Many factors affect its development and clinical course
- The only effective treatment for the symptoms and for the prevention of deterioration is pharmacological
- Rehabilitation, compliance and ligstyle affect prognosis

# Questions?