

# **CINP Edinburgh Meeting April 2009**

## **Major Psychoses and Substance Abuse**

**Prof. Tomas Palomo  
University Hospital “12 de Octubre”  
Madrid  
Spain**

## Dual Diagnosis

**Tomas Palomo  
and  
Douglas Blackwood  
1978  
*MRC Brain Metabolism Unit  
Edinburgh***



**cibersam**  
Centro de Investigación Biomédica En Red  
de Salud Mental

**Pure Malt  
15 years old  
whisky**

**Plan:** to present a real clinical case that we could use to review some of the important questions that have been dealt with at this CINP meeting.

I will present to you the case of a **36 years old chronic schizophrenic** patient who started abusing **drugs at the age of 14 until he was 22**. Despite stoping abusing drugs, he suffered as many as 12 psychotic episodes afterwards and continued **progressive deterioration**.

After years of aggressive disruptive behaviour in our Psychiatry Unit, he was then put on a special programme for Severe Mental Disorders and now he is nearly a normaly behaving person who is looking for a job.

We will take this case as an example to examine chronic schizophrenia from vulnerability and etiology to chronicity and deterioration, and from prevention to trreatment.

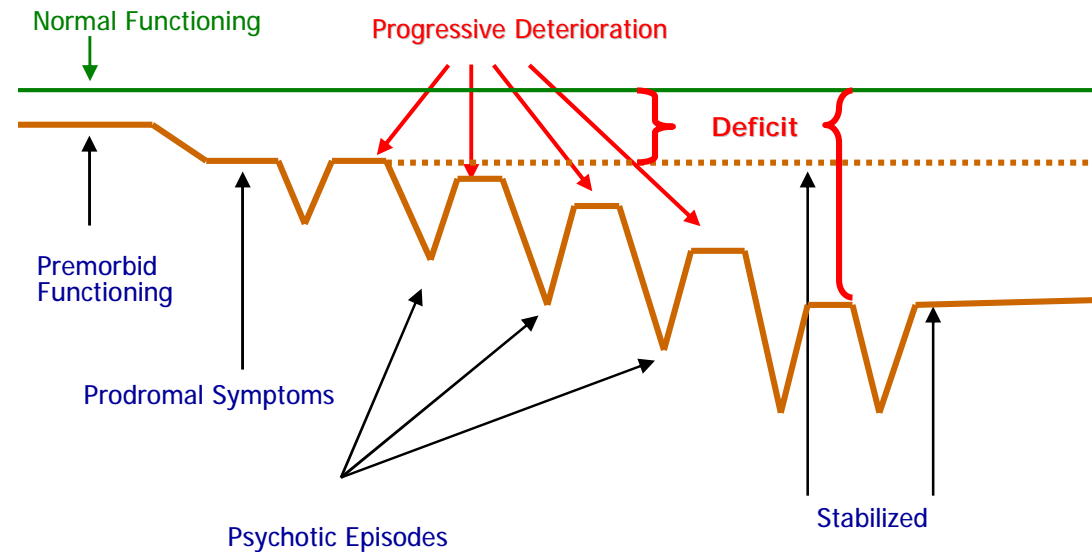
Main objective à to provoke thouhgts and questions that we can then discuss together.

# Chronic Psychoses

This real case will be used to examine the different **stages** as disease progress to chronic schizophrenia.

Following Patrick McGorry we will use this **staging approach** as a new paradigm with important implications for prevention and treatment

→ **Stages:** from premorbid to chronicity and deterioration



**Patient J.H.O.**

## **Cinical case**

Thirty-six-year-old single male, lives with his parents, diagnosed with Paranoid schizophrenia. He is the eldest of three brothers. He went to the primay school and continue to become a draughtsman. Unemployed, on disability allowance for the last year.

Family history: maternal grandmother attempted suicide, mother depressive and anxious, younger brother drug abuser

**Birth trauma** (complicated delivery)

First contact with Mental Health Care (Psychology) when 12 years old due to **withdrawn** and **oppositional behaviour**.

Began using **cannabis**, as well as **cocaine** and **alcohol**, at age 14 (all substance use stopped after age 22).

Patient J.H.O.

## Cinical case

When 19 years old his General Practitioner diagnosed a **depressive episode** and began treating him with antidepressant medication. From then on, his family noted a **progressive change in his character**; he became more socially withdrawn and irritable.

He had a relationship for a year and a half, and two months after breaking up visited the Emergency Room of 12 de Octubre Hospital, where he was admitted to the Psychiatry Inpatient Unit (age 21). His discharge diagnosis (October 1993) was **Adjustment disorder and Dissocial personality traits**. Despite recommendations, he did not attend the Outpatient Mental Health Services for follow-up after discharge.

**Patient J.H.O.**

## **Cinical case**

The patient had a second hospital admission in Gómez Ulla Hospital in Madrid in 1994, while in military service (age 22). On discharge, he received a diagnosis of **psychotic episode**, was treated with antipsychotic medication and was referred for follow-up in the Outpatient Mental Health Services, which he only attended for two months.

Since then, the patient underwent **repeated psychiatric hospitalisations** (up to a total of 12), which followed the same sequence: lack of insight at the time of discharge which led to non-compliance with treatment and follow-up, and progressive psychopathological and functional deterioration until polymorphic delusions, florid hallucinations and behavioural disorders were patent.

Patient J.H.O.

## Cinical case

The only exception to this pattern was a 6-year period, between age 27 to 33, when he remained relatively stable due to the fact that his mother hid his medication **(clozapine)** in an infusion.

From the onset of his illness, he has been treated with all **antipsychotic medications** available in both oral and injectable formulations, with little success in achieving either treatment compliance or illness insight.

**Patient J.H.O.**

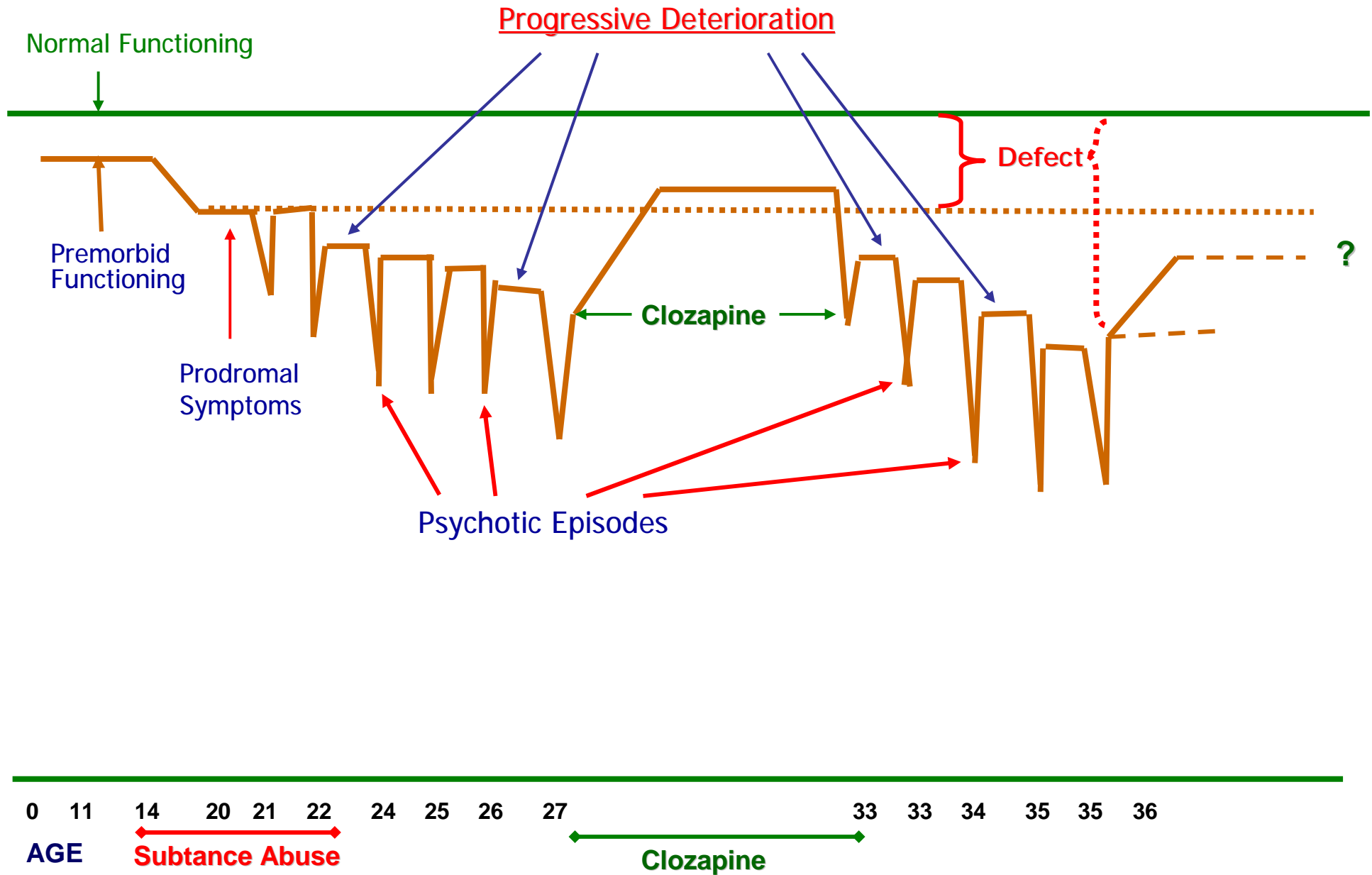
## **Cinical case**

Due to the unfavourable course of his illness, after his last hospital discharge in June 2008 the patient was referred to the **Severe Mental Disorders Program**. The programme includes intensive day hospital treatment (psychosocial, cognitive psychotherapy, group and family interventions treatment, etc). It is worth noting that the he has been attending the Program daily, with good compliance and participation in the different activities.

Regarding **pharmacological treatment**, his desire to be clinically stable in order to be referred to the local Work Rehabilitation Centre brought about negotiations which included changing his depot medication to oral risperidone and performing regular blood levels to ensure compliance. The patient is currently taking his medication every day.

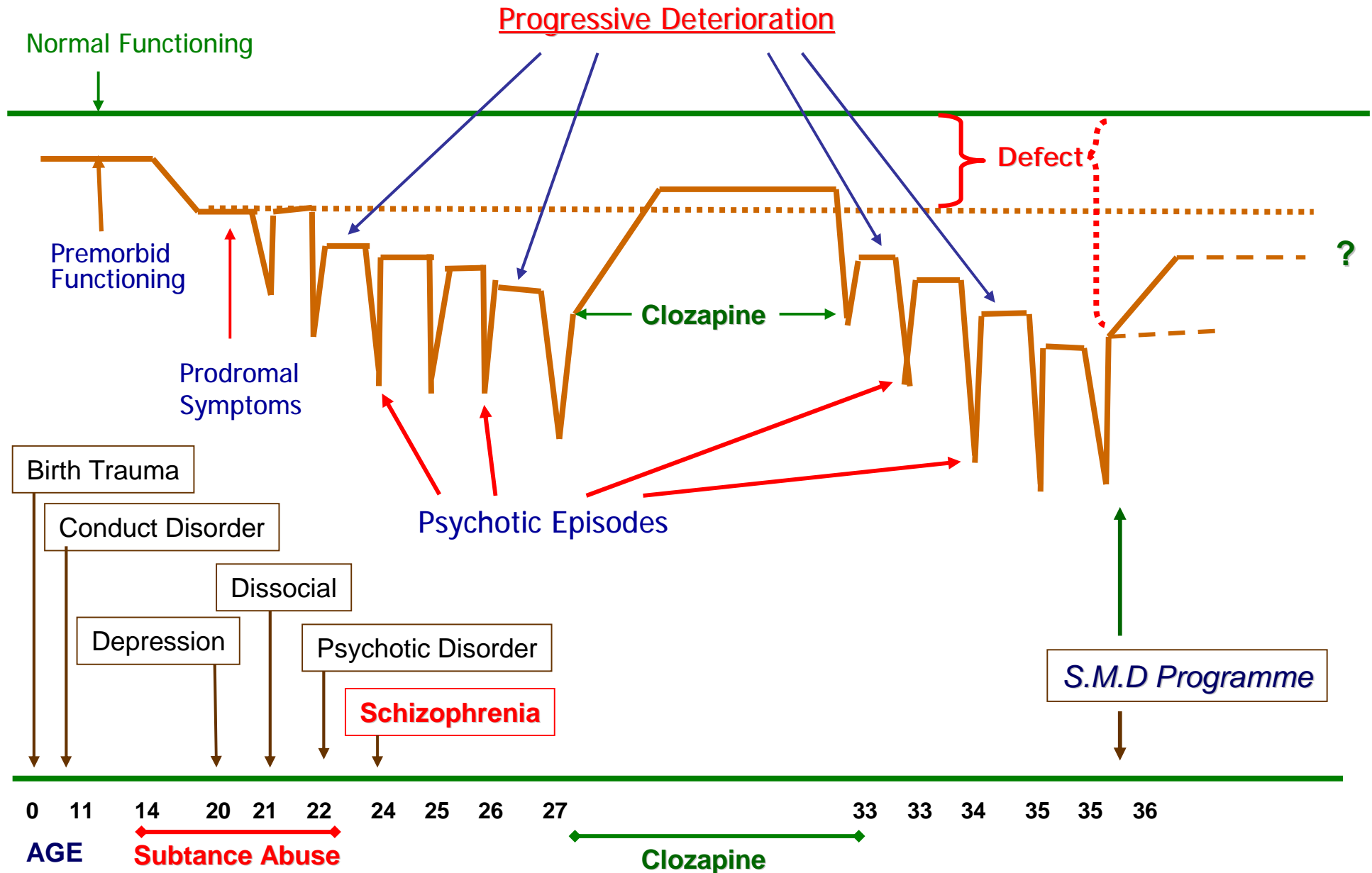
# Patient J.H.O.

→ **Stages:** from premorbid to chronicity and deterioration

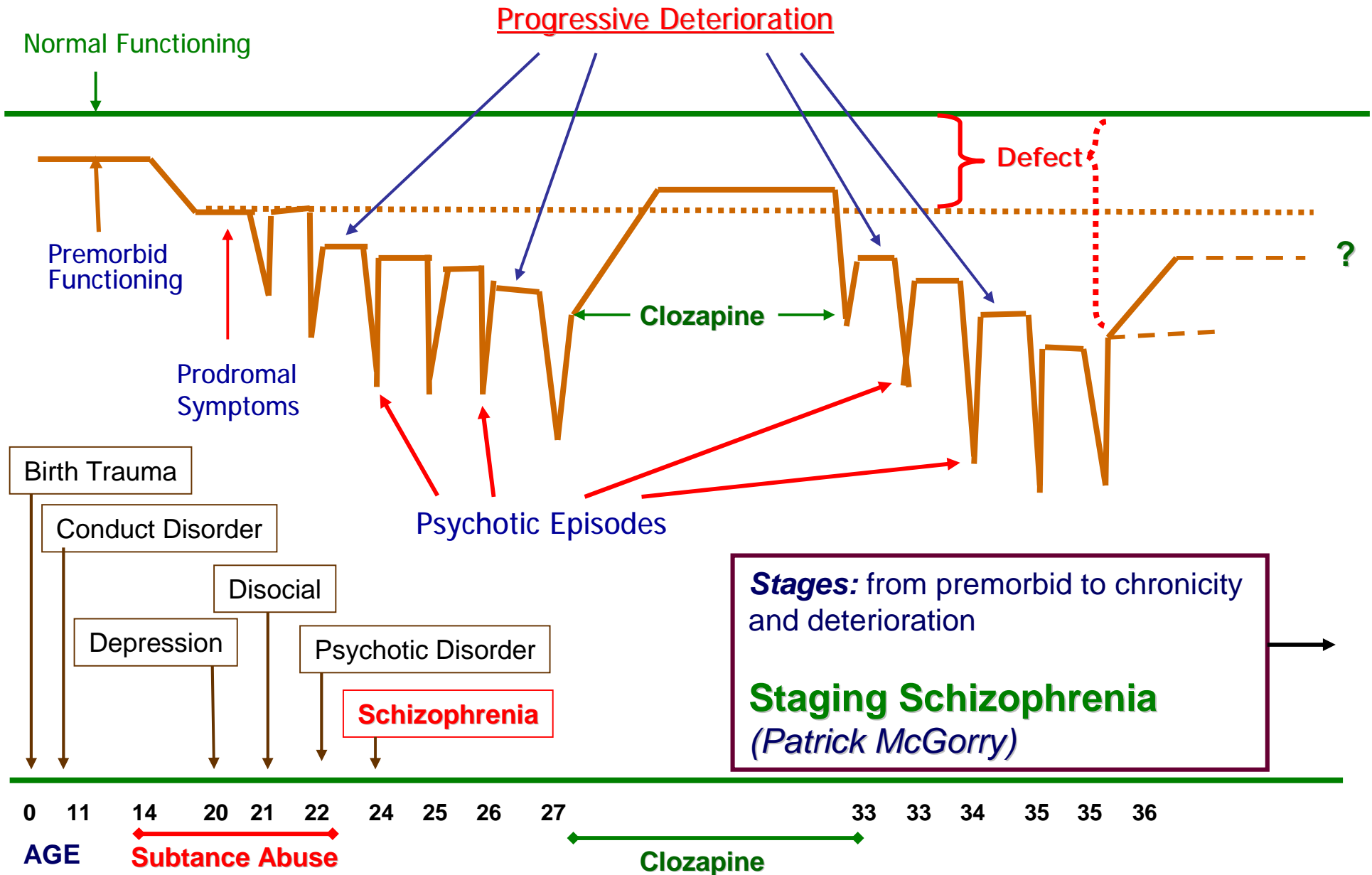


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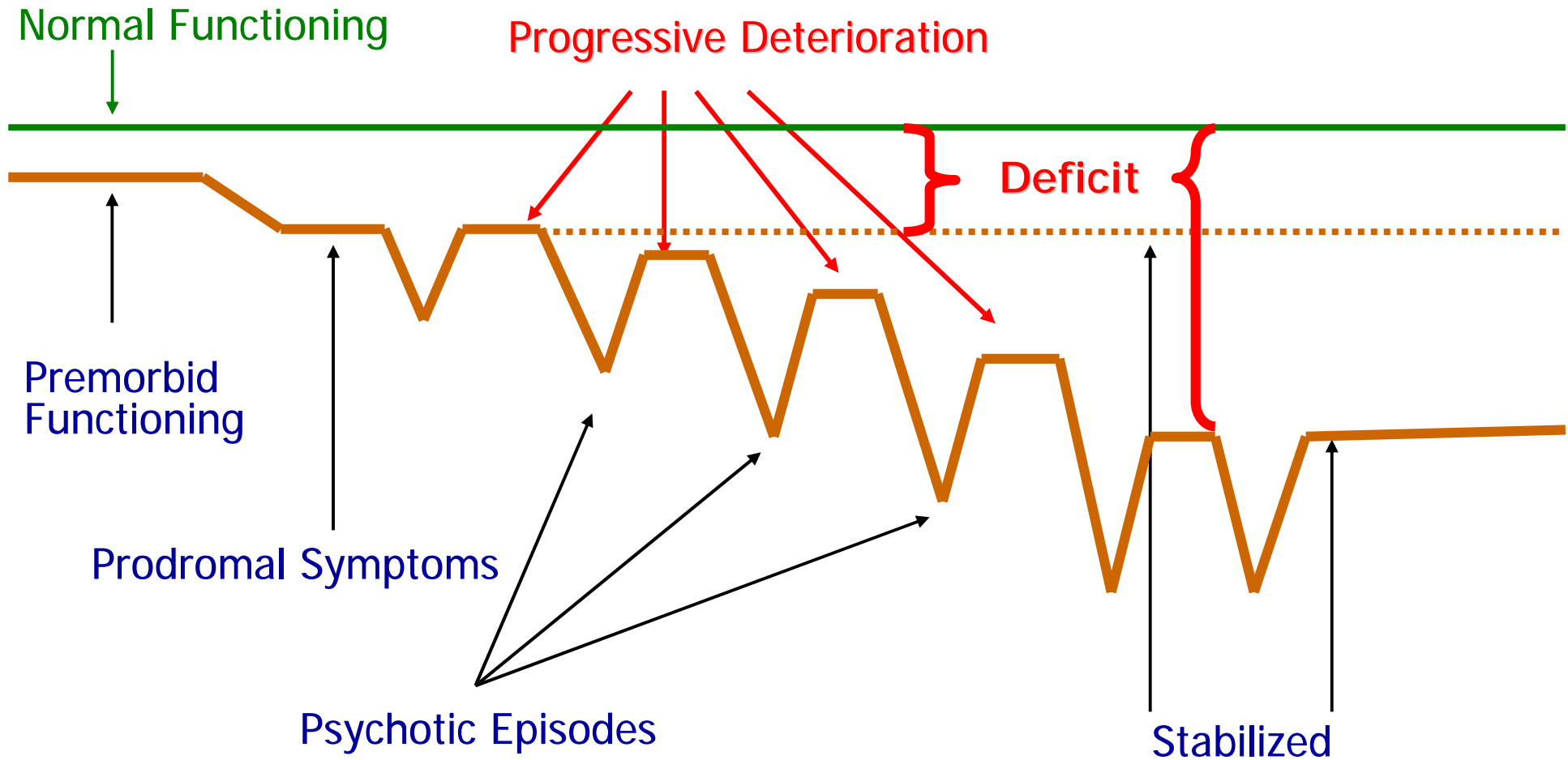


# Patient J.H.O.



# Schizophrenia Clinical Course

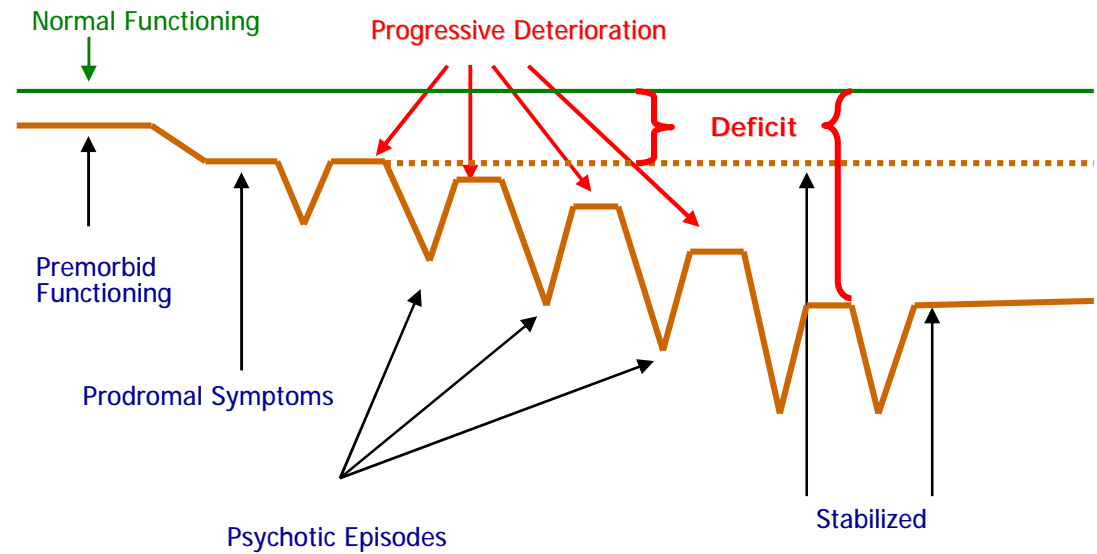
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# Schizophrenia Clinical Course

“staging” (Patrick McGorry)

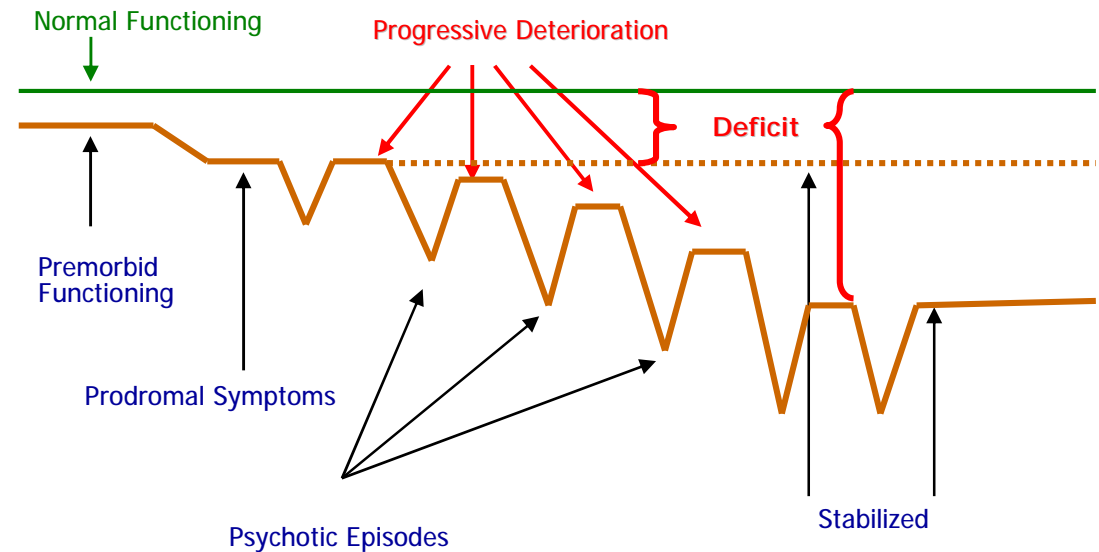
Progression from prodromal to the first psychotic episode to chronic psychosis and cognitive and social deterioration (stages)



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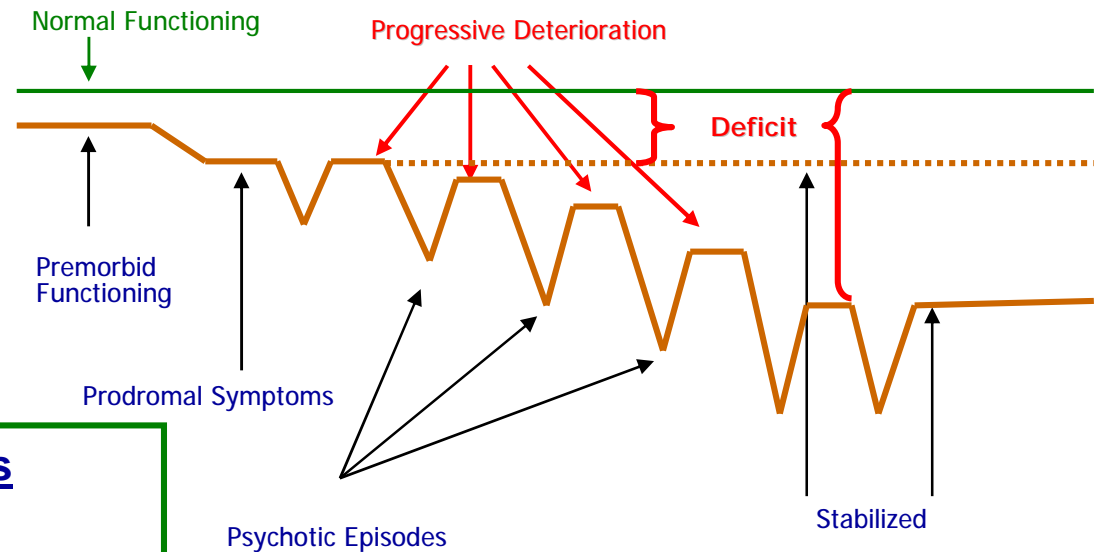


**Regarding psychosis, there are more clinical and biological similarities between first-episode psychotic bipolar disorder and first-episode schizophrenia than between early and chronic stages of schizophrenia.**

# Schizophrenia Clinical Course

“staging” (Patrick McGorry)

Progression from prodromal to the first psychotic episode to chronic psychosis and cognitive and social deterioration (stages)



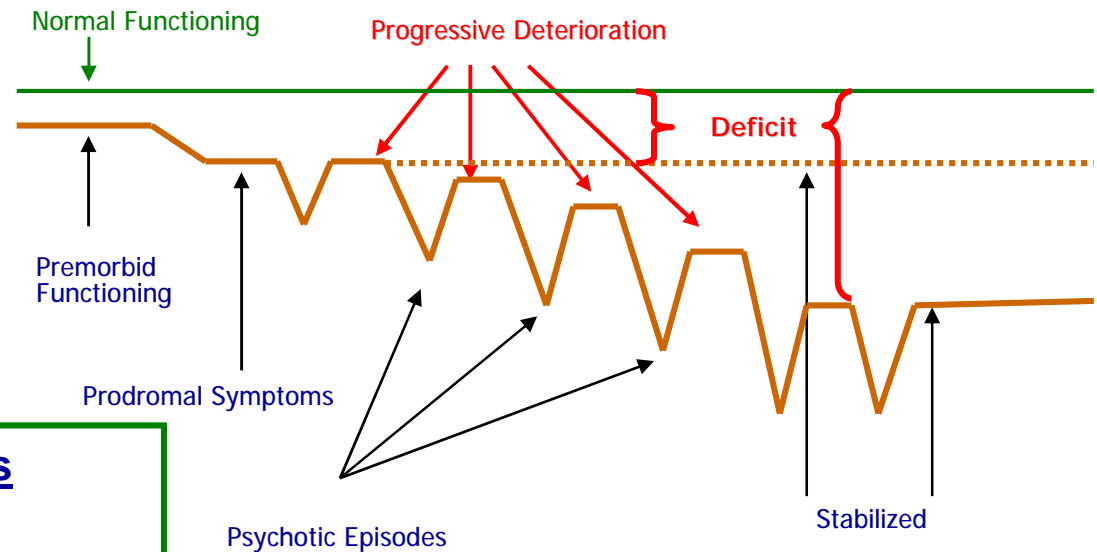
## SCIENTIFIC QUESTIONS:

- What are the **risk and protective factors** (social, biological, personal) that influence **movement across stages**?
  - What is their relative potency?
  - Can they be modified by treatment or interventions?
- How **environmental variables** (drug abuse, stress, cognitive style, medication adherence, social isolation) **interact with** genetic and other **biological risks factors at a particular time** in the pathogenesis of illness?
- Can patients be saved from the progression toward chronic psychosis and deterioration?

# Schizophrenia Clinical Course

“staging” (Patrick McGorry)

Progression from prodromal to the first psychotic episode to chronic psychosis and cognitive and social deterioration (stages)



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- Can patients be saved from the progression toward chronic psychosis and deterioration?

- **Is neurobiology different at different stages?**
- **Can we relate biological change to stage of illness?** (like in cancer or drug addiction)

### **Implications for treatment:**

- treat current symptoms
- treat to prevent progression to more advance stages
- treat to regress to previous stage

# SCHIZOPHRENIA

## Some questions

What happens in the brain of these youngsters?

Why some of them get trapped in disease and some not?

Is it because of **genetics**? à ex. **COMT** ?

Is it because of education or **environment** à ex. **Stress / drugs ...**

What is exactly going on inside schizophrenic brain? à ex. **Sensitization**

And above all, can we prevent it? à **Treatment** à **typical / atypical**

Is it at all possible to cure? At present, what do we know? à **Clozapine?**

## What we know:

- Many of the **genetic polymorphisms** involved to a different degree in etiology (neuregulin 1, dysbindin, DISC1, DAOA, DAAO, COMT, DRD2, ANKK1, SLC6A3 ...)
- Many of the **Risk factors** that increase an individual vulnerability to develop schizophrenia (prenatal, perinatal and postnatal)
- Many **estructural and functional brain anomalies** (prefrontal cortex, temporal lobes, límbic estructuras, talhamus, basal ganglia, cerebellum)
- Some **circuits involved** in abnormal brain functioning
- **Neurotransmitters** systems involved (glutamate, GABA, dopamine ...)
- We start to know that not only **neurones** but also **glial cells** are involved in pathogenesis.

### Once disease starts, today we know:

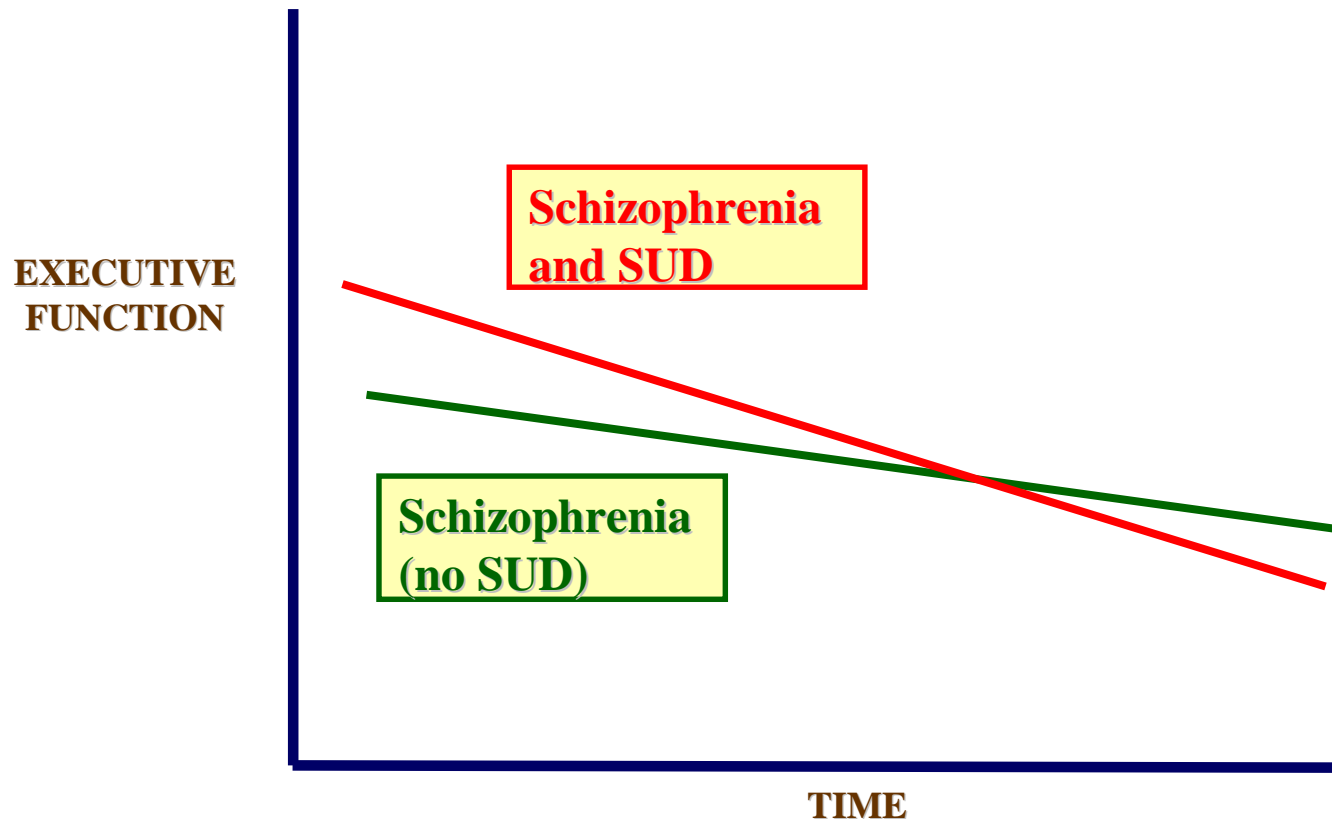
Once started, **the main factor for disease to continue, to progress to chronic and to worsen is disease itself.** That is to say: psychosis is toxic.

**Psychotic activity and episodes → dopamine sensitization → progressive deterioration**

Thus we know that there is no doubt that **antipsychotic treatment must start as soon as possible** in order to prevent or shorten psychosis toxic effect → better evolution

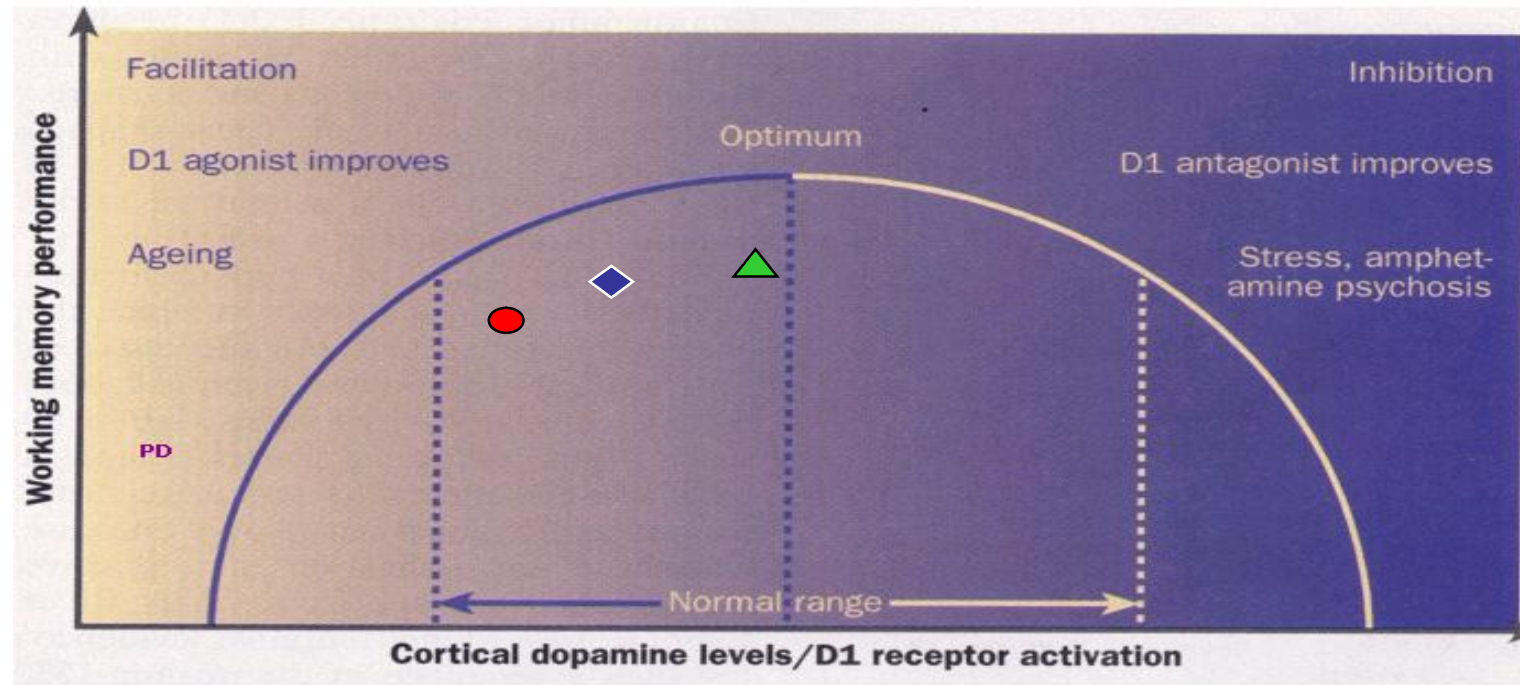
We have available **a large arsenal of therapeutic remedies** to treat psychosis.

**Cognitive decline cardinal symptom of schizophrenia**  
**Related to severity and chronicity and deterioration**  
**It depends on prefrontal dopamine activity**



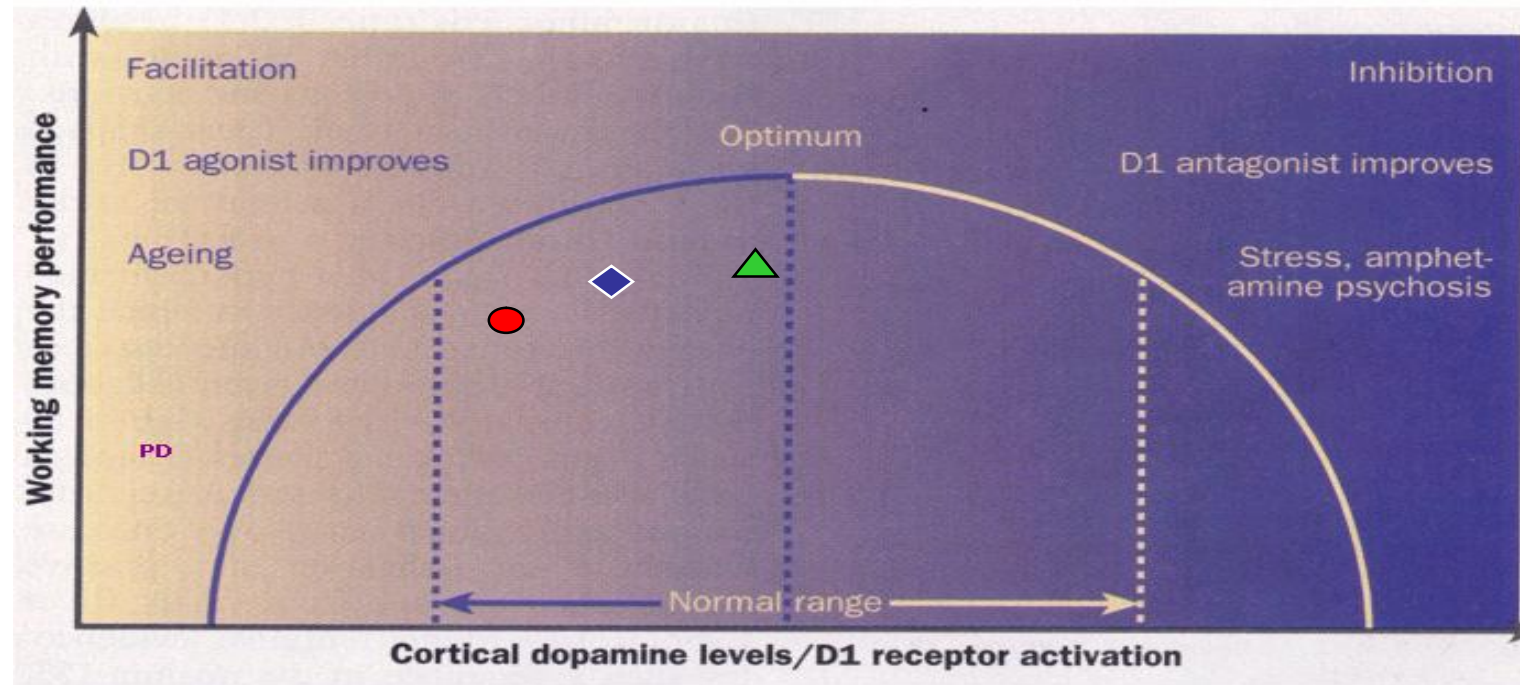
# Prefrontal Dopamine Activity and Cognitive Performance

COMT gene as an example of protection polymorphisms and as an example of gene-environment interaction



# Prefrontal Dopamine Activity and Cognitive Performance

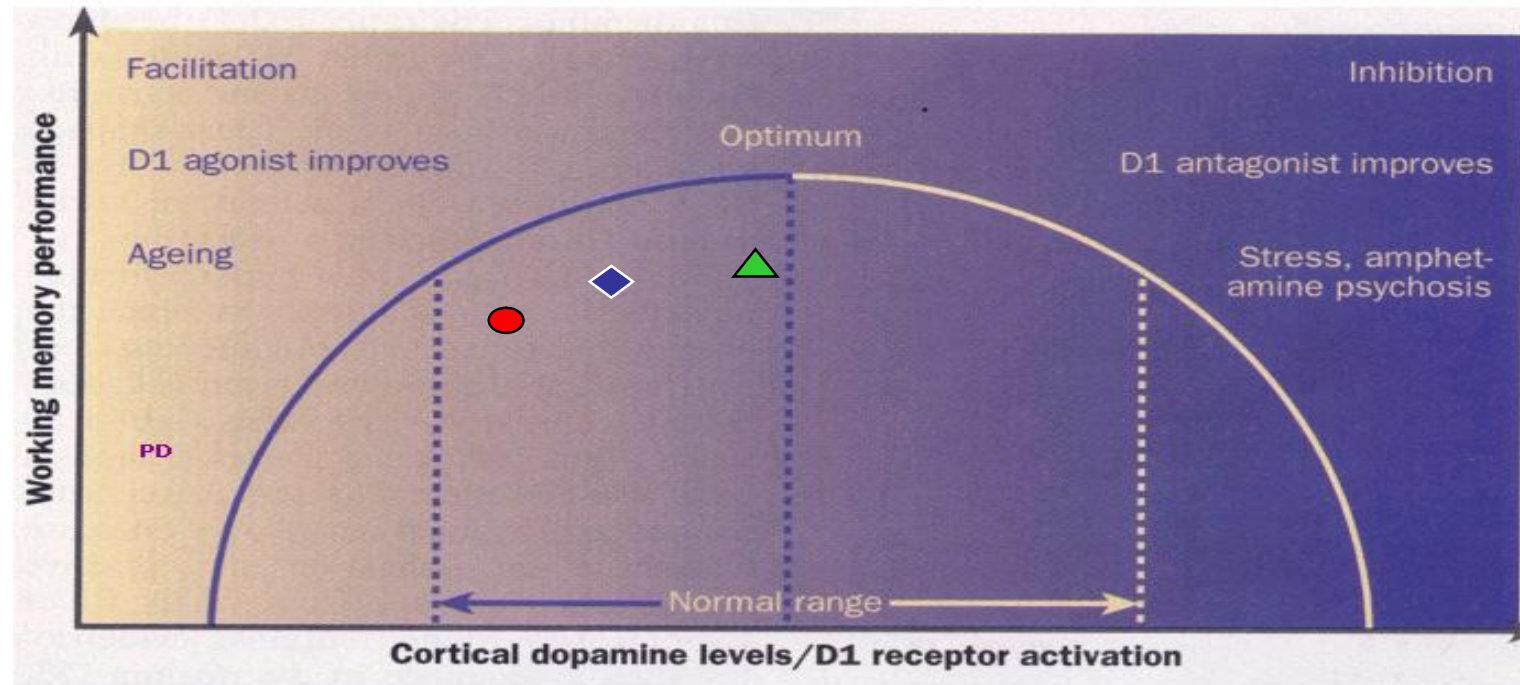
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COMT → dopamine metabolism → ↓dopamine → prefrontal DA activity control

# Prefrontal Dopamine Activity and Cognitive Performance

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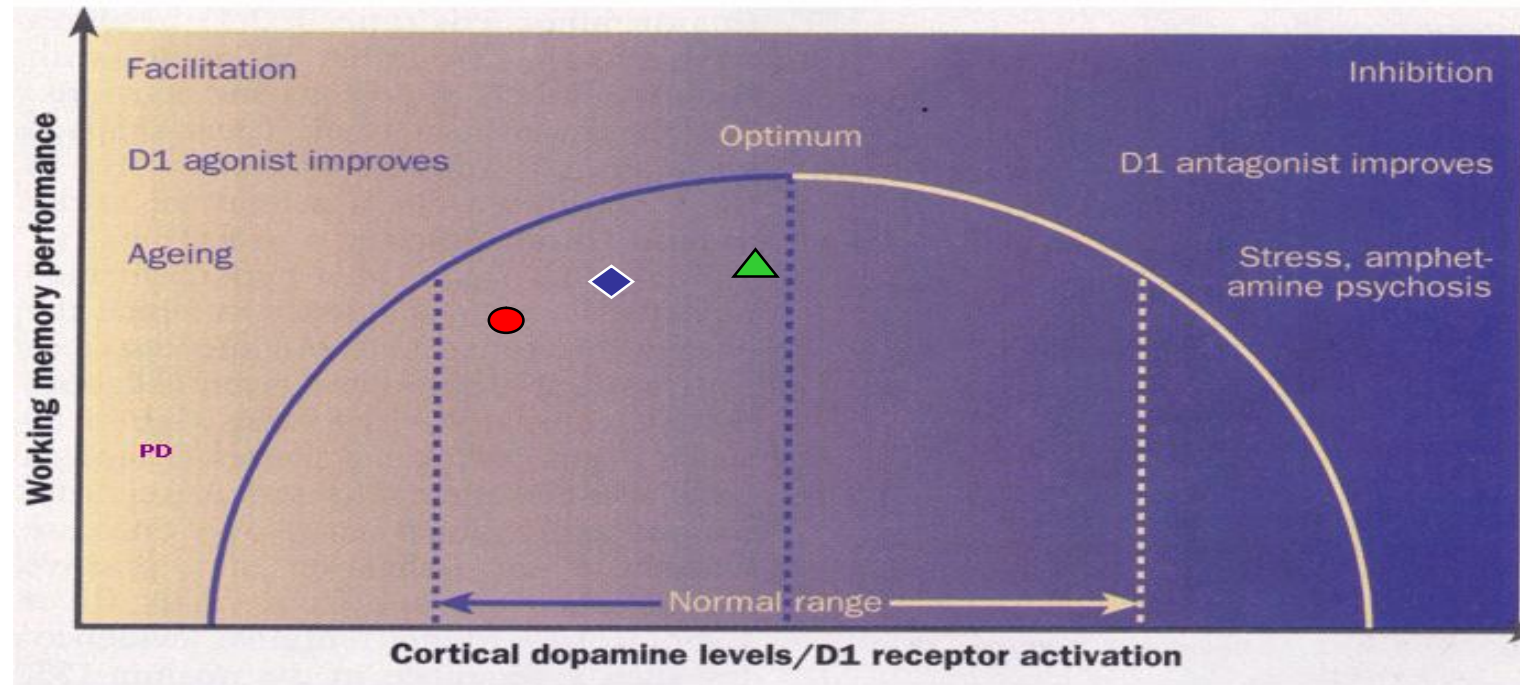
COMT → dopamine metabolism → ↓ dopamine → prefrontal DA activity control

Three genetic variants of **COMT** gene (polymorphisms Val108/158Met)

- Val-Val → less prefrontal dopamine ●
- Met-Met → more prefrontal dopamine ▲
- Val-Met → intermediate prefrontal DA ◆

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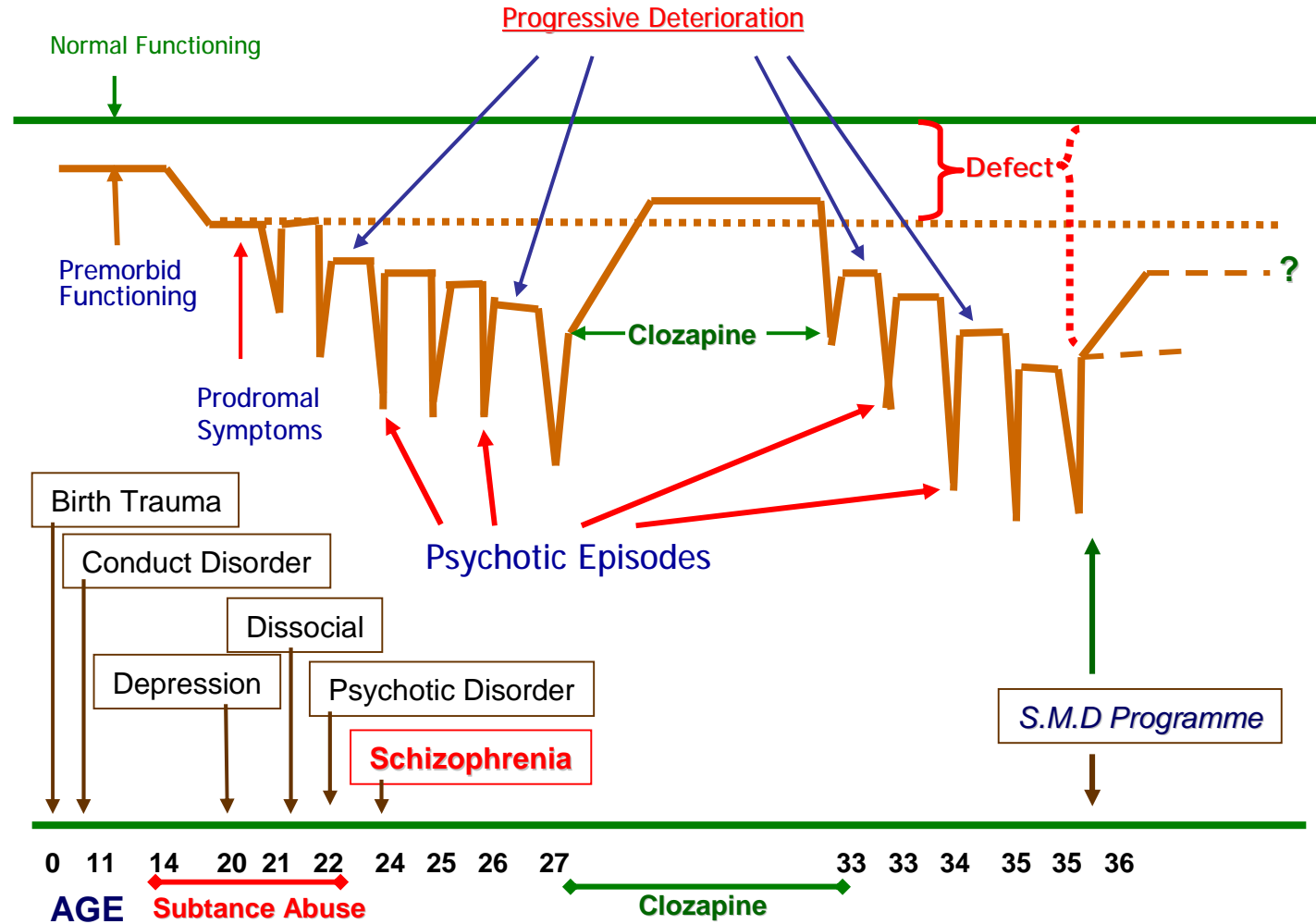
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Gene **COMT** associated to →

Schizophrenia  
Response to drugs in at risk individuals  
Response to stress in at risk individuals

→ **Stages:** from etiology to chronicity and deterioration



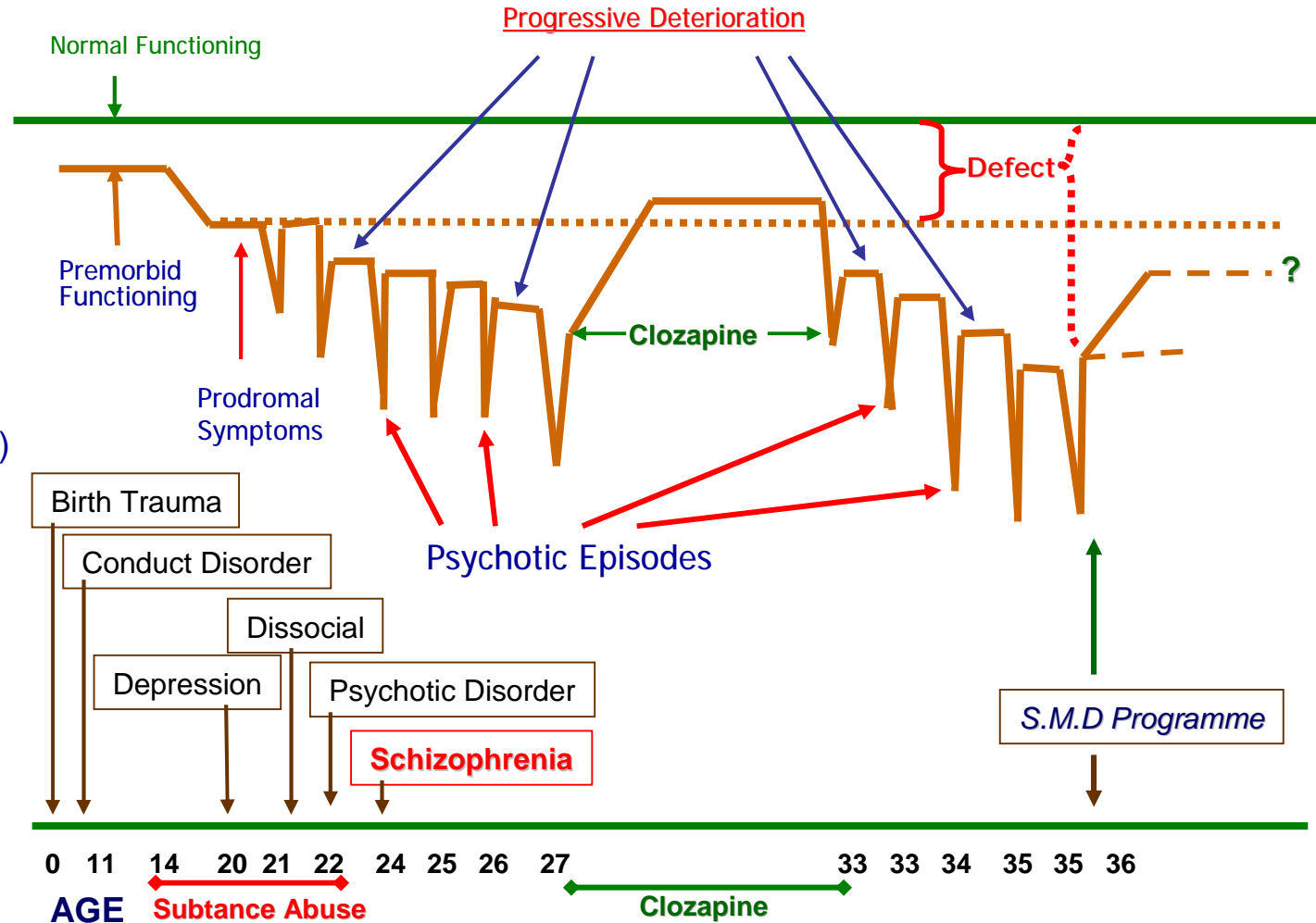
# Patient J.H.O.

## Back to our patient

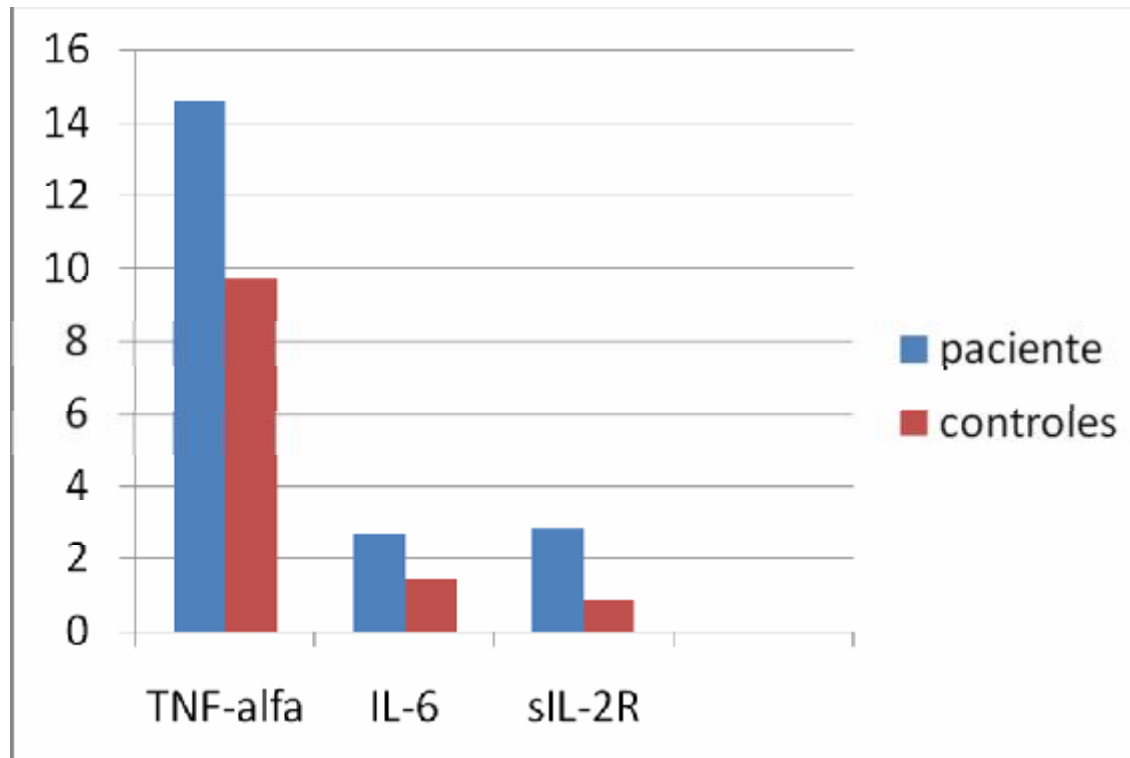
→ **Stages:** from etiology to chronicity and deterioration

### KEY ISSUES:

- Genetics (heredability)
- Environment
  - Perinatal
  - Stress sensitivity
  - Drugs sensitivity
- Early onset (adolescence)
- Cognitive decline
- Abnormal cognition
- Bizarre behaviour
- Heterogeneity
- Episodes along course
- Progressive chronicity
  - à defect
- Partial response to tx.
- Treatment resistance
- Clozapine

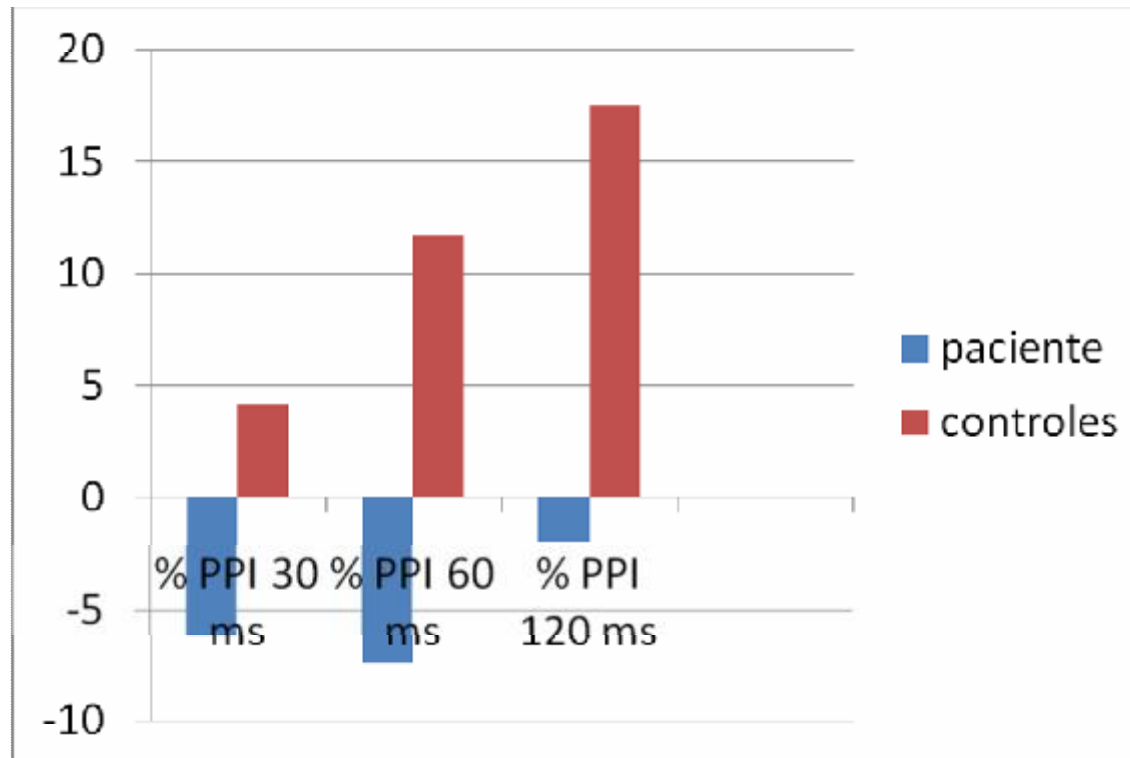


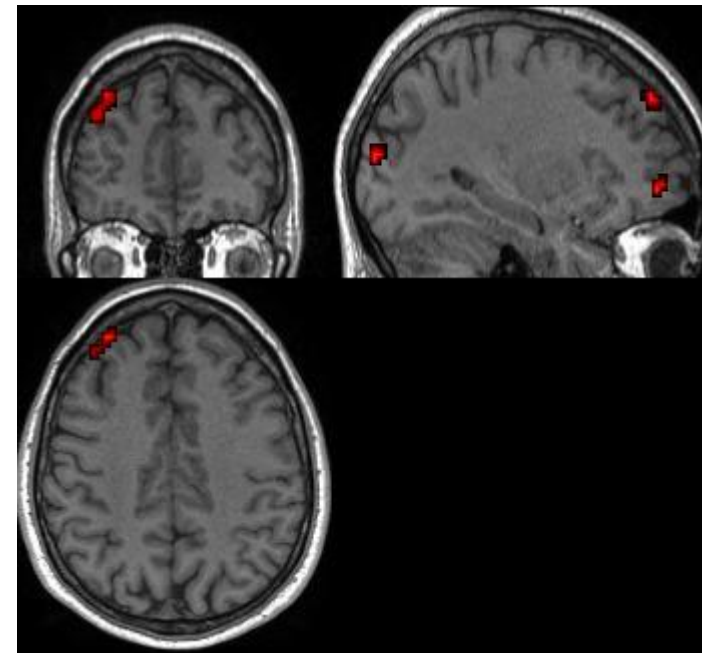
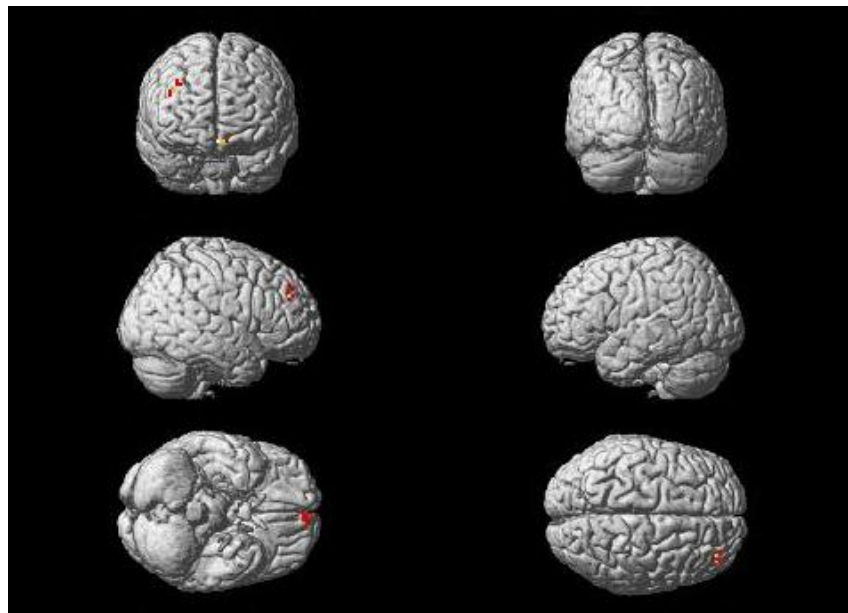
Citoquinas



# Cinical case

## Prepulse inhibition





**2-back FDR05 10c:** Durante tarea 2-back, FDR (más restrictivo que sin corrección)  $p < 0.05$ , clusters a partir de 10 vóxeles: Giro frontal medio izquierdo (BA 11).

## Jefe del Grupo: Tomás Palomo



Unidad de conductas  
adictivas y patología dual  
Miguel Ángel Jiménez-Arriero  
Guillermo Ponce  
Roberto Rodríguez-Jiménez  
María Aragüés  
Alexandra Bagny  
Javier Ballester  
Pilar Cano  
Justo Díez  
Pedro Holgado  
Isabel Martínez  
María Jesús Muñiz  
Javier Rodríguez-Torresano  
Gabriel Rubio  
Santiago Vega  
Iluminada Rubio

Laboratorio de Genética:  
Janet Hoenicka

Facultad de Medicina  
José Antonio Ramos

Hospital Cuenca:  
Jose Luis Santos  
Clara Villanueva  
Hospital Guadalajara:  
Eva M Sánchez Morla

Becarios pre-doctorales:  
Cristina García  
Laura España  
Rosa Jurado  
Alejandra Koencke  
Natalia Martín Suñé  
Diana Taboada

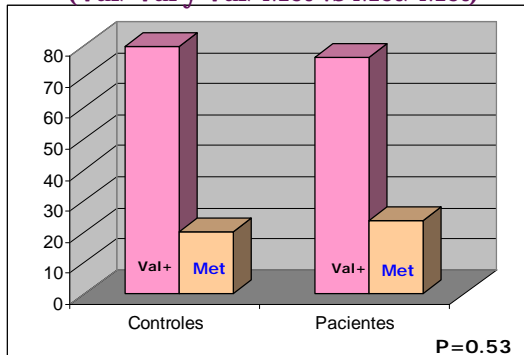
Facultad de Psicología  
Evelio Huertas

Soporte Técnico:  
Carmen Aguirre

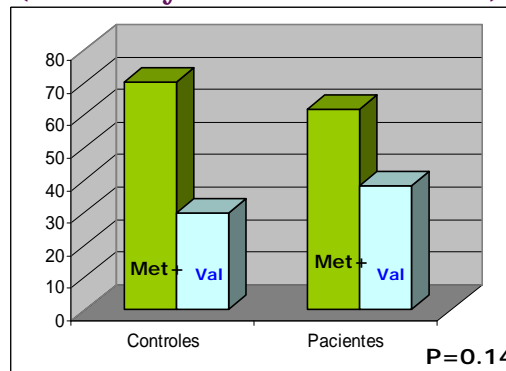
Servicio de Bioquímica:  
Natalia Suñé

El genotipo heterocigoto para el polimorfismo G674A (Val108/158Met) del gen *COMT*, presenta una disminución significativa en los pacientes españoles con esquizofrenia

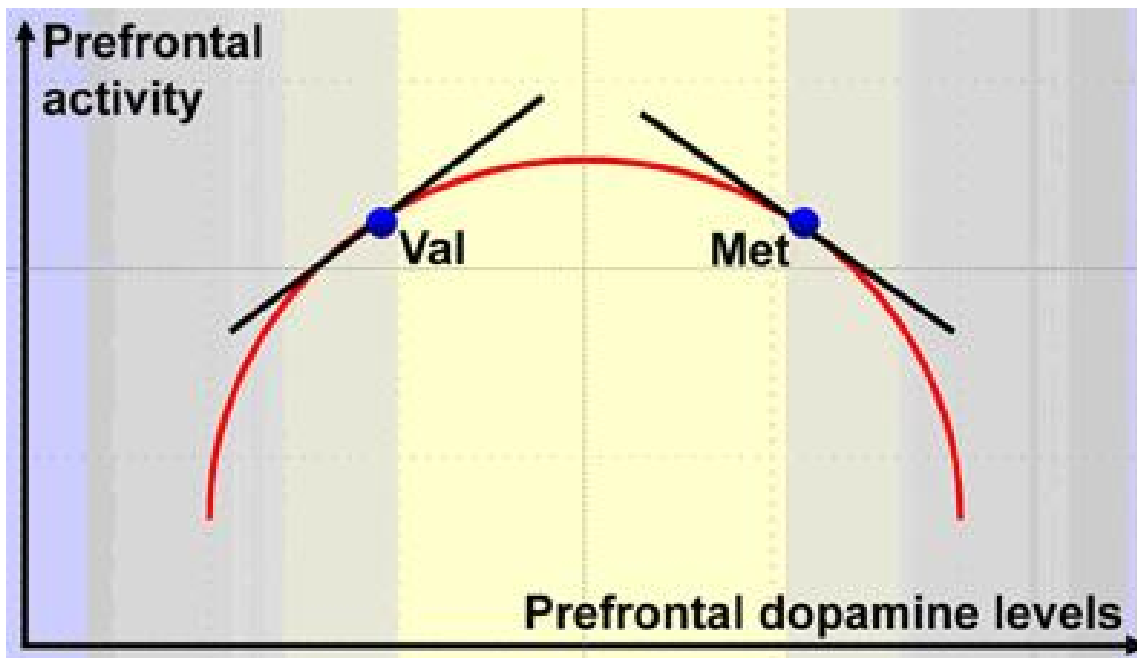
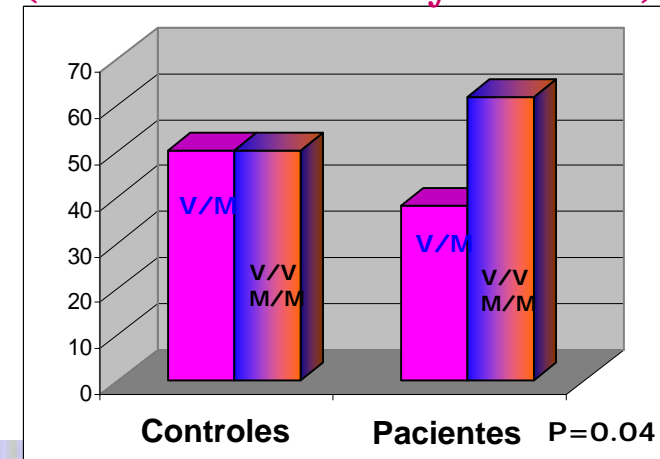
**Dominante**  
 (Val/Val y Val/Met vs Met/Met)



**Recesivo**  
 (Val/Met y Met/Met vs Val/Val)



**Heterosis**  
 (Val/Met vs Val/Val y Met/Met)



- Niveles intermedios de DA funcionalidad óptima para la CPf.
- Podría constituir un factor de protección para estos trastornos.

## CLOZAPINA (Neuroimagen)

- La **clozapina**, produce cambios cerebrales estructurales y funcionales **diferentes** a los producidos por los antipsicóticos típicos y atípicos.
- En la esquizofrenia, los **déficits** de volumen cortical asociados al progreso de la enfermedad pueden ser, al menos, parcialmente **reversibles** à potencial de aumentar la sustancia gris
- **clozapina en población resistente**: Relación directa entre la mejoría de sintomatología resistente y volumen de **materia gris** temporal
- Urgente estudiar efectos en **primeros brotes**

