Theories of Schizophrenia

Dr Bharat Shah

History

- Benedict Morel (1809-1873) a French psychiatrist, used the term demence precoce to describe deteriorated patients whose illness began in adolescence.
- Emil Kraepelin (1856-1926) translated Morels demence precoce into dementia precox. Patients with dementia precox were described as having a long-term deteriorating course and the clinical symptoms of hallucinations and delusions. Kraepelin distinguished these patients from manic-depressive psychosis and paranoia, which was characterized by persistent persecutory delusions and lacked the deteriorating course of dementia precox.

History

- A. Alzheimer (1864–1915) made detailed observations of the cerebral pathology of psychotic patients. Consequently, he found that patients with psychotic symptoms exhibited no gliosis.
- As an expression describing this prolonged era, it was said that “schizophrenia is a graveyard for neuropathologists.” At the 1st International Congress of Neuropathology in 1952 (in Rome), the conclusion that “there is no neuropathology of schizophrenia”

Bleuler's theory

- Eugene Bleuler (1857-1939) coined the term schizophrenia, which replaced dementia precox. He chose the term to express the presence of schisms between thought, emotion, and behavior in patients with the disorder.
- Fundamental (or primary) symptoms of schizophrenia: **A**ssociational disturbances of thought, especially looseness, **A**ffective disturbances, **A**utism, and **A**mbivalence. Accessory (secondary) symptoms: hallucinations and delusions.
- *"They have encased themselves with their desires and wishes, have cut themselves off as much as possible from any contact with the external world. This detachment from reality with the relative and absolute predominance of the inner life is autism"*

Psychoanalytical theory

- Schizophrenia is a regression to the oral stage when the ego has not emerged from the id. As there is no distinct ego, by regressing to the primary narcissistic stage, schizophrenics lose contact with the world.
- There is heightening of id impulses specially of sexual nature during adolescence. Lack of interpersonal relations and libidinal attachment are attributed to pt's heightened sensitivity to criticism. By trying to adapt with the demands of the id impulses and to have contact with some stimulus, symptoms of delusions, hallucination and thought disorders are found.

Psychoanalytical theory

- Freud named the illness as narcissistic neuroses. In his view, positive symptoms such as hallucinations and delusions were restitutional. His famous quote is - A delusion is like a patch applied over the tear between the ego and external world

Psychosocial theory

- Harry Sullivan viewed SCZ as disturbance in interpersonal relatedness. Severe anxiety that threatens sense of self and unrelatedness is rescued by distortions which lead to paranoia.

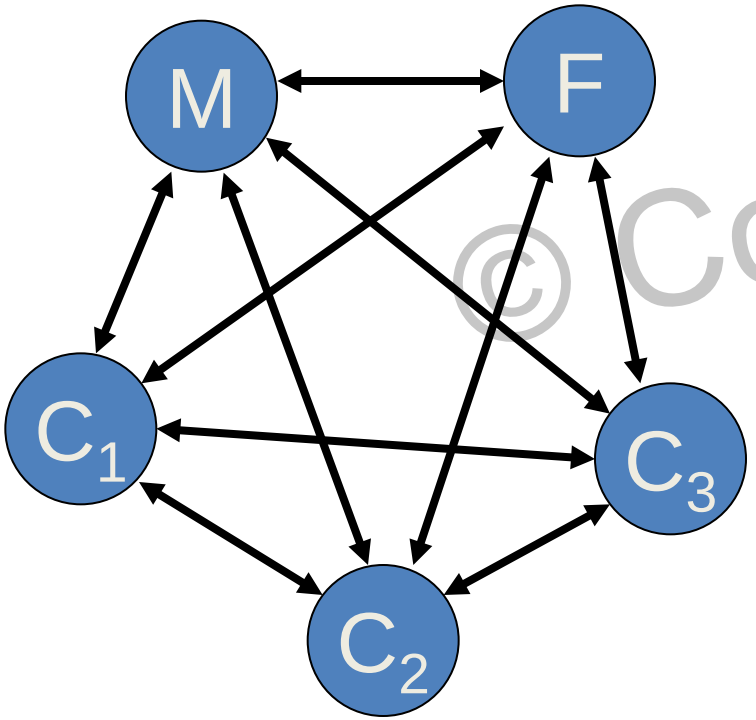
Family Systems

- An early, but since discredited theory, focused on the role of the ***schizophrenogenic*** mother.
- In what some feminists view as historic psychiatric sexism, the ***schizophrenogenic*** mother was described as cold, aloof, overprotective, and domineering.
- She was characterized as stripping her children of self-esteem, stifling their independence, and forcing them into dependency on her.
- Children reared by such mothers were believed to be at special risk for developing schizophrenia if their fathers were passive and failed to counteract the mother's pathogenic influences.

Family Systems Theory

- Origins in:
  - The psychoanalytical tradition (the influence of the family on abnormal behaviour)
  - Systems thinking (idea that things are best understood by looking at the relationships between a set of entities)

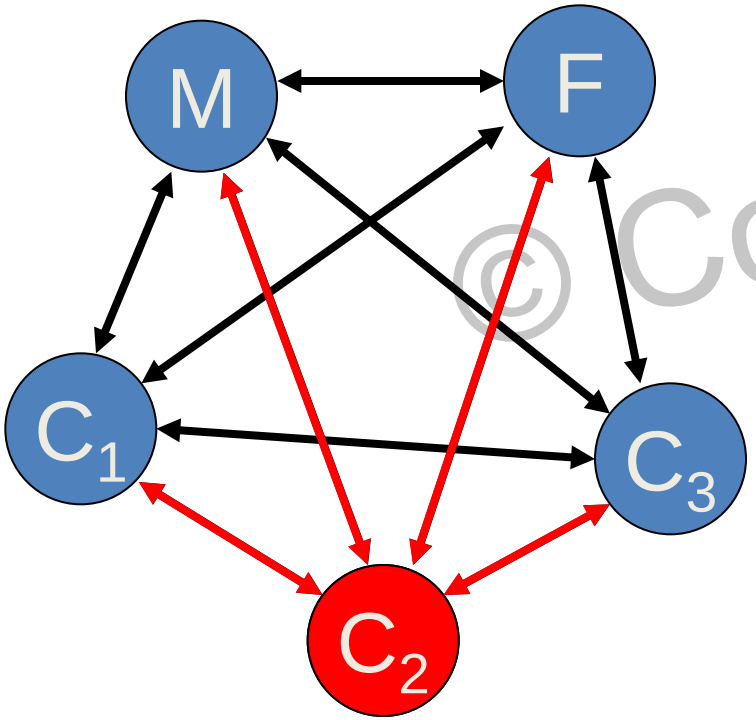
Family System



A family can be seen as a set of entities, each interacting with all the others.

The behaviour of each entity can only be understood by looking at its relationships with the others

Family System



If one person starts to behave abnormally the problem might not lie within that person

Their behaviour may be a manifestation of a problem occurring within the wider family system

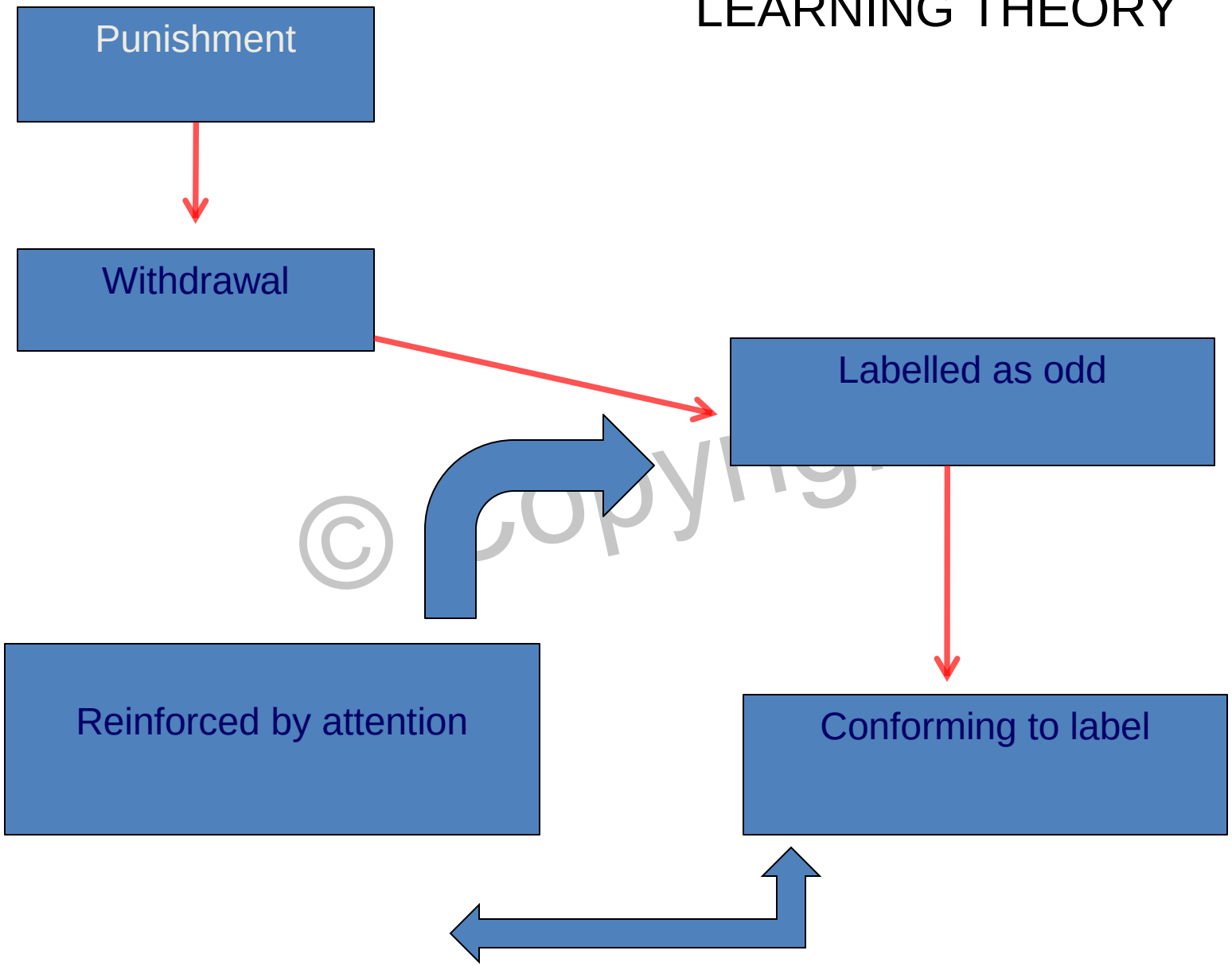
Double Bind Theory

- In a double bind situation a person is given mutually contradictory signals by another person
  - This places them in an impossible situation, causing internal conflict
  - Schizophrenic symptoms represent an attempt to escape from the double bind
  - The patient is a ‘symptom’ of a family-wide problem
  - They become ‘ill’ to protect the stability of the family system

Family System-EE

- Some evidence that family processes play a role in relapse of schizophrenia patients following stabilisation
  - Relapse more likely (58% vs. 10%) where family is high in 'expressed emotion'
  - Families high in
  - ✓ criticism,
  - ✓hostility
  - ✓over-involvement

LEARNING THEORY



Neuropathology

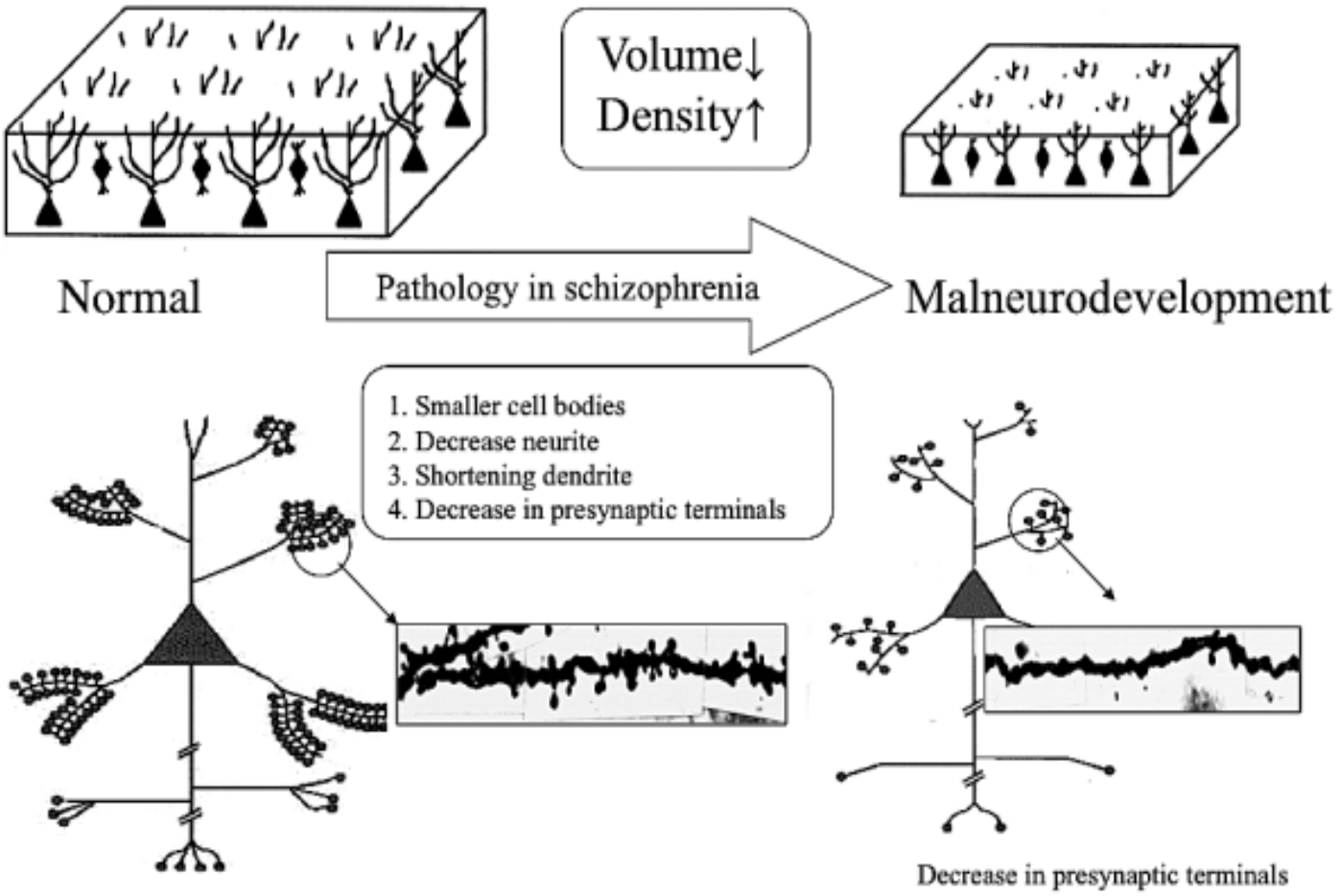
- Subsequently, in the 1980s, with progress in brain imaging technology such as CT, morphological abnormalities of schizophrenia were reported, and moreover, with MRI, PET, SPECT, and the like, detailed brain images including the functions of schizophrenia cases were examined.

- Neuropathological techniques such as image analysis with a computer, and immunohistological special staining and post 1990, genetic research added to the view of brain damage

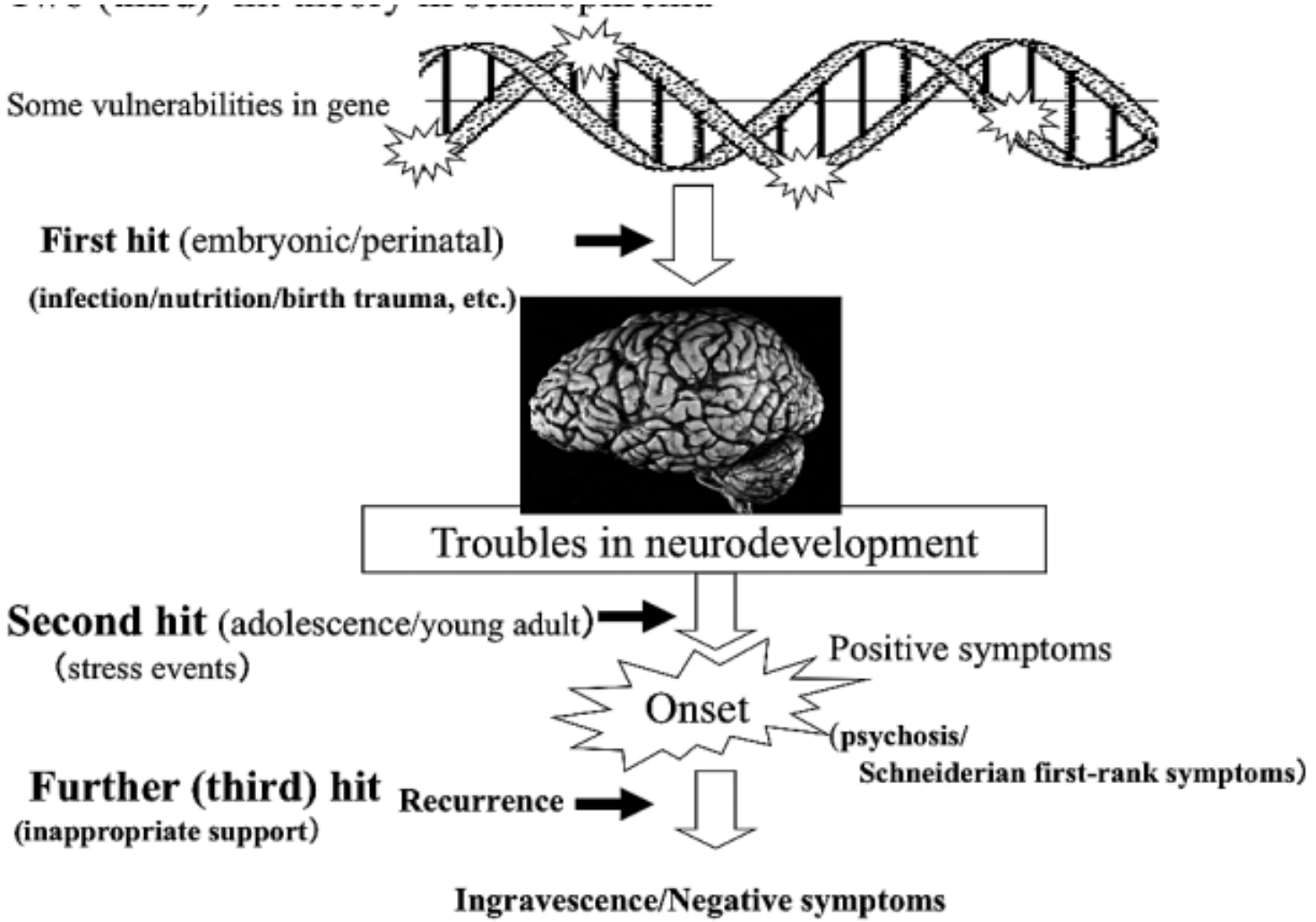
Neuropathology in SCZ,

Macroscopic findings	Strength of evidence
Enlarged lateral and third ventricles	shown by meta-analysis
Decreased cortical volume	shown by meta-analysis
The above changes present in first-episode patients	strong
Disproportionate volume loss from temporal lobe (incl. hippocampus)	strong
Decreased thalamic volume	good
Cortical volume loss affects grey rather than white matter	good
Enlarged basal ganglia secondary to antipsychotic medication	moderate
Histological findings	
Absence of gliosis as an intrinsic feature	good
Smaller cortical and hippocampal neurons	good
Fewer neurons in dorsal thalamus	good
Reduced synaptic and dendritic markers in hippocampus	good
Maldistribution of white matter neurons	moderate
Miscellaneous	
Alzheimer's disease is not more common in schizophrenia	Shown by meta-analysis

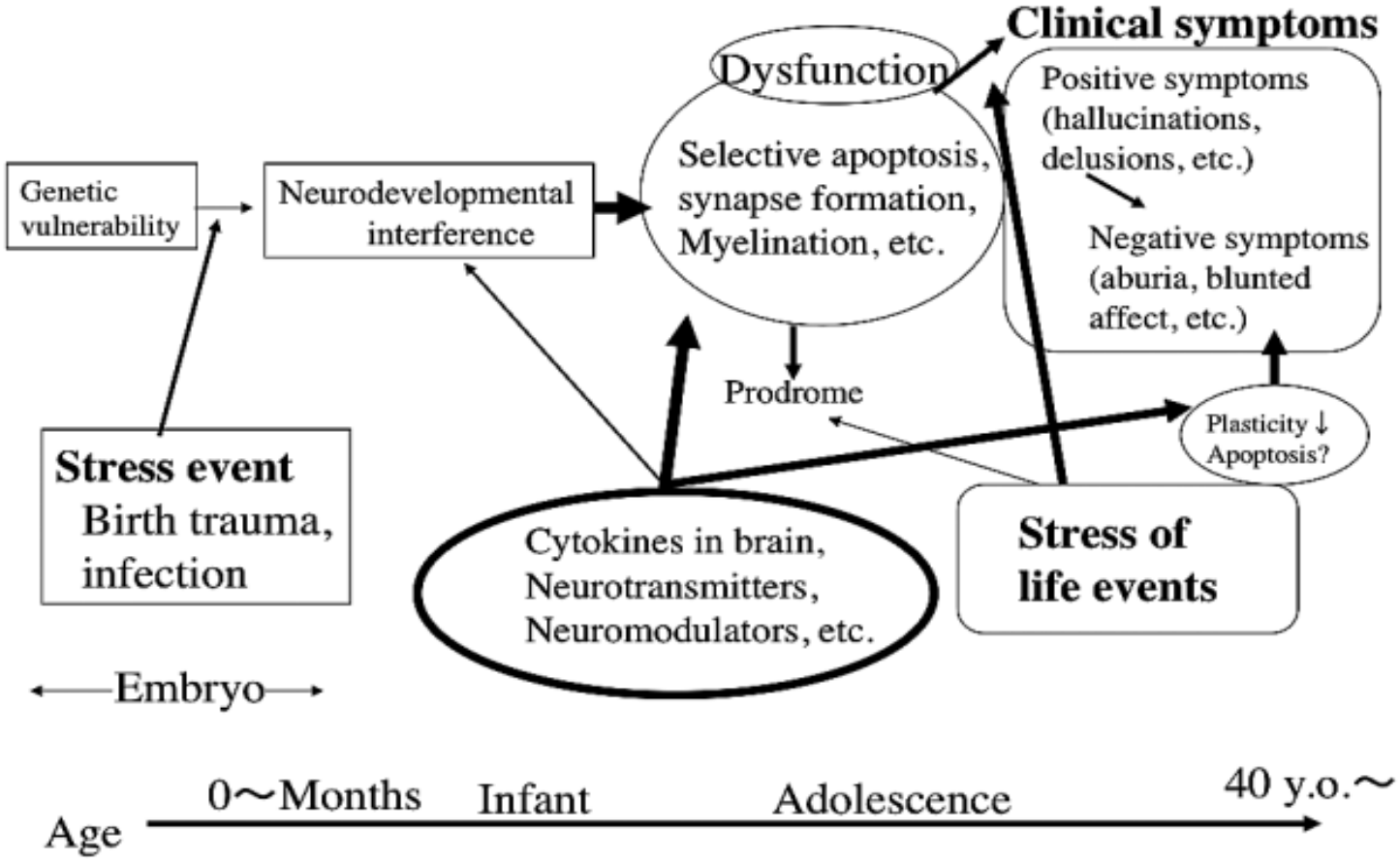
Brain volume loss in SCZ



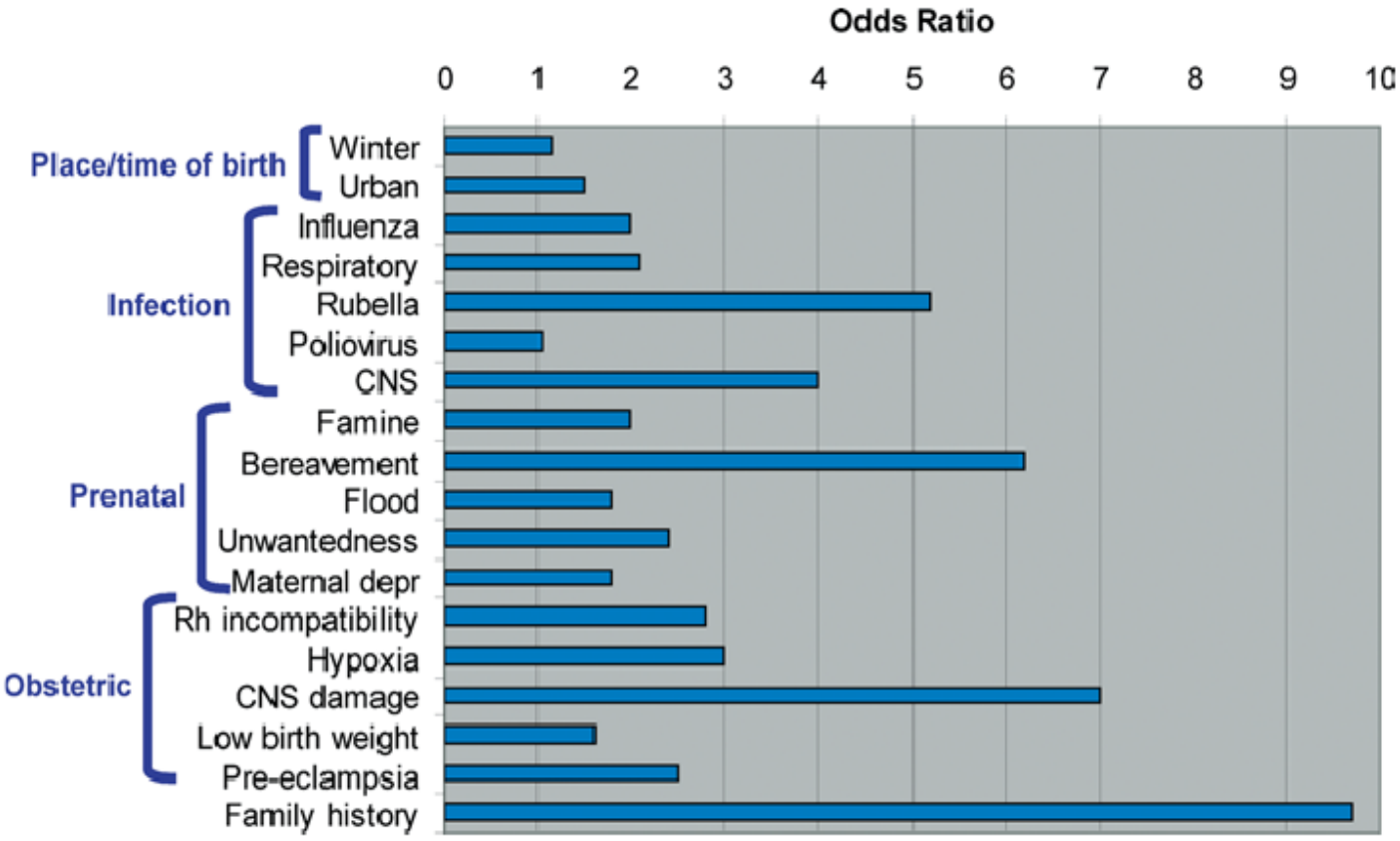
Two hit theory



Neuro developmental dysfunction hypothesis

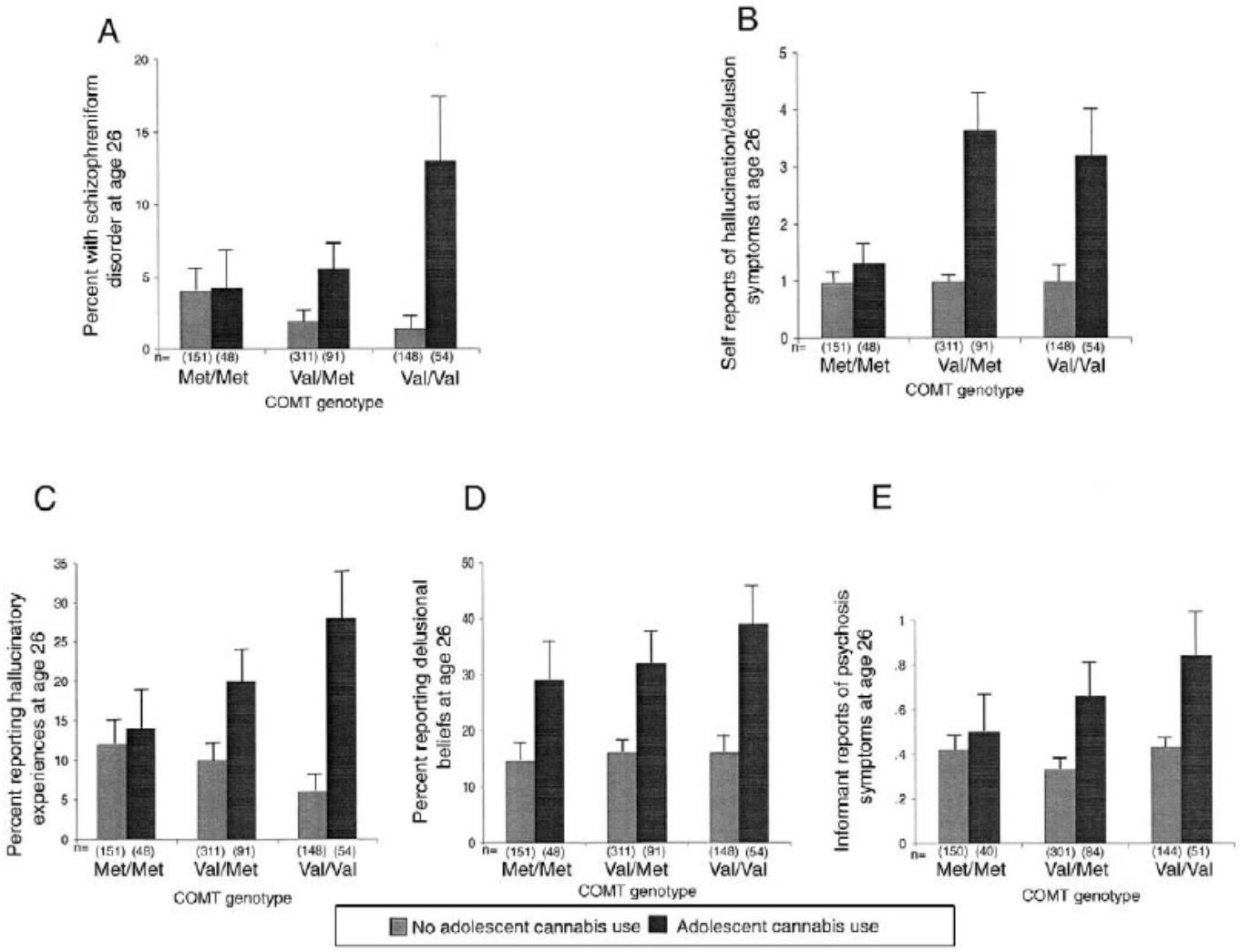


Environmental risk factors in schizophrenia

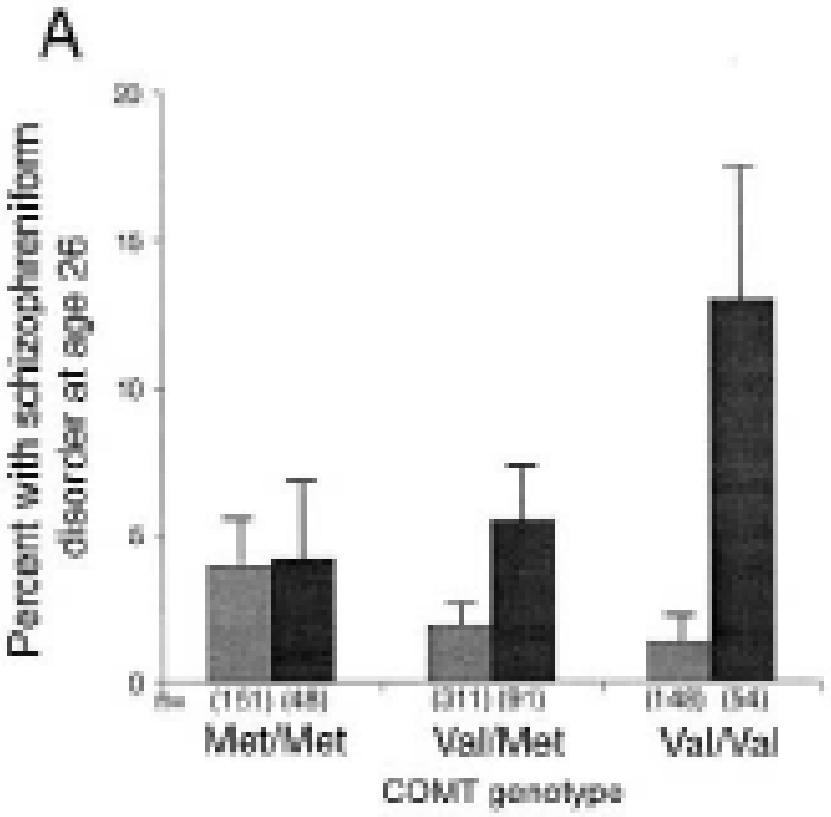


From: Sullivan, 2005. The Genetics of Schizophrenia. *PloS Medicine*

The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene



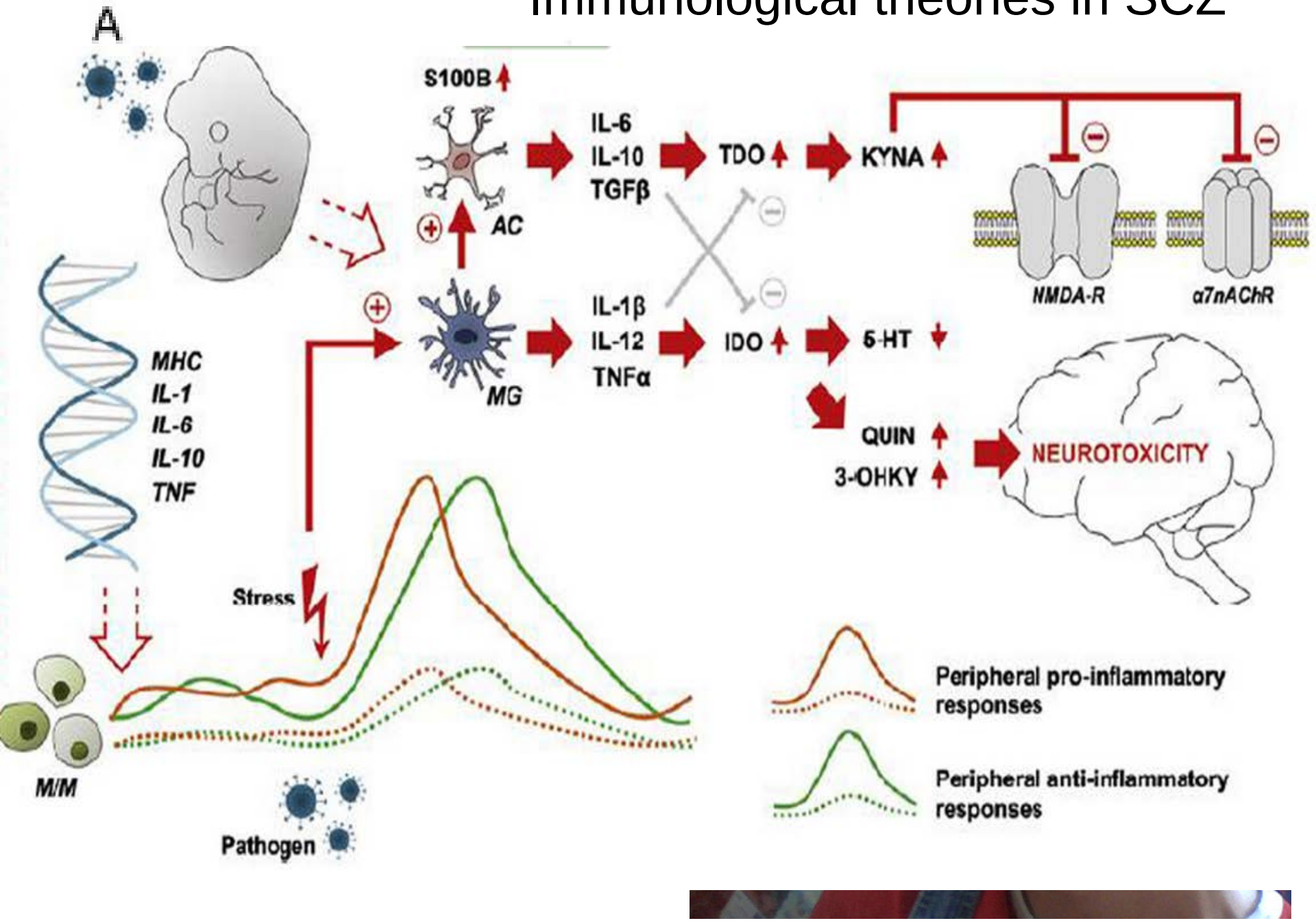
Caspi et al, 2005.

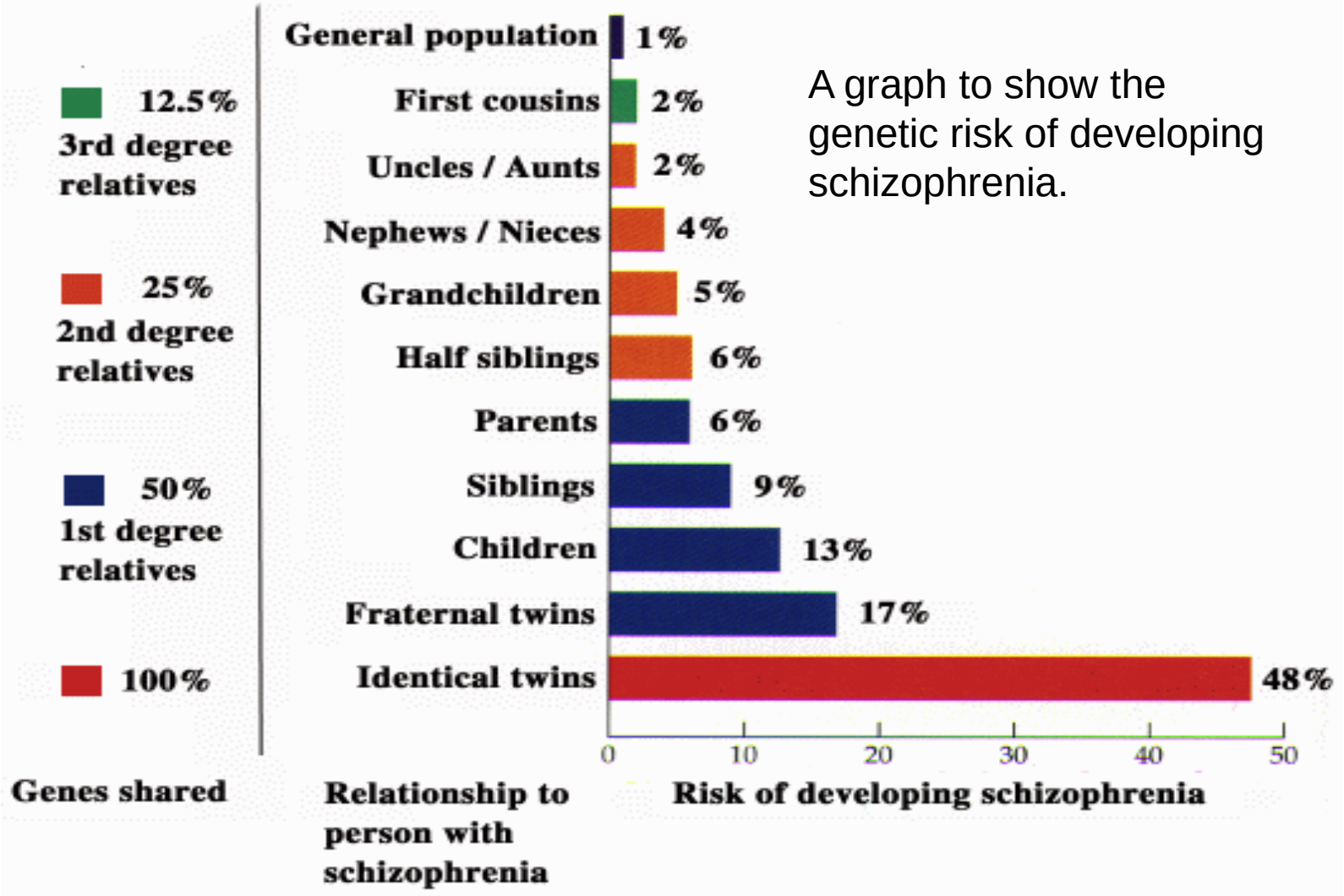


13% of individuals carrying the Val/Val genotype and using cannabis had schizophreniform disoder

Good idea to genotype yourself before you fly to Amsterdam.

Immunological theories in SCZ





A graph to show the genetic risk of developing schizophrenia.

The familial risk of schizophrenia

Genetics

- Generally speaking, the more closely one is related to people who have developed schizophrenia, the greater the risk of developing schizophrenia for oneself.

- **Monozygotic** (MZ) twins, whose genetic heritages are identical, are much more likely than **dizygotic** (DZ) twins, whose genes overlap by 50%, to be concordant for schizophrenia.

Genetics: The Copenhagen High-Risk Study

- Kety and collegues (1962) identified 207 offspring of mothers diagnosed with schizophrenia (high risk) along with a matched control of 104 children with ‘healthy’ mothers (low risk)
- Children aged between 10-18 years at start of study and matched on age, gender, parental socio-economic status and urban/rural residence.

- Follow-up studies conducted in 1974 and 1989

Results:

- Schizophrenia diagnosed in 16.2% of high risk group compared to 1.9% in low risk group
- Schizotypal personality disorder diagnosed in 18.8% of high risk group vs 5% of low risk group

Genetics: Twin Studies

- Compare concordance rates for identical (MZ) and dizygotic (DZ) twins
- Both share the same environment but only MZ twins have identical genetics
- Many studies conducted – all show much higher concordance rate in MZ than DZ twins
- To separate environment from genetic influences, researchers have sought out MZ twins reared apart where at least 1 has been diagnosed with schizophrenia

Genetics: Twin Studies

Gottesman & Shields (1982) used the Maudsley twin register and found 58% (7/12 MZ) twins reared apart were concordant for schizophrenia.

If the genetic hypothesis is correct, then the offspring of a non-affected discordant MZ twin should still be high-risk

A study found that 9.4% of such offspring developed schizophrenia, which is a much higher incidence than in the general population (1%)

Genetics: Adoption Studies

- More effective in separating effects of genetic and environmental factors
- Look at adopted children who later develop schizophrenia and compare to biological parents

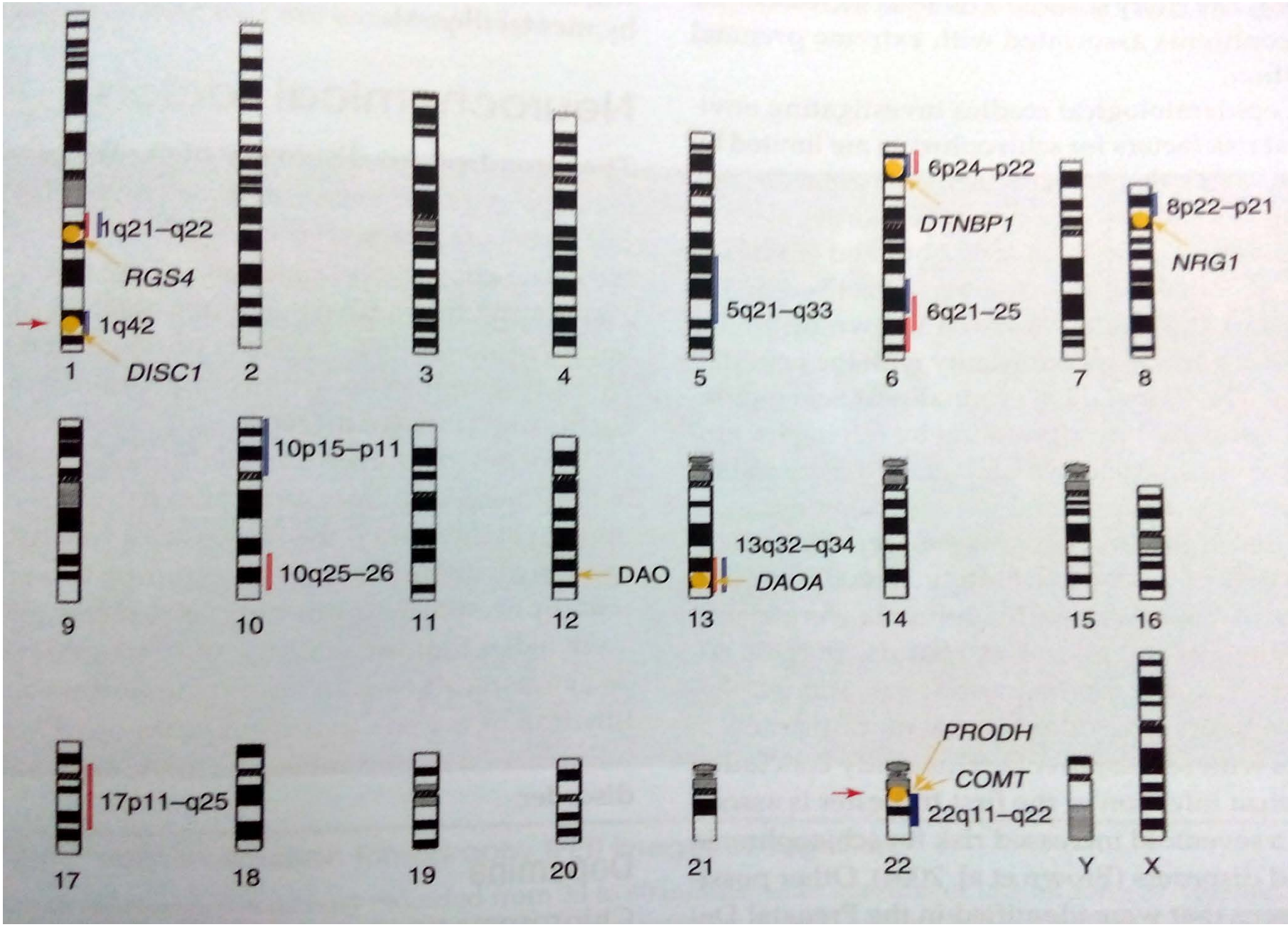
- **The Finish Adoption Study** (1969) identified adopted offspring of biological mothers with schizophrenia (112 cases)
- Matched control group (135 adopted offspring of non-schizophrenic biological mothers)
- Adoptees ranged from 5-7 yrs at the start of the study, and separated from mothers before 4
- Study checked children again in 1987
- Reported 7% of high risk group developed schizophrenia compared to 1.5% of controls.

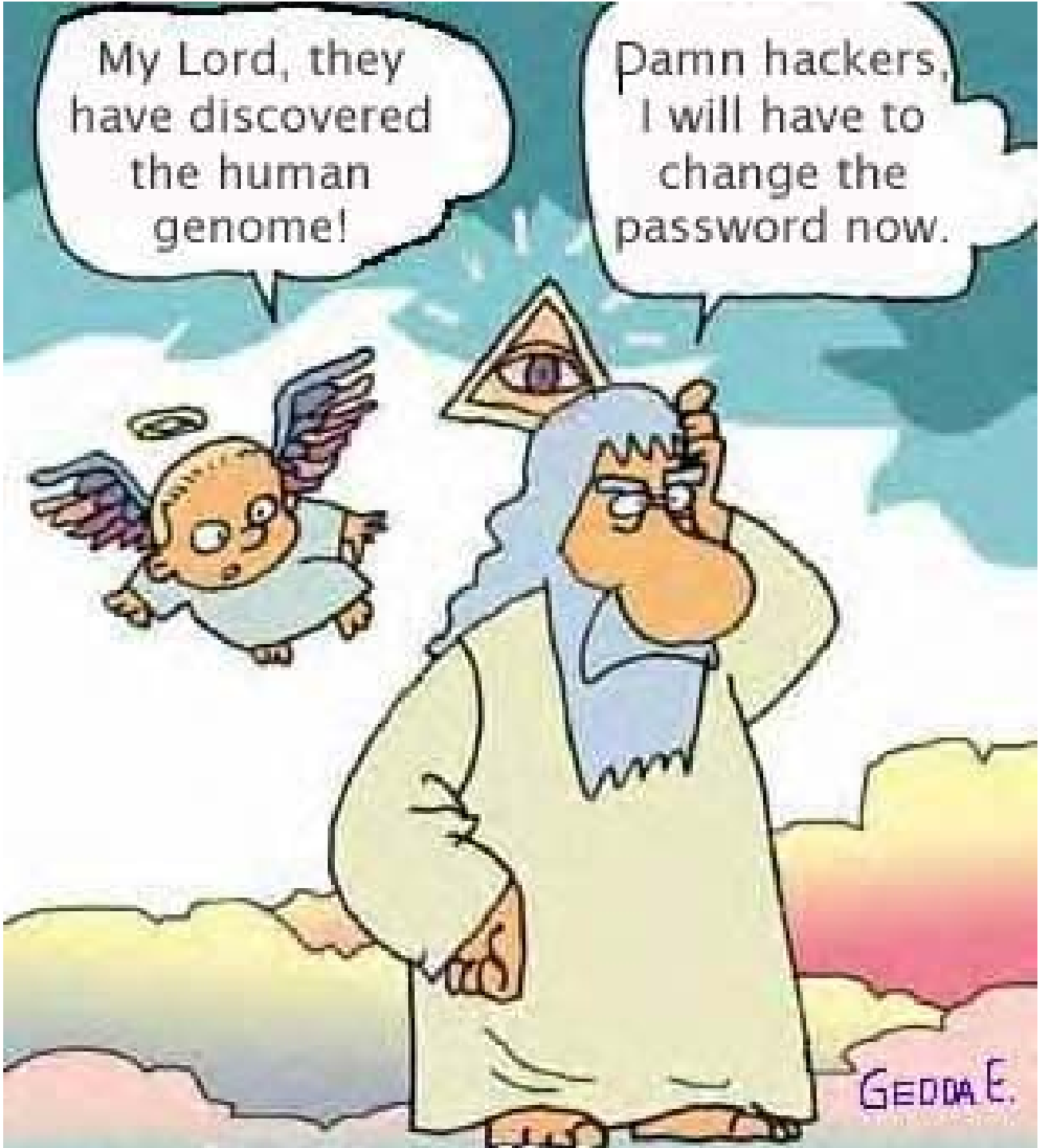
- **The Danish Adoption Study (1994)** took a national sample across Denmark
- Found high rates of diagnosis for chronic schizophrenia in adoptees whose biological parents had the same diagnosis, despite living with 'healthy' parents

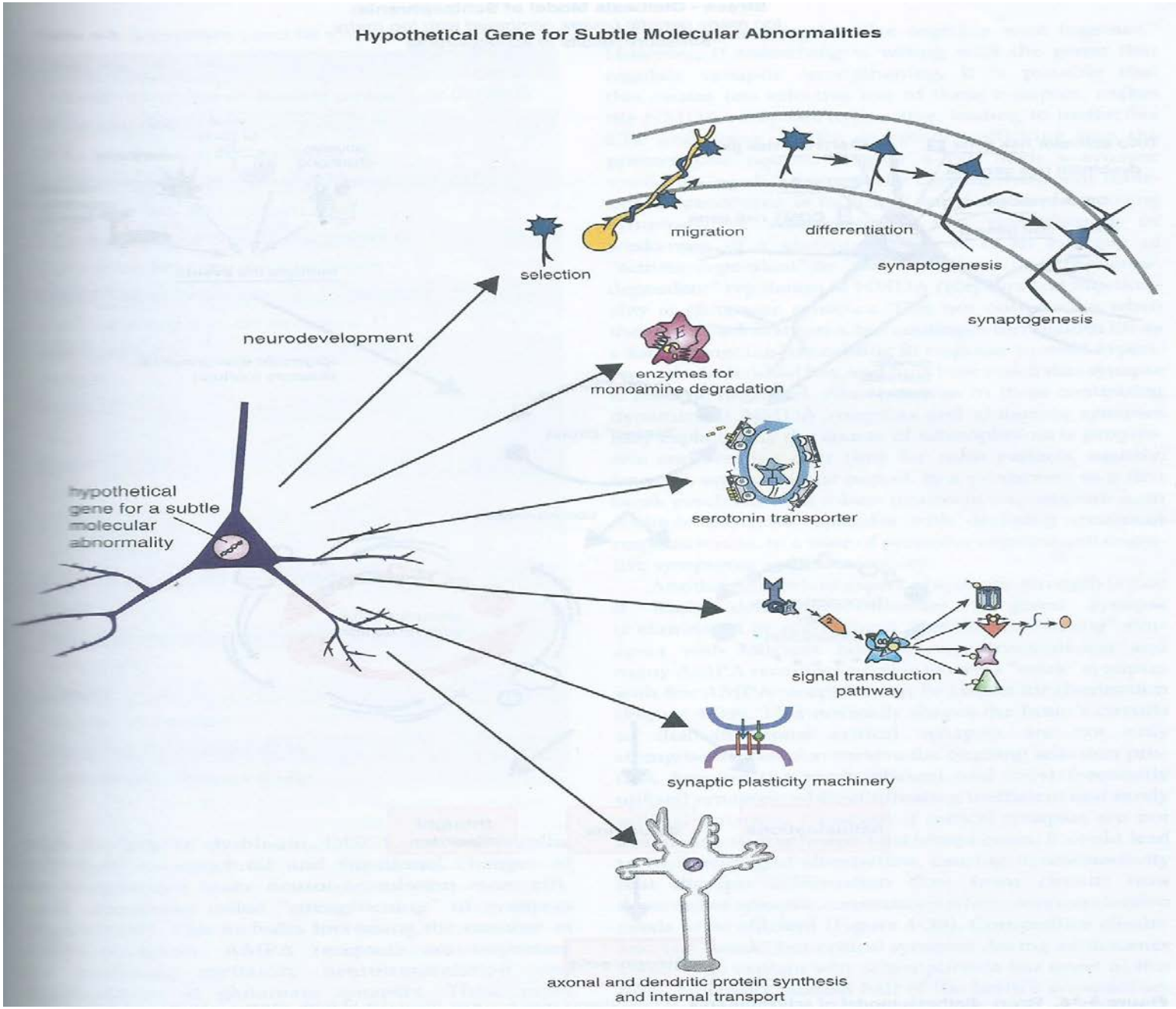
Genetics

- Strategies to find specific genes that cause SCZ:

✓ Linkage studies
✓ Association studies
✓ Single nucleotide polymorphism(SNP) genotyping
✓ Copy number variants

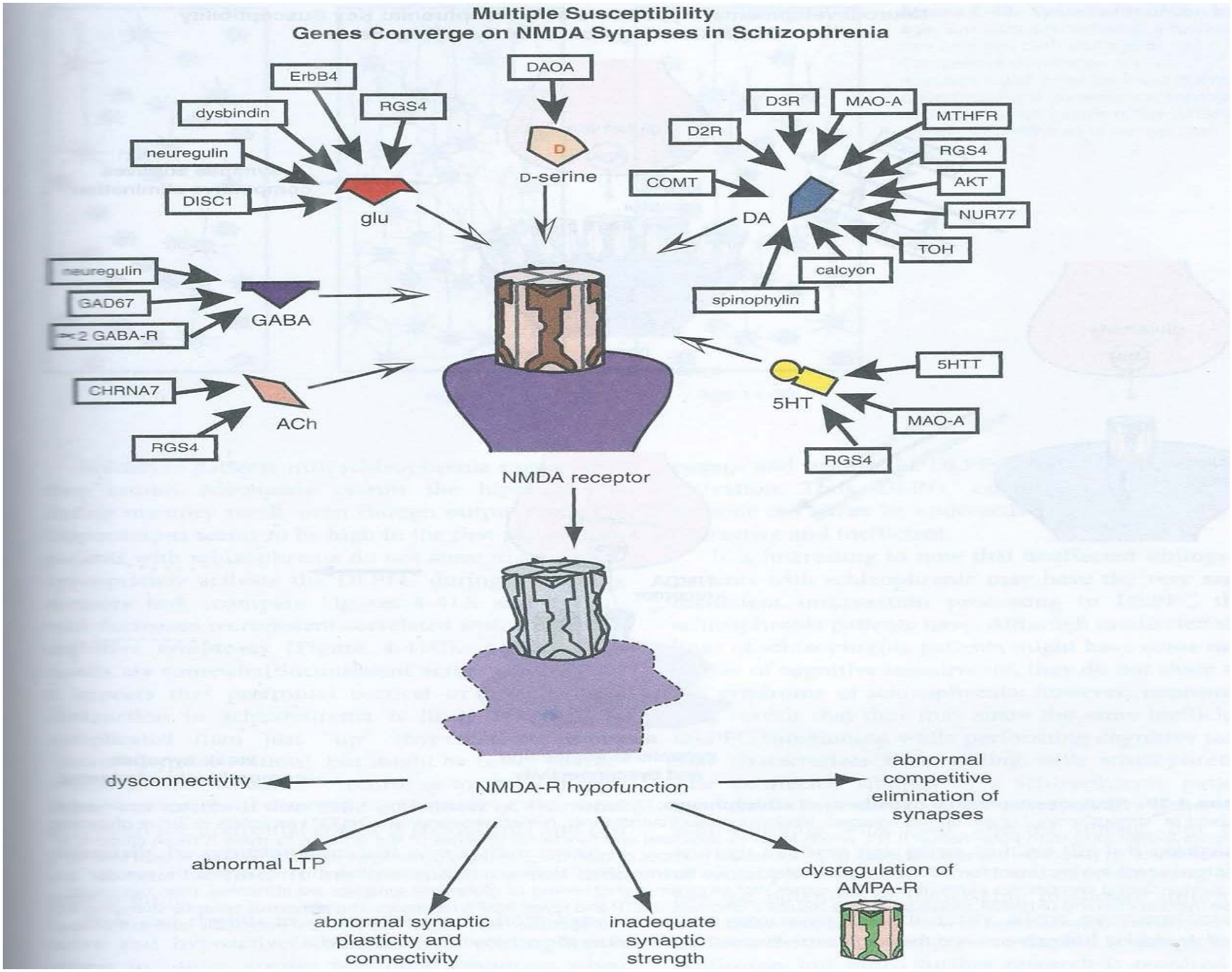

1q21–q22
RGS4
1q42
DISC1
1
2
3
4
5q21–q33
5
6p24–p22
DTNBP1
6q21–25
6
7
8p22–p21
NRG1
8
9
10p15–p11
10q25–26
10
11
12
DAO
13q32–q34
DAOA
13
14
15
16
17p11–q25
17
18
19
20
21
PRODH
COMT
22q11–q22
22
Y
X

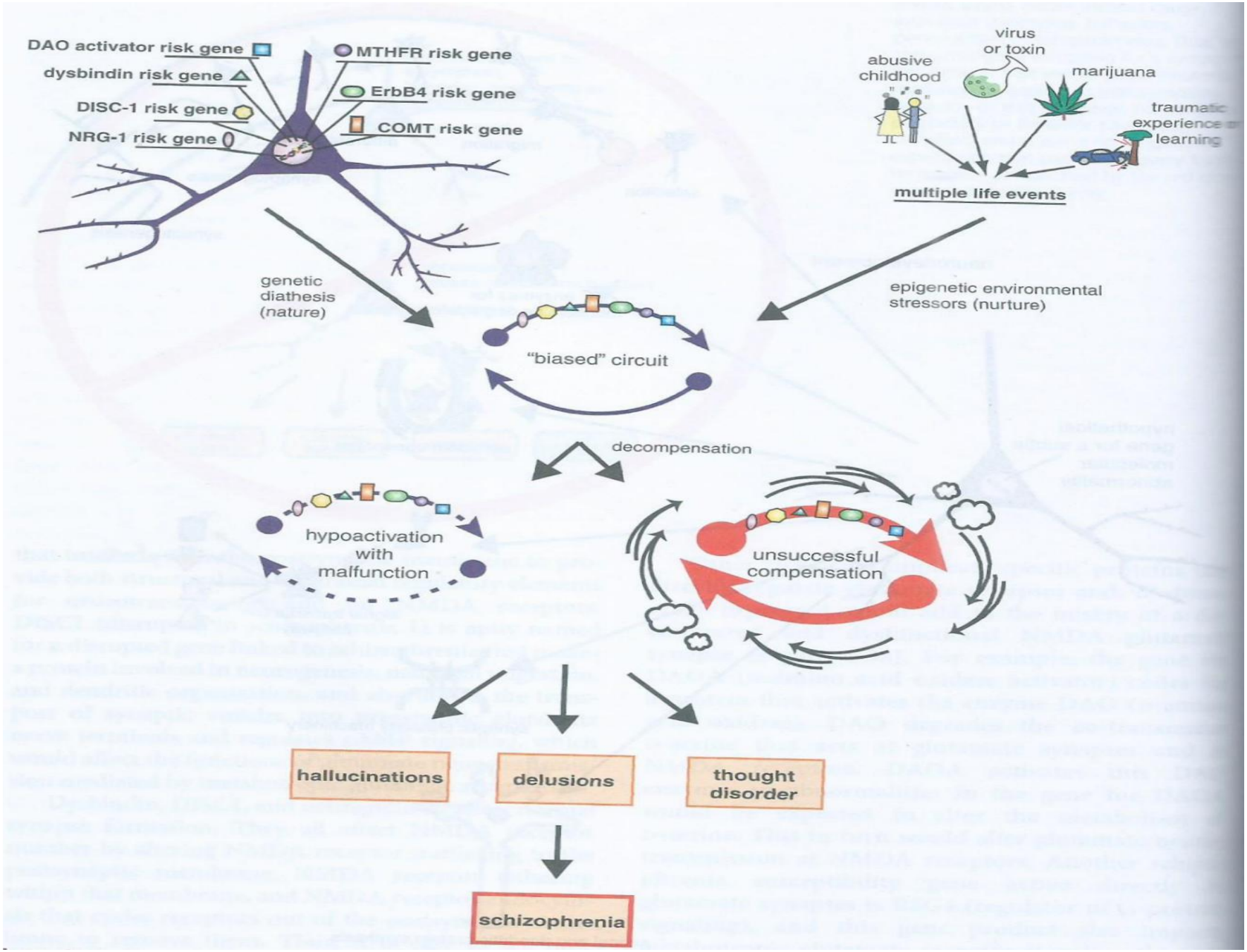

My Lord, they have discovered the human genome!
Damn hackers, I will have to change the password now.
GEDDA E.


Hypothetical Gene for Subtle Molecular Abnormalities
migration
differentiation
synaptogenesis
selection
synaptogenesis
neurodevelopment
enzymes for
monoamine degradation
hypothetical
gene for a subtle
molecular
abnormality
serotonin transporter
signal transduction
pathway
synaptic plasticity machinery
axonal and dendritic protein synthesis
and internal transport

Candidate genes in schizophrenia

Gene[1]	Description	Cytogenetic Band	Genome Scan Meta-Analysis[3]	Linkage Evidence[4]	Association Study Support[5]
AKT1	V-AKT murine thymoma viral oncogene homolog 1	14q32.33	No	No	2+ & 1– studies
COMT	Catechol-O-methyltransferase	22q11.21	Yes	Yes	Some studies +
DISC1	**Disrupted in schizophrenia 1**	1q42.2	No	Yes	Multiple studies +
DRD3	Dopamine receptor D3	3q13.31	No	Inconsistent	Meta-analysis +
DTNBP1	**Dystrobrevin binding protein 1**	6p22.3	Yes	Yes	Multiple studies +
G30/G72	Putative proteins LG30 & G72	13q33.2	No	Inconsistent	Multiple studies +
HTR2A	Serotonin receptor 2A	13q14.2	No	Inconsistent	Meta-analysis +
NRG1	**Neuregulin 1**	8p12	Nearby	Yes	Multiple studies +
PRODH	Proline dehydrogenase 1	22q11.21	Yes	Yes	-
RGS4	**Regulator of G-protein signaling 4**	1q23.3	Yes	Yes	Multiple studies +
SLC6A4	Serotonin transporter	17q11.2	Nearby	Inconsistent	Meta-analysis +
ZDHHC8	Zinc finger/DHHC domain protein 8	22q11.21	Yes	Yes	2+ & 1– studies


Multiple Susceptibility
Genes Converge on NMDA Synapses in Schizophrenia
ErbB4
dysbindin
neuregulin
DISC1
RGS4
glu
DAOA
D
D-serine
D3R
MAO-A
MTHFR
D2R
RGS4
COMT
AKT
DA
NUR77
TOH
calcyon
spinophylin
neuregulin
GAD67
2 GABA-R
GABA
CHRNA7
RGS4
ACh
NMDA receptor
5HTT
5HT
MAO-A
RGS4
dysconnectivity
NMDA-R hypofunction
abnormal competitive elimination of synapses
abnormal LTP
abnormal synaptic plasticity and connectivity
inadequate synaptic strength
dysregulation of AMPA-R


DAO activator risk gene
dysbindin risk gene
DISC-1 risk gene
NRG-1 risk gene
MTHFR risk gene
ErbB4 risk gene
COMT risk gene
virus or toxin
abusive childhood
marijuana
traumatic experience or learning
multiple life events
genetic diathesis (nature)
epigenetic environmental stressors (nurture)
"biased" circuit
decompensation
hypoactivation with malfunction
unsuccessful compensation
hallucinations
delusions
thought disorder
schizophrenia

Neurophysiological Evidence : Auditory P300 Abnormalities

One of the most consistently replicated neurophysiological abnormalities observed in schizophrenia.

- – Auditory P300 amplitude is reduced, often delayed

  Observed in chronic patients, first episode patients, schizophrenia spectrum patients, and first degree relatives of schizophrenic patients. Good Endophenotype (A possible marker of genetic vulnerability and/or neurodevelopmental insult)

Another abnormality is N100.

Interpretation is Pts are highly sensitive to incoming stimuli and compensate by blunting the processing at a higher cortical level.

PPI and MMN

- Inability to filter irrelevant sensory information is cognitive defect.
- A neuro physiological correlate of this deficit is evaluated by a pre-attentive paradigm called paired pulse inhibition (PPI). Subjects are presented a startling (test) stimulus with or without a preceding non-startling (conditioning) stimulus.
- In control subjects, the response to the test stimulus is suppressed by the conditioned stimulus, but this suppression is reduced in SCZ subjects

- Another ERP is MisMatch Negativity(MMN). An evoked potential generated in the supra-granular layer of primary auditory cortex called mismatch negativity is reduced in schizophrenia .

Dopaminergic theory:History

- How did chlorpromazine work ?
- Role of dopamine.
- The relation between the clinical effectiveness of antipsychotic drugs and their affinity for dopamine receptors.

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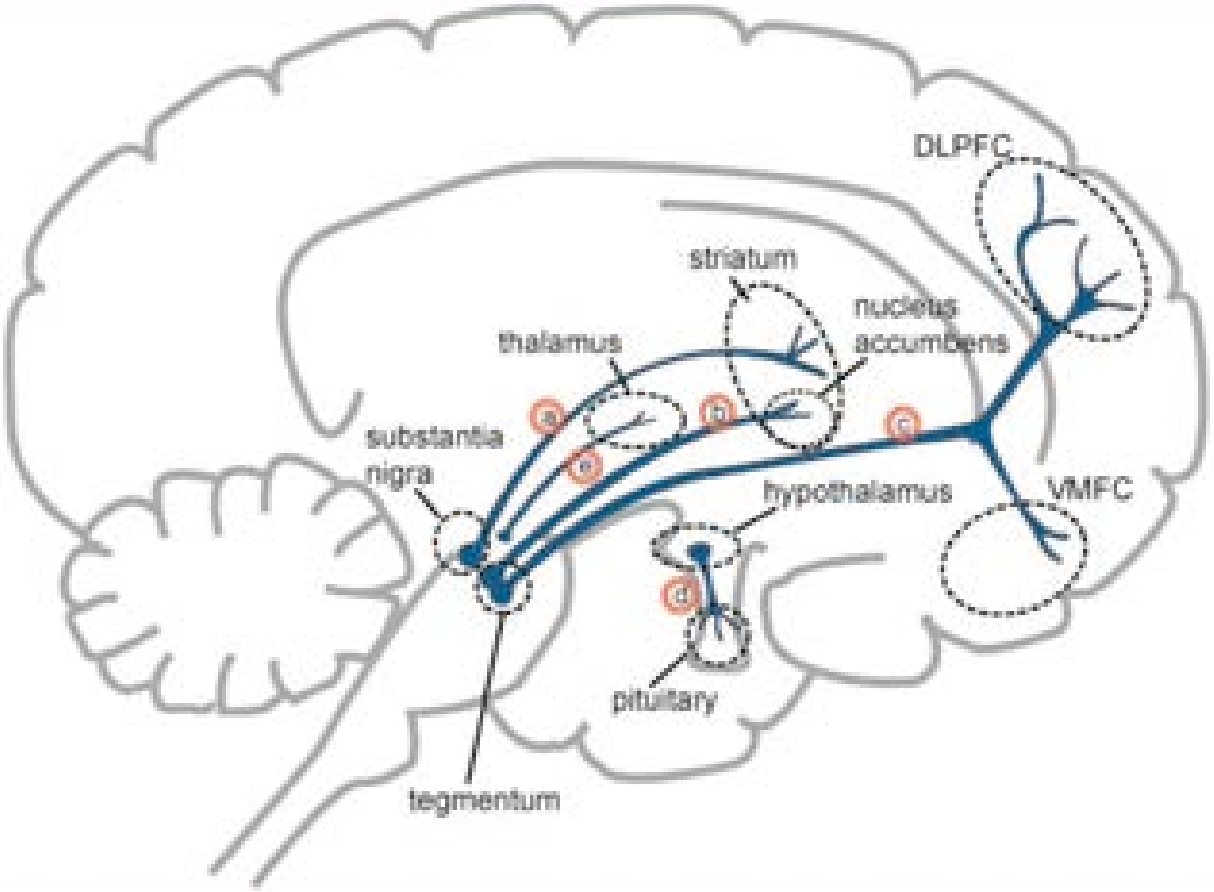
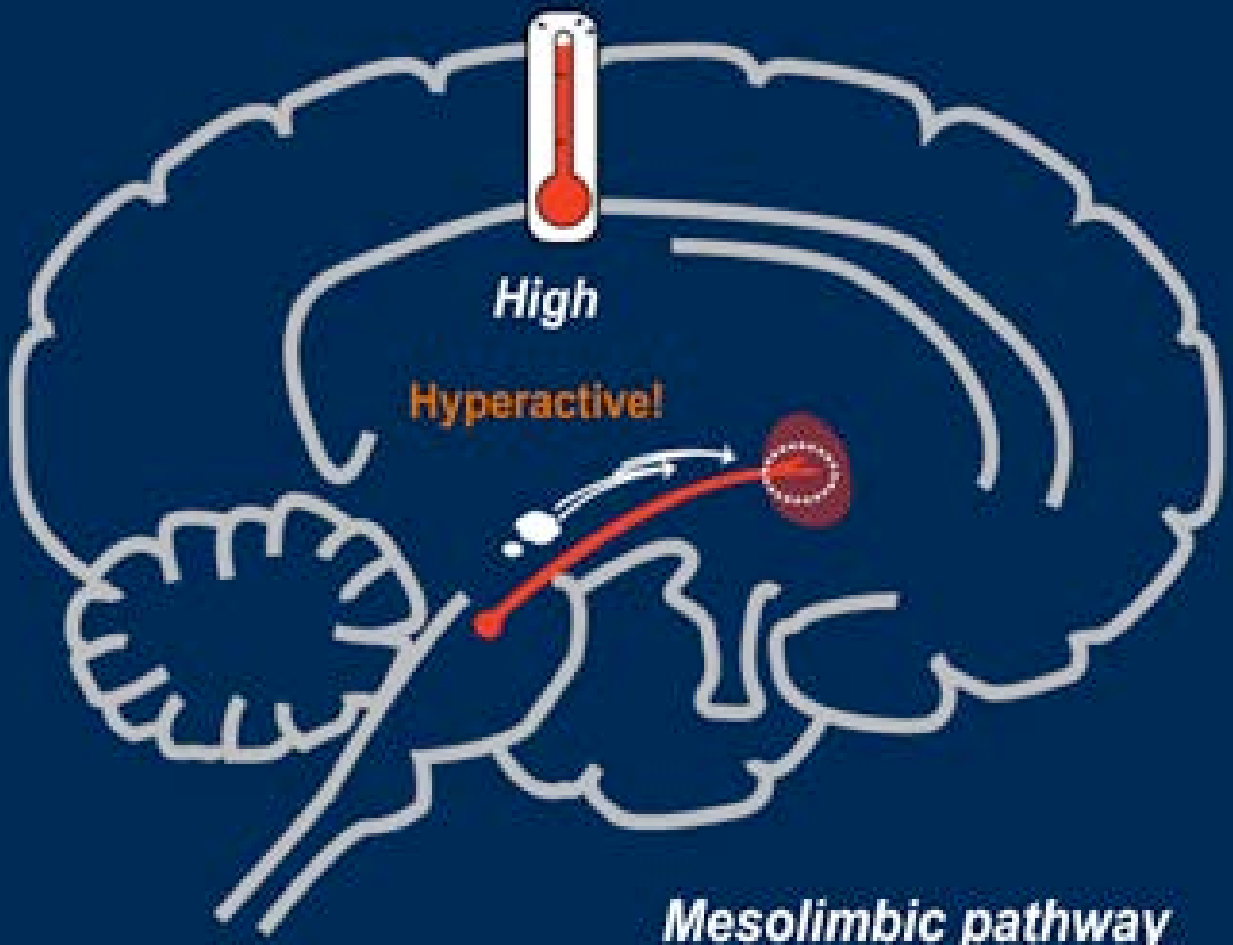
Dopamine Pathways and Key Brain Regions



Courtesy of Stahl SM. *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications.* 3rd ed. Cambridge University Press; 2008.

Schizophrenia: Too Much Dopamine?

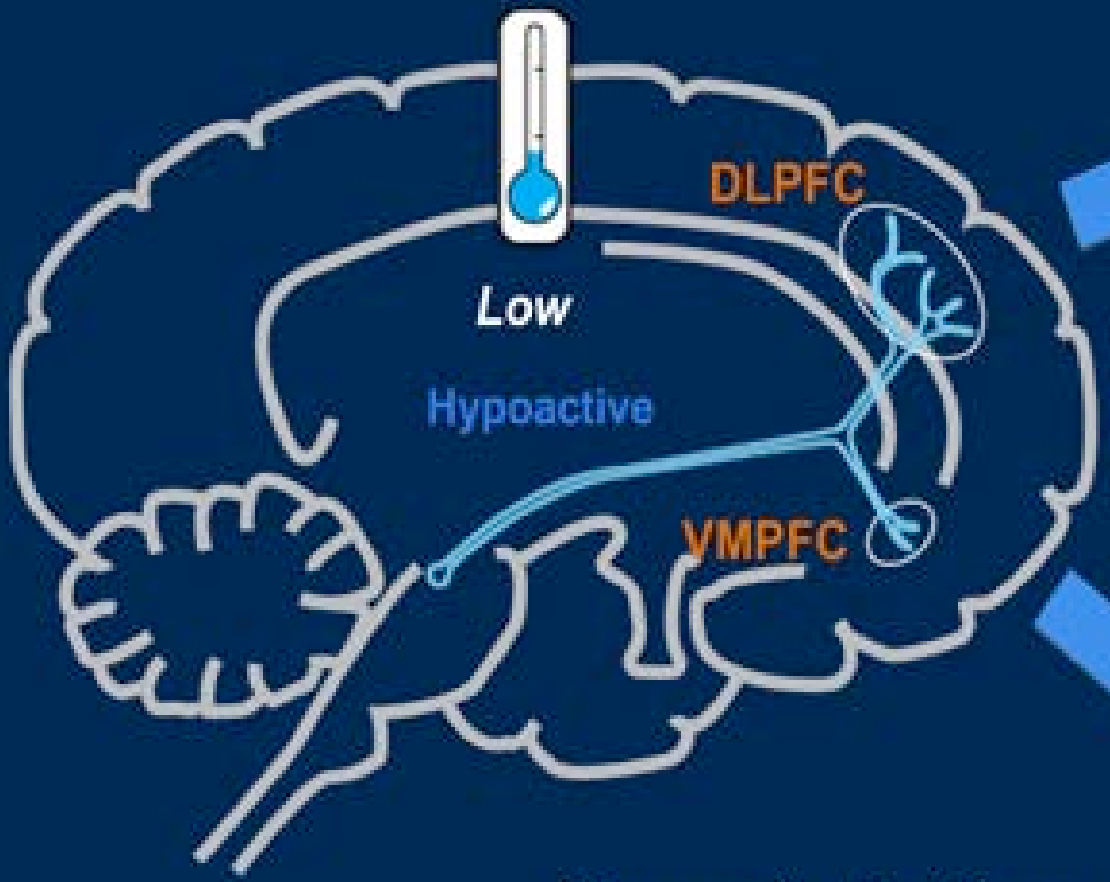


Positive symptoms

Mesolimbic pathway

Courtesy of Stahl SM. *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications.* 3rd ed. Cambridge University Press; 2008.

Schizophrenia: Too Little Dopamine?



Mesocortical pathway

Cognitive symptoms

Negative symptoms

Affective symptoms

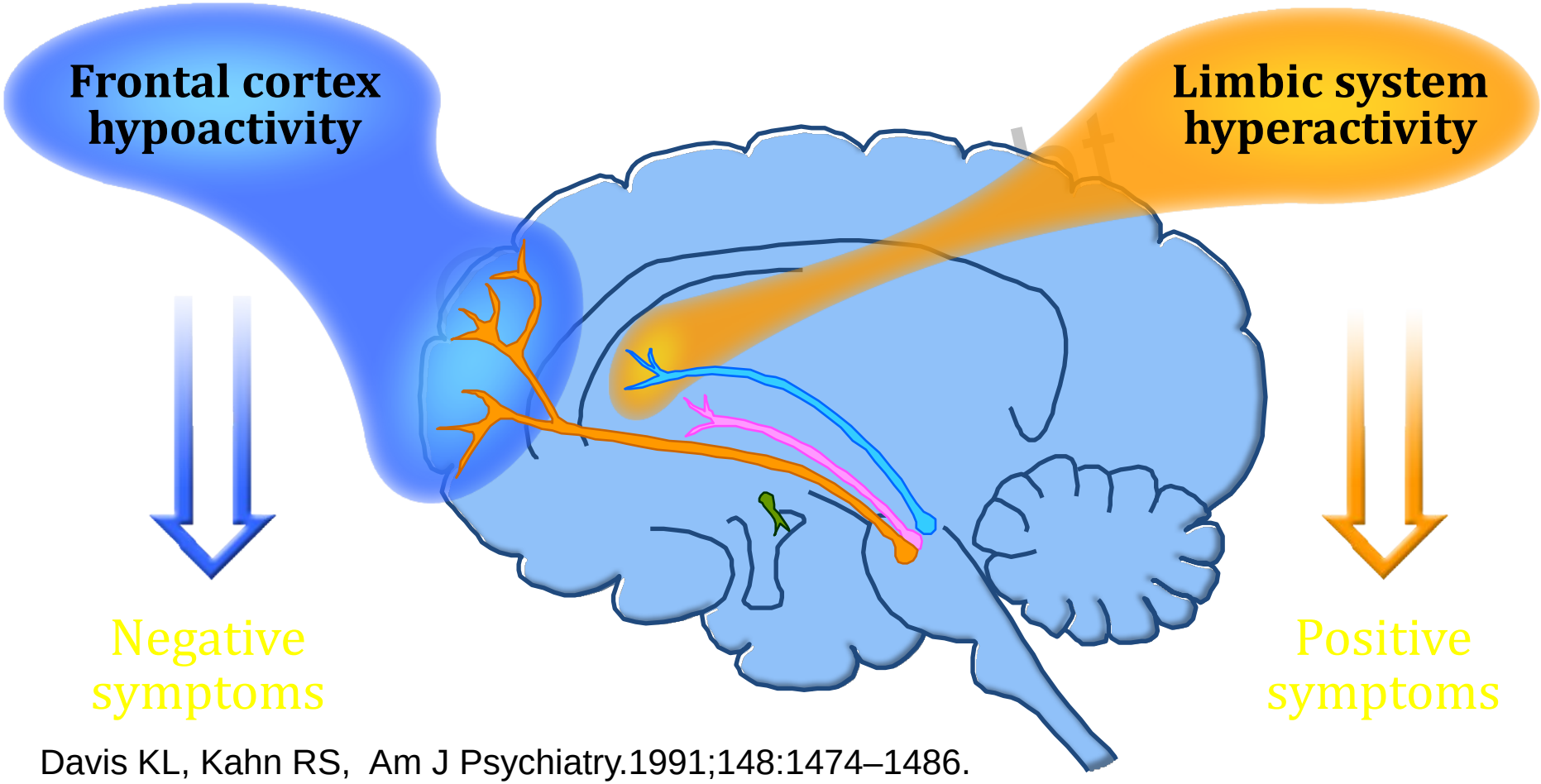
Courtesy of Stahl SM. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. 3rd ed. Cambridge University Press; 2008.

"Revised" dopamine hypothesis of schizophrenia:

Prefrontal deficit and subcortical hyperdopaminergia

- ***Mesocortical DA projections to the prefrontal cortex might be hypoactive -> hypostimulation of D1 receptors -> negative symptoms and cognitive impairment***

Subcortical mesolimbic DA projections might be hyperactive-> hyperstimulation of D2 receptors -> productive symptoms



Davis KL, Kahn RS, Am J Psychiatry.1991;148:1474–1486.

Dopamine in schizophrenia

- Patients with schizophrenia have elevated synthesis and storage of dopamine in presynaptic dopaminergic nerve terminals in striatum.

  This is the most consistent finding. The increased levels are linked with increase in psychosis.

- Increased dopamine release at synapses and baseline increased occupancy of D2 receptors by dopamine.

- There is some evidence of D1 receptor levels in PFC and that reflects chronic low dopamine levels in PFC and relates with negative and cognitive defects.

Moore RY, Brain Res. 2003;982:137–145.

Abi-Dargham A, J Neurosci. 2002;22:3708–3719.

Aberrant Salience

- "Salience" refers to the motivational properties of a stimulus, which can cause it to attract attention and drive behavior.

- Aberrant salience refers to the tendency for irrelevant stimuli to be attributed motivational salience and thus to attract attention and influence behavior inappropriately

Roiser JP, Schizophrenia Bulletin , 2013,vol. 39 no. 6: 1328–1336.

Aberrant Salience

- Increasing evidence of dopamine's role in motivational incentive salience.
- Abnormal firing of dopamine neurons and the abnormal release of dopamine leads to an aberrant assignment of salience to innocuous stimuli.
- Over time the individual's own explanation of the experience of aberrant salience leads to formation of delusions and hallucinations

Kapur S, Mizrahi R, Li M. Schizophr Res. 2005;79:59–68.

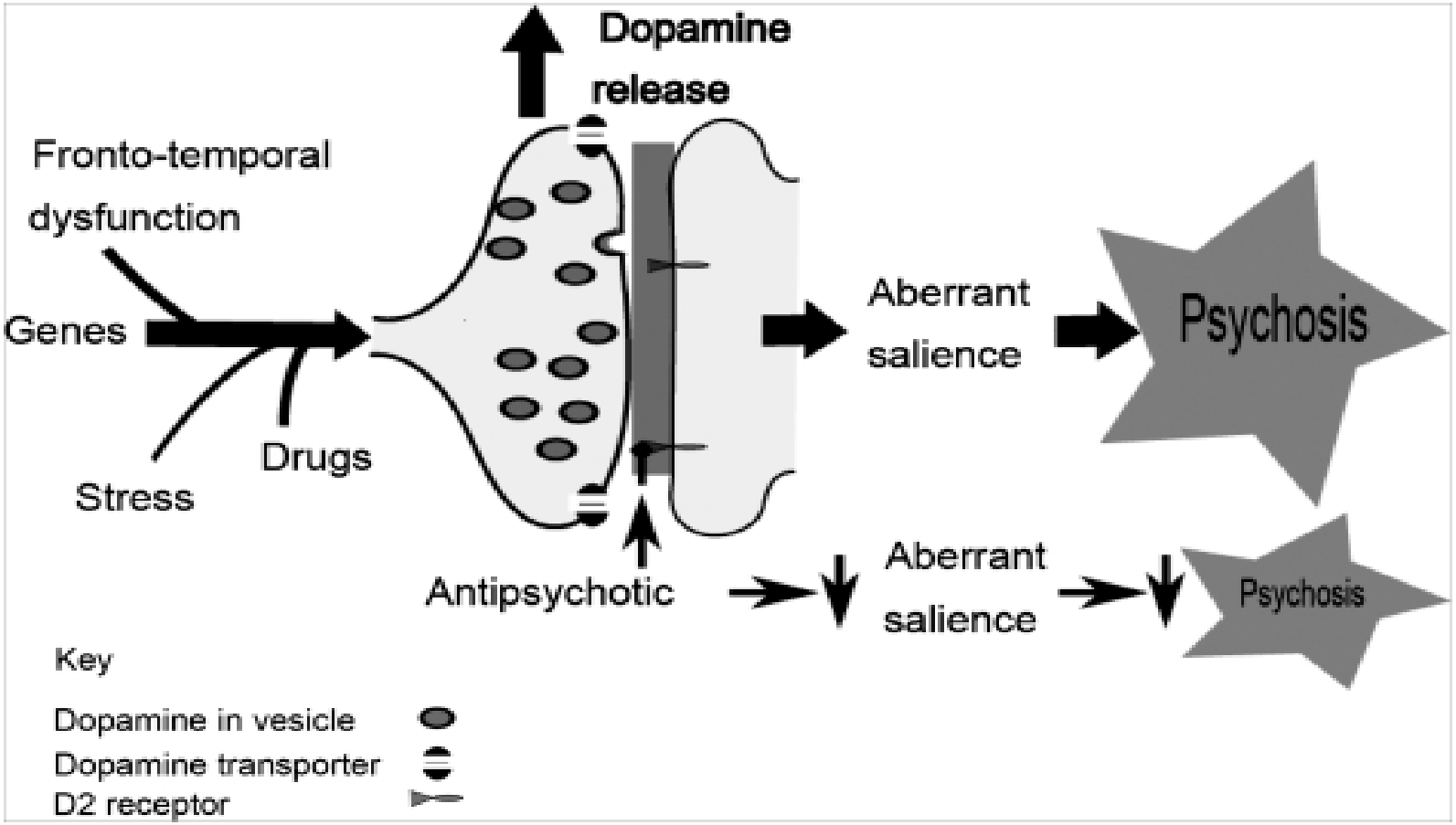
Environmental factors and Dopamine

- Late environmental markers of adversity such *as migration, unemployment, urban upbringing, lack of close friends, and childhood abuse*

  are all associated with a well-established increased risk for schizophrenia

- Animal Studies of social isolations and subordination find that these factors lead to dopaminergic overactivity.

Dopamine model of psychosis



Oliver D. Howes and Shitij Kapur
Schizophr Bull. May 2009; 35(3): 549–562.

Glutamate hypothesis

- Phencyclidine (PCP): dissociative anesthetic: Noncompetitive NMDA antagonist (blocks Ca2+ channel)
- 2 weeks PCP in monkeys → schizophrenia-like symptoms
  - Including poor performance on frontal lobe-sensitive task
- Ketamine (NMDA antag)→ similar effects

- In Schizophrenia is there a pathology that is causing NMDA hypofunction ?

Glutamate system and schizophrenia

(1) NMDA Receptors Hypofunction Hypothesis of Schizophrenia

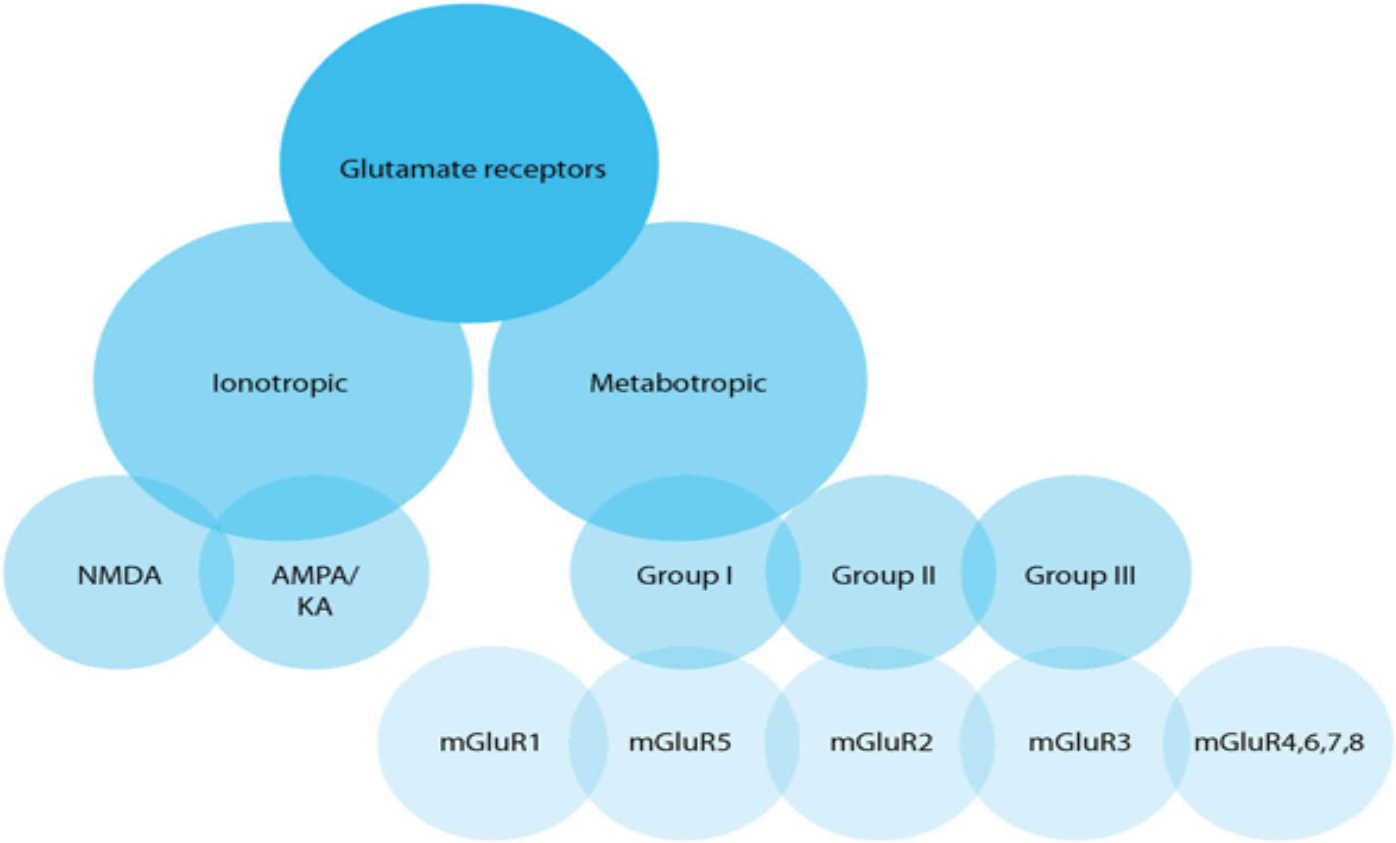
- (The Glutamate theory vs the Dopamine theory in schizophrenia)

(2) The Glutamate Excitotoxicity as part of the Neurodevelopmental Theory of Schizophrenia

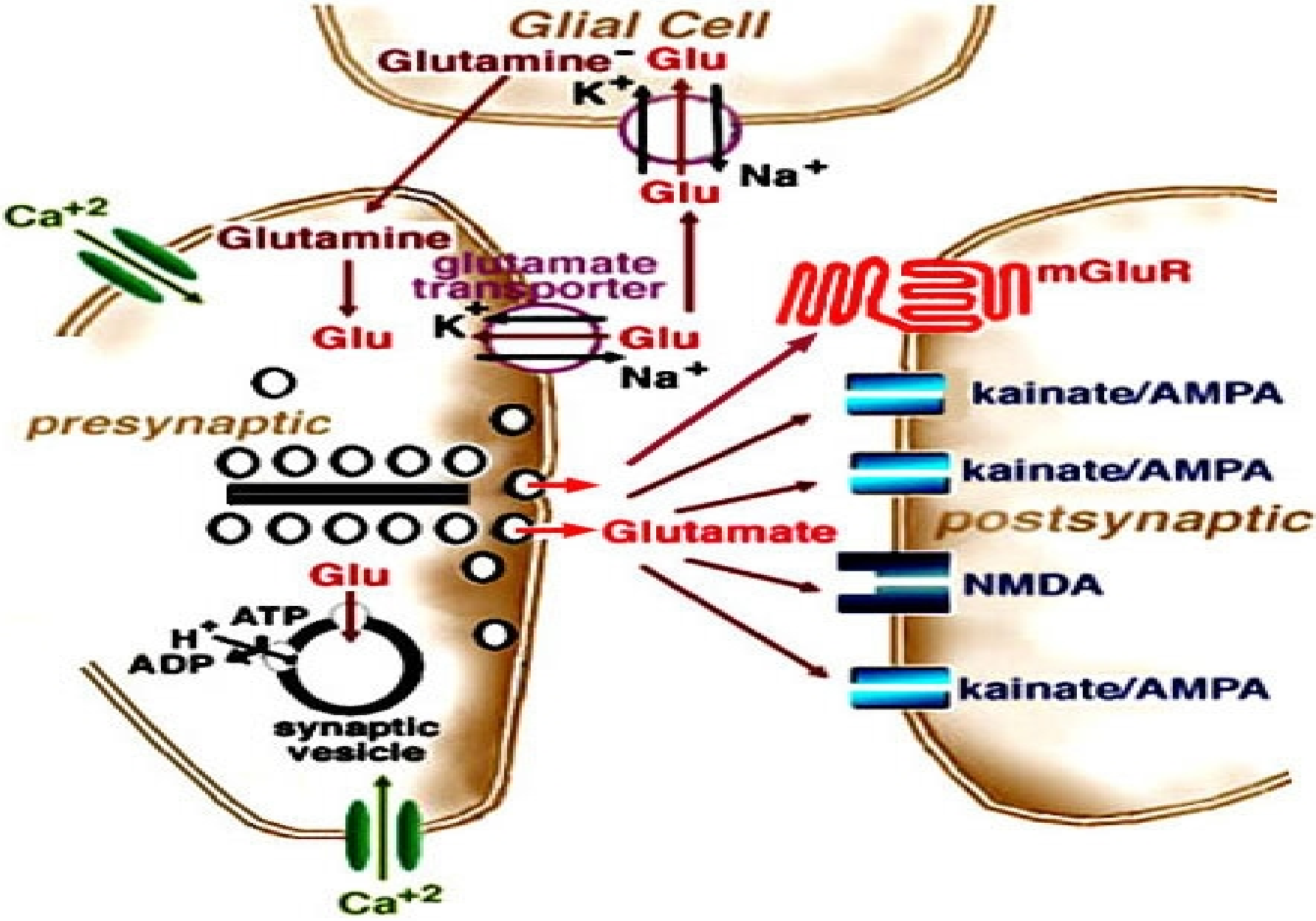
- The excessive pruning theory

Gluamate

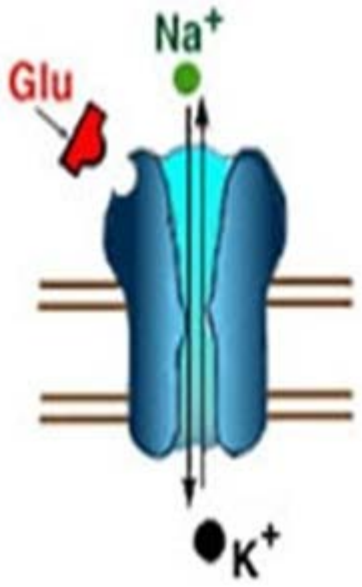
- Glu is an aminoacid involved in building proteins, and in energy metabolism. It is aslo a NT
- Glu is the workhorse transmitter for excitatory signaling in the nervous system
- > 60% receptors in brain
- Involved in many behavioral and physiological functions, but perhaps the most important is synaptic plasticity
  - Changes in the strength of connections
  - Learning and memory



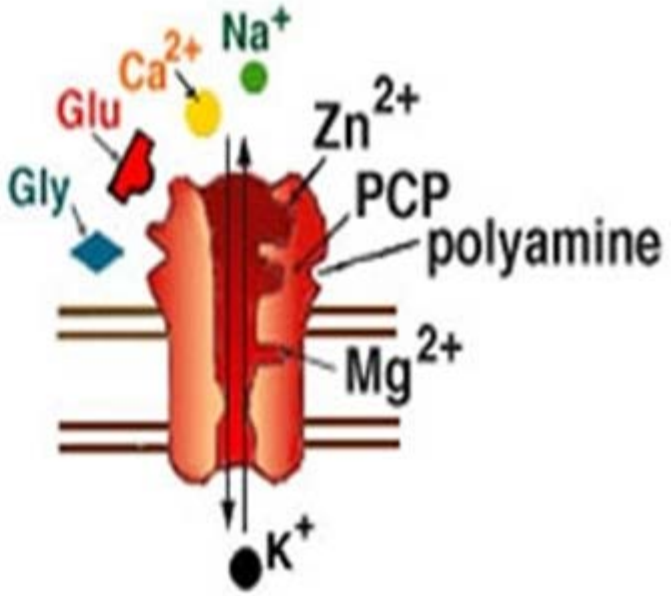
Glutamate receptors may be divided into 2 broad categories: ionotropic (cation channels) and metabotropic receptors (G-protein coupled receptors). Three classes of ionotropic glutamate receptors have been identified, which were named on the basis of agonist selectivity: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA), and kainate (KA). To date, 8 metabotropic glutamate receptors (mGluRs) have been identified; they are generally categorized into 3 groups (groups I, II, III) based on related effects on messenger cascades and homology.


Glial Cell
Glutamine
Glu
K+
Na+
Glu
Ca+2
Glutamine
glutamate transporter
Glu
K+
Glu
Na+
mGluR
kainate/AMPA
kainate/AMPA
presynaptic
Glutamate
postsynaptic
Glu
NMDA
ATP
H+
ADP
kainate/AMPA
synaptic vesicle
Ca+2

non NMDA receptor



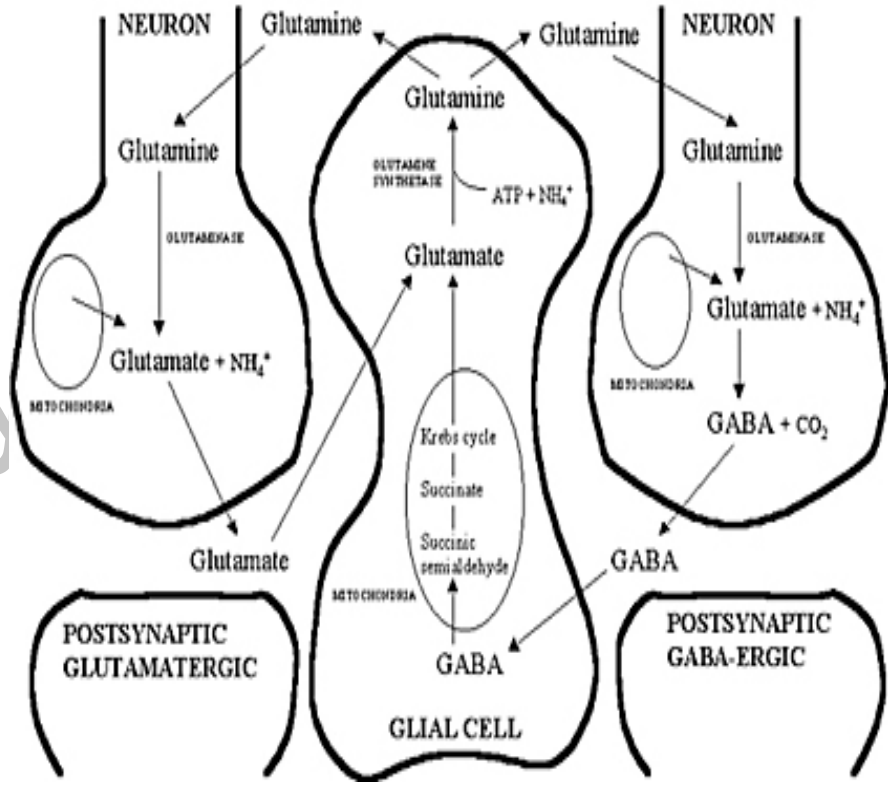
NMDA receptor



NMDA receptors

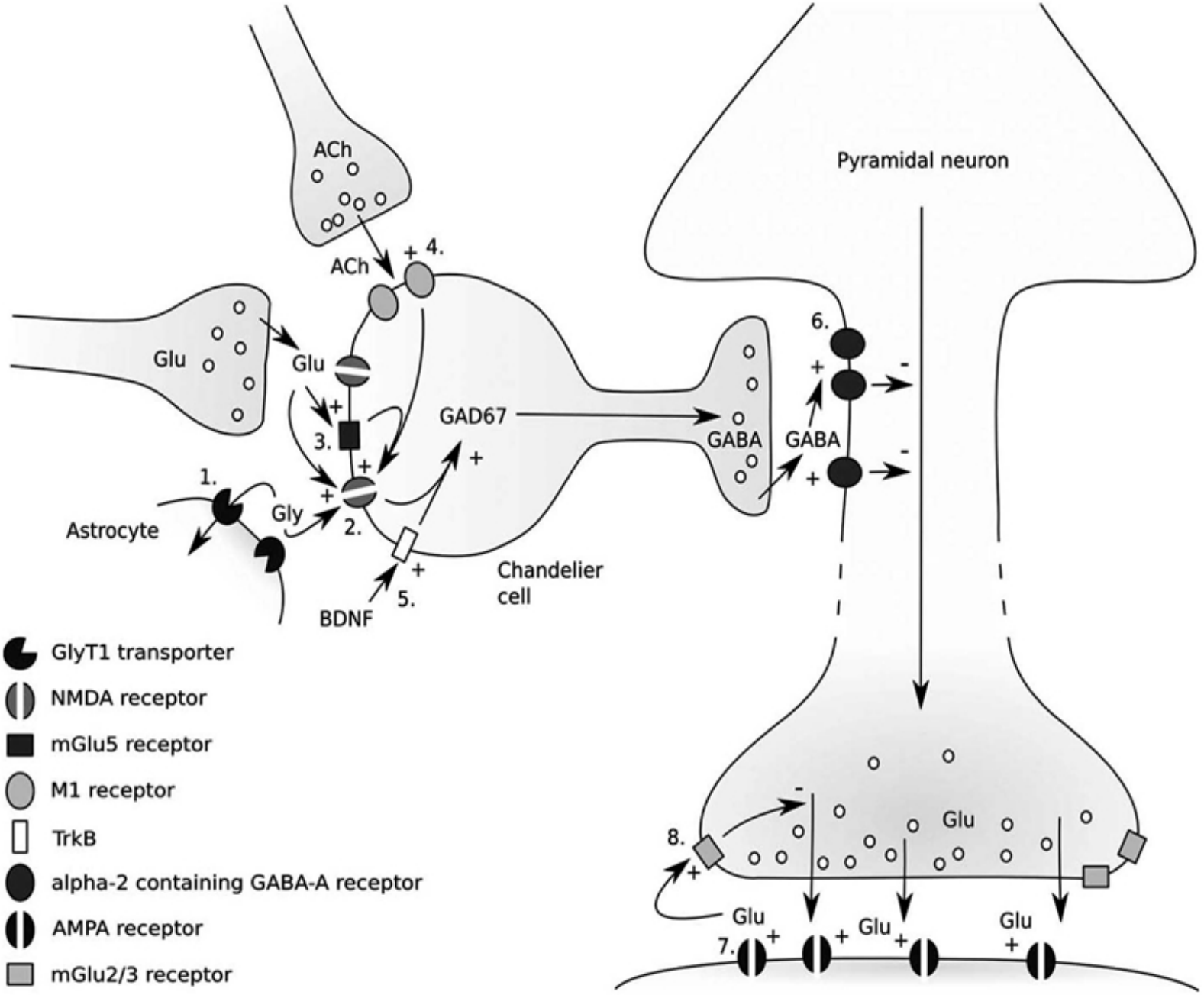
- NMDA receptors require two different neurotransmitters to open the channel
  - 1) Glutamate
  - 2) Glycine or D-serine
- Glycine (or D-serine) has its own binding site.
  - Thus glycine (or D-serine) is considered to be a co-agonist.
- Usually the co-agonist binding site is occupied though, so the presence or absence of glutamate determines channel opening

GABA receptors



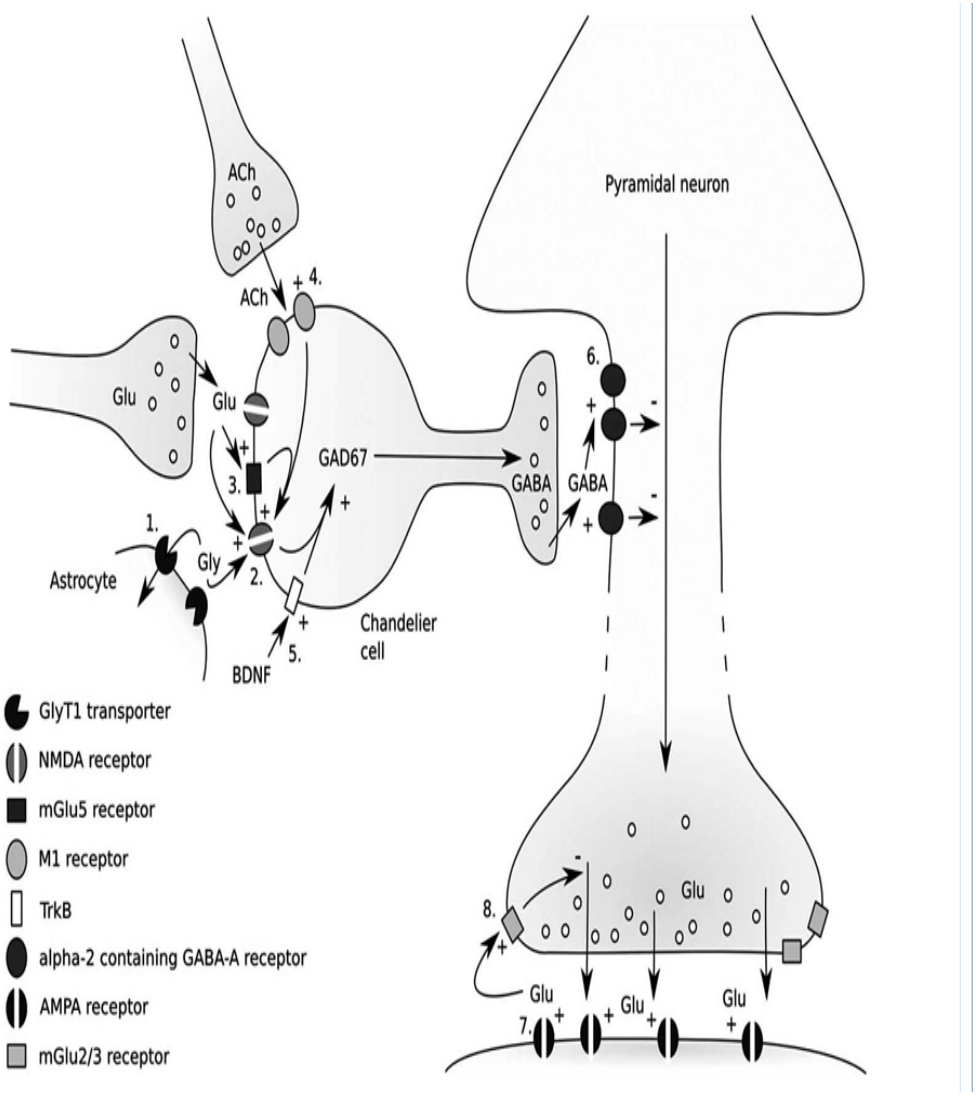
GABA interneurons

- Most Gabaergic cortical interneurons can be divided into three distinct subgroups based on several neurochemical markers: parvalbumin- (PV+), somatostatin- (Sst+), or calretinin-expressing(CR+) interneurons.
- PV+ are fast-spiking (FS) and comprise two major subtypes: basket and chandelier cells.


ACh
ACh
4.
Glu
Glu
3.
GAD67
GABA
GABA
6.
1.
Gly
2.
Astrocyte
Chandelier
cell
BDNF
5.
Pyramidal neuron
8.
Glu
Glu
Glu
Glu
7.
GlyT1 transporter
NMDA receptor
mGlu5 receptor
M1 receptor
TrkB
alpha-2 containing GABA-A receptor
AMPA receptor
mGlu2/3 receptor

Evidence:
Neuropatholgy in GABA cells

- There is decreased expression of GABA synthesizing enzyme-Glutamic acid decaroxylase (GAD)esp its isoform GAD67 in paravalbumin containing GABAergic chandelier and basket cells in DLPC, hippocampus.
- These cells innervate Glutamatergic Pyramidal cells and inhibit them.



GABA and Epigenetics

- GAD67 levels are tightly controlled by neural activity via transcriptional regulation of *GAD1, the* gene encoding GAD67. Different levels of *GAD1 transcription maybe linked to genetic* variability, and polymorphisms in the 5′ region of *GAD1 have been associated with s*chizophrenia and decreased GAD67 transcription.
- In the cortex of a subset of schizophrenia patients, methylation of histones (the core proteins of chromatin) near the promoter region of *GAD1 shows a shift from transcription-open to transcription repressive* chromatin structure, which is accompanied by a reduction in GAD67 mRNA in the same individuals.

GABA and cortical oscillations

- GABA-mediated inhibition may play roles in addition to oscillatory synchronization of neuronal activity.
- GABA mediated inhibition are important to maintain and terminate persistent activity. Persistent activity is viewed as the cellular basis of working memory, a form of memory that is altered in schizophrenia and is essential for cognitive function.

GABA and cortical oscillations

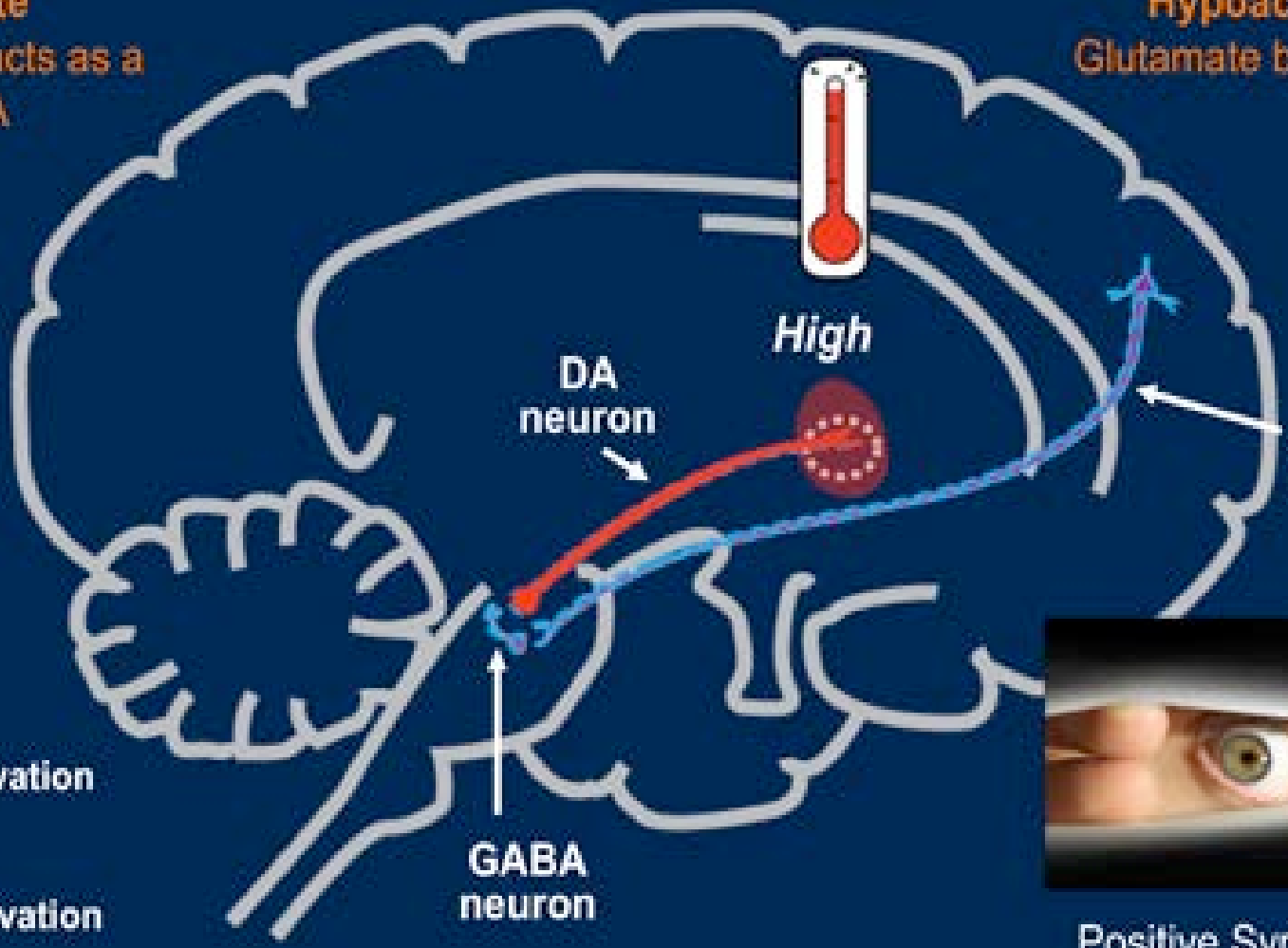
- Mice were genetically engineered to express light-sensitive ion channels exclusively in pyramidal cells or PV neurons in order to selectively drive cell activity by means of light flashes. Selective activation of PV cells in these mice produced γ band oscillations, whereas inhibiting PV neurons suppressed them.

- Moreover, nonrhythmic stimulation of pyramidal neurons drives PV cells to produce feedback inhibition generated a γ rhythm. These and other elegant optogenetics experiments show that PV cell activity, possibly driven by pyramidal cells via AMPARs, generates γ oscillations.

NMDA Receptor Hypofunction in Cortico-Brainstem Projections: Hyperactivity of Mesolimbic Dopamine Pathway

Normal state
Glutamate acts as a brake on DA

Hypoactive state
Glutamate brake is off

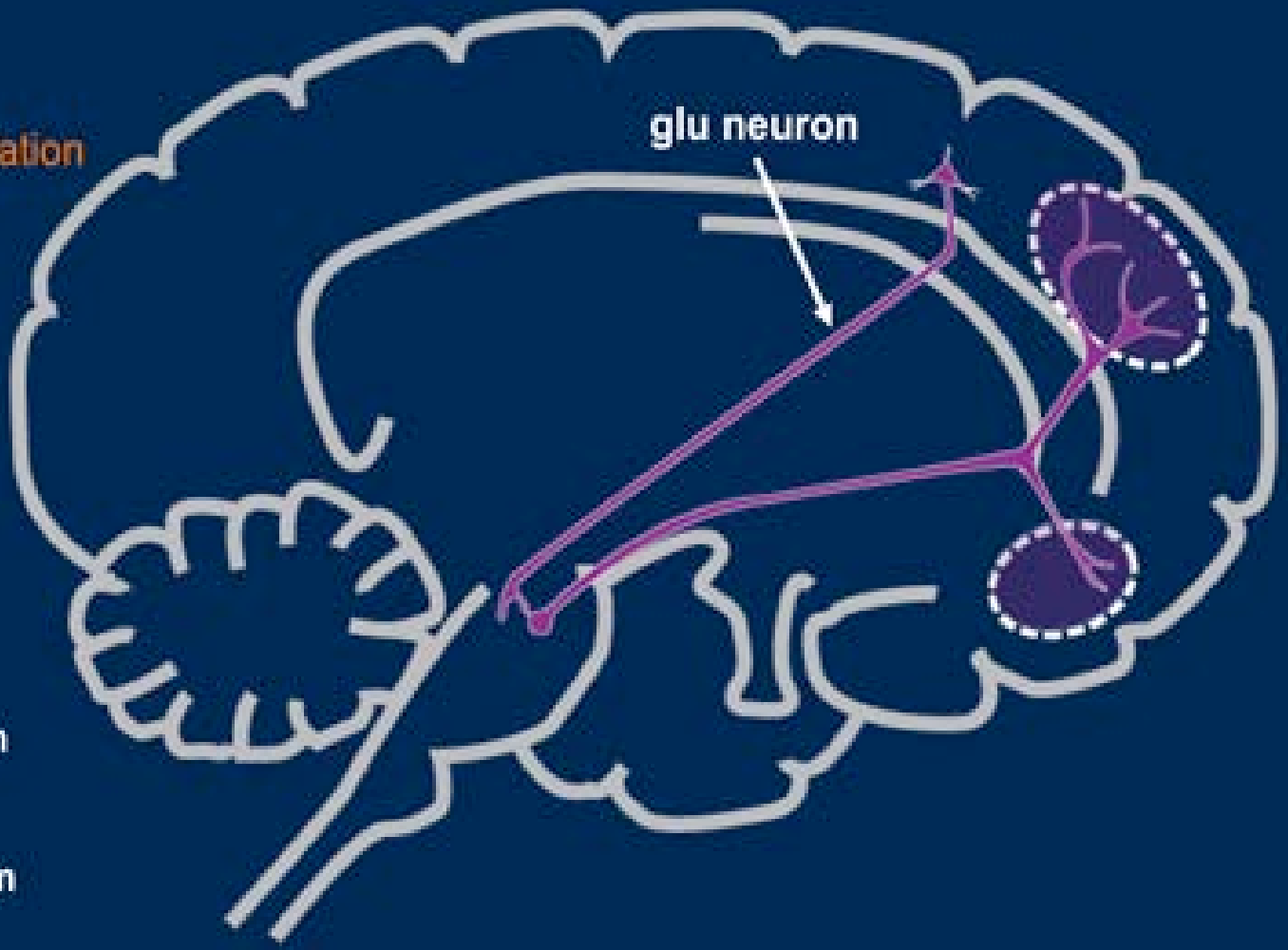


Positive Symptoms

Courtesy of Stahl SM. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. 3rd ed. Cambridge University Press; 2008.

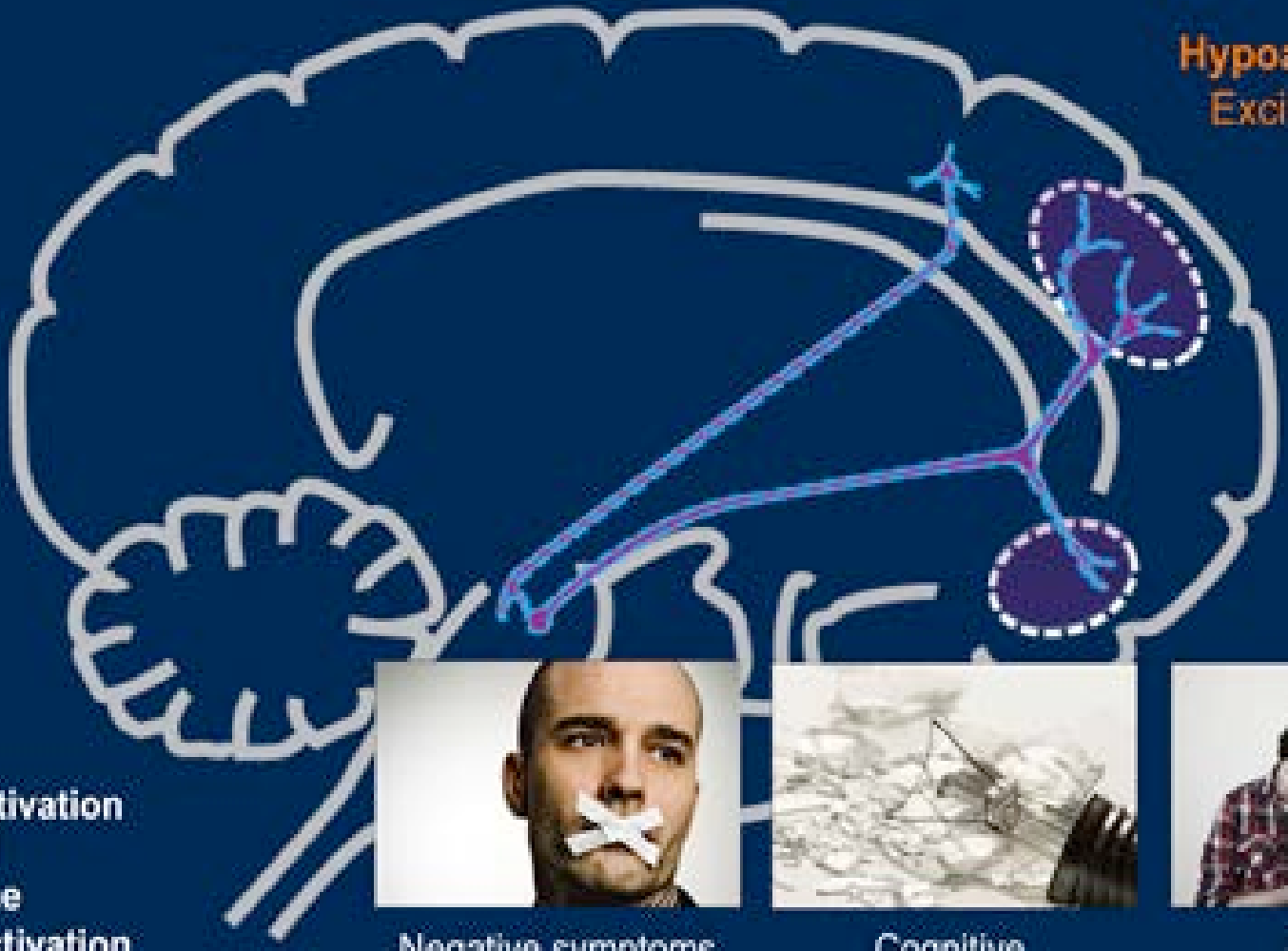
NMDA Receptor Regulation of Mesocortical Dopamine Pathways: Tonic Excitation

Normal state
Cortical glutamate provides tonic excitation of mesocortical DA



Courtesy of Stahl SM. *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications*. 3rd ed. Cambridge University Press; 2008.

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



Courtesy of Stahl SM. *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications*. 3rd ed. Cambridge University Press; 2008.

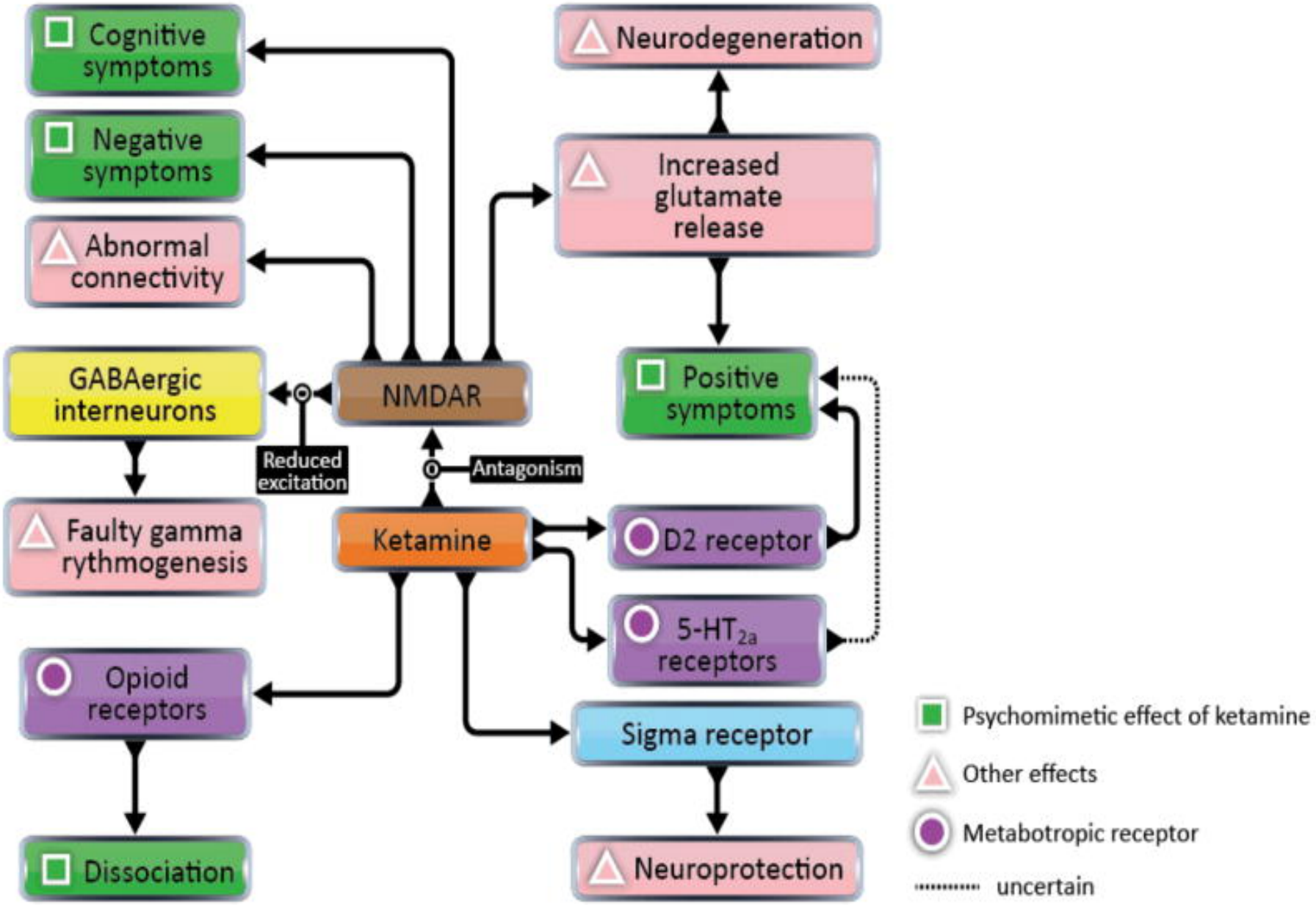
Coyle JT. *Cell Mol Neurobiol*. 2006;26(4-5):365-384.

Ketamine & Sigma receptor

- Ketamine has mild sigma R blocking action.
- The sigma receptor is a nonopioid receptor found in the endoplasmic reticulum. The sigma-1 receptor is involved in mitochondrial Ca2+ signaling, neuroprotection, neuroplasticity, and neurite outgrowth, thus leading to the hypothesis that it is also necessary for optimal cognition and cerebral metabolism.
- Sigma receptor ligands can protect dopaminergic cells from the excitotoxic effects of NMDA.
- Mice that are repeatedly administered PCP show fronto-cortical reductions of the sigma-1 receptor.

Ketamine & Kappa opioid receptor

- Ketamine to be an agonist of the kappa opioid receptor. Salvinorin A is a kappa receptor agonist and the most potent naturally occurring hallucinogen. Many studies report a positive correlation between levels of dynorphins, endogenous kappa receptor ligands, in the cerebrospinal fluid of schizophrenia patients and psychotic symptoms.
- An abnormal laminar distribution of kappa receptors in the hippocampus has also been reported for schizophrenia patients.
- Finally, kappa receptor agonists administered to rats have varied effects on prepulse inhibition, which is reduced in schizophrenia.


Cognitive symptoms
Negative symptoms
Abnormal connectivity
Neurodegeneration
Increased glutamate release
GABAergic interneurons
NMDAR
Positive symptoms
Reduced excitation
Antagonism
Faulty gamma rythmogenesis
Ketamine
D2 receptor
5-HT2a receptors
Opioid receptors
Sigma receptor
Dissociation
Neuroprotection
Psychomimetic effect of ketamine
Other effects
Metabotropic receptor
uncertain

THANK YOU