SCHIZOPHRENIA: AN UPDATE

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CONTENTS

Clinical features

Update on etiology

- Genetic factors v/s Environmental factors
- Dopamine v/s Glutamate hypothesis

Treatment strategies:

- Pharmacological
- Community based

SCHIZOPHRENIA

History- schz-source of bewilderment
Possessed by demons; teased, tormented, locked up, exiled,…

Stigma- violent behaviours
Distress to patient & family
Media protraying

Schizophrenia…

as protrayed by the media

- Misperceptions
- Prejudices

- Better understanding of the disease
- More effective treatment
- Better quality of life of patients

- Demystify the illness
- Beat the stigma

Schizophrenia…

…to the medical world

- **Complex brain disease**
  - **impairments in perception, thought, cognition, etc**
  - **Symptoms clusters**
    - Positive symptoms
    - Negative symptoms
    - Cognitive dysfunction
- **No one characteristic is common to all.**
  - Paranoid
  - Hebephrenic
  - Catatonic
  - Simple

SCHIZOPHRENIA

DISTRESSING THOUGHT & PERCEPTUAL ABN

- **Distressing delusions**

1. **“I have been pregnant with the devil’s child for past 14 years and delivering in 2028”**
2. **“being stalked by a dwarf in a government conspiracy”**
3. **“Neighbour and his orchestra playing violin on my head”**

- **Distressing hallucinations**

DISTORTED VISUAL PERCEPTION

A 20th-century artist, Louis Wain,

fascinated by cats,

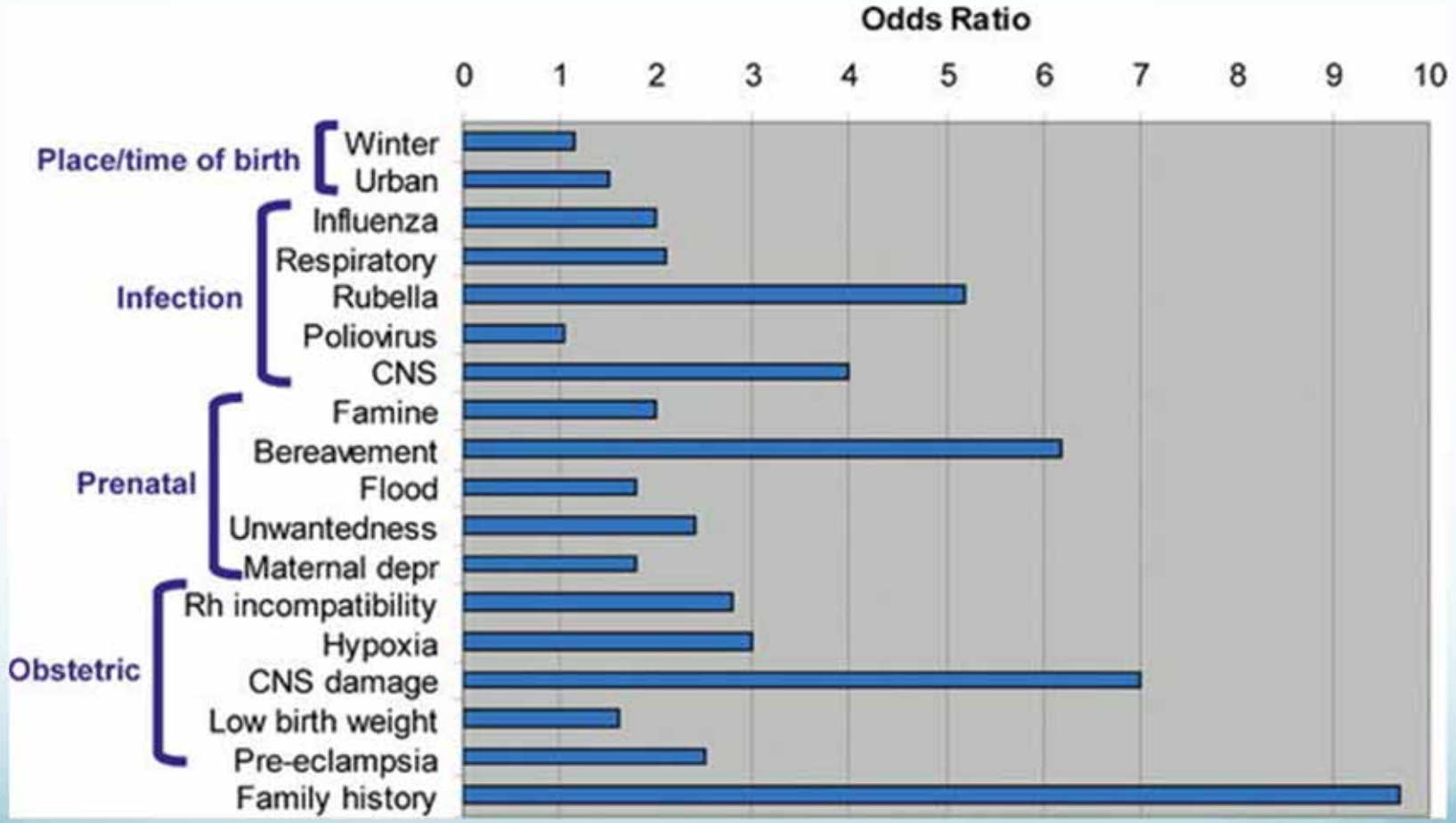
painted these pictures over a period of time in which he developed schizophrenia.

progressive stages in the illness

and exemplify what it does to the patient's perception.

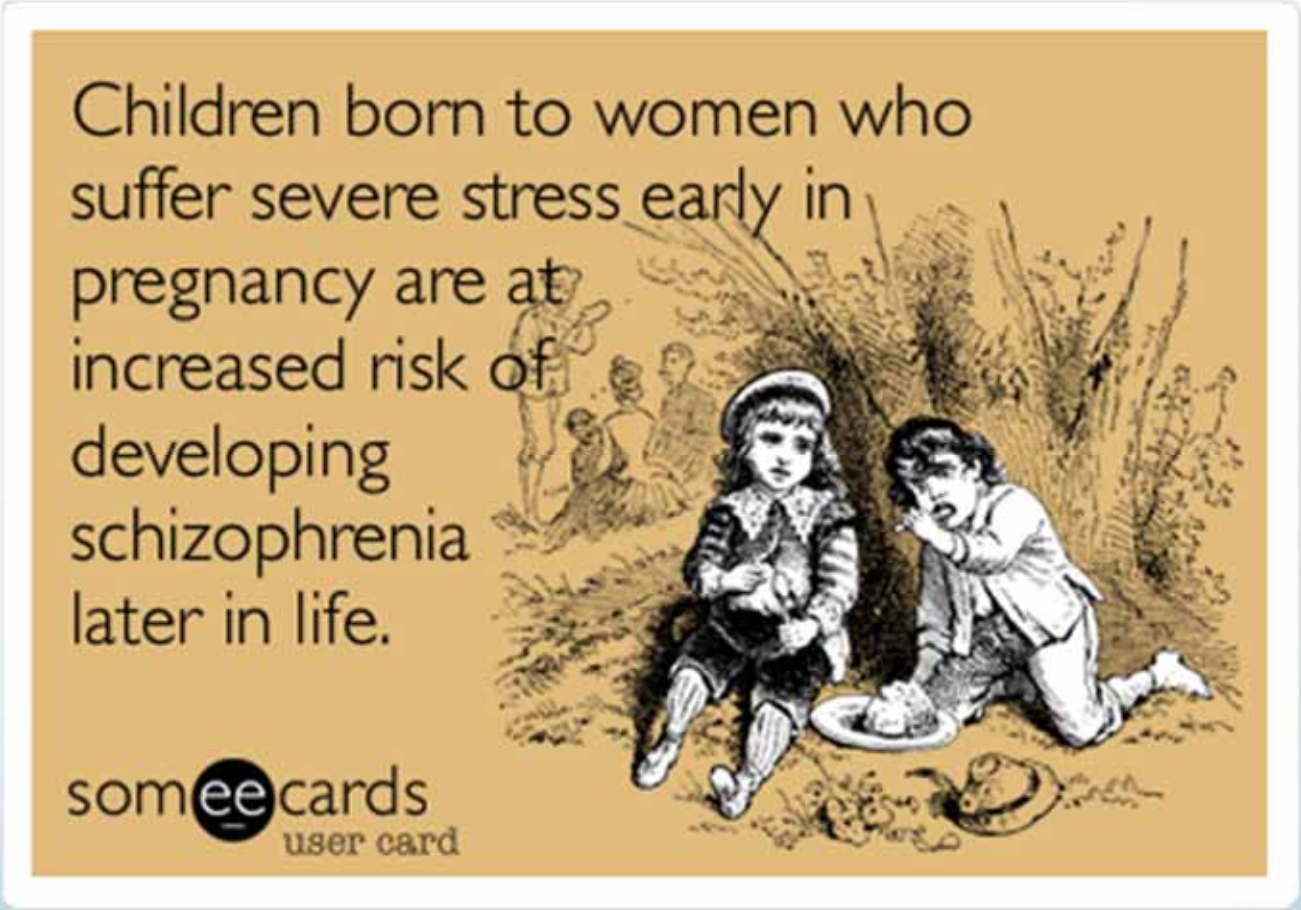
RISK FACTORS

RISK FACTORS



Maternal stress…

…no conclusive findings



Increasing paternal age

Stefánsson et al, 2012 (Iceland)

40-year-old father v/s 20-year-old father: Risk doubled

Increase in the number of de novo mutations in the sperm

Schizophrenia perpetuates itself not thru procreation but thru mutation

BRAIN CHANGES IN SCHIZOPHRENIA

This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

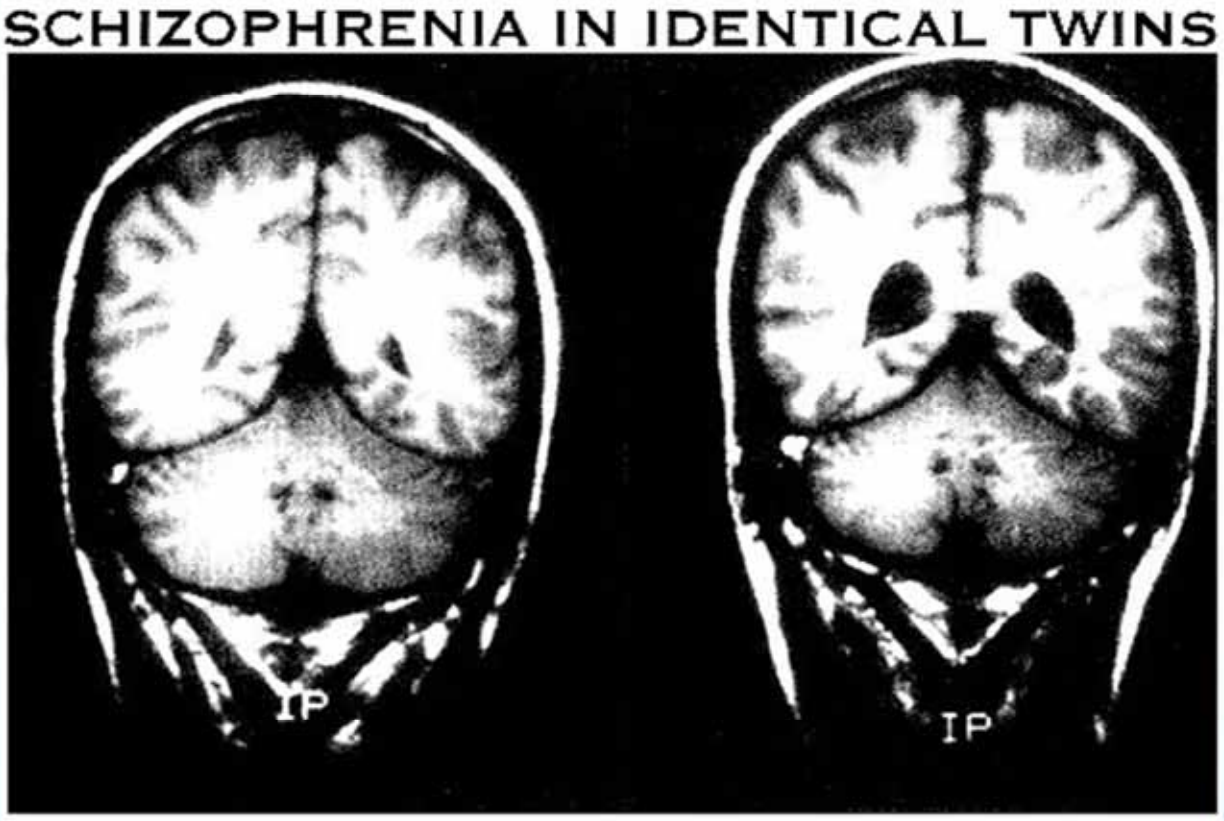
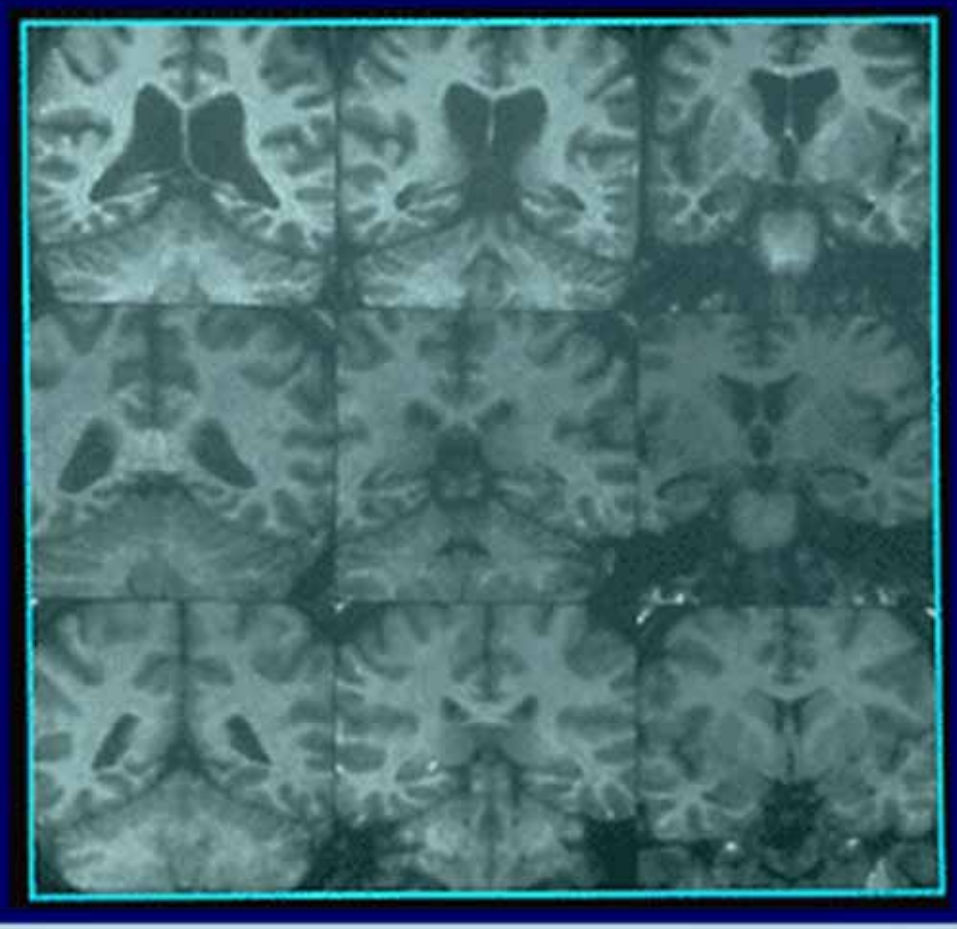


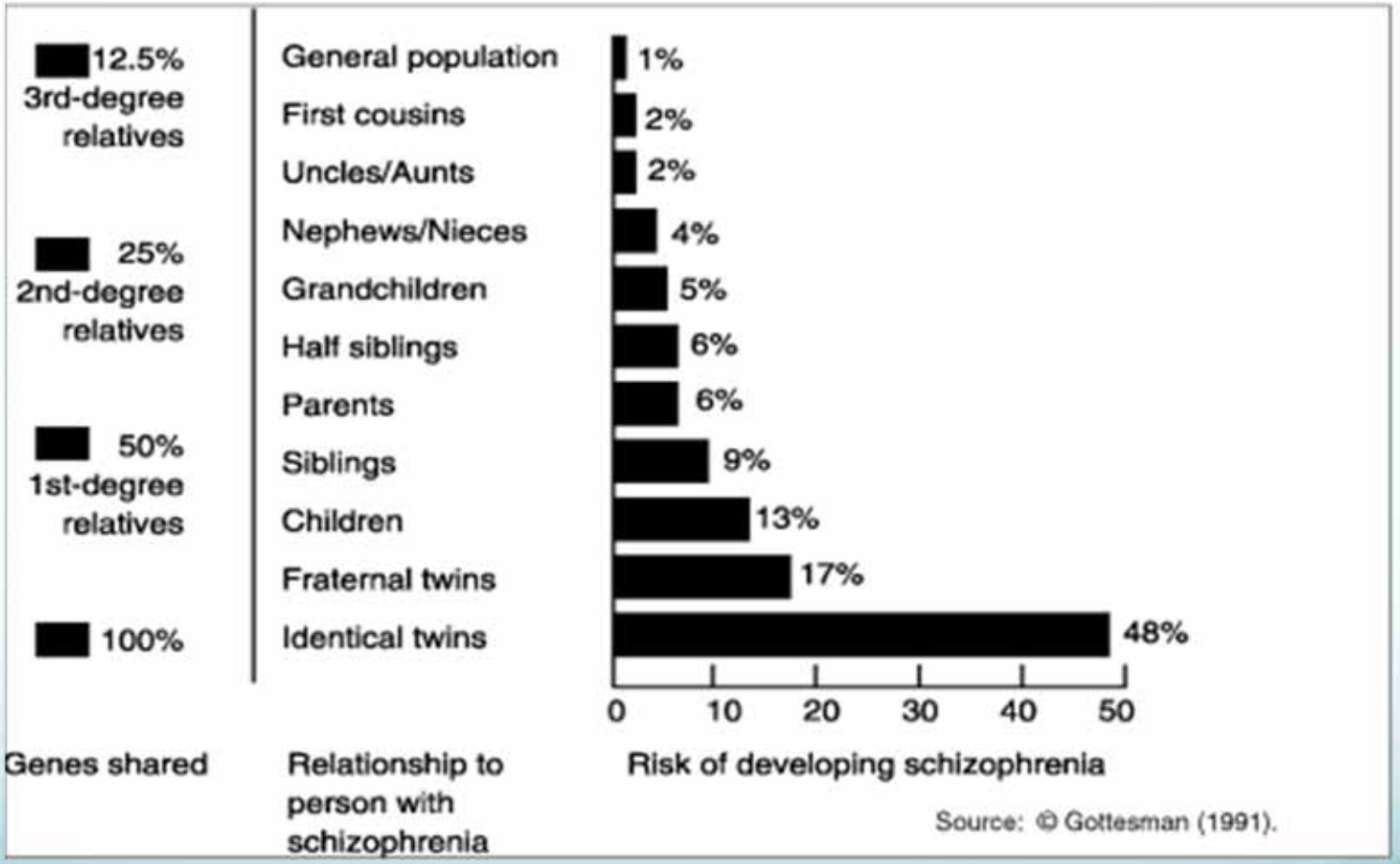
Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

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).

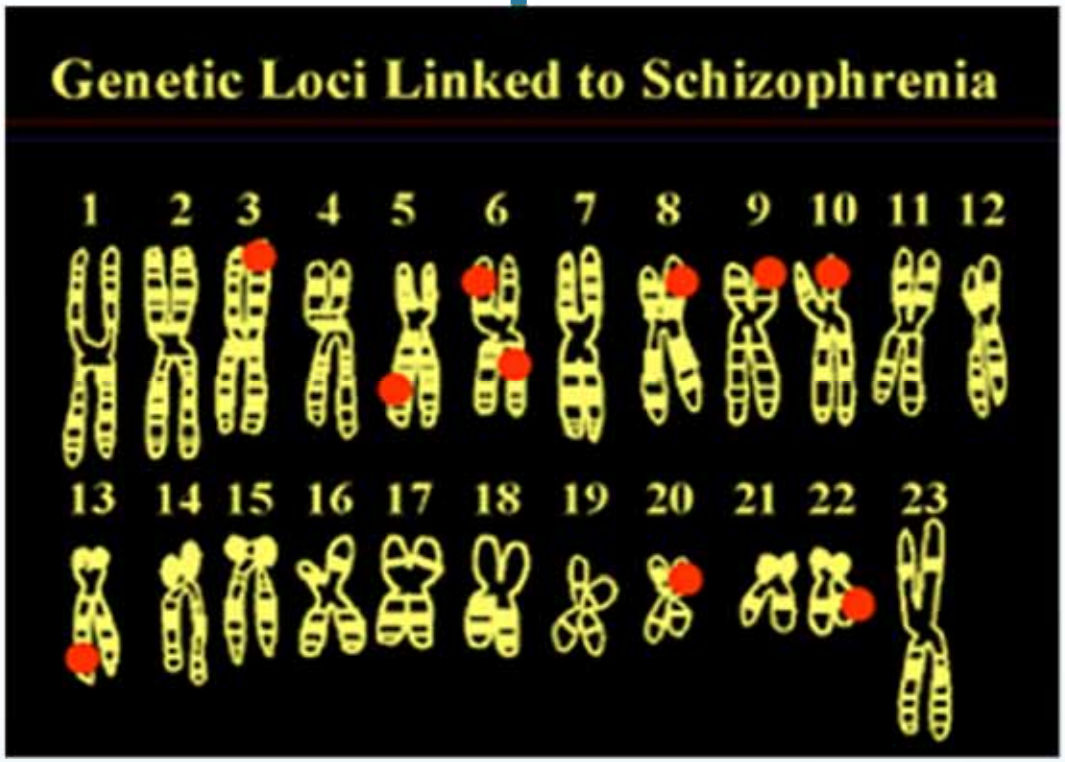
MRI of Ventricular System



GENETIC FACTOR



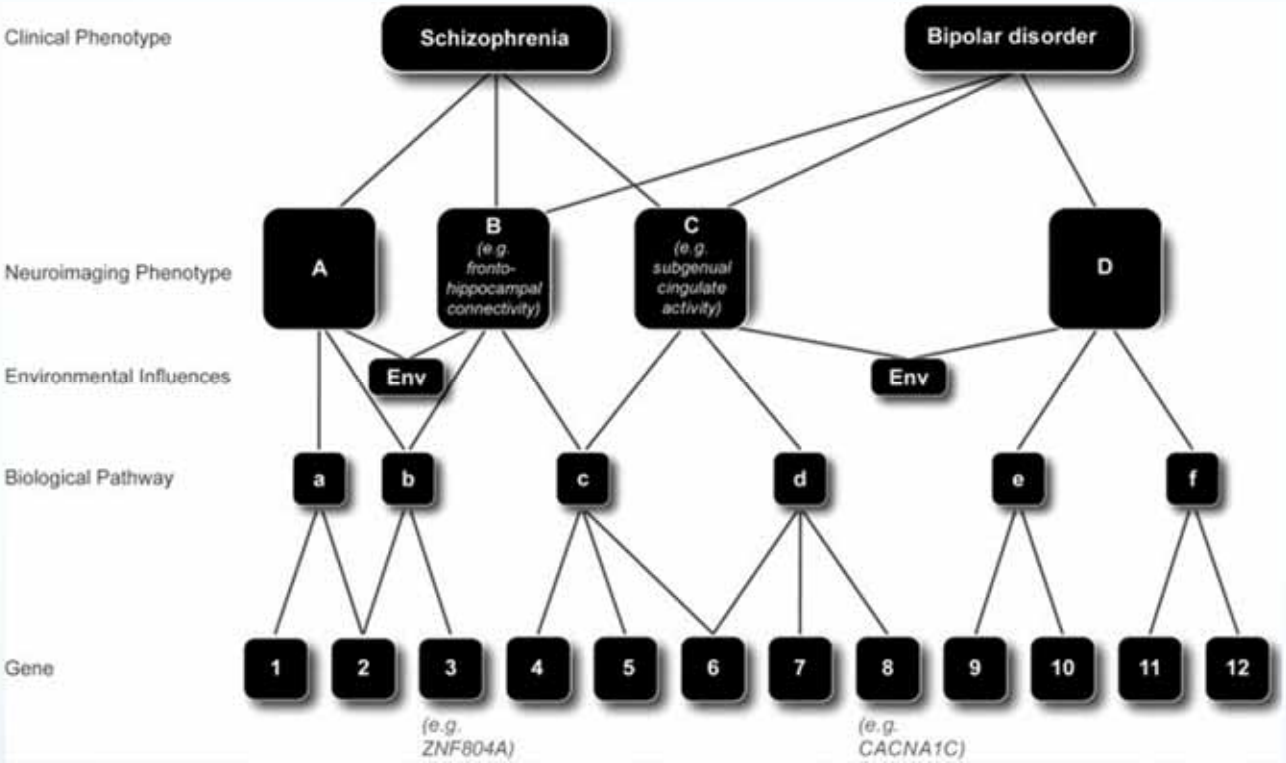
Genetic heterogeneity of schizophrenia



- There is no single gene but a **large number of susceptibility genes**, each with a **small effect** which contribute to the predisposition for the illness. **APA cf, 2012**
- Vast **majority of genes** discovered so far are associated with **glutamatergic pathways** and not with the dopamine or serotonin pathways
- Powerful indicator that glutamate pathways hold the key to finding an **effective treatment** for schizophrenia especially the **negative symptoms**

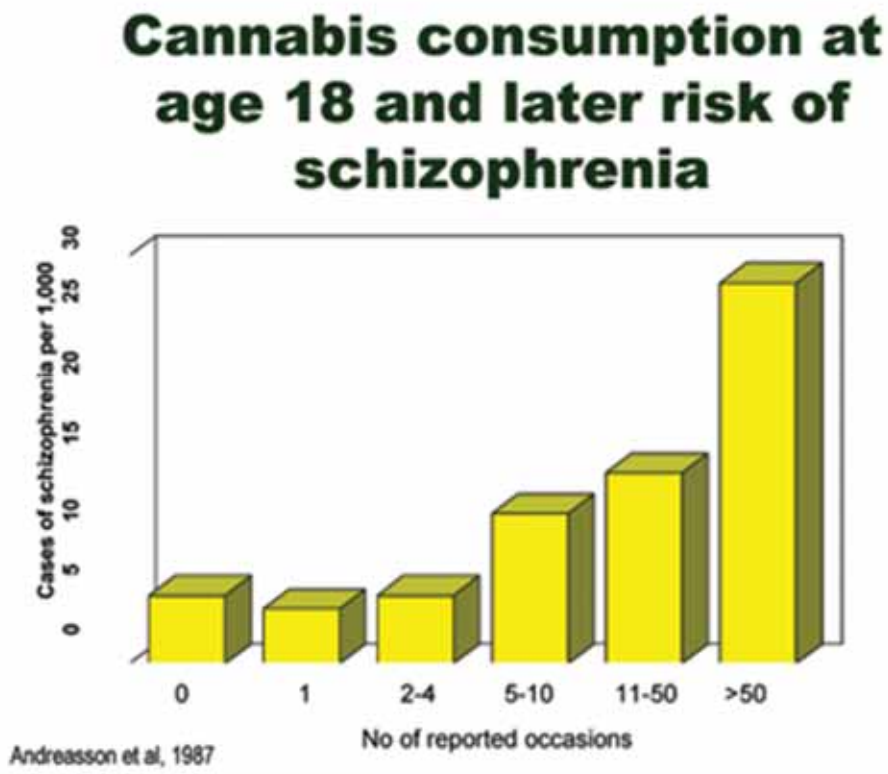
Schizophrenia & Bipolar disorder Share Common Genetic Cause

Hultman et al, 2009, Sweden



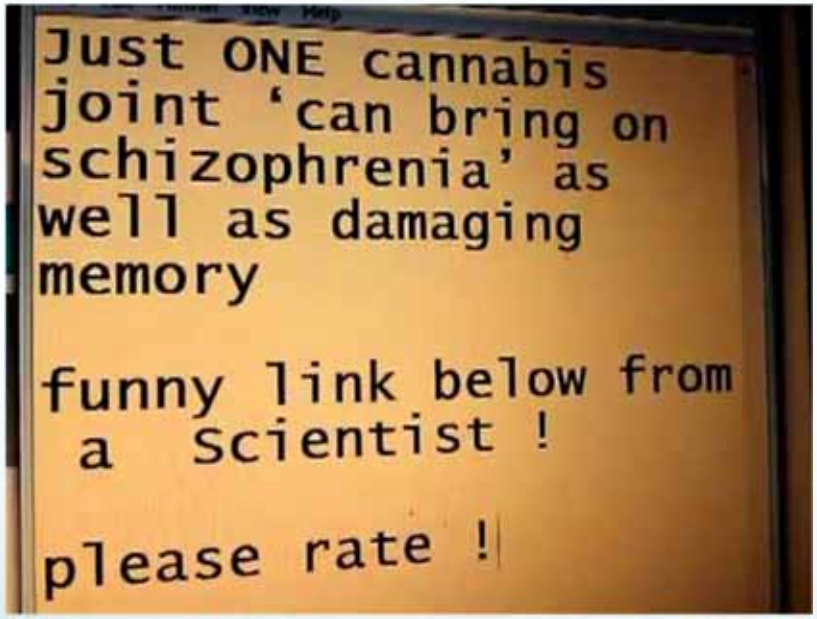
- **Largest family study of schizophrenia and bipolar disorder ever conducted**
  - 9 million individuals (2 million families) over a 30-year period
- **Investigators found that full siblings were**
  - **9 times** more likely than the general population to have **schizophrenia** &
  - **8 times** more likely to have **bipolar disorder.**
  - **Share a common genetic cause and not separate and distinct conditions.**

Cannabis & Schizophrenia



- Andreasson et al, 1987
- 50 000 army conscripts
- Aged 18-20 years
- Followed up in time
- Ordinary users (1.3X)
- Heavy users (6.7X)
- Secondary schools
- Recreational drugs

Cannabis & Schizophrenia

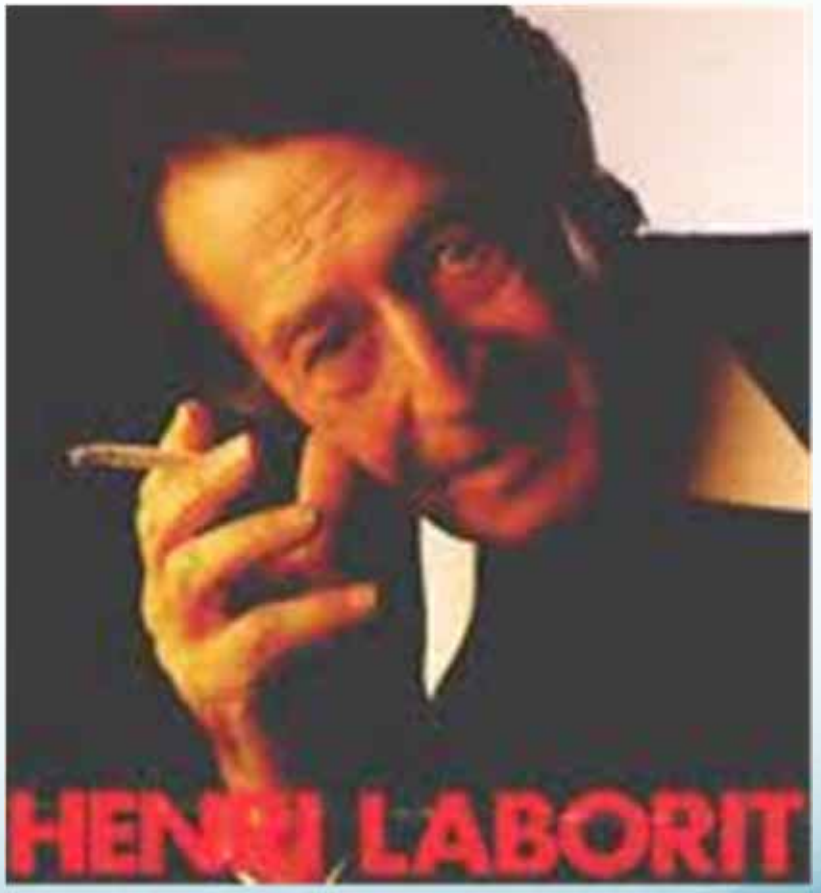


- Murray et al, 2005 (London)
  - 15-year study of 750 adolescents
  - **4.5X for regular cannabis smokers**
  - 1.6X for those with no regular use
- New Zealand study, 2007
  - Young cannabis users 3X
  - **Heavy users were 7X**
  - more likely to develop schizophrenia
- boosts levels of dopamine in the brain

NEW TREATMENT STRATEGIES & RELAPSE PREVENTION

CURRENT ANTIPSYCHOTICS

- First generation (typical)
  - Chlorpromazine
  - Haloperidol
- Second generation (atypical)
  - Olanzapine
  - Risperidone
  - Quetiapine
  - Aripiprazole
  - Clozapine



COMBINATION TREATMENTS

Olanzapine + Risperidone	Small study suggests that some patients may benefit after sequential failure of each drug alone (Suzuki et al, 2008)
Olanzapine + Aripiprazole	Single case report suggest benefit (Duggal, 2004)
Olanzapine + Lamotrigine	Reports contradictory and rather unconvincing (Kremer et al, 2004)
Olanzapine + Olanzapine (30-60 mg/day)	Contradictory findings in the literature but possibly effective. High dose olanzapine: •is not atypical (Bronson et al, 2000) •can be poorly tolerated (Kelley, 2003) •causes gross metabolic changes (Meltzer, 2008)
Olanzapine + Glycine	Small double-blind crossover trial suggests clinically relevant improvement in negative symptoms (Heresco-Levy, 2004)
Olanzapine + Fish oil	Suggested efficacy but very limited data (Puri et al, 1998)

FISH OIL

- Omega-3 fatty acids
  - Eicosapentanoic acid (EPA)
  - Docosahexanoic acid (DHA)
- Neuronal membrane
  - Modulation of membrane proteins
  - Production of PG and leukotrienes.
- Double-blind randomised comparison of EPA (2g daily) and placebo (12 weeks) suggest
  - **useful efficacy** (Mellor et al, 1995)
  - **significant improvement in symptoms** (Peet et al, 2001)
- Research dwindled past few years
- Residual symptoms
- Cheap/ ?try as adjunct few months
- Benefit physical health

NEW DEPOT ANTI-PSYCHOTIC

RISPERIDONE MICROSPHERES

- Not an esterified form
- Coated in polymer
- Microspheres
- Suspended in aq base b4 use
- Stored if fridge
- Cumbersome
- Expensive
- Paliperidone (9-0H risperidone)
- Paliperidone palmitate
- Deltoid muscle

OLANZAPINE PAMOATE

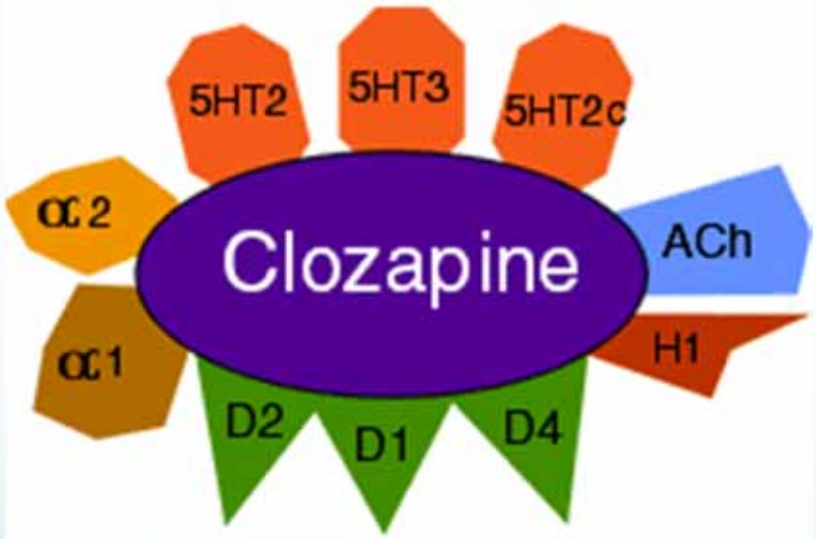
- Poorly soluble salt
- Aq suspension
- Sedation syndrome
- Metabolic syndrome

ARIPIPRAZOLE DEPOT

- going to be commercialized very soon in USA.
- “Intramuscular depot aripiprazole is a **safe and tolerable** option for long-term maintenance treatment of schizophrenia.” Kane et al, 2012
- adult outpatients receiving once-monthly im injections of aripiprazole had a
  - significantly greater **delay in time to relapse**
  - significantly **lower rate of relapse**

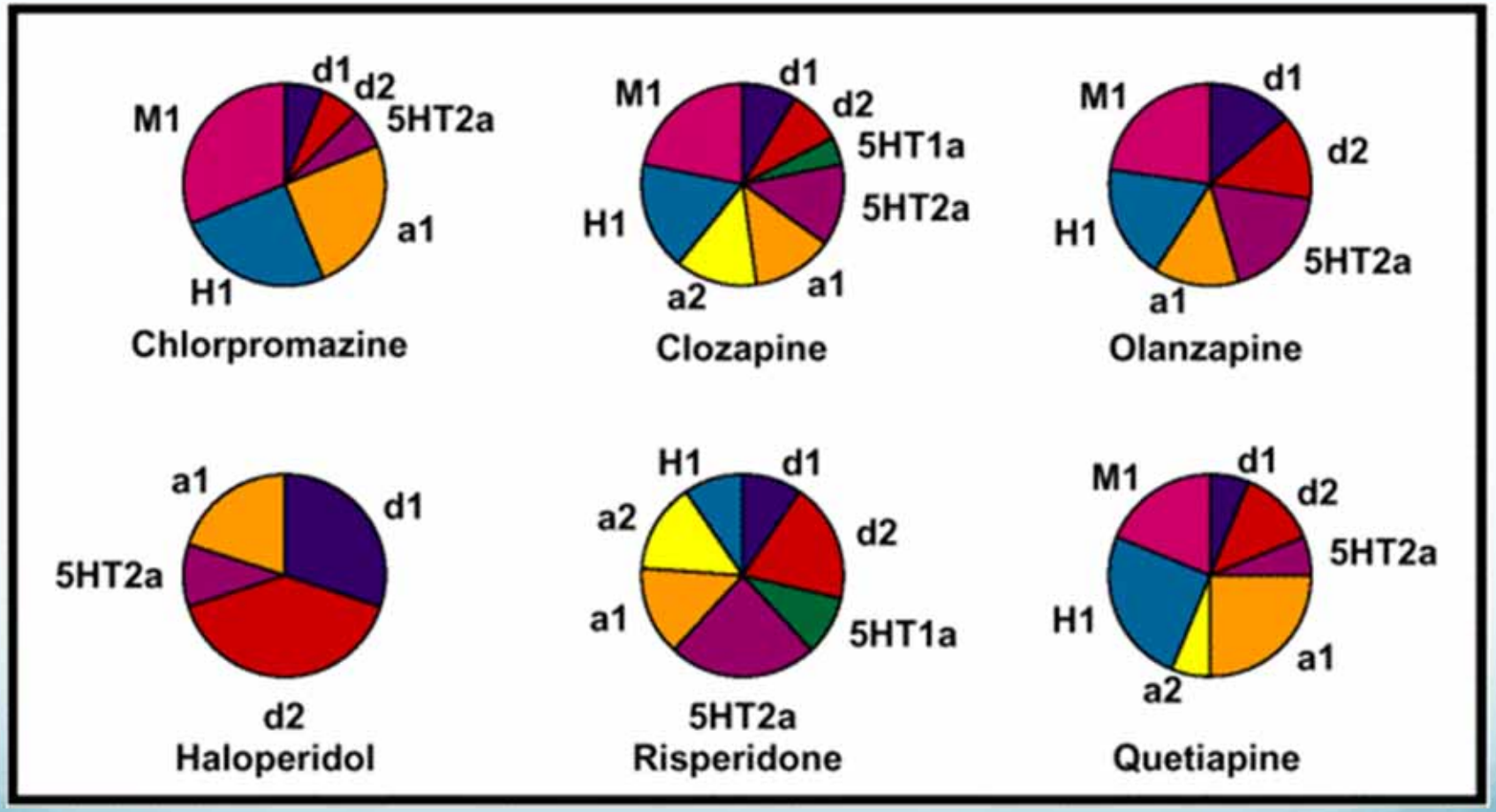
  compared with the participants who received placebo.”

CLOZAPINE



- Used in treatment resistant cases
- 1st used 1971
- Removed 1975
- Restarted 1989
  - Rx- resistant cases
  - WCC (weekly/monthly)
    - Neutropenia
    - Agranulocytosis
  - HbA1C
- Titrate from low dose
  - To lessen side effects
- Broad spectrum anti-psychotic.
- Superior efficacy

Receptor blockade



Non-compliance with medication increases relapse rate & hosp adm rate

- **Leucht et al, 2012**
- **Meta-analysis**
- **65 RCT** with data for **6500 pts stable on anti-psychotic (A/P)**
- **Treatment gp:**
  - **Maintained on A/P**
- **Control gp:**
  - **Withdrawn from A/P and put on placebo**
- **Primary outcome**
  - **Relapse within the year**

	A/P	Placebo
Relapse rate	25%	69%
Hosp admission rate	10%	25%

MECHANISM OF ACTION

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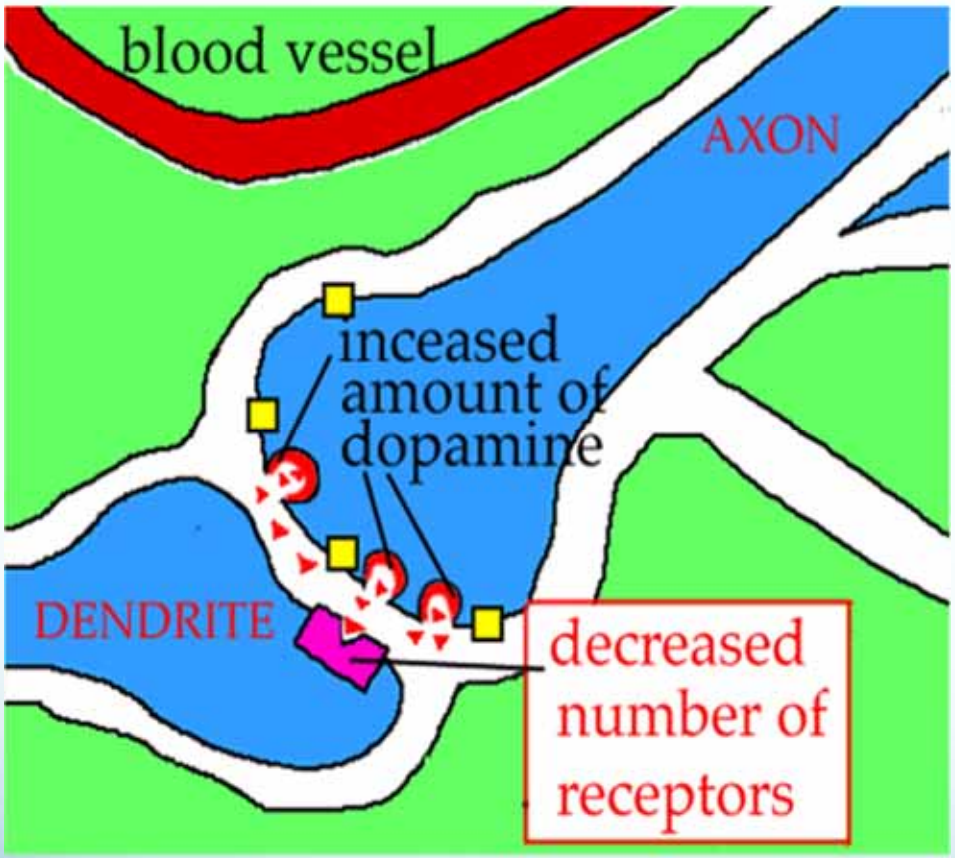
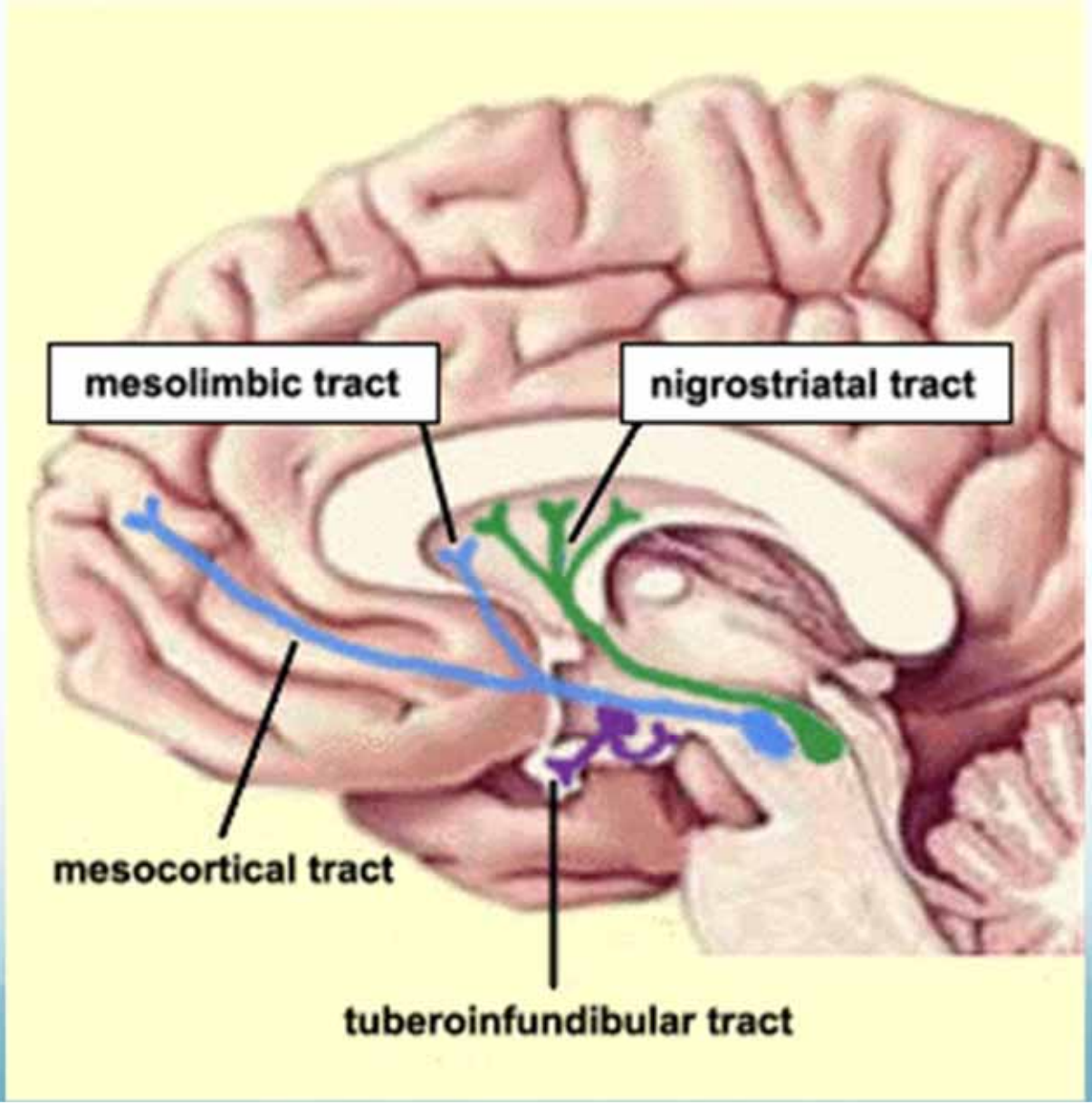


- “Amphetamine psychosis”
- Dopamine blocking drugs
- **Dopamine hypothesis**
- Mesolimbic-mesocortical tracts

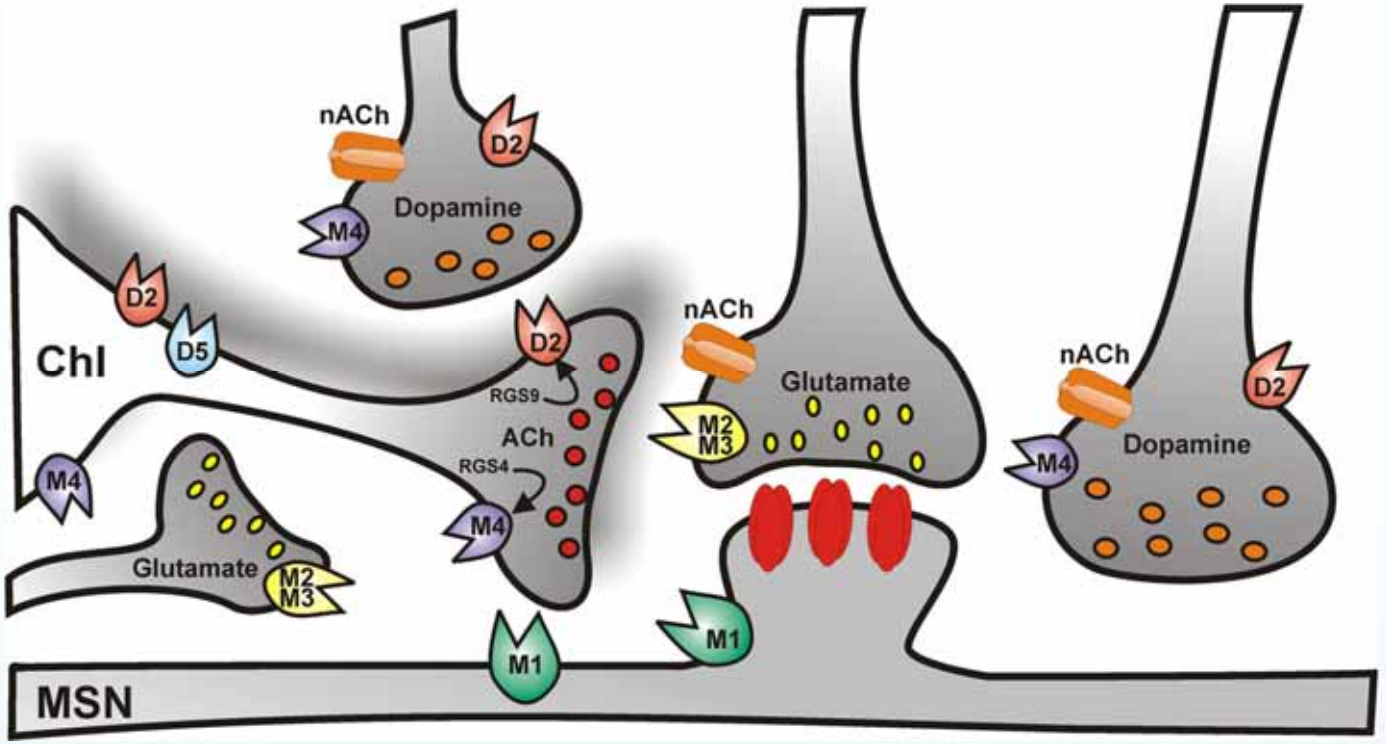
DOPAMINE TRACTS



Limitations of the dopamine model

- **No consistent dopamine abnormalities found.**
- Some agents with **no D_2 binding affinity, yet reduce positive symptoms.**
- **No impact on negative symptoms or the cognitive deficits** associated with schizophrenia.

BEYOND THE DOPAMINE HYPOTHESIS



Growing body of evidence implicating the hypofunction of the glutamatergic N-methyl-D aspartate (NMDA) receptor and its major role in the pathophysiology of schizophrenia.

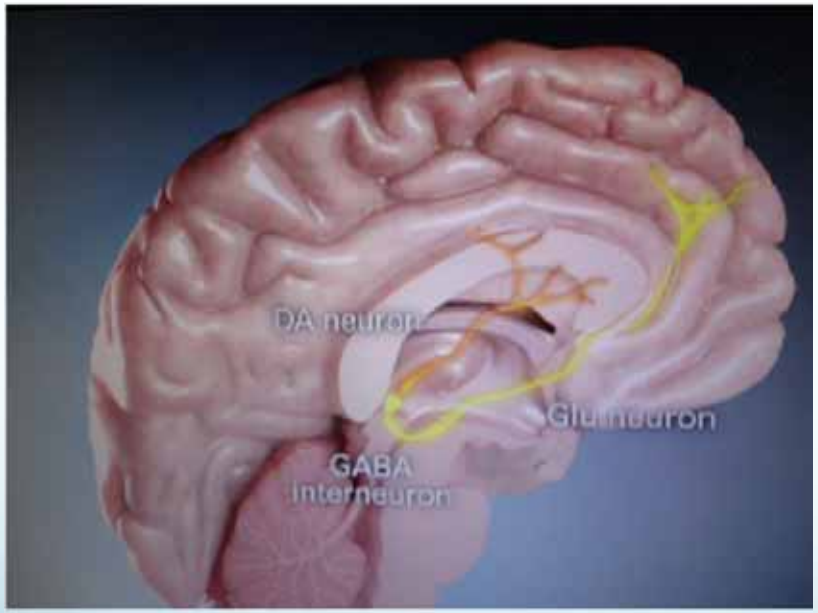
Why the glutamate system?

- **Ketamine (Glutamate antagonist)**
  - **can induce positive, negative and cognitive symptoms** in healthy volunteers
  - **exacerbates psychotic and cognitive symptoms** in patients with schizophrenia

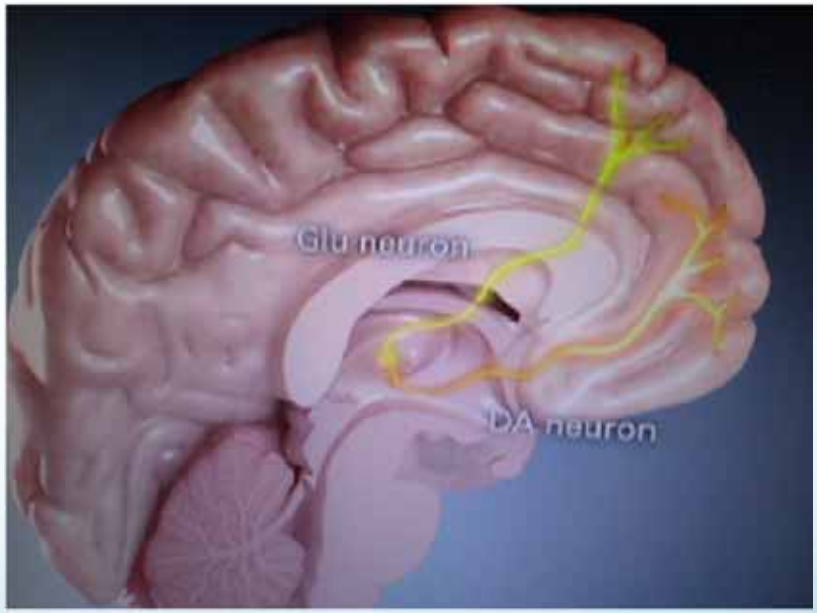
- Glutamate system regulates dopamine system

GLUTAMATERGIC-DOPAMINERGIC PATHWAYS

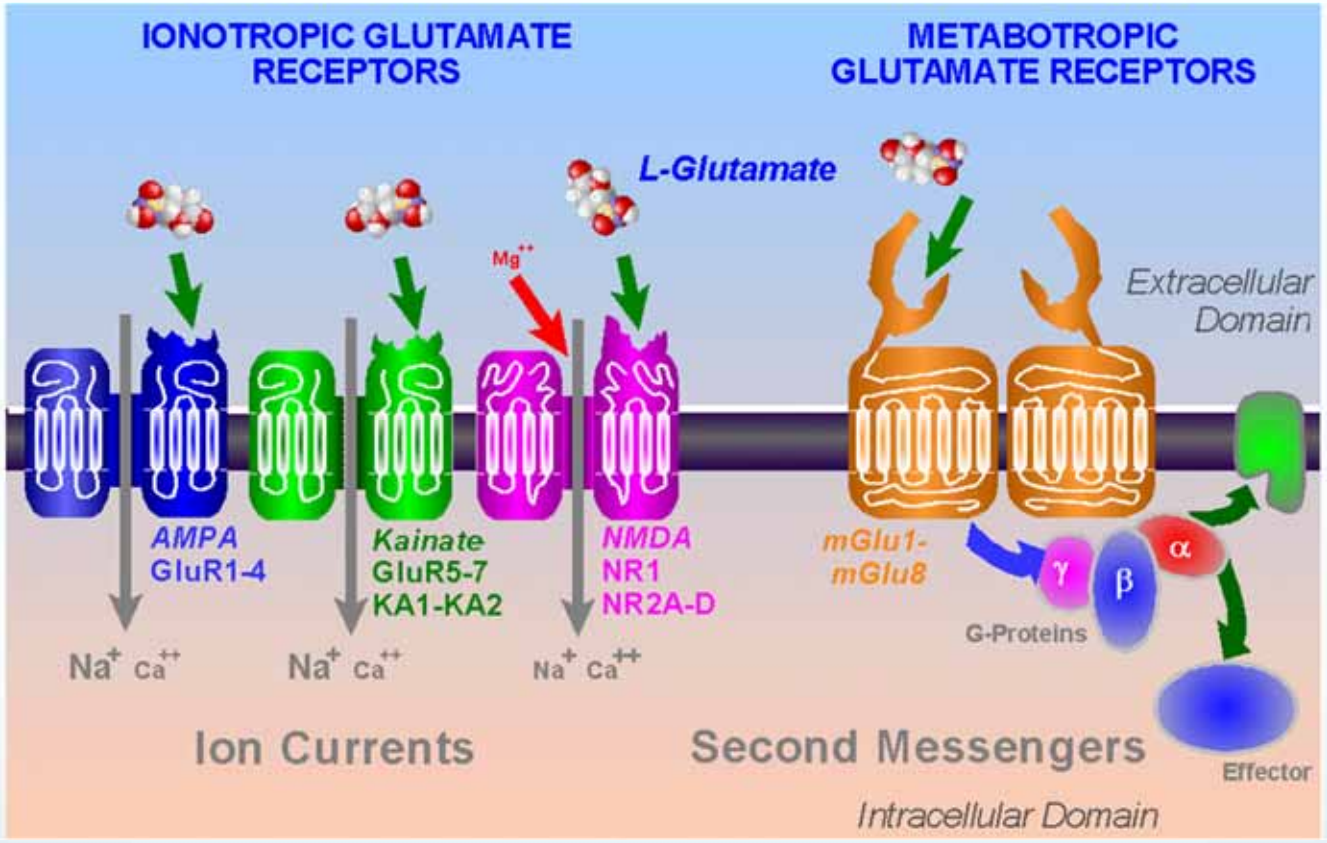
MESOLIMBIC TRACT



MESOCORTICAL TRACT

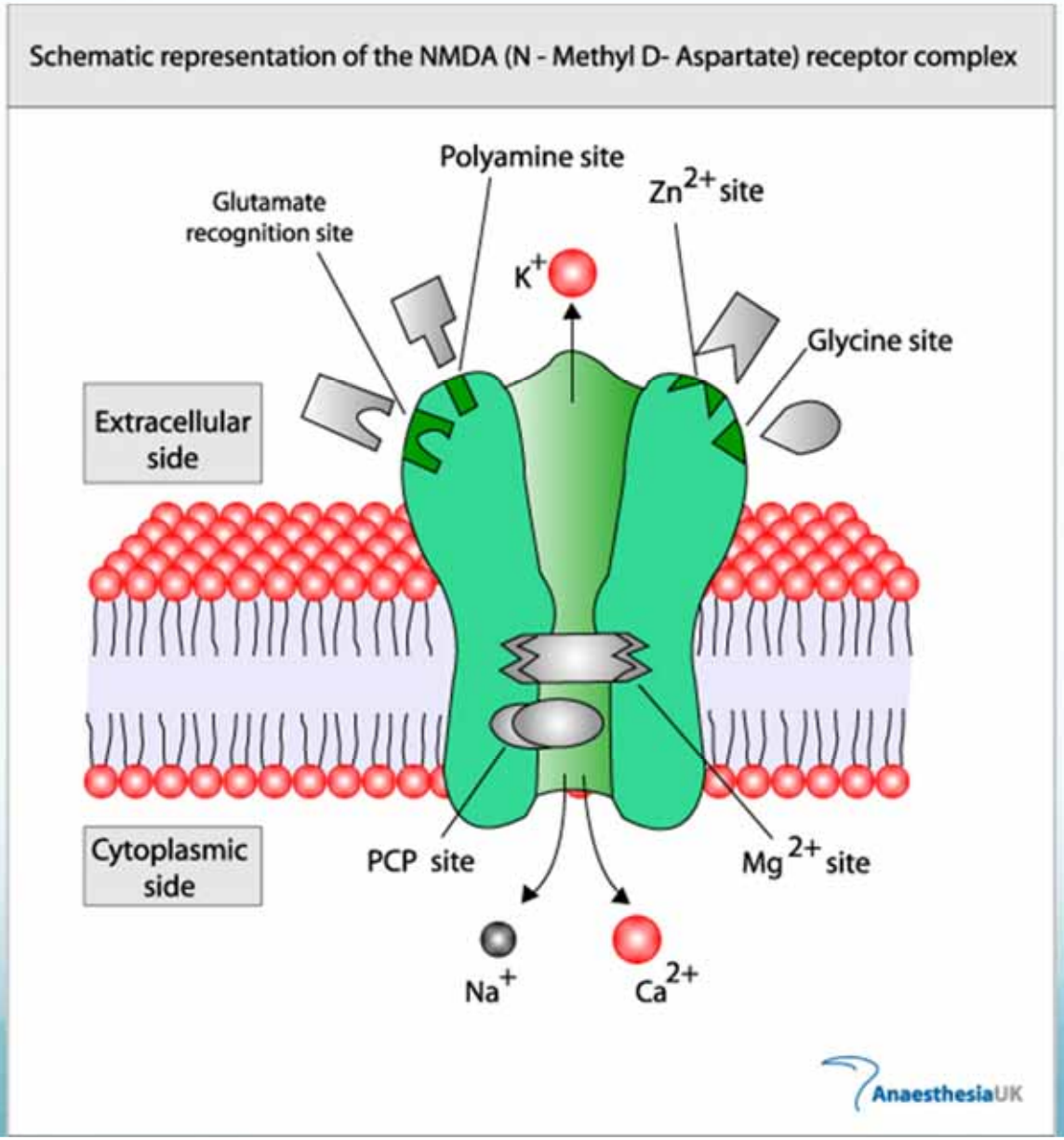


GLUTAMATE RECEPTORS



If blocking NMDA receptors induces psychosis and cognitive deficits…
then stimilating NMDA receptors should be beneficial

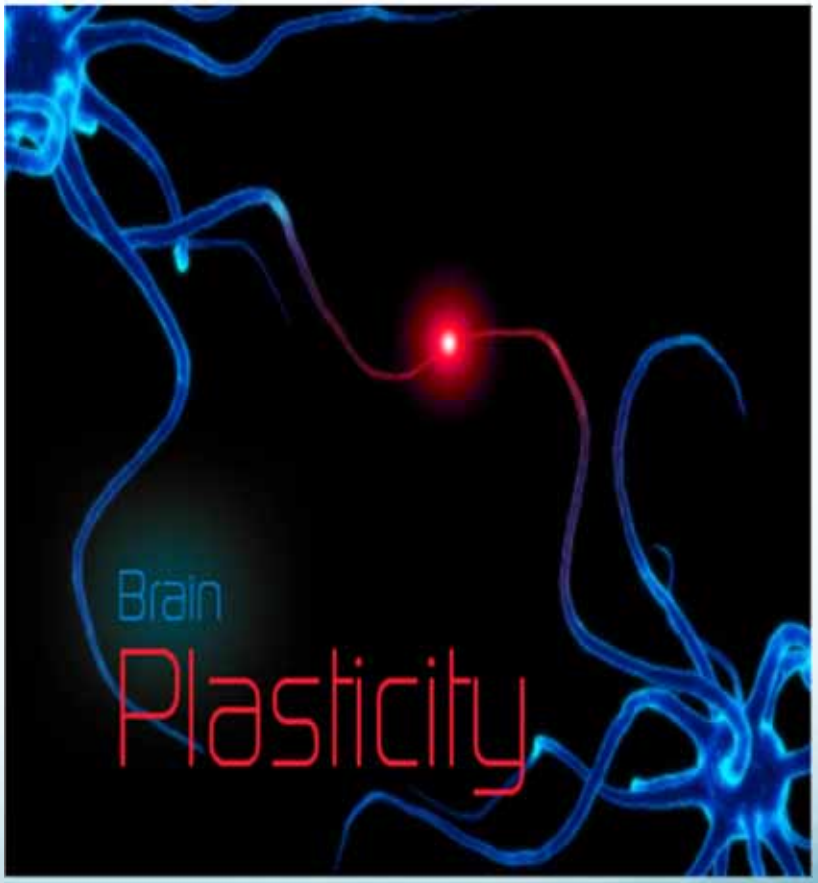
NMDA RECEPTOR



New strategies of treatment

- **Glutamate receptor agonists**
  - **Metabotropic receptor agonists**
  - **NMDA agonists**
- **Glycine**
  - **Glycine reuptake inhibitors**
  - **Glycine transport inhibitors** e.g sarcosine (Roche)
- clozapine blocks glycine

  ?adding sarcosine to glycine
- Rx may **enhance plasticity**
  - **Brain is a plastic organ**
  - **Early Rx ➔better outcome**
  - **Exciting time for research**
  - **Future promising**
- **Nicotinic receptor agonist**
  - A7 stimulating N receptor



OUTCOME OF RESEARCH
Glutamate receptors

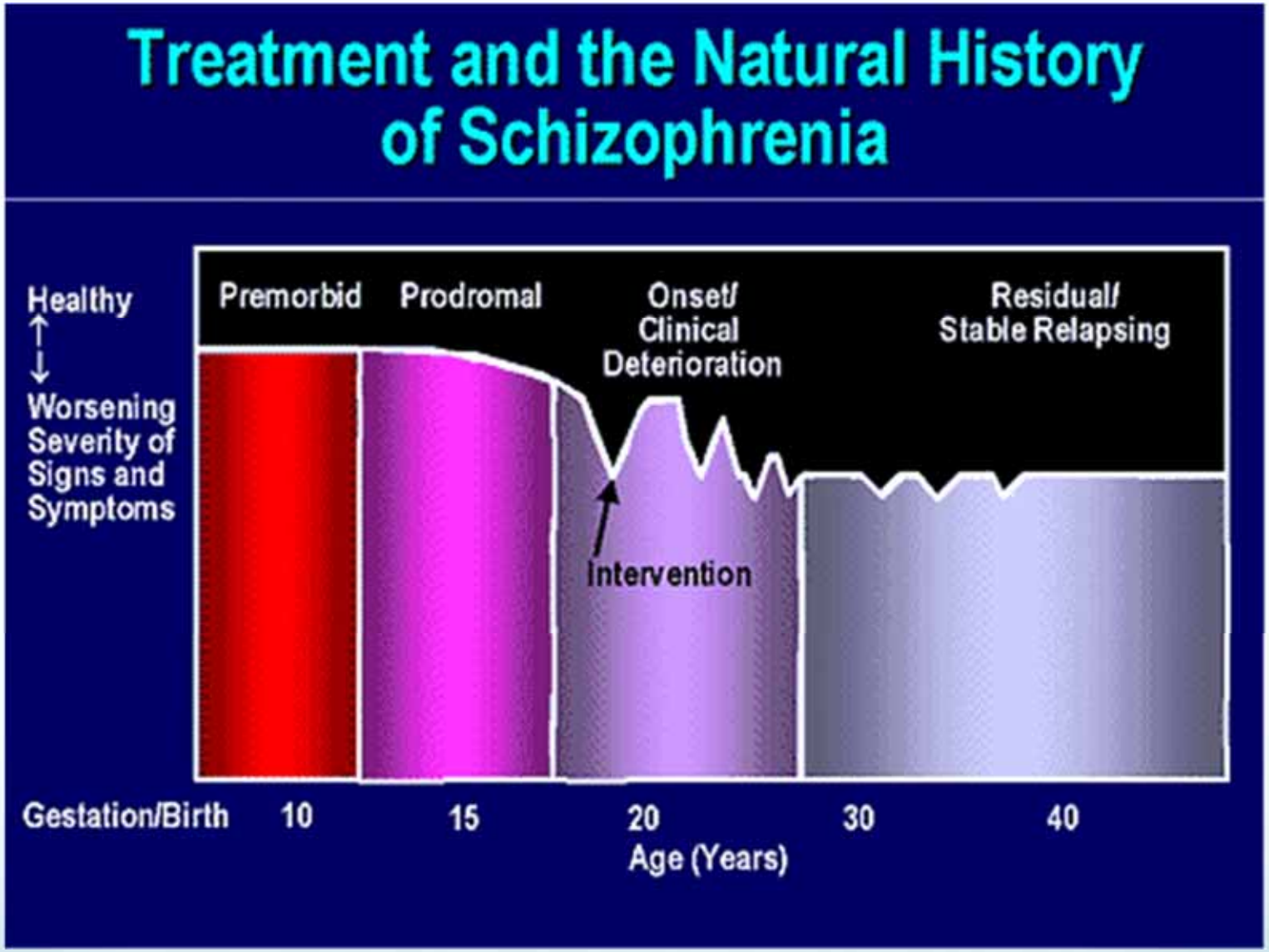
Metabotropic

- **POMAGLUMETAD METHIONIL**
  - Eli Lilly and co. said its experimental schizophrenia drug known as mGlu2/3 **did not work** in a late stage clinical trial. (Reuters, 11 Jul 2012)
  - The schizophrenia **trial failure** "adds another, albeit modest, disappointment," he said.

Ionotropic

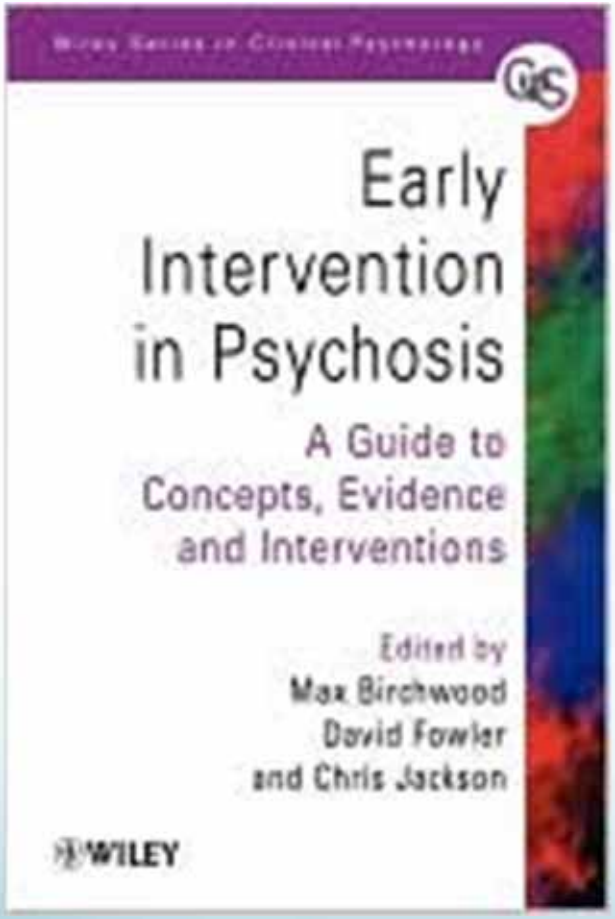
- NMDA agonists
  - Awaiting results of trials
- Glycine reuptake inhibitors
  - Awaiting results of trials
- Glycine transport inhibitor
  - Sarcosine (Roche)
  - Reduction in –ve symptoms

COMMUNITY TREATMENT & REHABILITATION



Role of early intervention

better outcome



- Birchwood et al,1997
- Identify early signs
  - Prodromal phase
- Treat early…better prognosis
- **Early interventions team**
  - Education of GPs
  - Identify patients at risk
  - Treat patients at risk

HOME VISIT BY COMMUNITY TEAM MEMBER

- Home treatment team
  - Visit in pairs (for safety reasons)
  - Referral from GP
  - Self referral of chronic patients
  - Engage patients in taking medication
  - Problem solving & crisis intervention
  - Educate family & offer advice
  - Help with hospital admission
  - Cost effective as lessen hosp adm rate
- Community Mental Health Team consists of
  - Doctors
  - Nurses
  - Health care assistants
  - Social workers
  - Occupational therapists
  - Psychologists
- Purpose
  - Out-patient clinics
  - Administering depot
  - More likely to attend than distant mental hospital.

Expressed emotion

- Vaughn & Leff, 1976
- Family environment
  - Critical comments
  - Hostility
  - Emotional over involvement
- Relapse rate 45% in HEE
- Relapse rate 25% in LEE
- When combined with non-compliance to medication,
- 85% relapse within 12 months.
- Psychoeducation
  - Strategies to reduce EE.

Crisis intervention

COMMUNITY MENTAL HEALTH CENTRES