Granollers , 18 de novembre de 2010
Centre de Medicina Avançada del Vallès

El cervell humà i la seva modulació per la interacció dels gens i les experiències vitals

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Universitat de Barcelona

Institut de Biomedicina de la UB (IBUB)

La malaltia mental no és aliena a la condició humana

PLASTICITY

Environment

BEHAVIOUR

Genes

By an apparent contradiction, *human brain maintains its stability only if it is* excitable and capable of modifying itself according to external stimuli, and adjusting its response to the stimulation.
In a sense, human brain is stable because it is modifiable

W.B. Cannon, 1929

Evolutive process- History of our genes

The recent origin of *Homo sapiens sapiens*
(200.000 years b.p.)

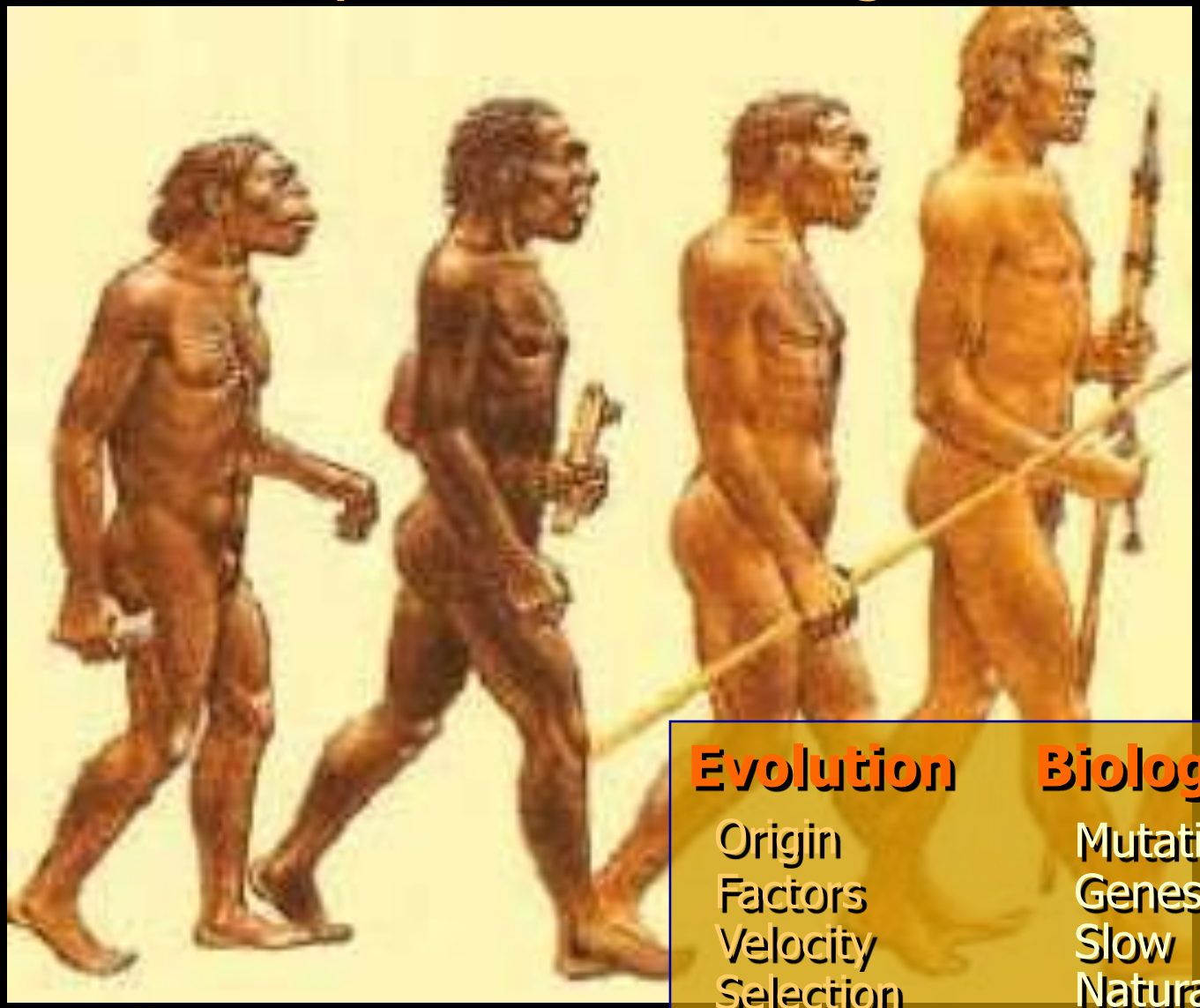
Origin of *Homo* (~2.10^6 y)

Origin of Hominids (~5.10^6 y)

(~6.10^6 y)

Chimpanzees

The history of human lineage



Evolution	Biological	Cultural
Origin	Mutation	Invention
Factors	Genes	Culture
Velocity	Slow	Fast
Selection	Natural	Social
Sense	Random	Deliberate
Results	"Hominize"	"Humanize"

Els reptes socials han constituit el factor selectiu més important a favor de l'evolució del nostre cervell

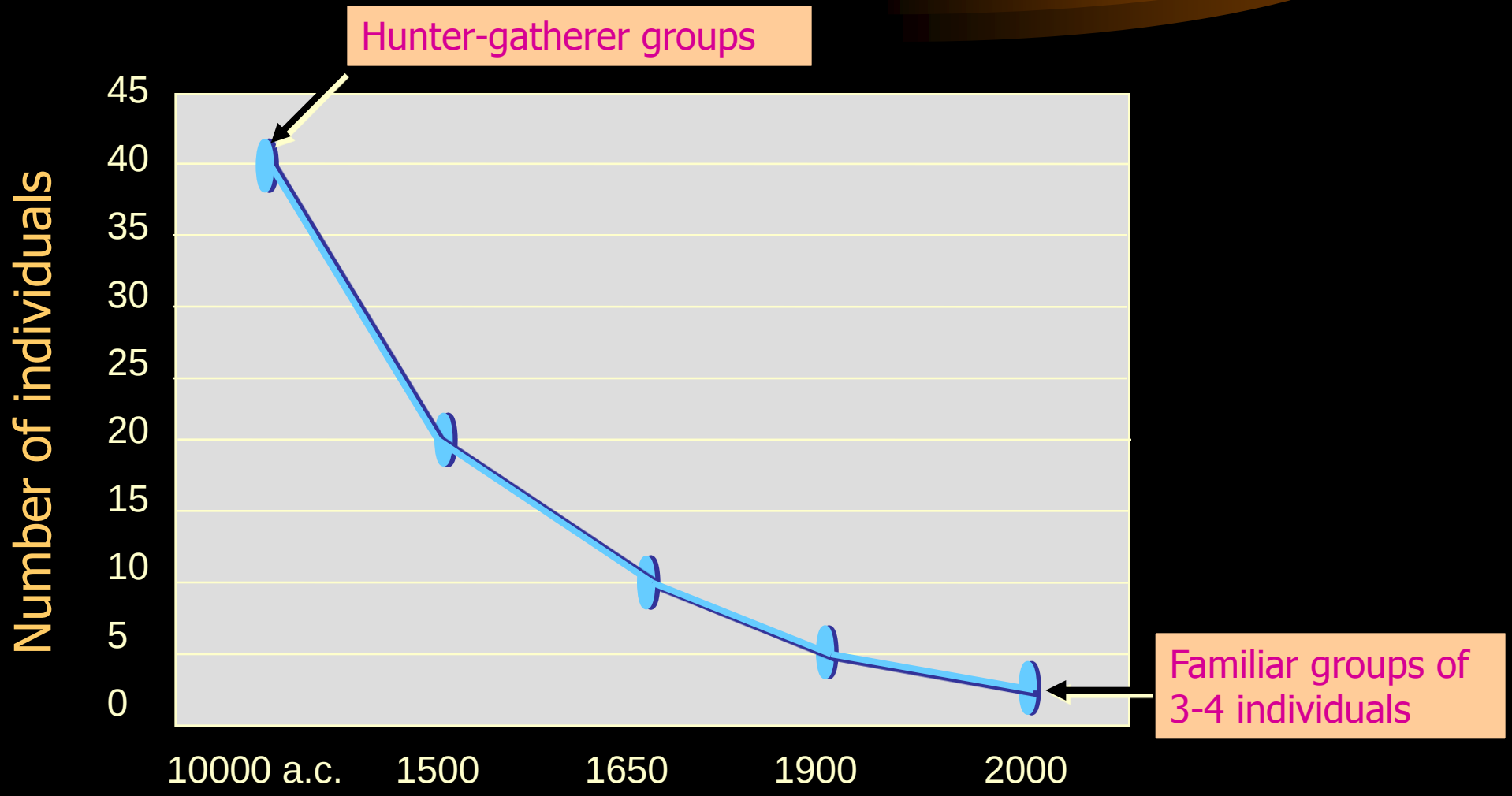
By the sea at Klaises River Mouth in South Africa, 100.000 years ago

MODERN HUMANS HISTORY

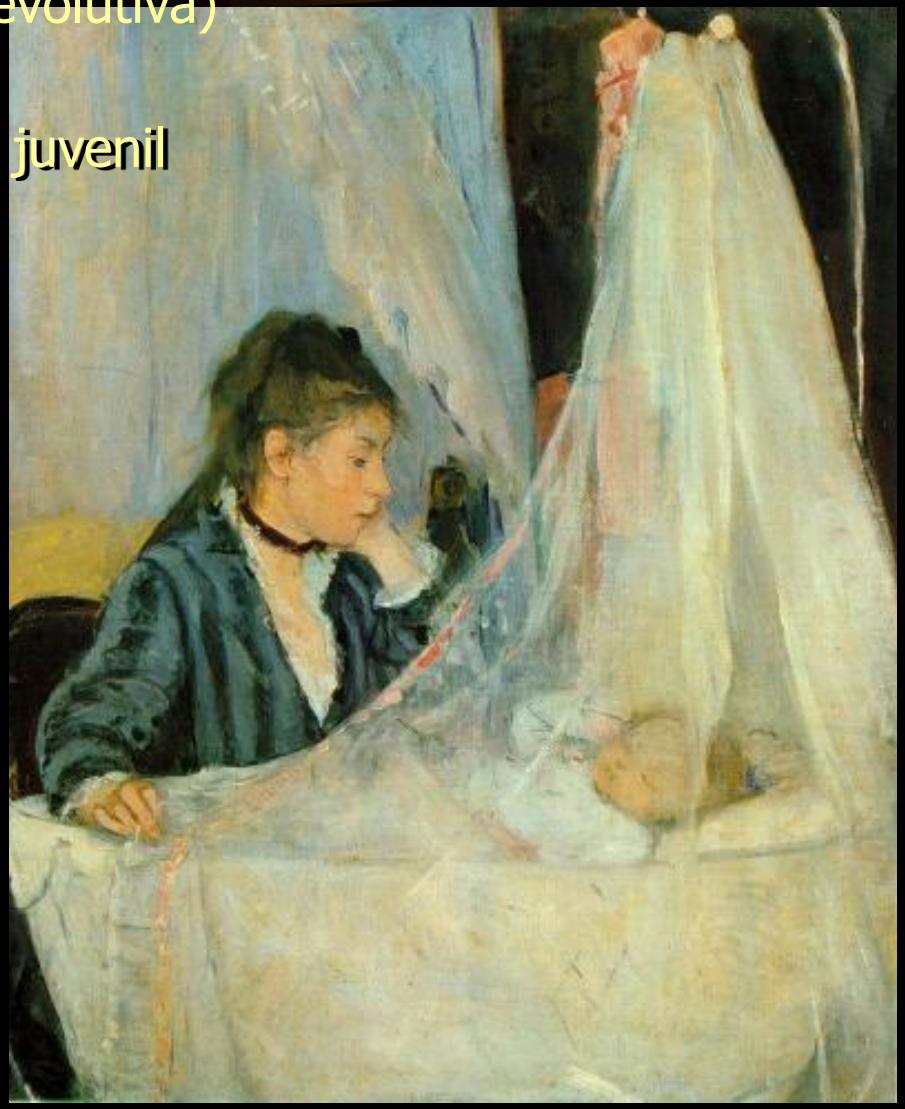
100.000 years 40.000 years 10.000 years Present

PALEOLITHIC NEOLITHIC

From Neolithic to now: Evolution of the group living



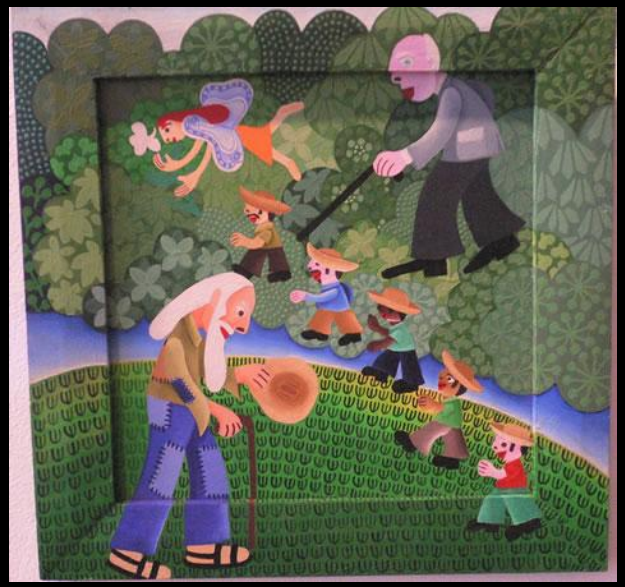
- ✓ Major immaduresa cerebral en el nounat humà que en qualsevol altre primat (estratègia evolutiva)
- ✓ Desenvolupament cerebral fins a l'edat juvenil



El neonat humà neix amb un desenvolupament neurològic insuficient per a adaptar-se activament al seu entorn i, per aquesta raó la seva maduració cerebral és un procés permanent i continu depenent alhora del vagatge genètic i de la informació i material posats a la seva disposició per l'ambient, especialment per la mare.

Marcelli i De Ajuriaguerra, 1996

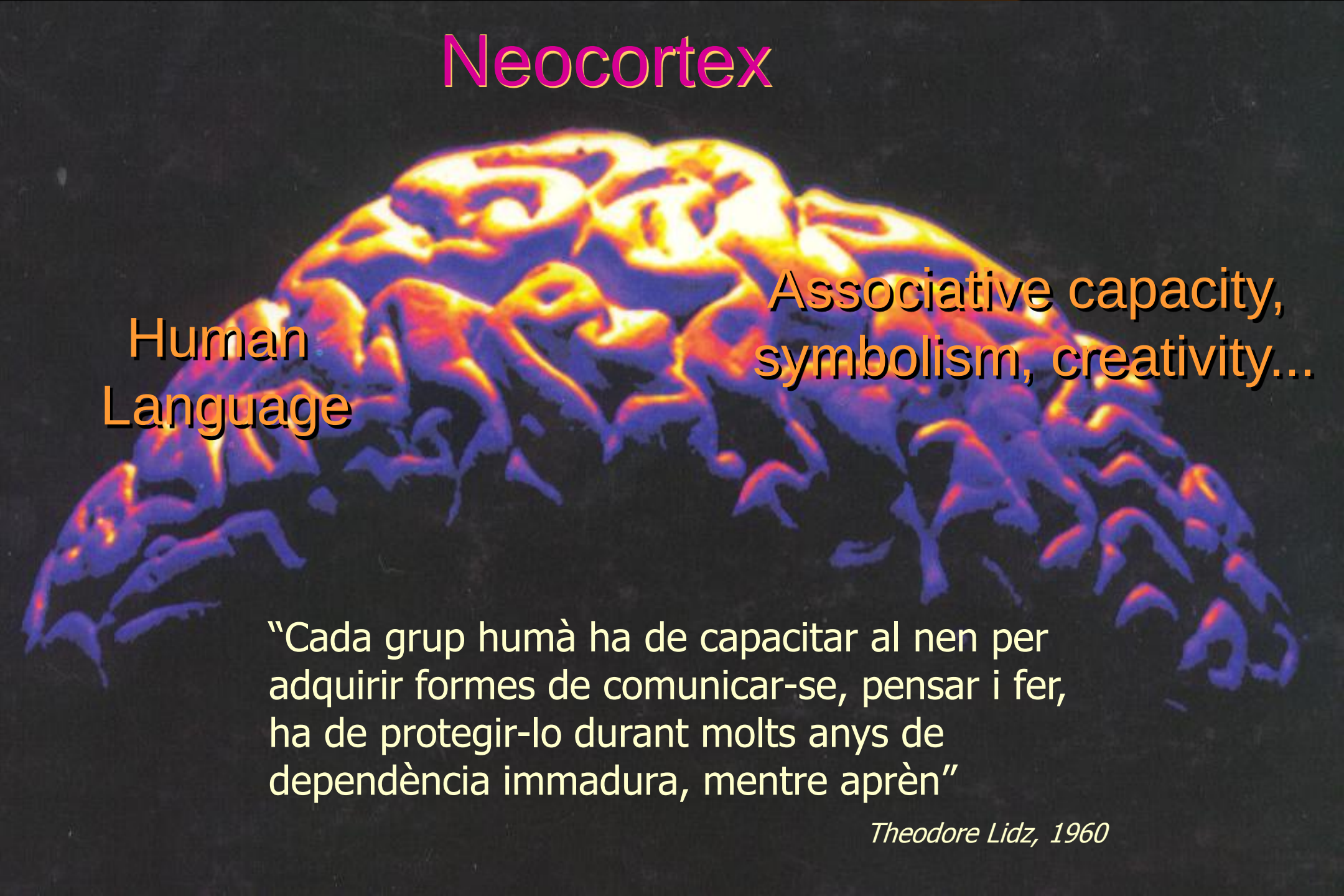
Manteniment de la parella reproductora (supervivència dels fills)



Major longevitat post-reproductora que qualsevol altra espècie (augment del període de contacte entre generacions)

Lahdenpera et al., 2004. Nature, 428

Neocortex



Human Language

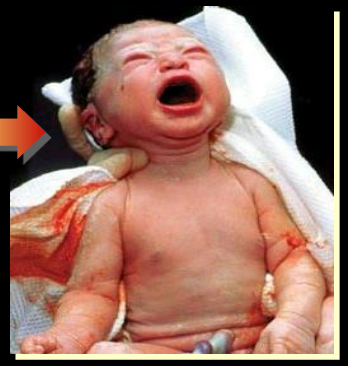
Associative capacity, symbolism, creativity...

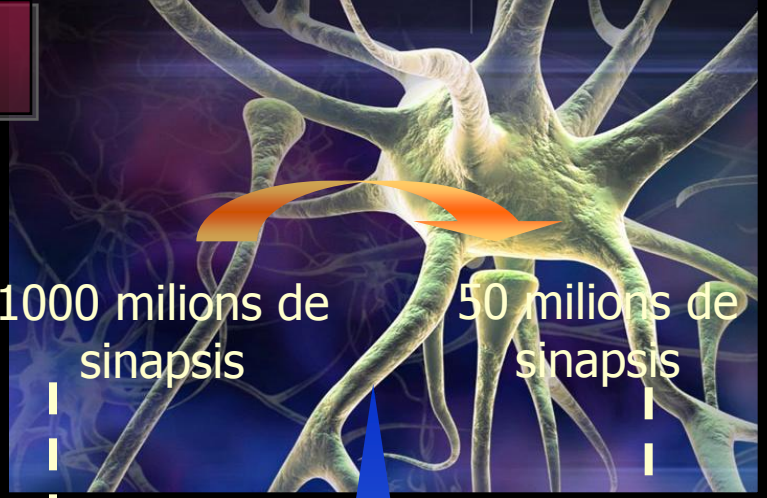
"Cada grup humà ha de capacitar al nen per adquirir formes de comunicar-se, pensar i fer, ha de protegir-lo durant molts anys de dependència immadura, mentre aprèn"

Theodore Lidz, 1960

FUNCIONS BÀSIQUES

~ 100.000 milions neurones x 10-50 cèl·lules glials





PRENATAL **INFANCIA I PUBERTAT**

NEUROGÈNESI

MIGRACIÓ

DIFERENCIACIÓ I ARBORITZACIÓ

APOPTOSI

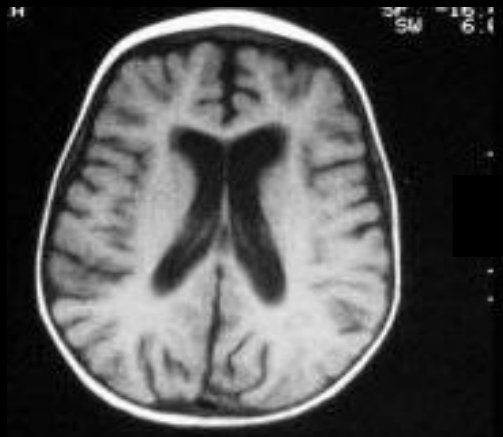
SINAPTOGÈNESI

MIELINITZACIÓ

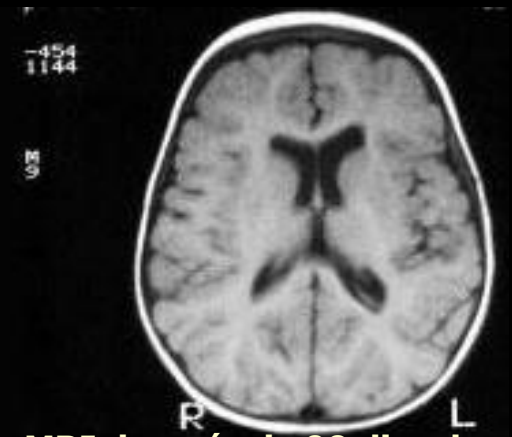
ELIMINACIÓ SINÀPTICA

G E N S A M B I E N T

- ✓ MALNUTRICIÓ
- ✓ NEGLIGÈNCIA



nen 14 mesos ingressat per malnutrició



MRI després de 90 dies de rehabilitació nutricional

Gunston 1992; Kar Mores and Wiley 1997; Phillips 2000

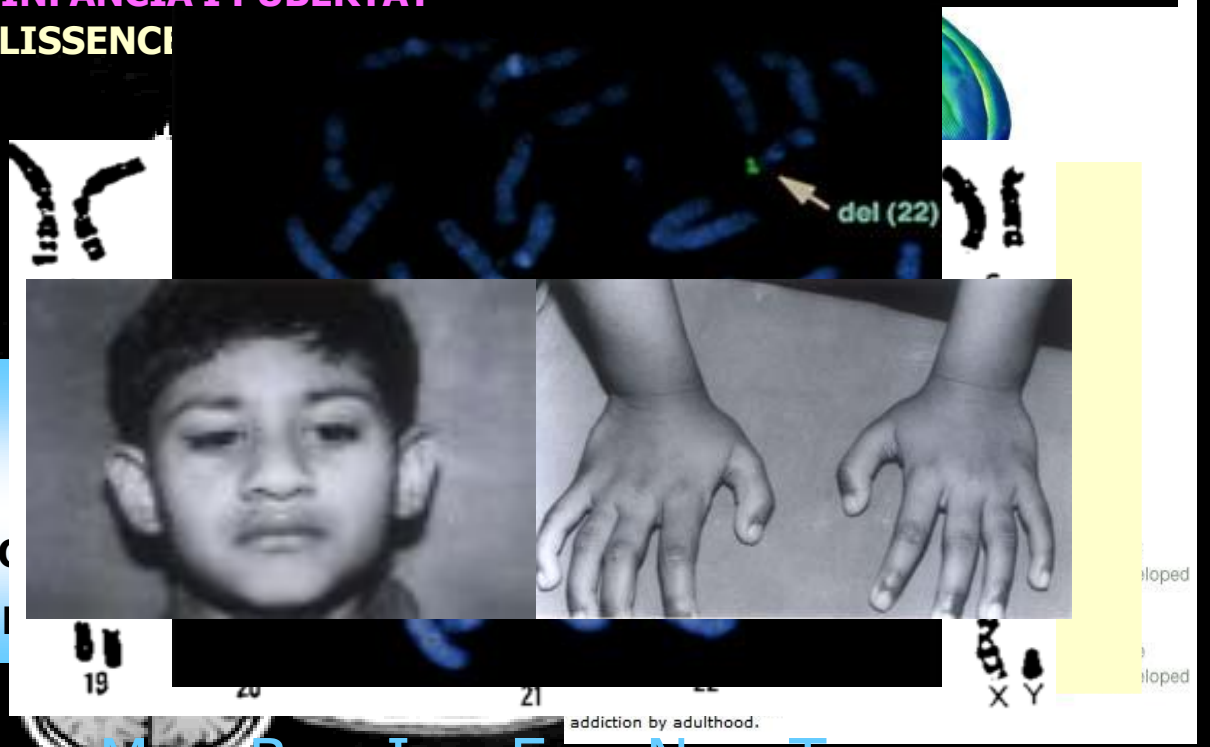
PRENATAL

- ✓ TRISOMIA 21
- ✓ DELECIÓ 22q11
- ✓ MUTACIÓ LIS-1 (17p13.3)

INFANCIA I PUBERTAT

LISSENCI

- ✓ INFECCIONS
- ✓ TÒXICS
- ✓ COMPLICACIÓ
- OBSTÈTRIQU



G E N S A M B I E N T

Gogtay 2004

Article

The Caregiving Environments Provided to Children by Depressed Mothers With or Without an Antisocial History

Julia Kim-Cohen, Ph.D.

Avshalom Caspi, Ph.D.

Michael Rutter, M.D., F.R.C.P.

Mónica Polo Tomás, M.Sc.

Terrie E. Moffitt, Ph.D.

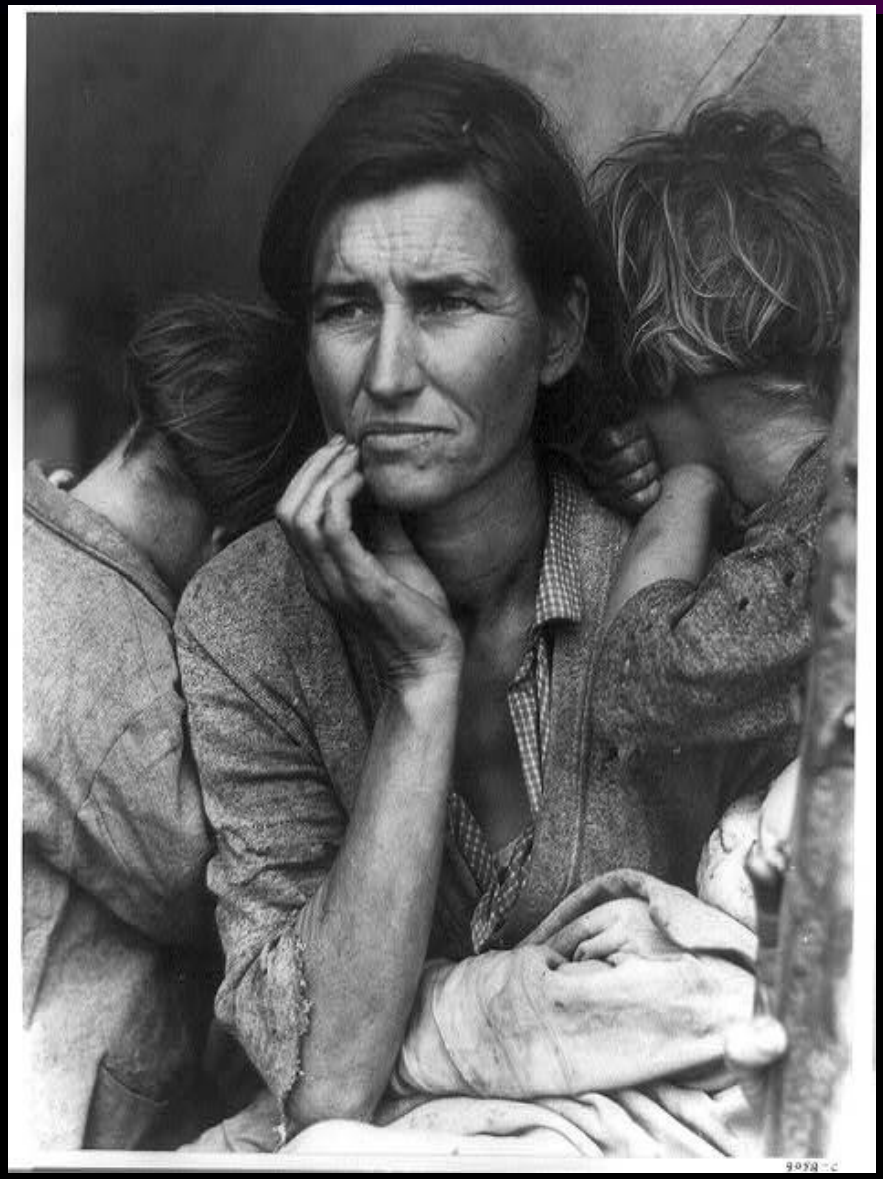
Objective: Many depressed women have a history of antisocial behavior, but research into maternal depression has not ascertained if this has implications for children of depressed mothers. This study compared the developmental outcomes in and caregiving environments provided to children by depressed mothers with or without an antisocial history.

Method: In the Environmental Risk Longitudinal Twin Study, a nationally representative study of 1,106 families, mothers were administered the Diagnostic Interview Schedule for Major Depressive Disorder and interviewed about their lifetime history of antisocial personality disorder symptoms. Mothers and teachers provided information regarding the children's behavior problems at 5 and 7 years of age. The authors assessed the quality of the caregiving environment through maternal reports and interviewer observations.

Results: Compared with children of mothers with depression only, the children of depressed and antisocial mothers had significantly higher levels of antisocial behavior and rates of DSM-IV conduct disorder, even after the authors controlled for numbers of symptoms and chronicity of maternal major depressive disorder. The children of depressed and antisocial mothers were at an elevated risk of experiencing multiple caregiving abuses, including physical maltreatment, high levels of maternal hostility, and exposure to domestic violence.

Conclusions: If one ignores the common co-occurrence of an antisocial history in depressed mothers, it may obscure the significantly elevated risks in children's development. Clinicians treating women's depression should be aware that children of depressed and antisocial mothers constitute a group at extremely high risk for early-onset psychopathology.

(Am J Psychiatry 2006; 163:1009–1018)



Durant la nostra avaluació, la Sra A no es va moure del llit. Es mostrava plorosa, tenia mal aspecte,semblava absent, fumava i renegava constantment.

El seu metge li havia prescrit antidepressius el darrer any, però ella havia considerat que no l'ajudaven, i va decidir no prendre'ls.

Va explicar que havia conegut el pare biològic dels seus fills quan tenia 19 anys en un centre de desintoxicació on tots dos hi anaven. El pare no s'havia quedat amb ella quan els bessons van néixer. Els nens (ara 7 anys) no passaven massa temps a l'apartament i solien voltar pel barri sense supervisió fins la nit. No obstant, els nens no tenien problemes a l'escola, i s'havien adaptat bé a l'ajuda que els oferia un treballador social que els visitava cada mes.

The Environmental Risk Longitudinal Twin Study (E-Risk)

AIM: The quality of the caregiving environment provided to children by depressed mothers (with or without antisocial history)

Sample:

1.106 famílies (mothers and their twins with same sex)

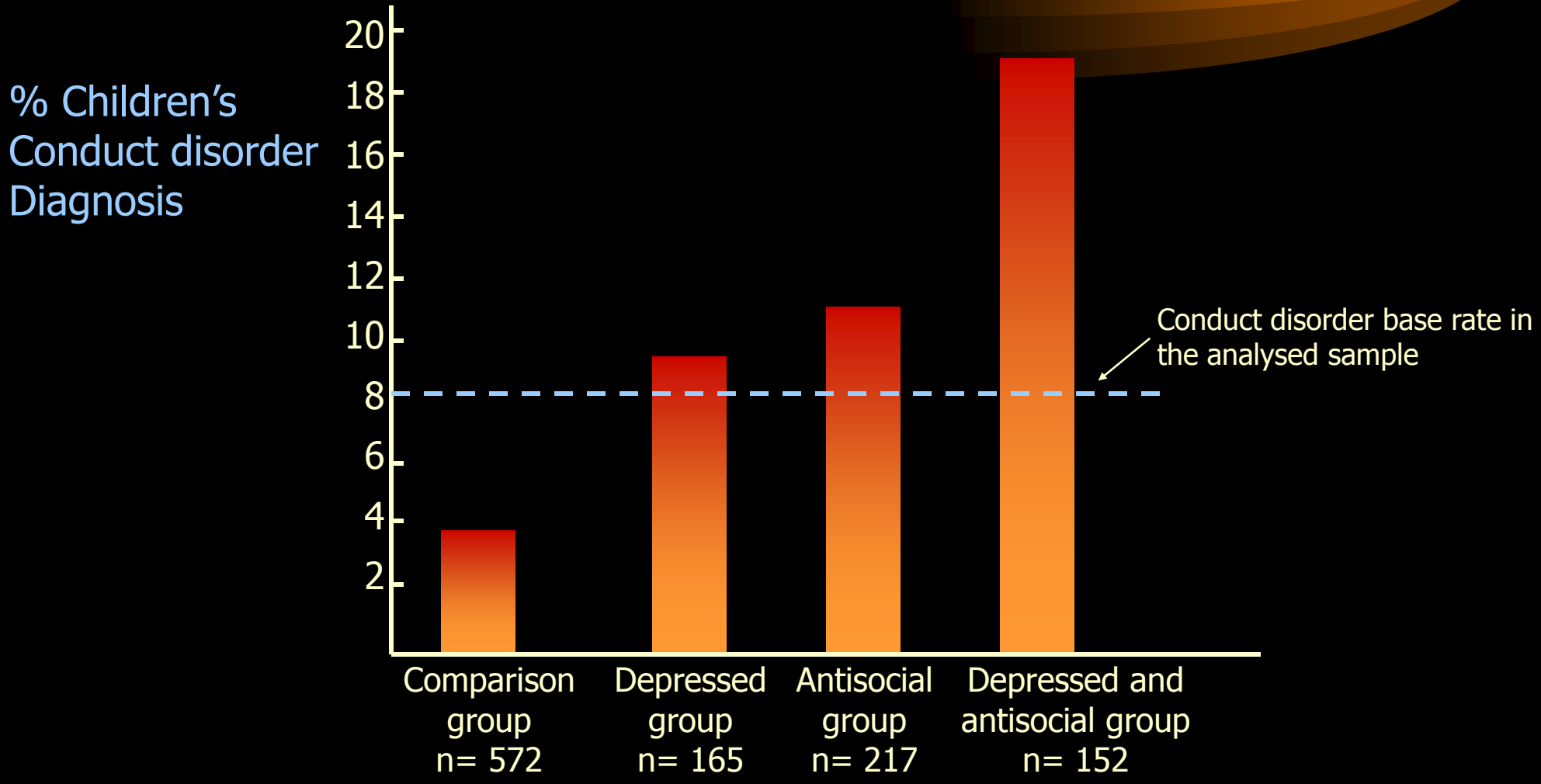
Mother assessment:

The Diagnostic interview Schedule for Major Depressive disorder and antisocial personality disorder symptoms

Children assessment:

Mothers and teachers provided information regarding children's behavior problems at 5 and 7 years old.

Prevalence of Children's conduct disorder Diagnosis Among Children of Depressed Mothers with and without Antisocial History



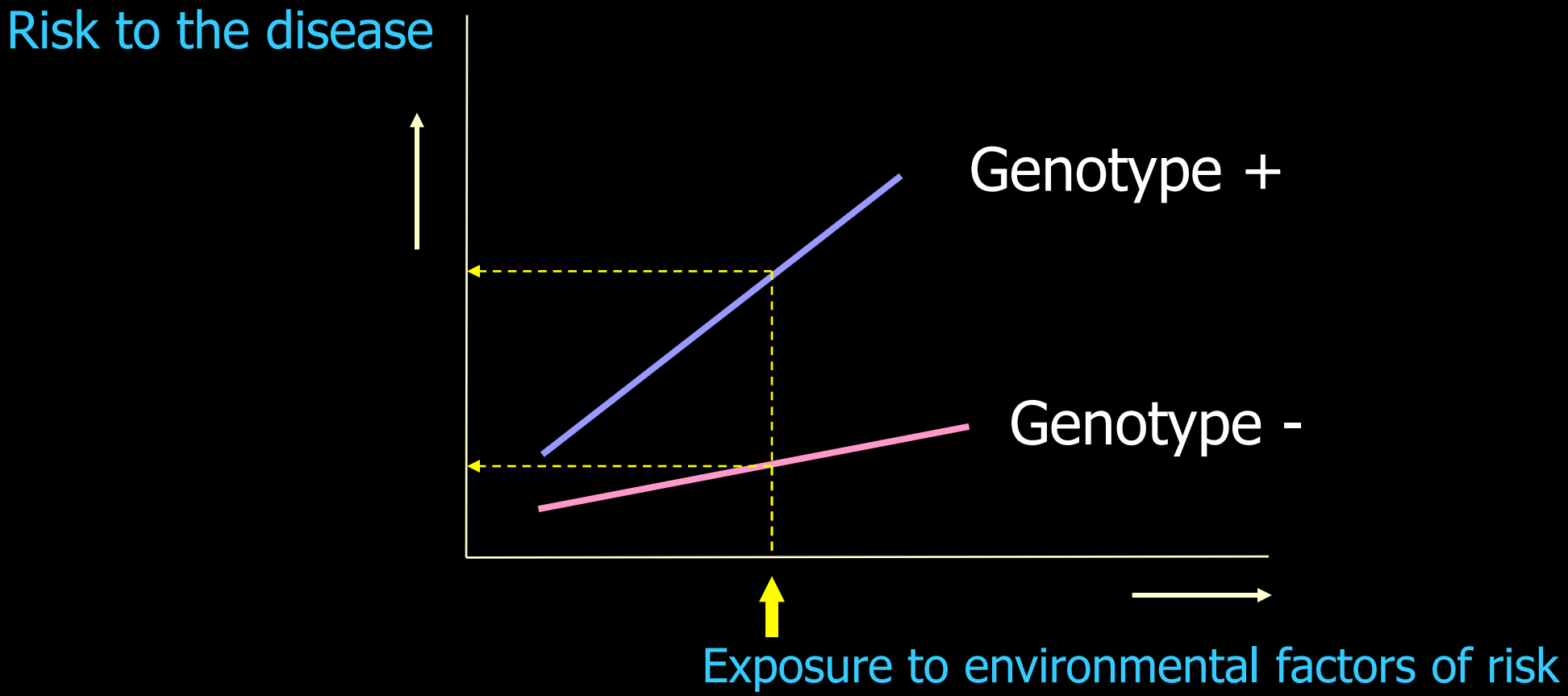
Kim-Cohen et al. Am J Psychiatry 163: 1009-1018

Vulnerable:

Susceptible de ser ferit o vulnerat, de prendre mal o perjudici de ser afectat, commogut, convençut o vençut per alguna cosa que s'expressa.

Gene-environment interaction (GxE):

(Genotypes are differentially sensitive to environmental influence)



Van Os and Marcelis 1998

DEPRESSIÓ MAJOR: Símptomes clínics

(DSM-IV, APA, 1994)

Emocionals

- Humor deprimit
- Poc interès o satisfacció en la majoria d'activitats

Somàtics

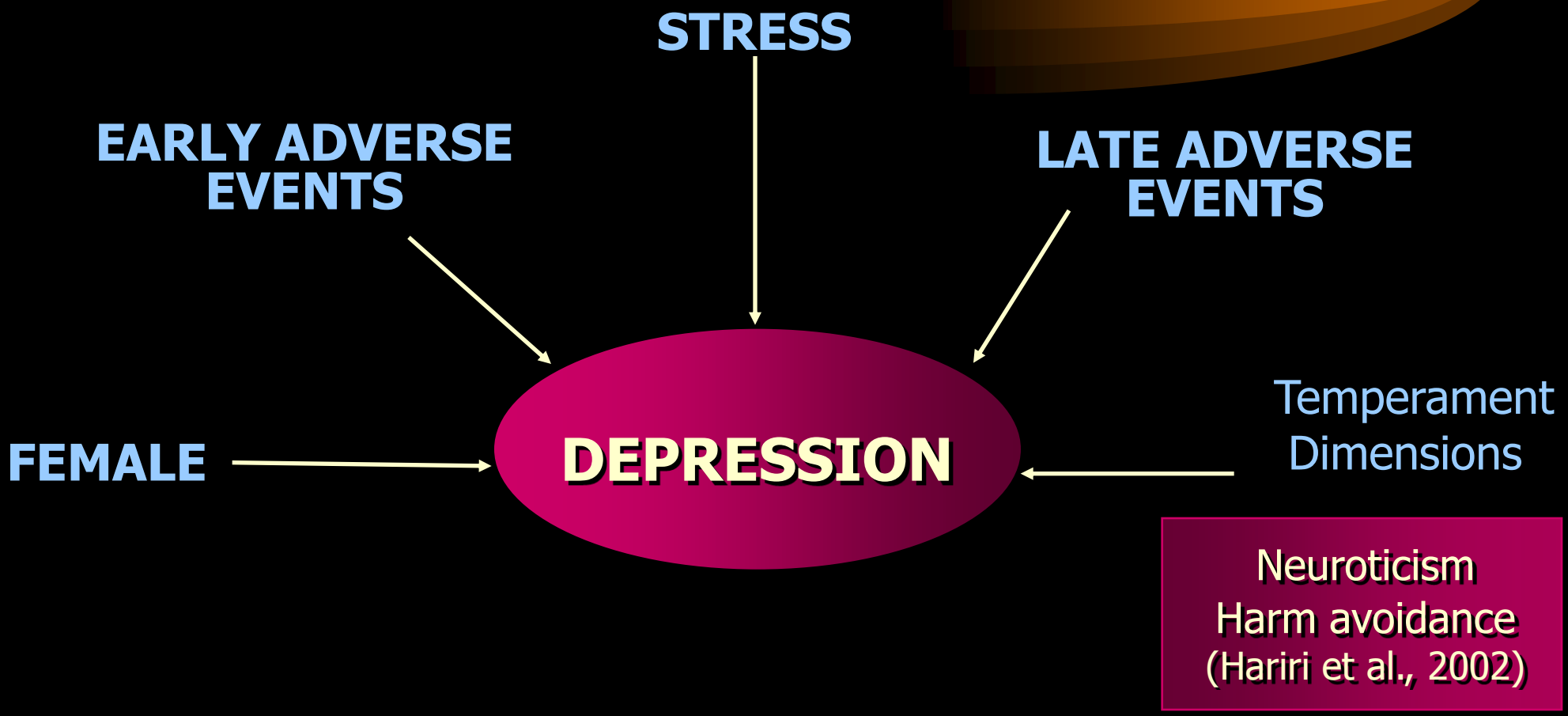
- Pèrdua o augment de pes, canvi de gana
- Insomni o hipersòmnia
- Moviments agitats o més lents
- Fatiga, cansament o pèrdua d'energia

Cognitius

- Sentimients d'infravaloració o de culpabilitat excessiva
- Menor capacitat de pensar o concentrar-se
- Pensaments recurrents de mort o suicidi

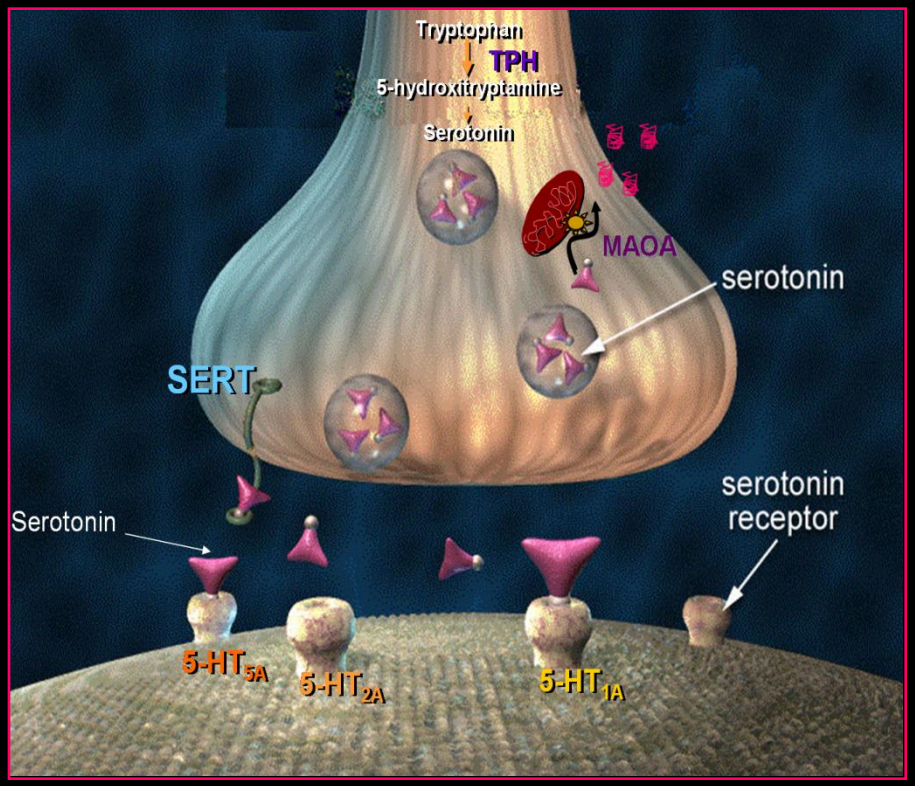
* Aquests símptomes han de ser presents cada dia al menys durant dues setmanes

Risk factors for depression

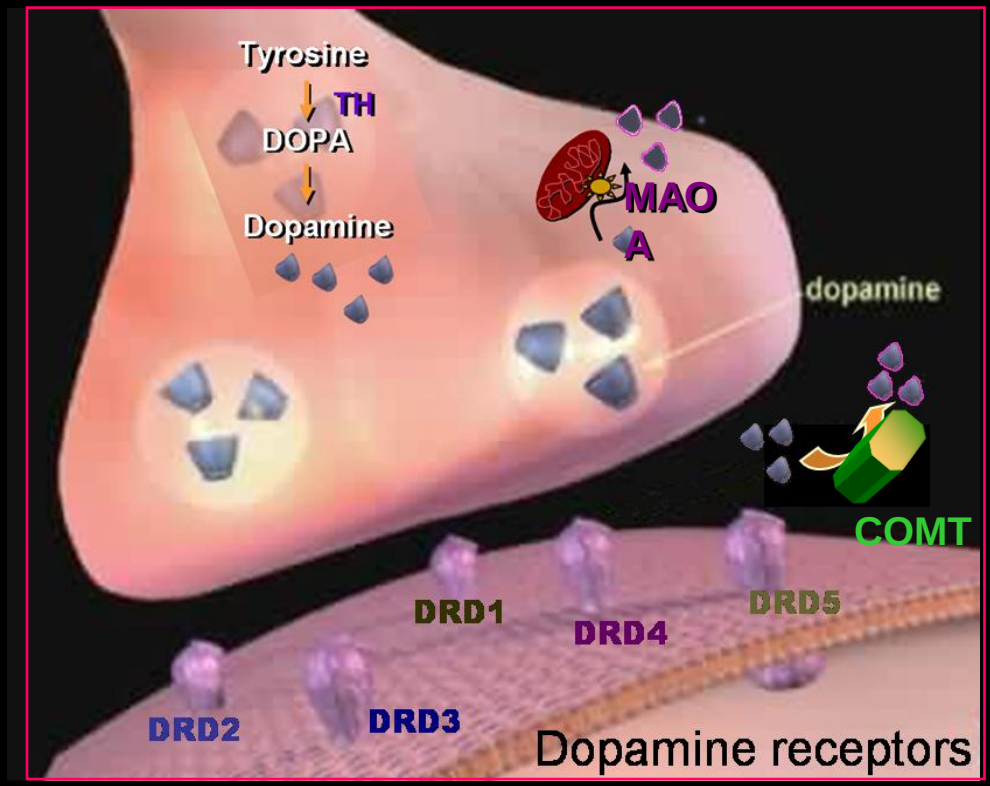


Most of the GxE studies have focused on polymorphisms in MAOA and 5-HTT

Serotonin Neurotransmission



Dopamine Neurotransmission

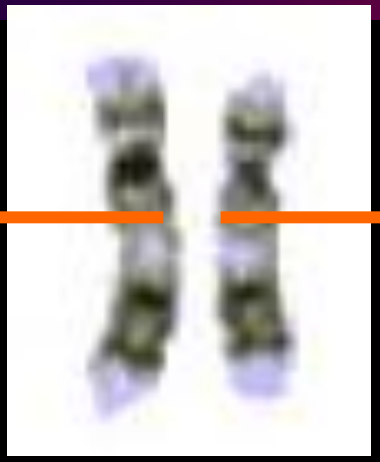


Two principal genes implicated in early brain maturation and the regulation of mood, behavior, and stress response

Serotonin transporter (5-HTT o SERT)

Cr. 17 materno

Cr. 17q12



Cr. 17 paterno

Cr. 17q12

Allele variants

L **S**

Genotype variants

L/L L/S S/S

L S

5-HTT

5′ Promoter 3′

5′ Promoter 3′

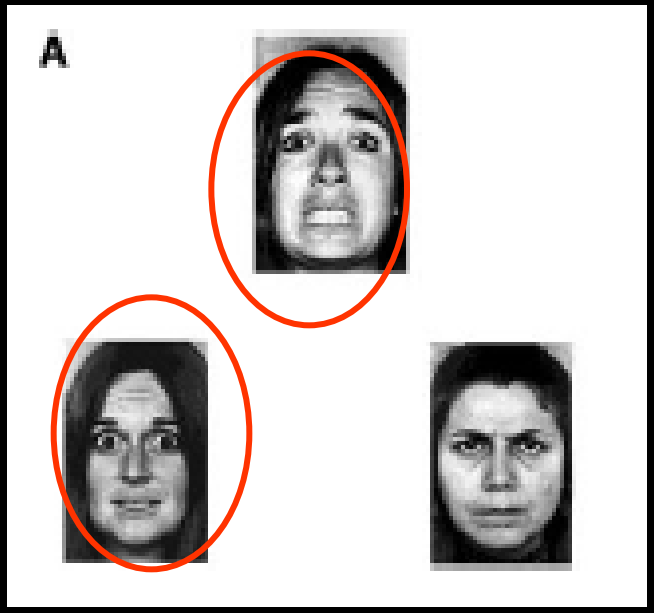
L S

Short allele (S) has been related to low expression and function (Heils et al., 1997) and increased fear and anxiety

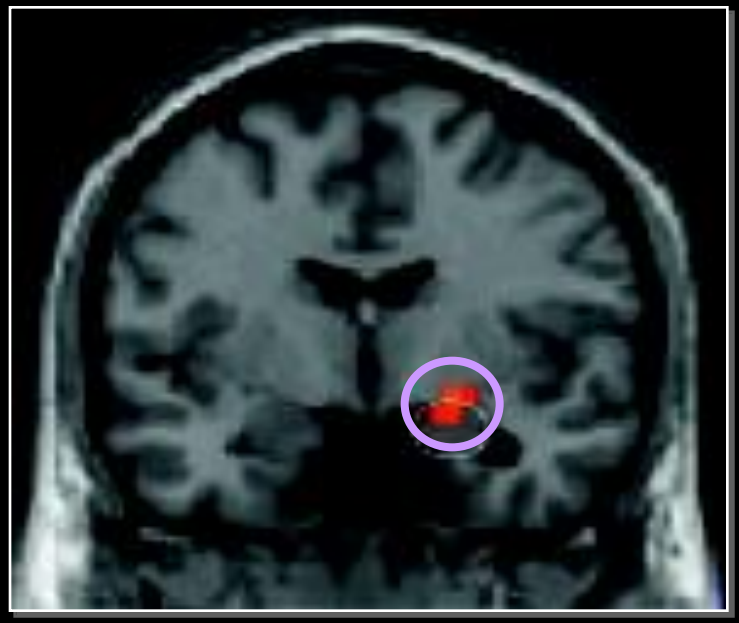
Serotonin transporter (5-HTT) genetic variation and the response of the human amygdala.

Hariri, AR, Mattay, VS, Tessitore, A, Kolachana, B, Fera, F, Goldman, D, Egan, MF, Weinberger, DR. **Science, 2002,** 297: 789-796.

EMOTION TASK



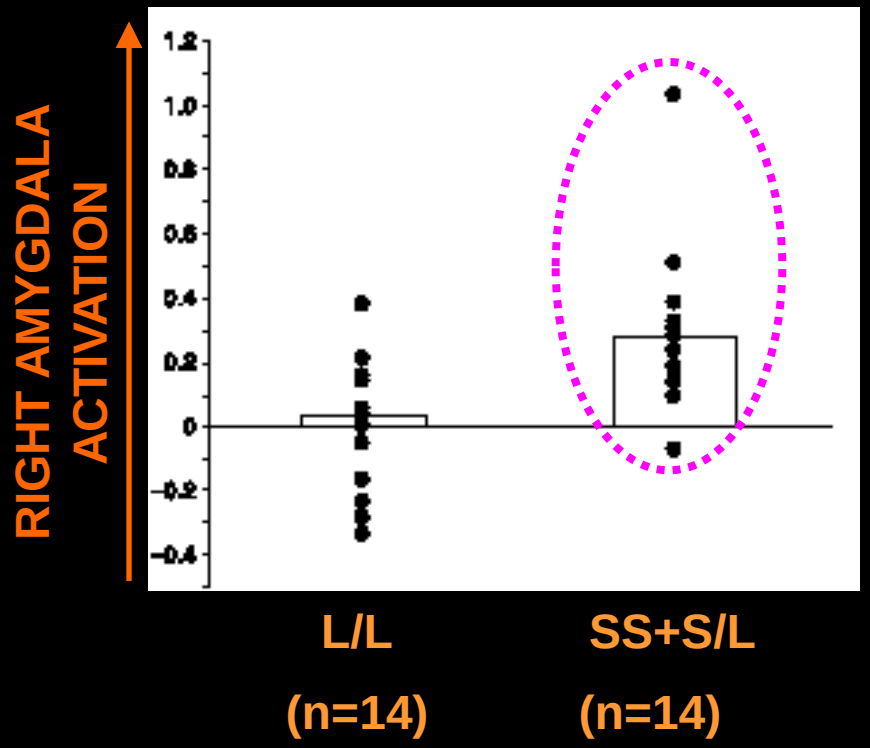
Subjects viewed a trio of faces and selected one of two faces (bottom) that expressed the same emotion as the target face (top)



AMYGDALA ACTIVITY

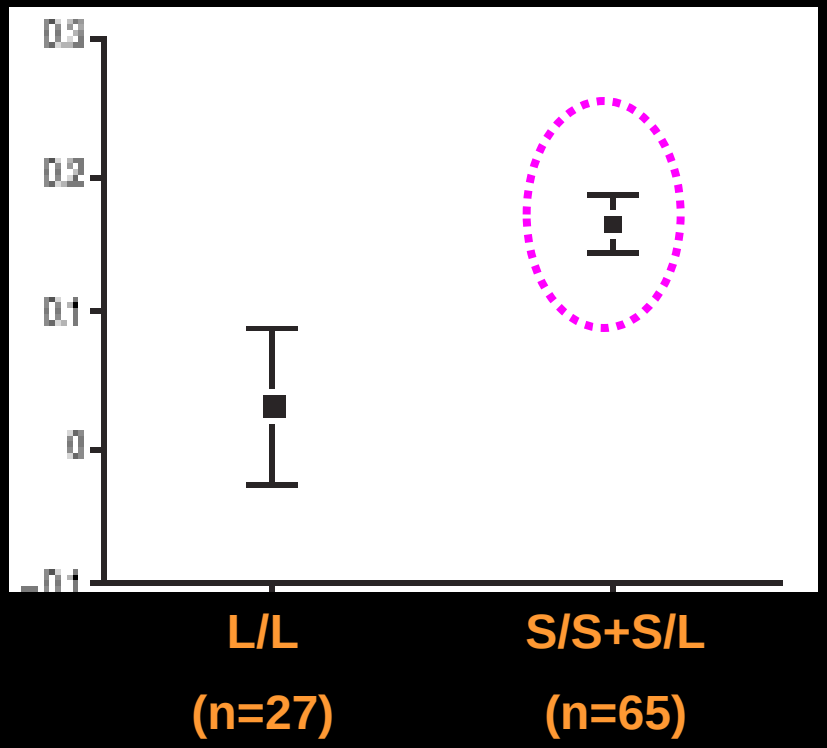
Right amygdala response to fearful stimuli according to Serotonin Transporter polymorphism status:

short allele carriers (SS+SL) *versus* long/long homozygous (L/L)



Hariri et al., 2002.

Science 297:400-3



Hariri et al., 2005.

Archives of General Psychiatry 62: 146-52

Caspi et al. (2003) Science 301:386

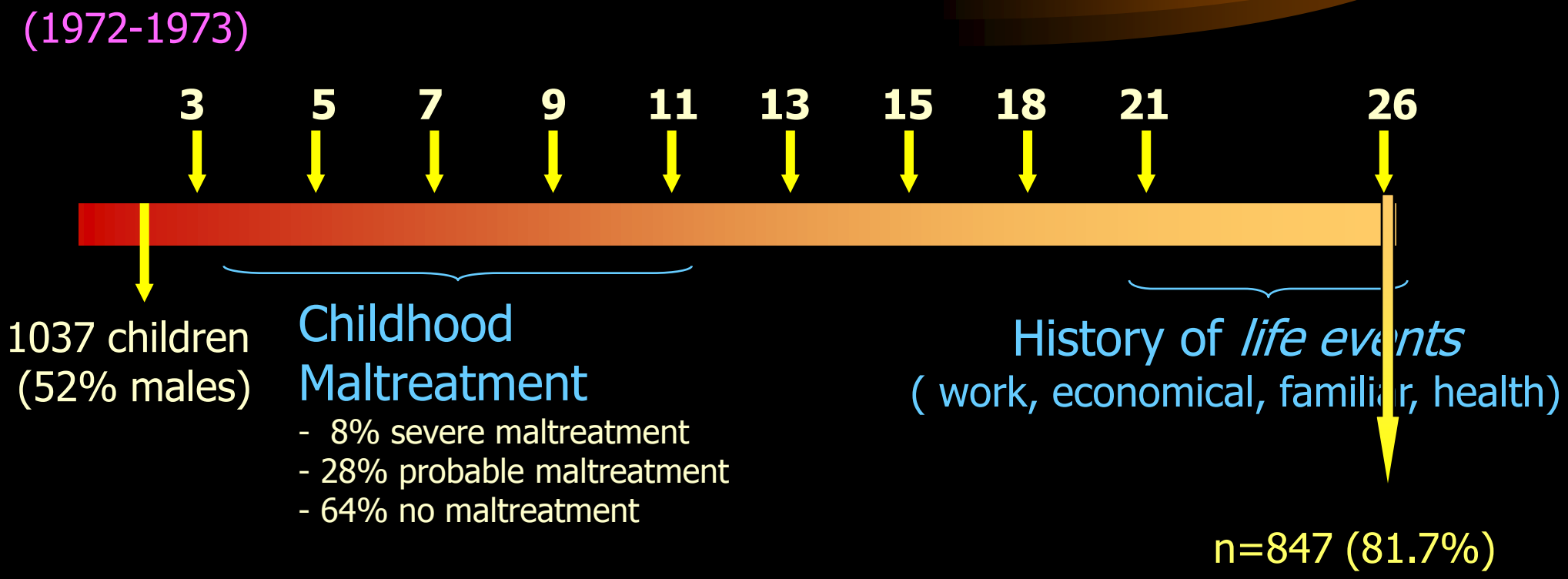
Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2*]
Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2]
Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3]
Antony Braithwaite,[4] Richie Poulton[3]

In a prospective-longitudinal study of a representative birth cohort, we tested why stressful experiences lead to depression in some people but not in others. A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

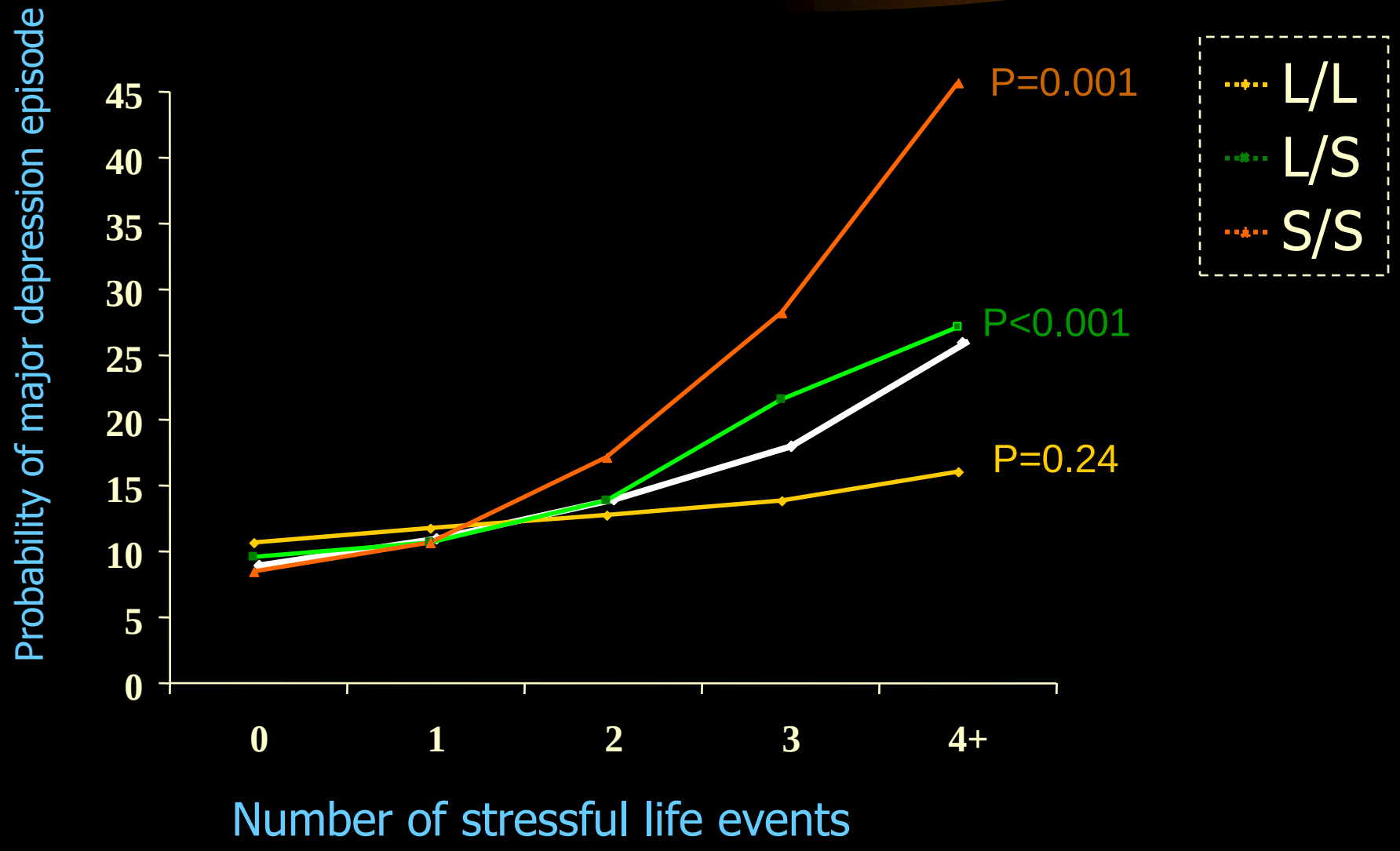
Dunedin Multidisciplinary Health and Developmental study

Dunedin Multidisciplinary Health and Developmental study

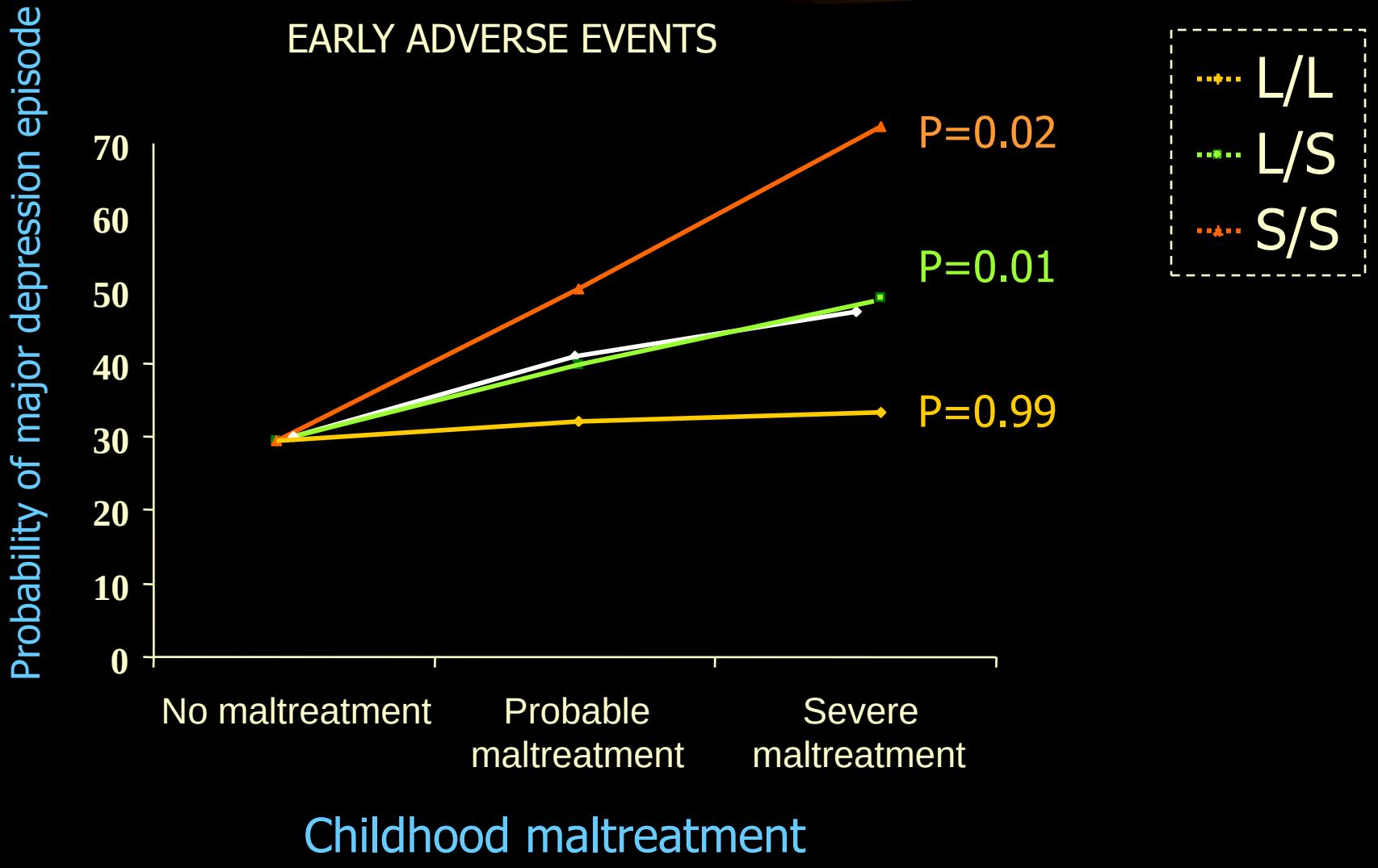


- 17% of study members (N=140) met criteria (DSM-IV) for a past-year major depressive episode.

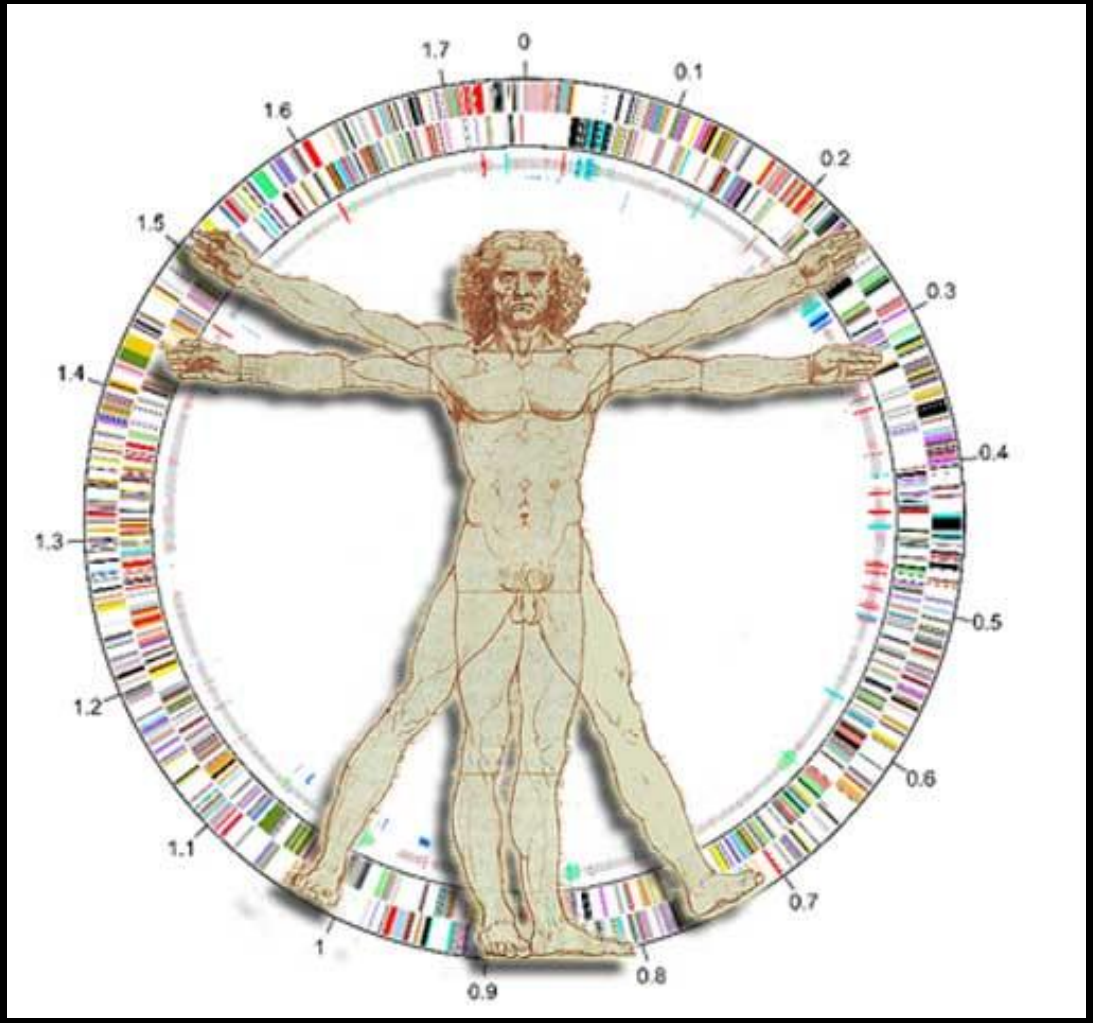
Prediction of major depression by gene- environment interaction (5HHT – stressful life events)



Prediction of major depression by gene- environment interaction (5HHT – childhood maltreatment)



This epidemiological study provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insult is moderated by his or her genetic make up.



Caspi et al. (2002) Science 297: 851-853

Role of Genotype in the Cycle of Violence in Maltreated Children

Avshalom Caspi,[1,2] Joseph McClay,[1] Terrie E. Moffitt,[1,2*] Jonathan Mill,[1] Judy Martin,[3] Ian W. Craig,[1] Alan Taylor,[1] Richie Poulton[3]

We studied a large sample of male children from birth to adulthood to determine why some children who are maltreated grow up to develop antisocial behavior, whereas others do not. A functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (*MAOA*) was found to moderate the effect of maltreatment. Maltreated children with a genotype conferring high levels of *MAOA* expression were less likely to develop antisocial problems. These findings may partly explain why not all victims of maltreatment grow up to victimize others, and they provide epidemiological evidence that genotypes can moderate children's sensitivity to environmental insults.

MAOA gene: Xp11.23-11.4

Location:

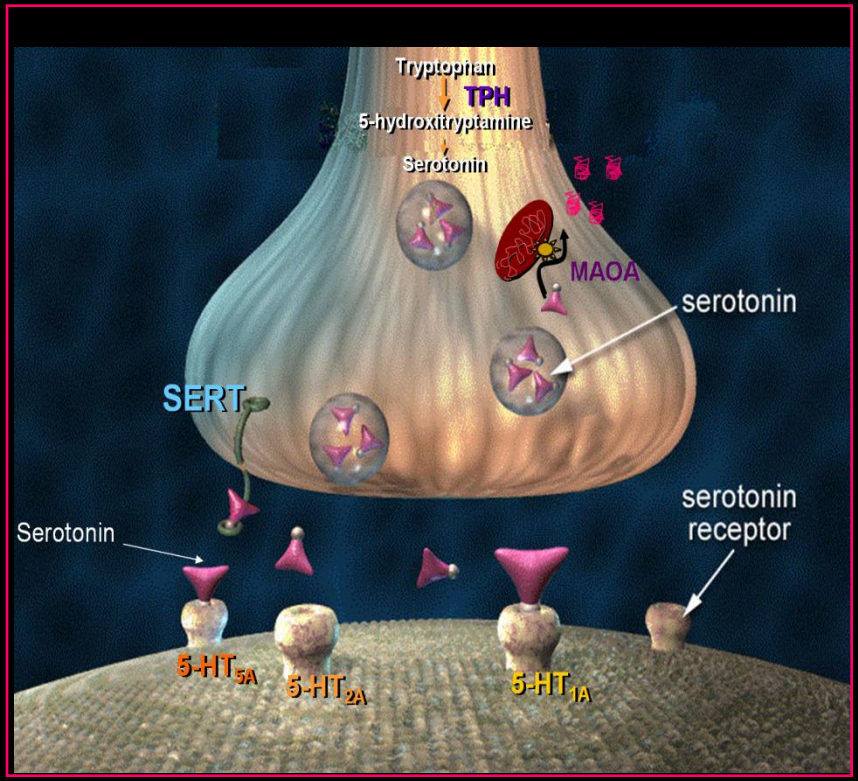
- Enzime of mitochondrial outer membrane
- High levels in catecholaminergic neurons

Function:

- Degradative deamination of biogenic amines
- High affinity for 5-HT and NE

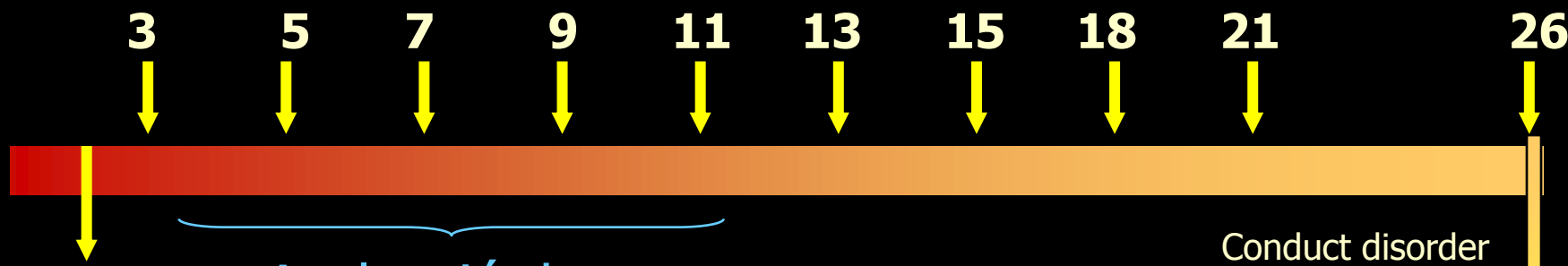
Knock-out mice:

- Effect on CNS: ↑5-HT, ↑DA, ↑NE
- Effects on mice behaviour: ↑ Aggressivity



Dunedin Multidisciplinary Health and Developmental study

(1972-1973)



1037 nens
(52% mascles)

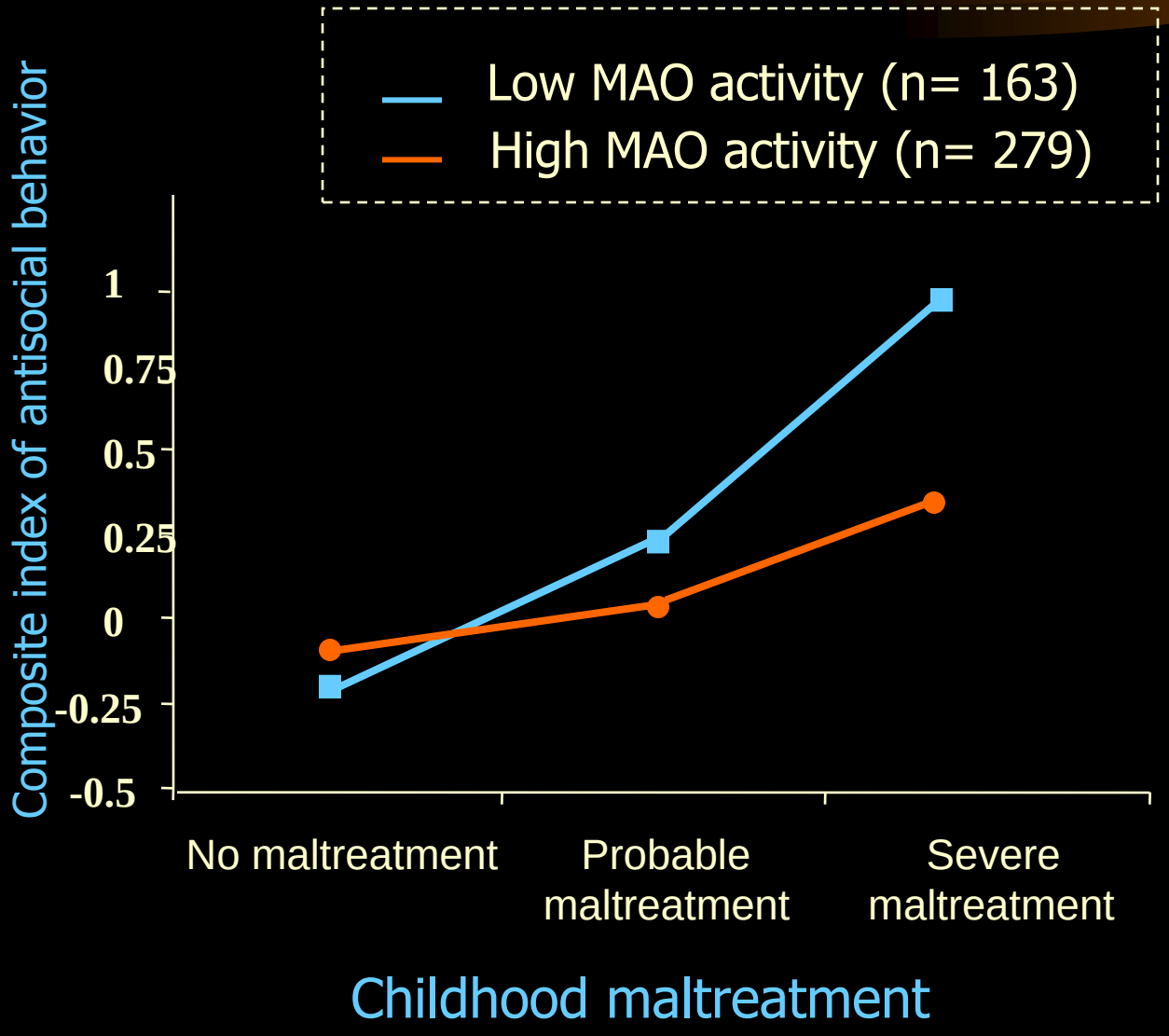
Avaluació de Maltractament

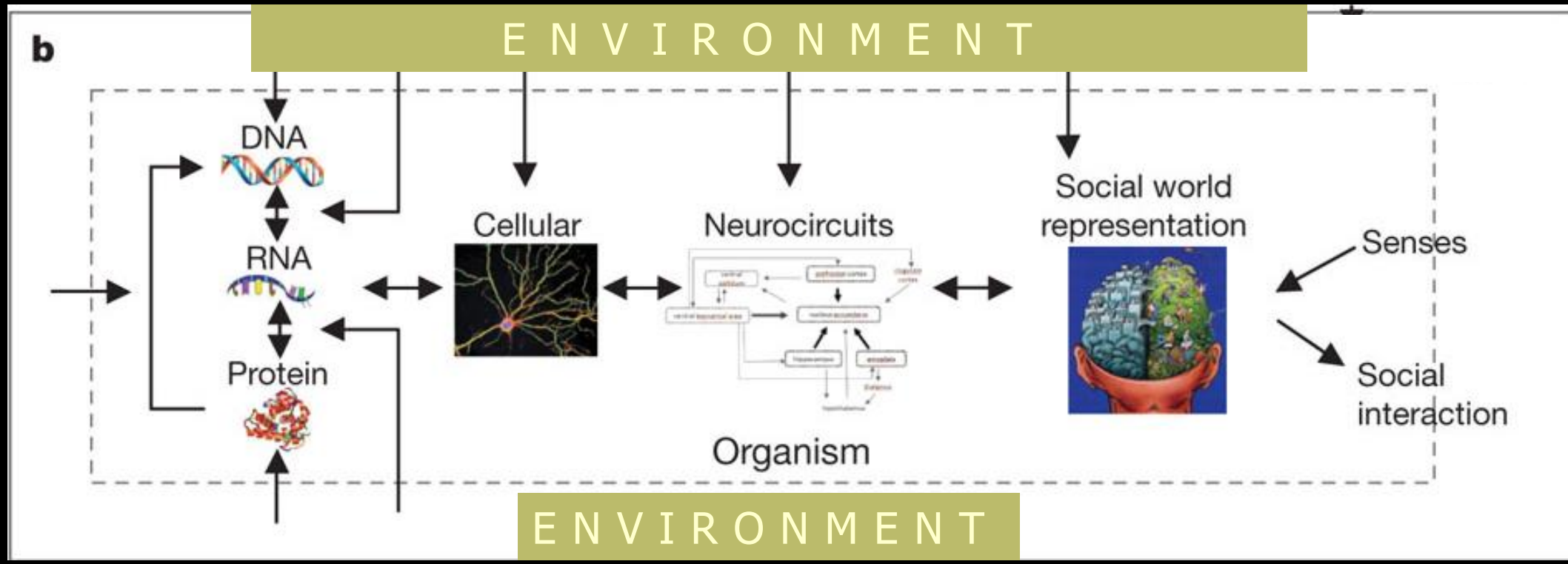
- 8% severe maltreatment
- 28% probable maltreatment
- 64% no maltreatment

Conduct disorder
Convicted or violent offense
Disposition toward violence
Antisocial personality disorder

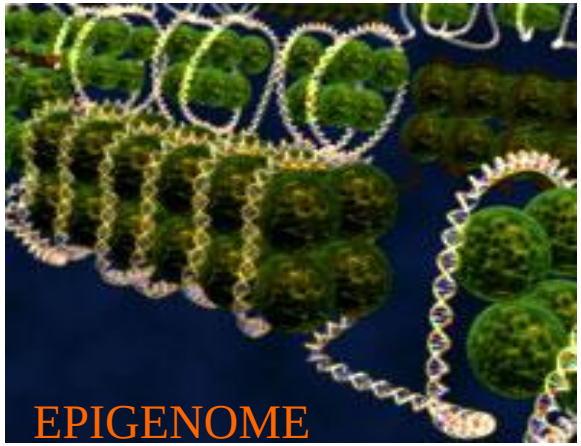
n=847 (81.7%)

Antisocial behavior as a function of MAOA activity and childhood history of maltreatment

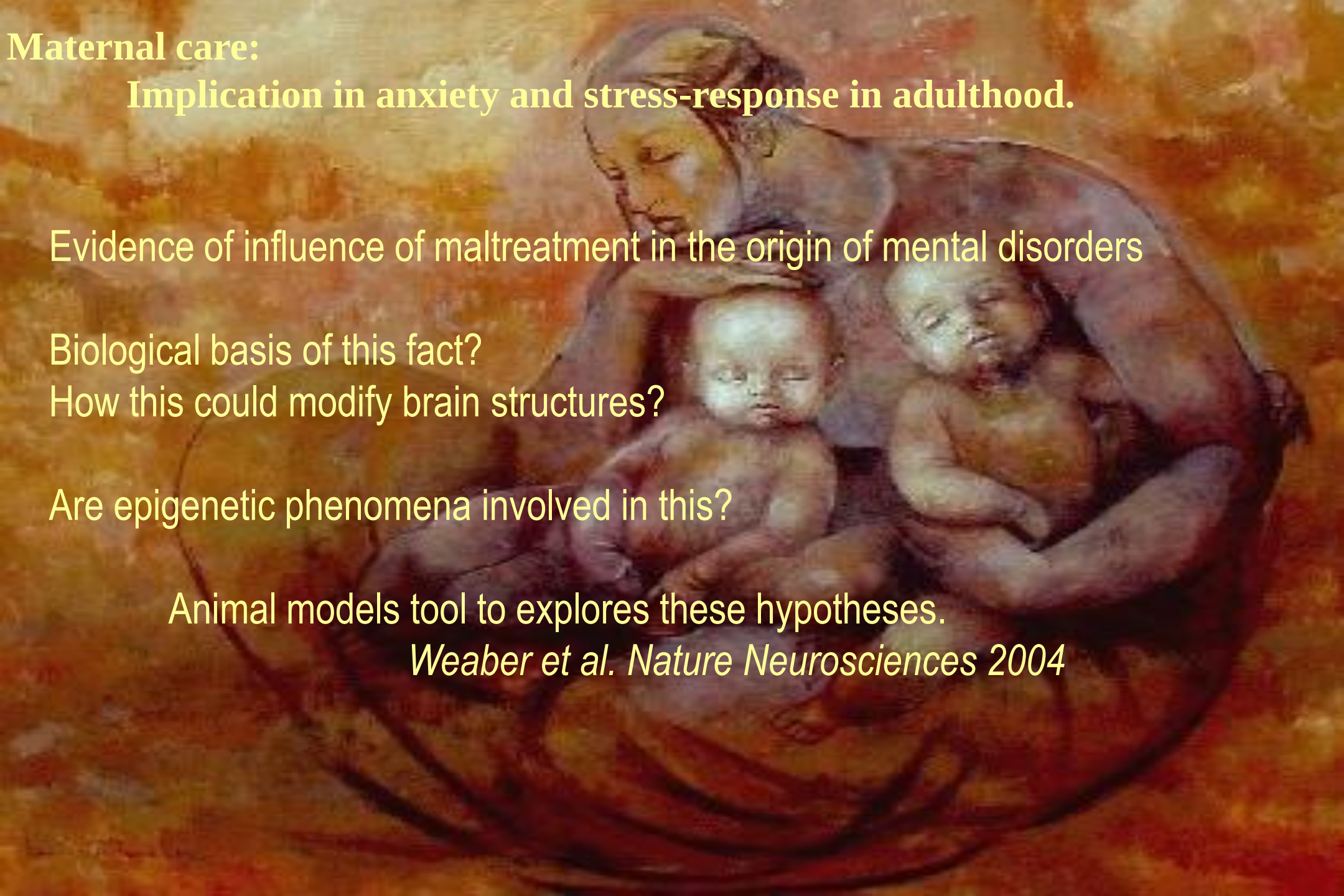



b
ENVIRONMENT
DNA
RNA
Protein
Cellular
Neurocircuits
Social world representation
Senses
Social interaction
Organism
ENVIRONMENT

The Epigenotype plays a critical role along with the Genotype and Environmental factors in determining phenotypes



PHENOTYPE



Maternal care:

Implication in anxiety and stress-response in adulthood.

Evidence of influence of maltreatment in the origin of mental disorders

Biological basis of this fact?
How this could modify brain structures?

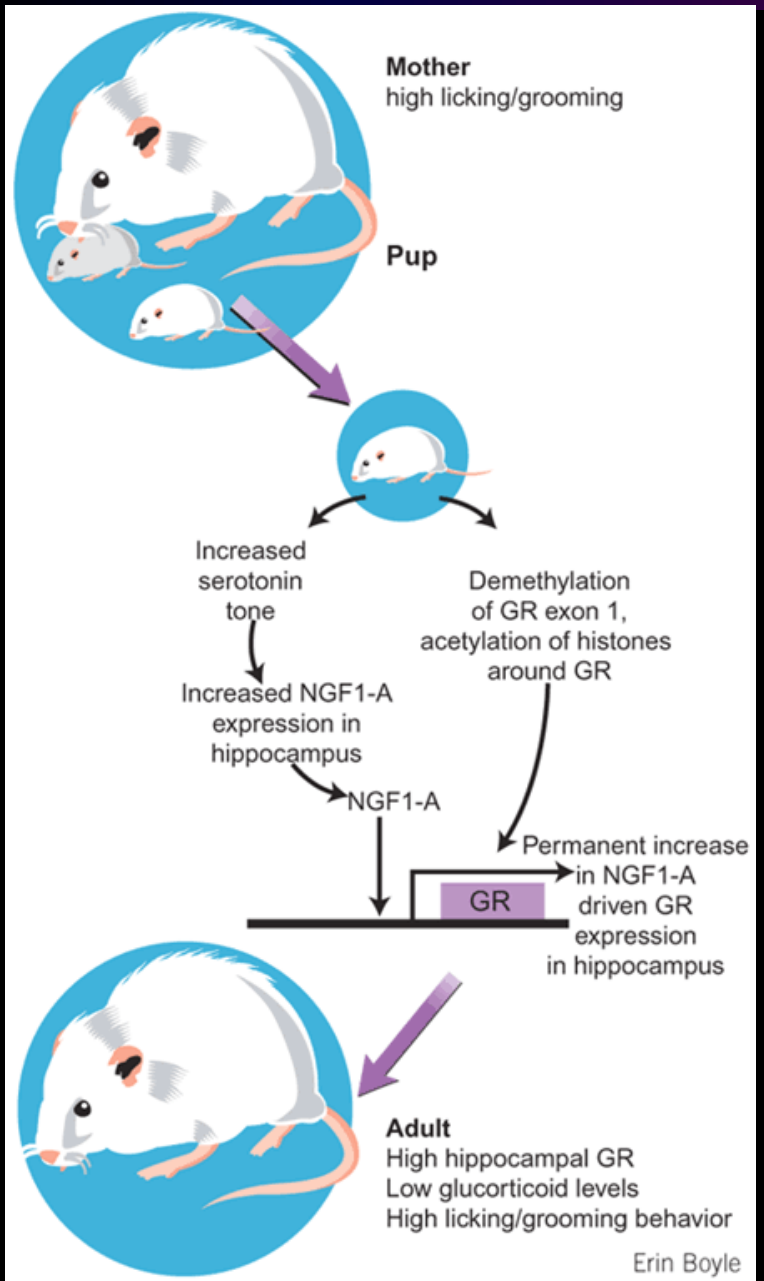
Are epigenetic phenomena involved in this?

Animal models tool to explores these hypotheses.

Weaber et al. Nature Neurosciences 2004

The importance of a well-groomed child

R.M Sapolsky. Science 277: 1620-1621 (1997)



Maternal licking and grooming

INFANCY

Less glucocorticoid secretion

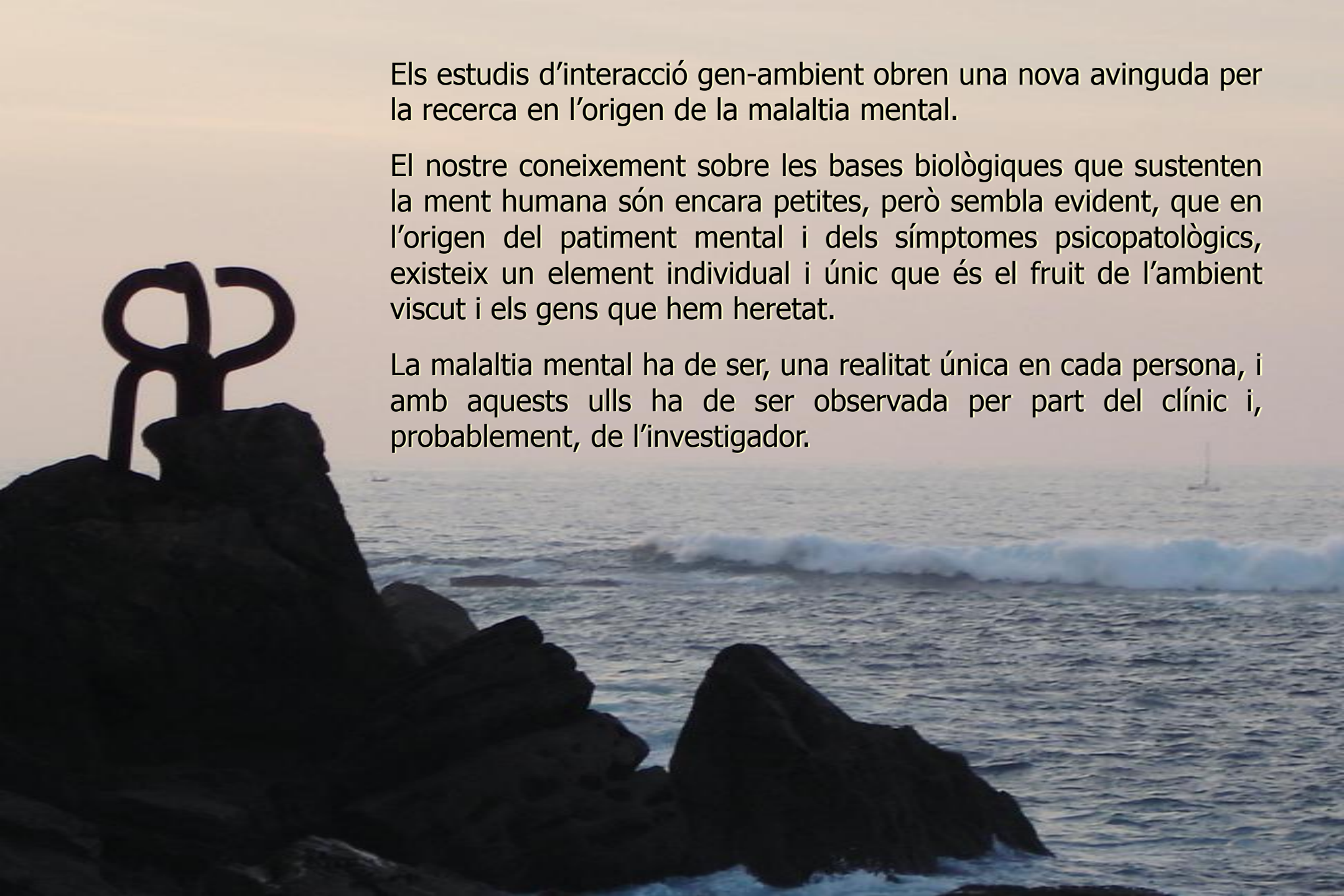
Less glucocorticoid mediated neurodegeneration and more intact cognition

ADULTHOOD

Increase in hippocampal glucocorticoid receptor number

Greater negative-feedback sensitivity of glucocorticoid secretion

OLD AGE



Els estudis d'interacció gen-ambient obren una nova avinguda per la recerca en l'origen de la malaltia mental.

El nostre coneixement sobre les bases biològiques que sustenten la ment humana són encara petites, però sembla evident, que en l'origen del patiment mental i dels símptomes psicopatològics, existeix un element individual i únic que és el fruit de l'ambient viscut i els gens que hem heretat.

La malaltia mental ha de ser, una realitat única en cada persona, i amb aquests ulls ha de ser observada per part del clínic i, probablement, de l'investigador.