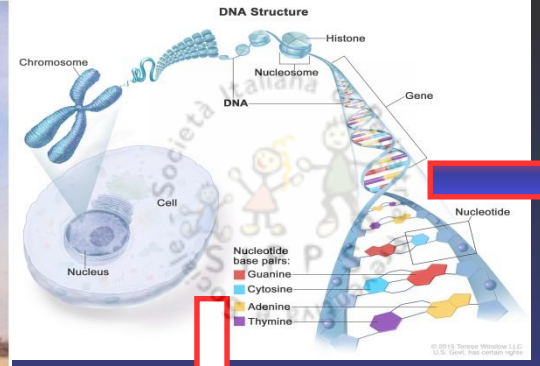
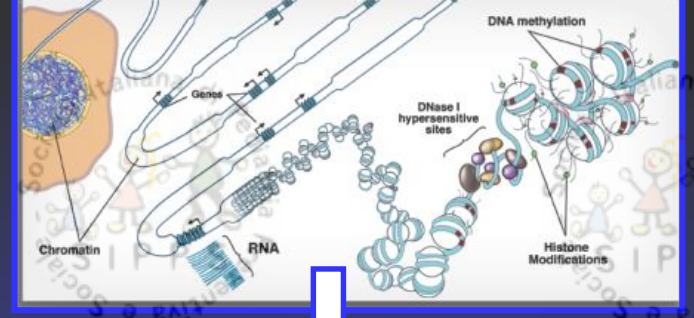
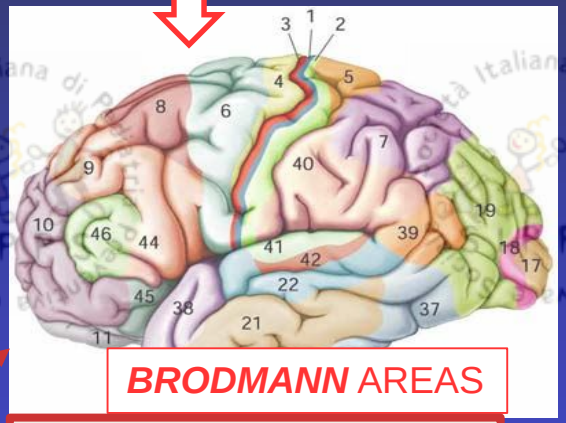
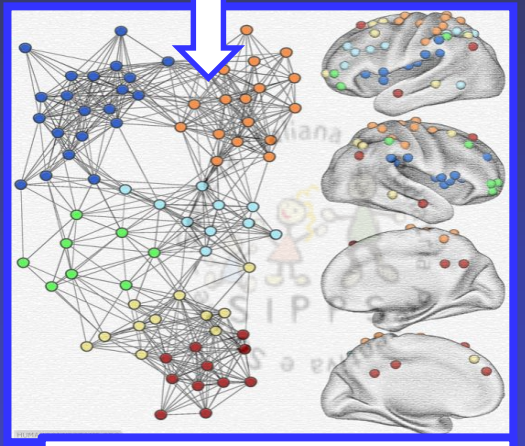




(I) The building of the *hardware* is under ***genetic control***

(Ib) The building of the *software* (the ***connectome***) is ***epigenetically*** modulated

**Early/late-life adversities and behavioural phenotypes: insight into metabolomics, genomics and connectomics**


# *The raise of Neurodevelopmental Disorders:* From ***GENETICS*** to ***EPIGENETICS***

**ERNESTO BURGIO**
**ISDE Scientific Committee**
**ECERI - European Cancer and Environment Research Institute**

Executive Healthcare Management
www.executivehm.com

# autism the great modern health concern

**Autism spectrum disorders** (**ASDs**) are a group of developmental disabilities that can cause significant social, communication and behavioral challenges. People with **ASDs** handle information in their brain differently than other people. **ASDs** are "spectrum disorders." That means **ASDs** affect each person in different ways, and can range from very mild to severe. There are three different types of **ASDs**: **Autistic Disorder** (also called "classic" autism), **Asperger Syndrome** and **Pervasive Developmental Disorder** – Not Otherwise Specified (PPD-NOS; also called "atypical autism")

1980 1 : 1500

## Autistic Disorder

What most people think of when hearing the word "autism." People with autistic disorder usually have significant language delays, social and communication challenges and unusual behaviors and interests.

## Asperger Syndrome

Usually have some milder symptoms of autistic disorder. They might have social challenges and unusual behaviors and interests. However, typically do not have problems with language or intellectual disability.

## Pervasive Developmental Disorder

The symptoms might cause only social and communication challenges. People with PDD-NOS usually have fewer and milder symptoms than those with autistic disorder.

2002 1 : 150

**1 in 150** children in the US have an ASD CDC estimated ave

meaning

**1%** of the population of children aged 3-17 have an ASD

2014 1 : 68

with

ASDs 4 to 7 times more likely to occur in BOYS than in GIRLS

2006 1 : 110

There is no medical test to diagnose ASDs, doctors look at the child's behavior and development to make a diagnosis.

About half of parents of children with ASD notice their child's unusual behaviors by age 18 months

about four-fifths notice by age 24 months

A person with an ASD might:

Not respond to their name by 12 months | Avoid eye contact and want to be alone | Have delayed speech and language skills | Repeat words or phrases over and over (echolalia) | Give unrelated answers to questions | Get upset by minor changes

2008 1 : 88

ASDs are the fastest-growing developmental disability **1,148%** growth rate with **10-17%** annual growth

Reports of autism cases per 1,000 children

| 1997 | 1999 | 2001 | 2003 | 2005 | 2007 |
|---|---|---|---|---|---|
| 0.8 | 1.3 | 2 | 2.8 | 3.9 | 5.2 |

Lifetime cost to care for an individual with an ASD Estimated from recent studies **$3.2m** with **$4,110–$6,200** per year of medical expenditures for an individual with an ASD than one without

2014 1 : 68

Sources: CDC | www.

http://arstechnica.com/science/2012/04/new-autism-studies-find-new-mutations-many-genes-behind-the-disorder/

# AUTISM
# (ASD :Autism Spectrum Disorders)

**ASD is the fastest-growing developmental disorder in the world, the prevalence of diagnosis having increased by 600% over the last 20 years**

New diagnosed cases (**incidence**) in US increased **from 15,580 in 1992 to 163.773 in 2003**

The estimated **prevalence** is **of 8-12 cases/1000 children (2012)**

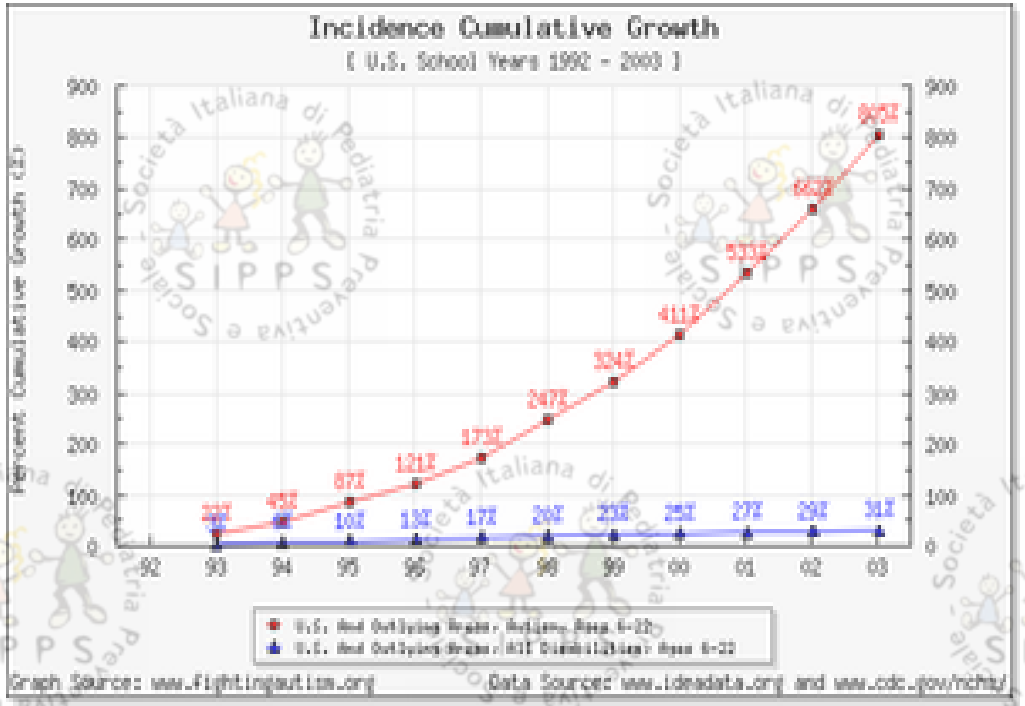
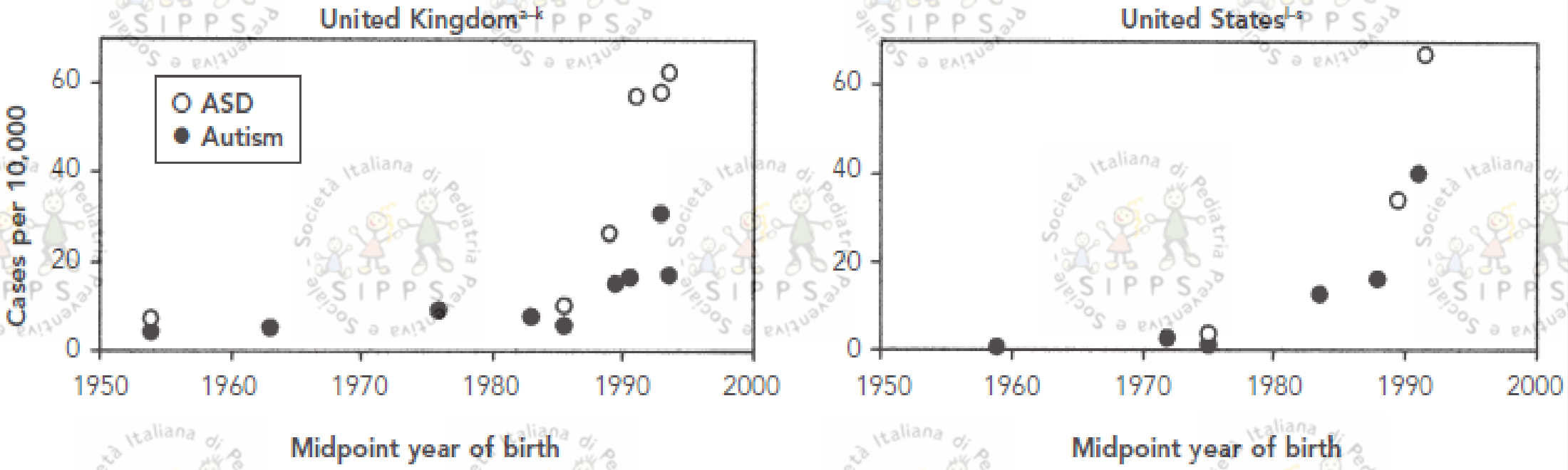


**Figure 1. Reported prevalence of autism and autistic spectrum disorders (ASDs), by midpoint year of birth, United Kingdom and United States, 1954–1994**




NOTE: These graphs show prevalence estimates from 11 U.K. and 8 U.S. studies. For studies with survey populations spanning a range of birth years, the midpoint of the birth year range is used.

[a]Lotter 1966[35]

[b]Wing and Gould 1979[42]

[c]Deb and Prasad 1994[82]

[d]Webb et al. 1997[89]

[e]Taylor et al. 1999[20]

[k]Baird et al. 2000[78]

[l]Treffert 1970[36]

[m]Ritvo et al. 1989[53]

[n]Burd et al. 1987[45]

[o]California Department of Developmental Services 2003[2]

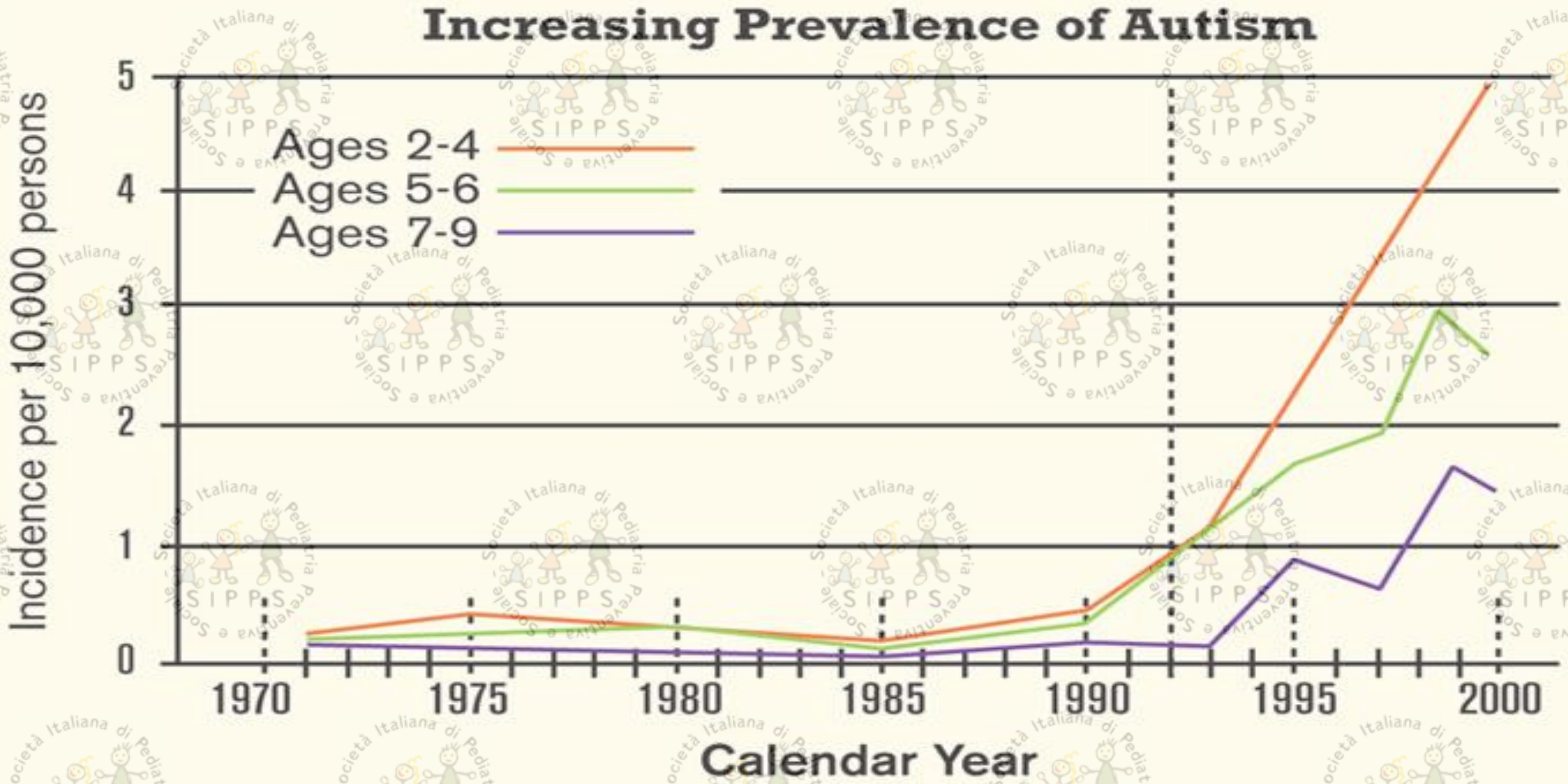



FIGURE 1. Incidence of autism by age and calendar year[89]

# Autism Prevalence Since 2000


Many scientists and researchers claim that Autism is **the fastest-growing developmental disorder**

**Centre for Disease Control (CDC)**

***Autism and Developmental Disabilities Monitoring Network 2014***

**1 of 68 children aged 8 years had been diagnosed as autistic**

*Prevalence of Autism Spectrum Disorders in EU*: 0,62 - 0,7%

***Autism*. Lai MC, Lombardo MV, Baron-Cohen S. Lancet. 2014 Mar.**

1:119 Finlandia *Mattila et al., 2011*

1:87 Svezia *Idring et al., 2012*

1:59 Gran Bretagna Russel et al., 2014

# The autism "epidemic"

## Ethical, legal, and social issues in a developmental spectrum disorder

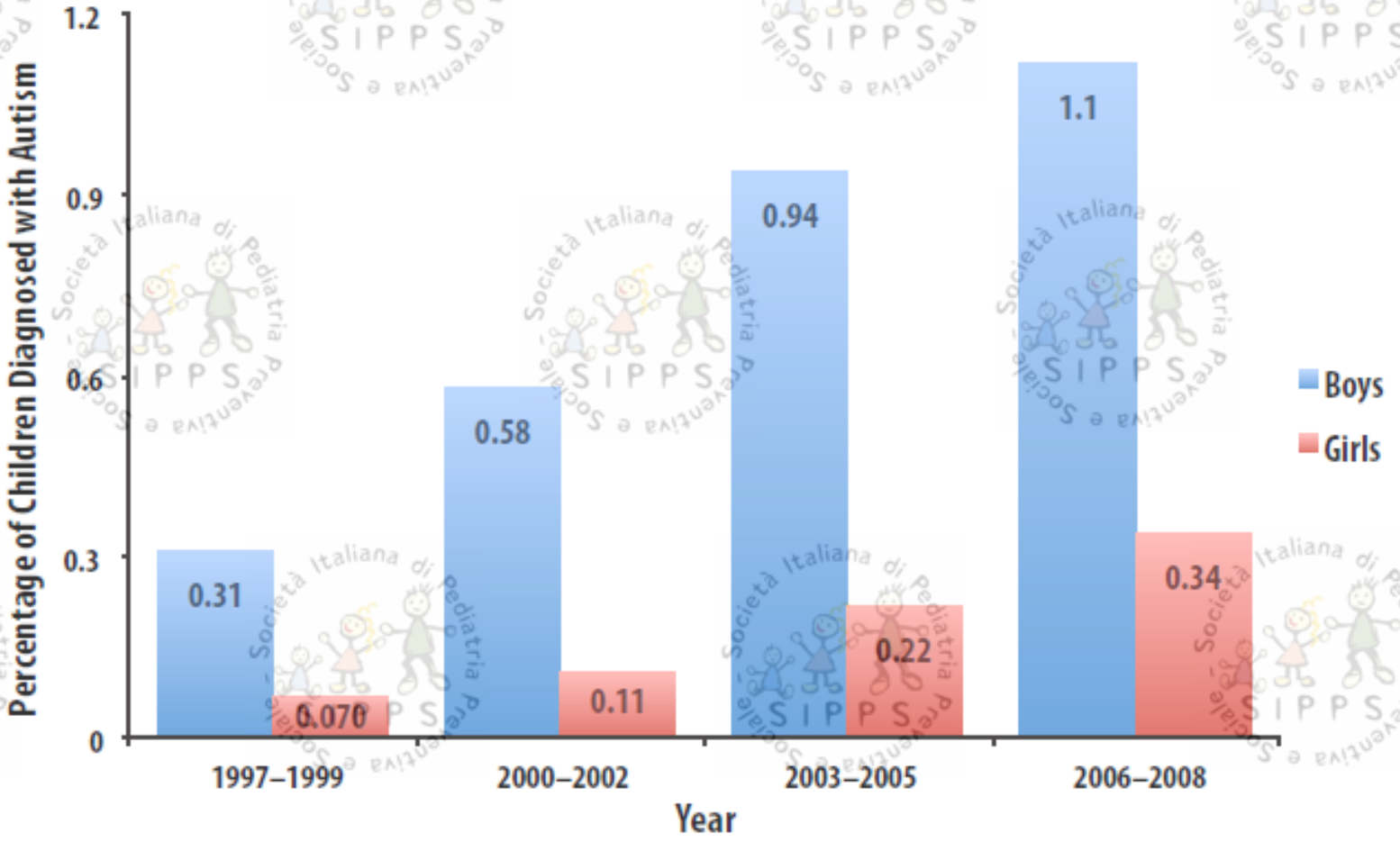
William D. Graf, MD
Geoffrey Miller, MD
Leon G. Epstein, MD
Isabelle Rapin, MD

Correspondence to
Dr. Graf:
wgraf@connecticutchildrens.org

**ABSTRACT**

Classic autism has gradually evolved into the concept of a larger "spectrum disorder." The rising prevalence of autism and autism spectrum disorder (autism/ASD) diagnoses can be largely attributed to broader diagnostic criteria, adoption of dimensional assessment strategies, increased awareness, linking of services to diagnosis, and the inclusion of milder neurodevelopmental differences bordering on normality. The spectrum disorder diagnosis raises numerous bioethical issues for individuals and society. Three groups of caregivers have important ethical, legal, and social obligations to individuals with autism/ASD: (1) families and advocates of individuals with autism/ASD; (2) health care and other professionals; and (3) governments. Each group may have different views of autism/ASD diagnostic criteria, screening, testing, and the effectiveness of various interventions. All see timely diagnosis as desirable, but earlier diagnosis may not be better, morally or practically. The growing practice of genetic testing in milder ASD raises ethical questions because of its uncertain scientific validity and limited clinical utility. Individuals with autism/ASD have various kinds of needs but all want acceptance and most deserve better accommodations. Governments struggle to provide a fair allocation of appropriate special education and supportive services. This article examines the evolving dimensions of the autism/ASD diagnosis, outlines certain bioethics principles related to its evaluation and management, reviews relevant laws and disability rights, and emphasizes the societal obligation to recognize neurodevelopmental variation and human neurodiversity. Future directions in the evaluation and care of autism/ASD should attempt to integrate the roles and responsibilities of all agents caring for each unique autistic individual. *Neurology*® 2017;88:1371-1380

**Figure 3:** Autism Prevalence among Children Ages 3 to 17, from 1997–2008




Rates of autism have risen dramatically in the past decade. While overall prevalence is higher among boys, the rate of increase is higher among girls. Source: C. Boyle et al, "Trends in the Prevalence of Developmental Disabilities in U.S. Children, 1997–2008."

## Il 17% dei bambini US < 18° a. ha un disturbo dello sviluppo, per lo più a carico del SN

Disturbi dell'apprendimento

ADHD

Disordini dello spettro autistico

Ritardo mentale

Problemi comportamentali

Analoghe sono le cifre europee

Il cervello è un organo prezioso e vulnerabile e, poiché il suo funzionamento ottimale dipende dalla sua integrità, anche danni limitati possono avere conseguenze serie ( Grandjean 2006)

Grandjean P.

# A Silent Pandemic

## Industrial Chemicals Are Impairing

## The Brain Development of Children Worldwide

**For immediate release: Tuesday, November 7, 2006**

Landrigan Ph

THE LANCET
Volume 368, Issue 9553, 16 December 2006-22 December 2006, Pages 2167-2178

### Developmental neurotoxicity of industrial chemicals

P Grandjean*, PJ Landrigan**

Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common, costly, and can cause lifelong disability. Their causes are mostly unknown. A few industrial chemicals (eg, lead, methylmercury, polychlorinated biphenyls [PCBs], arsenic, and toluene) are recognised causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brain function. Recognition of these risks has led to evidence-based programmes of prevention, such as elimination of lead additives in petrol. Although these prevention campaigns are highly successful, most were initiated only after substantial delays. Another 200 chemicals are known to cause clinical neurotoxic effects in adults. Despite an absence of systematic testing, many additional chemicals have been shown to be neurotoxic in laboratory models. The toxic effects of such chemicals in the developing human brain are not known and they are not regulated to protect children. The two main impediments to prevention of neurodevelopmental deficits of chemical origin are the great gaps in testing chemicals for developmental neurotoxicity and the high level of proof required for regulation. New, precautionary approaches that recognise the unique vulnerability of the developing brain are needed for testing and control of chemicals.

A few industrial chemicals (eg, **lead, methylmercury, polychlorinated biphenyls [PCBs], arsenic**, and **toluene**) are recognised causes of neurodevelopmental disorders and subclinical brain dysfunction.

**…**

Seven years ago two well known experts in Environmental Health, a pediatrician and an epidemiologist, launched an alarm from the pages of *the Lancet*, saying that a ***silent pandemic*** of ADHD, autism and other neurodevelopmental disorders was spreading also due to the ***shortage of funds in this area of research***

The Lancet Neurology, Volume 13, Issue 3 , Pages 330 - 338, March 2014

# Neurobehavioural effects of developmental toxicity

Philippe Grandjean, Philip J Landrigan

Lancet Neurol 2014; 13: 330–38
Published Online
February 15, 2014
http://dx.doi.org/10.1016/S1474-4422(13)70278-3

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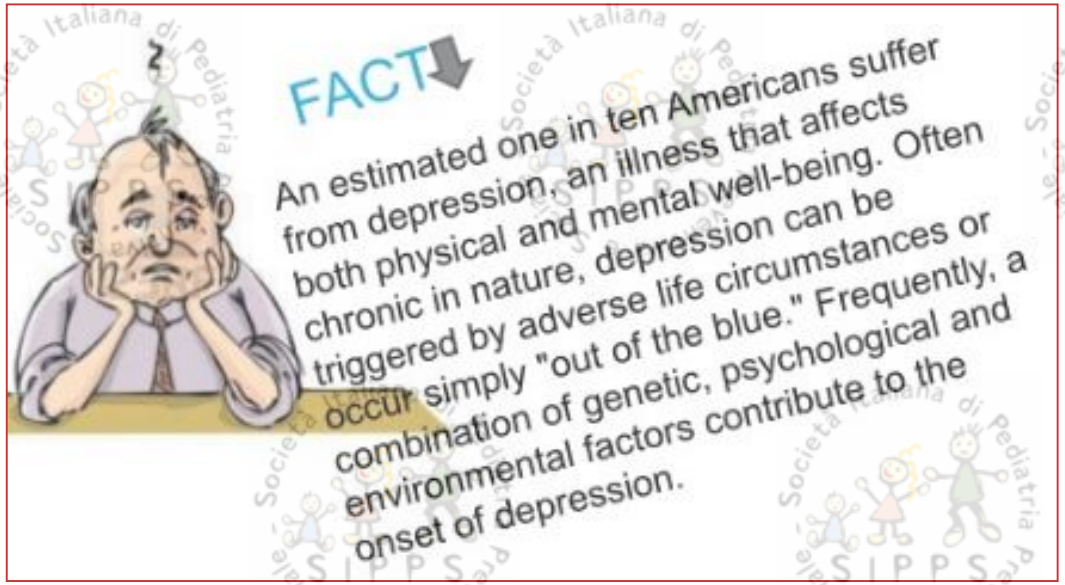
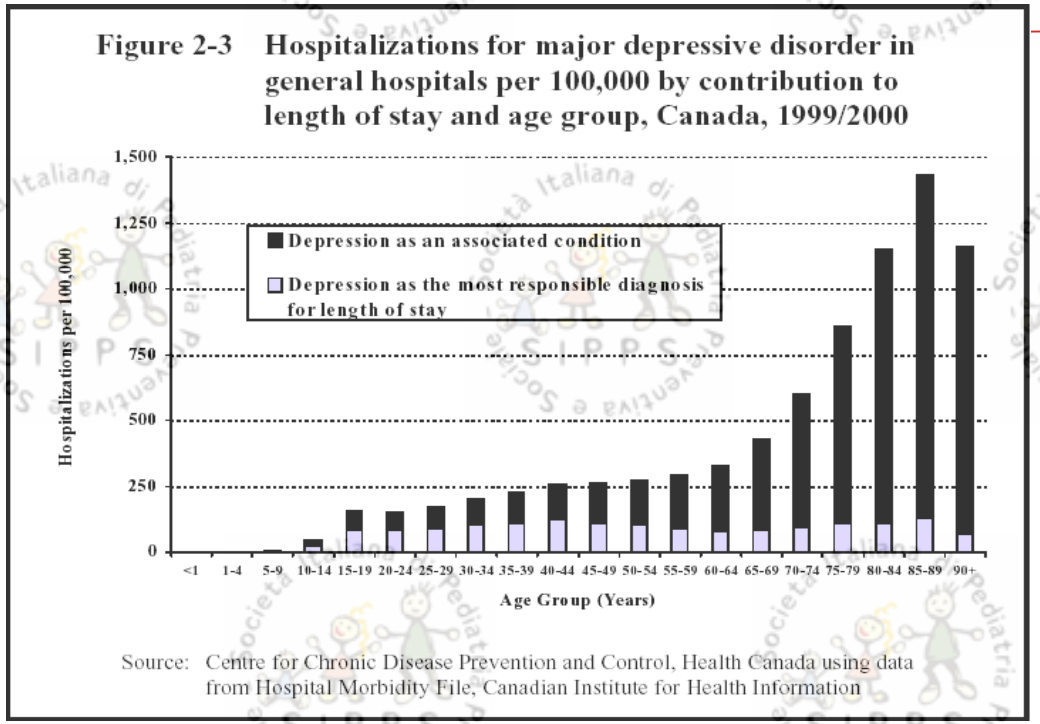
Correspondence to:
Dr Philippe Grandjean, Environmental and Occupational Medicine and Epidemiology, Harvard School of Public Health, 401 Park Drive E-110, Boston, MA 02215, USA
pgrand@hsph.harvard.edu

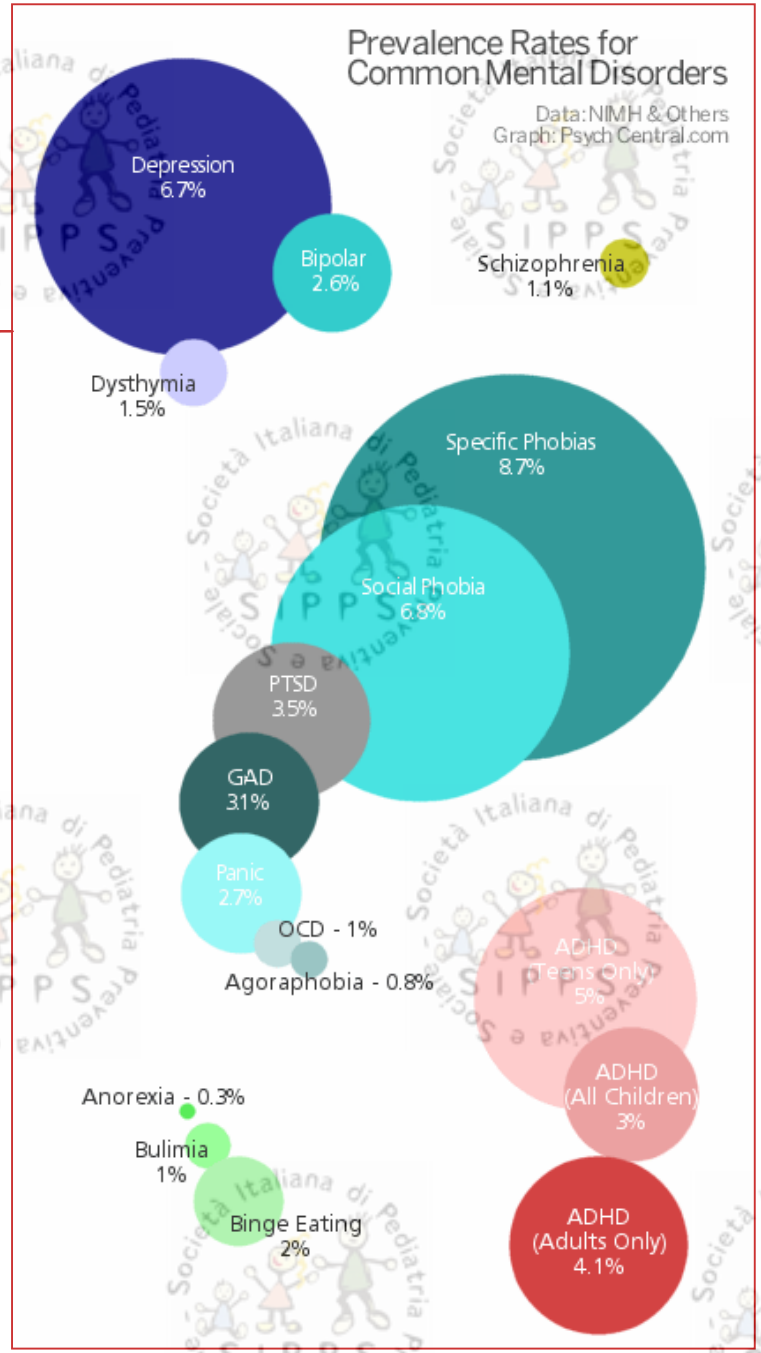
Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, we did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants—manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethane, tetrachloroethylene, and the polybrominated diphenyl ethers. We postulate that even more neurotoxicants remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed to be safe to brain development, and chemicals in existing use and all new chemicals must therefore be tested for developmental neurotoxicity. To coordinate these efforts and to accelerate translation of science into prevention, we propose the urgent formation of a new international clearinghouse.

**Since 2006**, epidemiological studies have documented **six additional developmental neurotoxicants — manganese, fluoride, chlorpyrifos, tetrachloroethylene, dichlorodiphenyltrichloroethane,, and the polybrominated diphenyl ethers.**
We postulate that even more neurotoxicants remain undiscovered

http://www.slideshare.net/CMoondog/depression-powerpoint-13945746



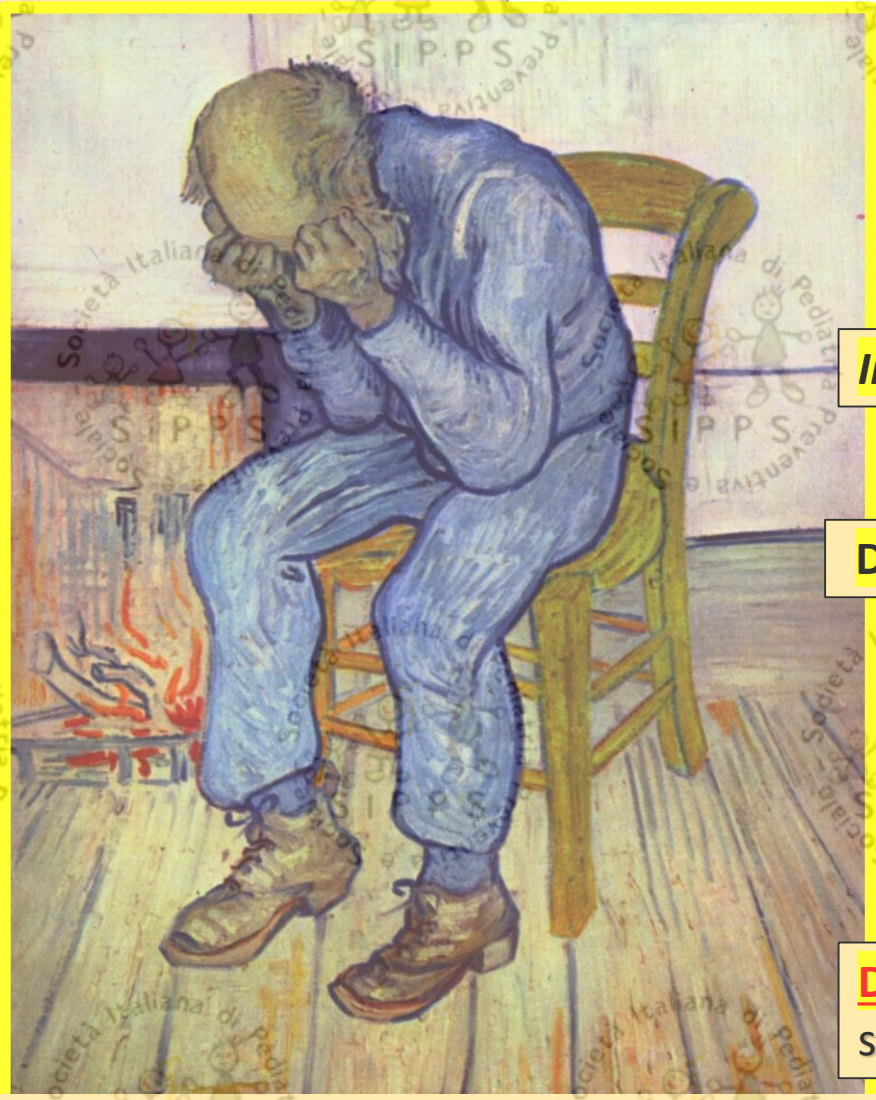

http://psychcentral.com/blog/archives/2009/10/05/prevalence-of-common-mental-disorders/

# Dépression majeure

*Major depressive disorder*

Facteurs **psychologiques, psychosociales environnementaux** (héréditaires)

**biologiques (génétique - épigénétique métagénomique) (Psycho-neuro-endocrino Immuno…**



**Tristesse persistante, anxiété ou un sentiment de «vide»**

**Sentiments de culpabilité, dévalorisation, faible estime de soi**

Sentiment de **désespoir. Pessimisme**

***Anhédonie* (*perte d'intérêt ou de plaisir dans les activités normalement agréables*)**

***Diminution de l'énergie, fatigue***

***Irritabilité, nervosité***

Agitation, **difficulté à rester assis**

Mouvements et langage ***ralentis***

**Difficulté à se concentrer**, prendre des décisions, réfléchir

**Troubles du sommeil/réveil, hypersomnie**

Changements dans **l'appétit, l'alimentation**, le **poids**

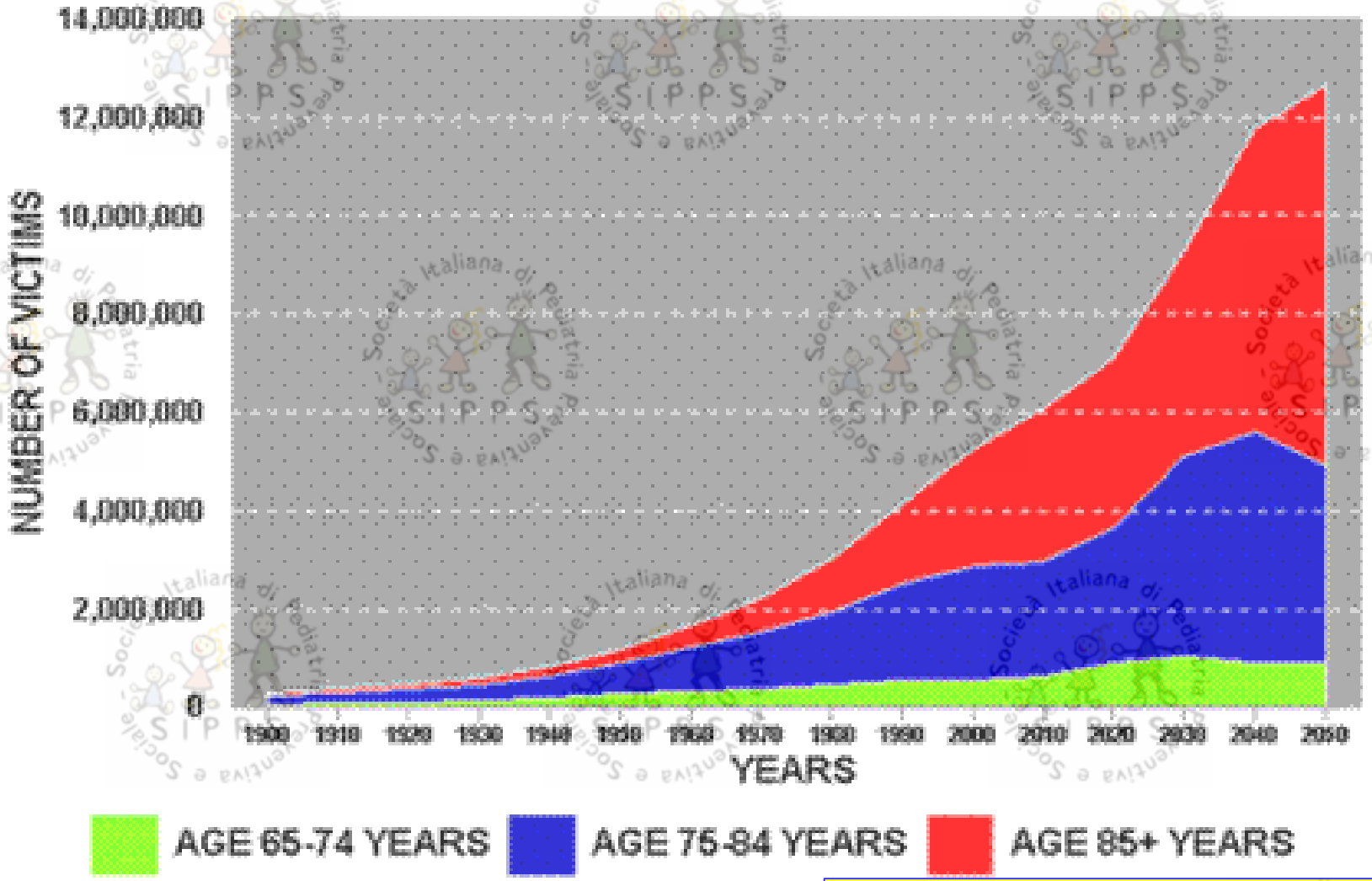
**Pensées de mort ou de suicide**. Tentative de suicide

**Douleurs, maux de tête, crampes, problèmes digestifs** sans cause physique claire **sans relief avec le traitement**

Le **cours est très variable**: à partir **d'un seul épisode de la durée de quelques semaines jusqu'à un trouble persistant tout au long de la vie avec des épisodes dépressifs majeurs récurrents.**

# PREVALENCE OF ALZHEIMER'S DISEASE

## (BY DECADES IN U.S.A. FROM 1900-2050)




This graph portrays how many Americans over the age
Alzheimer's, and a projection of how many more will b

An equally dramatic trend show **neurodegenerative diseases** and in particular **Alzheimer's disease**

Since 2000 there has been a **66% increase in Alzheimer's diagnoses**.
**6th leading cause of death** in the United States.
**5.4 million Americans** are living with the disease.
**15-20 million more Americans will be diagnosed by 2040**

BioEssays Vol. 18 no. 9
© ICSU Press 1996 pp. 695–696 BIO1029

# Are there 'Kuhnian' revolutions in biology?

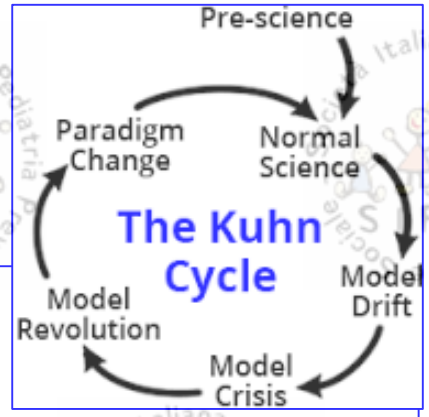
**Adam S. Wilkins**

The recent death, on 17 June 1996, of the noted philosopher of science, Thomas Kuhn, at age 73, provides a suitable occasion to remember and commemorate his contributions to the philosophy of science. It also provides an appropriate moment to ask how well the Kuhnian idea of scientific revolutions, which was developed principally from study of the physical sciences, applies to biology.

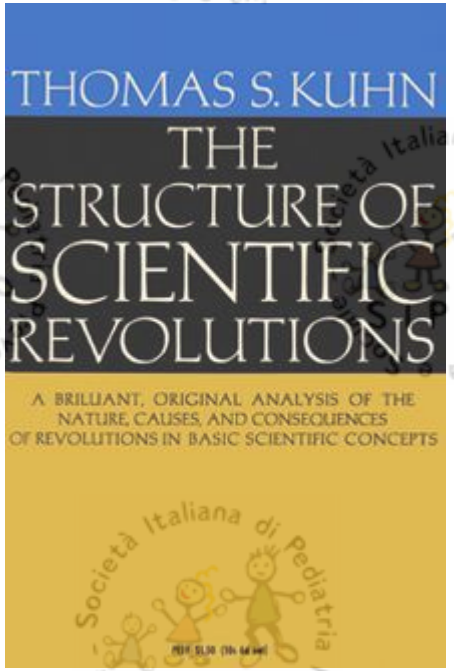
Kuhn, a professor emeritus at MIT in recent years, had written or coauthored five books and numerous scholarly articles, but he is undoubtedly best known, and will be best remembered, for *The Structure of Scientific Revolutions*[1], first published in 1962. In this seminal work, Kuhn argued persuasively against the traditional idea of 'scientific progress', the notion that scientific knowledge involves the steady growth of understanding through the application of something called 'The Scientific Method'. He argued that, in reality, science involves two distinctly different processes. For the most part, scientists work within certain conceptual frameworks or models, 'paradigms'. This work serves to embellish and strengthen the central paradigm at the heart of each field and is essentially conservative in nature. Kuhn termed such activities 'normal science'. Yet, the continued practice of normal science within a field often shows up weaknesses in the central paradigm. When these weak-

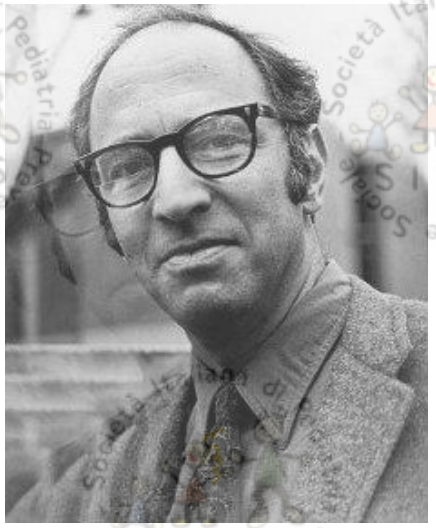
digms' and the like. The notion that what scientists believe at any one time is determined in part by group consensus – in some corridors, there were mutterings that the idea involved little more than 'mob rule' in deciding scientific truth, a notion vehemently denied by Kuhn himself[3] – was unsettling. Furthermore, the neurological implications – that young brains are much more likely to generate and be receptive to major conceptual breakthroughs – though not new, could not have been comforting to those past their first youth. Nevertheless, the impact of Kuhn's idea was immediate and pervasive. It would not be inappropriate to refer to the 'Kuhnian revolution' in the philosophy of science.

The question of generality, however, still nags. In contrast to many earlier, *a priori*, philosophical theories of knowledge, Kuhn built his case from examples, in effect inductively. (Kuhn's ideas co-exist uneasily today with those of Karl Popper, an arch-foe of argument from induction; it is, in fact, impossible to be both a Kuhnian and a Popperian, at least at the same instant.) Kuhn's primary examples were all drawn from physics and chemistry – Kuhn had taken his bachelor's degree in physics – and involved some of the classic discoveries in those sciences: the Copernican, Newtonian and Einsteinian revolutions and Lavoisier's disproof of the phlogiston theory.

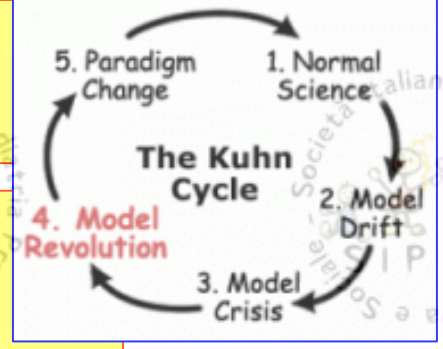



The recent **death**, on **17 June 1996**, of the noted philosopher of science, **Thomas Kuhn**, at age 73, provides a suitable occasion to remember and commemorate **his contributions to the philosophy of science.** It also provides an appropriate moment **to ask how well the Kuhnian idea of scientific revolutions, which was developed principally from study of the physical sciences, applies to biology**.



# We are currently facing a *paradigm shift* in biomedicine

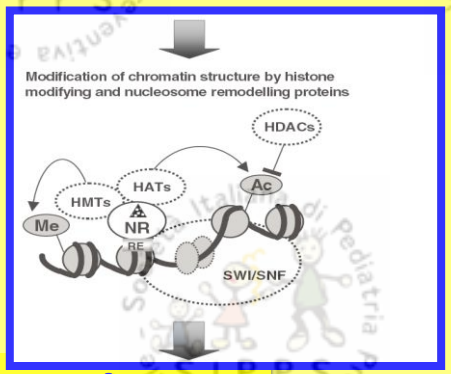



For the last 50 years it was agreed to consider **DNA as the code and the key project for the assembly of our phenotype**.

**In the last ten years** and especially since the appearance of **the first molecular epigenetic studies** we have begun to understand

that **the construction of the phenotype is the result of the interaction** between the **information** coming from the **environment**

and the **information** deeply inscribed **inside the DNA**




**thanks to a very complex molecular network surrounding the DNA: the *epigenome***

Therefore it can be argued that **there is no stable change in our phenotype (both physiological and pathological)** which is not

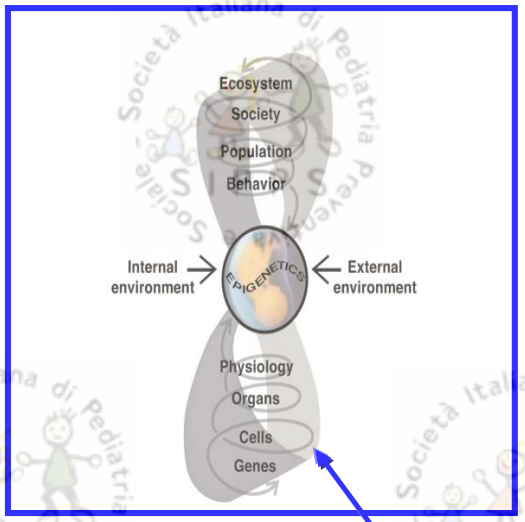
- ***environmentally*** induced
- ***modulated by the epigenome***
- ***conditioned*** by DNA

The other **key concepts** (obviously interdependent) are:

- ***developmental plasticity***
- ***fetal programming***

allowing us to understand how **the fetus epigenetically program (for life) all its cells in a *predictive* and *adaptive* way**

**responding to information coming from the *environment*** (through the ***mother bias*** )




It is important to note that during this period

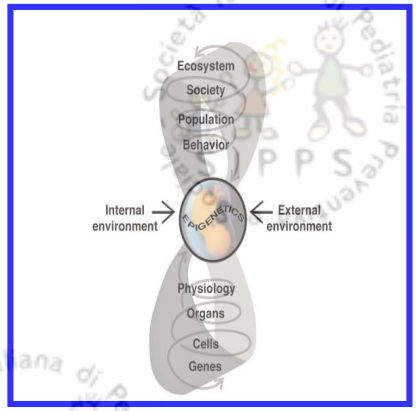
***incorrect information*** **( *pollutants, endocrine disruptors* ..)** and /or

***discrepancies*** between the **information** that the baby receives before and after birth **(*mismatch*)**

may create **epigenetically bad programmed cells** (including **gametes**), thus causing **chronic diseases in adulthood** or **even in subsequent generations**

This theory (***DOHaD Developmental Origins of Health and Disease***) could help us to **explain the current epidemiological transition** ..

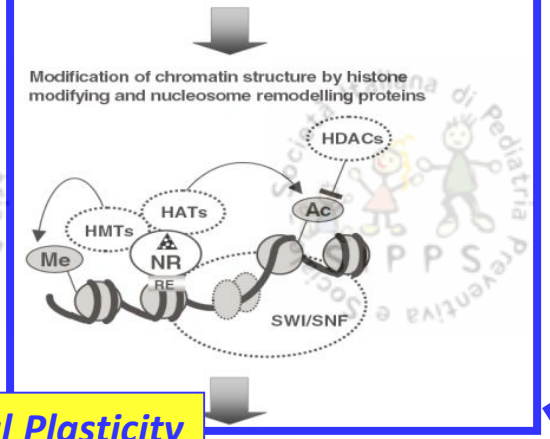
# The 7 keywords: from genetics to epigenetics




3

Ontogeny*

4




Developmental Plasticity

Fetal programming

Phylogeny*

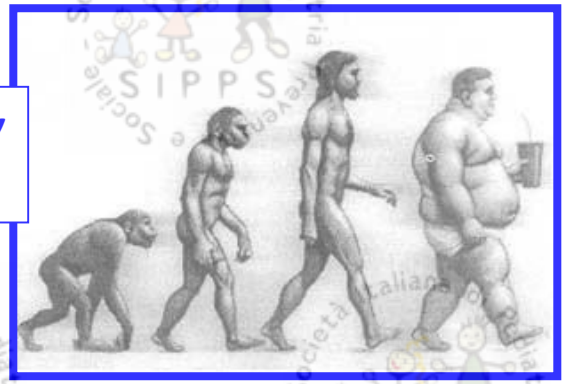
Devo → Evo

2

Environment

5

Evolutionary Medicine



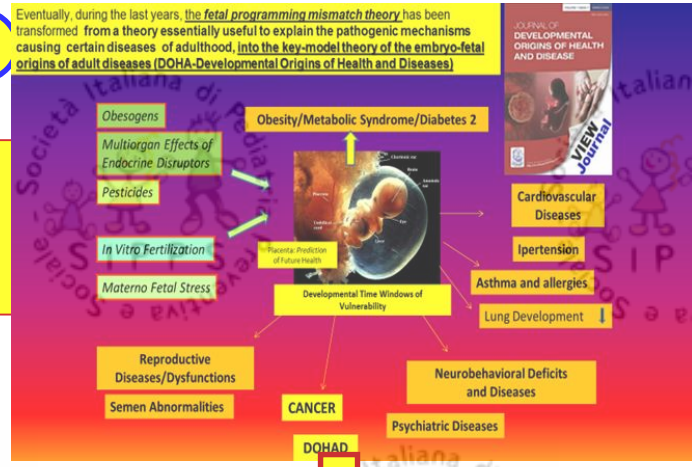
1

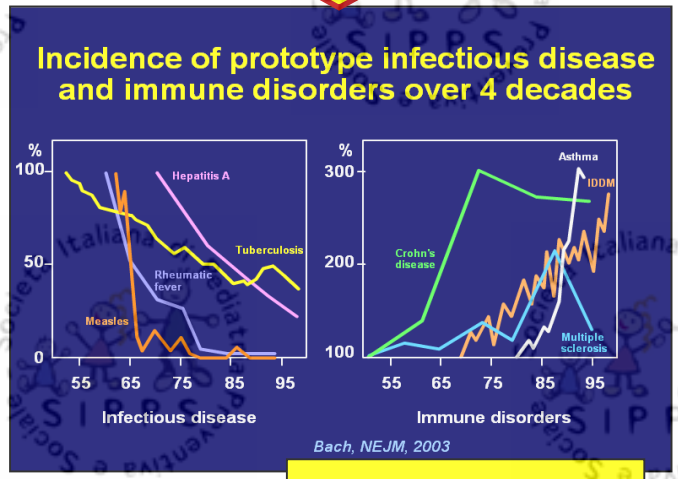
From Genetics to Epigenetics


Towards a paradigm shift in biomedicine.
Environmental interference with the human (epi)genome

6

Epi-genetic Mismatch DOHA




7

XXI Century Epidemiological Transition

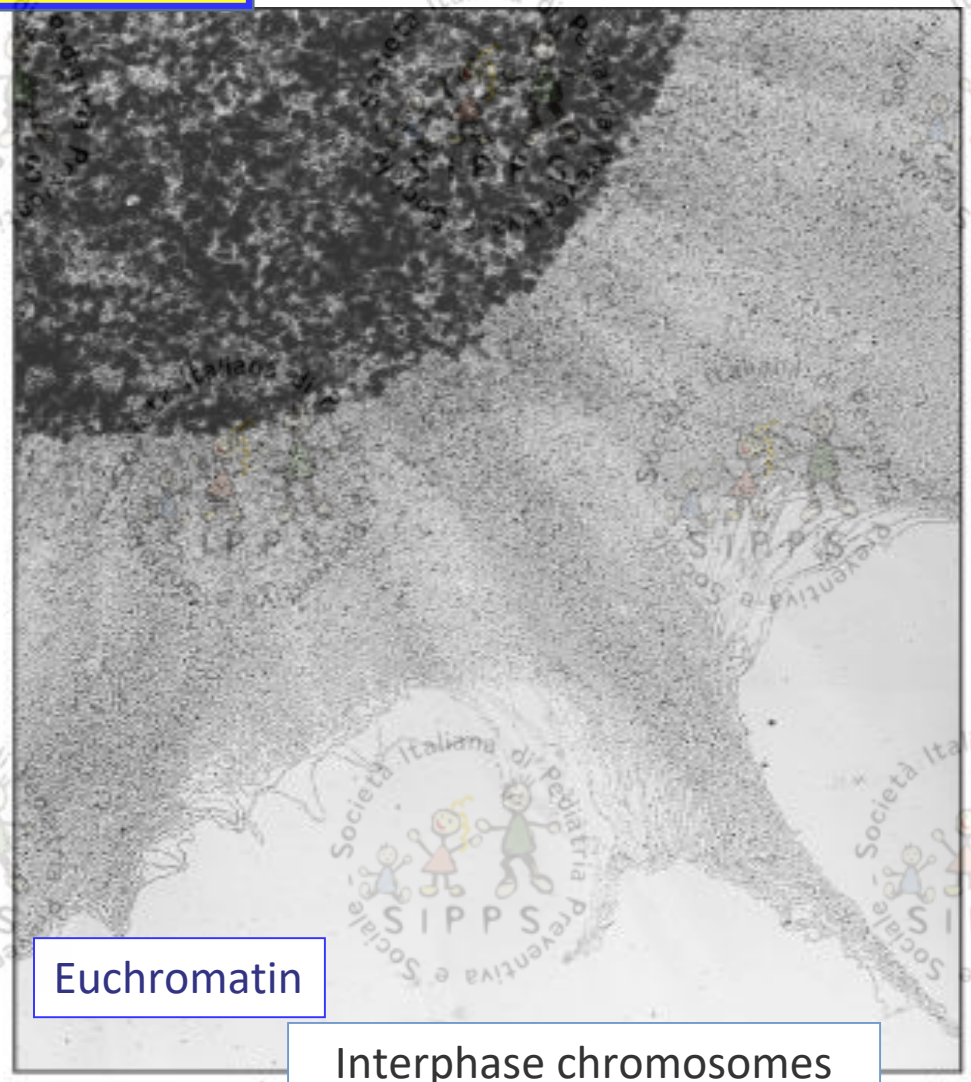

ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee


ECERI
European Cancer and Environment Research Institute

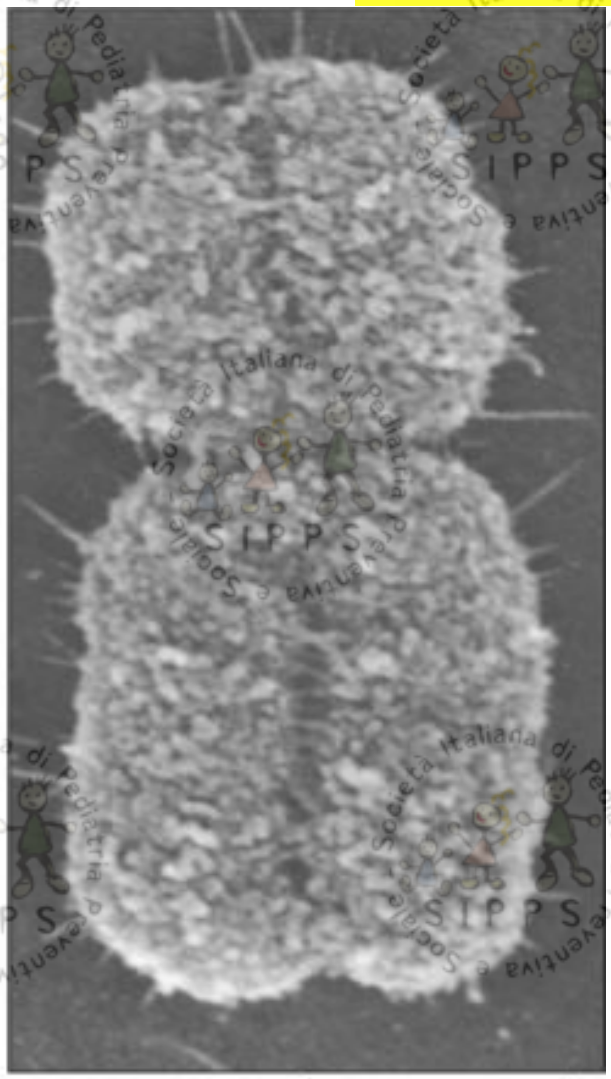
# The first keyword: **Epigenetics**

Heterochromatin

***Epigenetics*** appears to be the most appropriate and **powerful tool to build up a new systemic model of genome ..**




Mitotic chromosome




.. finally understood as a **dynamic and fluid molecular network** which can interact within itself and with the outside

Figure 4–21. Molecular Biology of the Cell, 4th Edition.

**Towards a Kuhnian Revolution in Biology**

nature biotechnology



COMMENTARY

EPIGENESIS AND COMPLEXITY

# The coming Kuhnian revolution in biology

*Richard C. Strohman*

The Watson-Crick era, which began as a narrowly defined and proper theory and paradigm of the gene, has mistakenly evolved into a revived and thoroughly molecular form of genetic determinism.

2

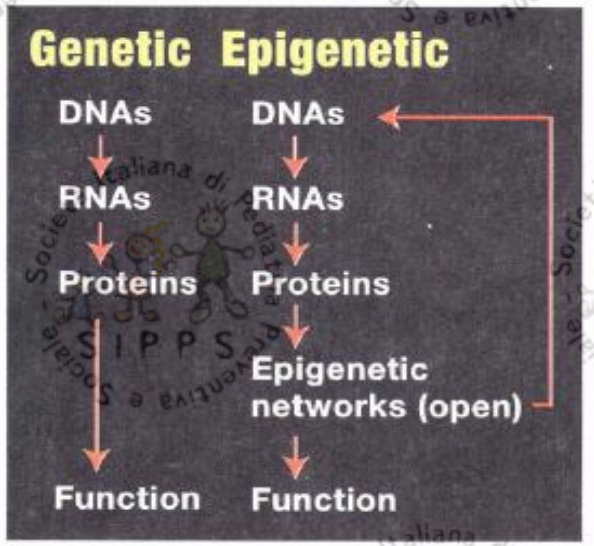



Figure 1. Genetic and epigenetic theories of information processing.

1

In 1997 the well known molecular biologist **R. Strohman** attempted an oblique **attack against the *central dogma* of molecular biology**; the **deterministic, linear, uni-directional pathway from DNA to RNA to proteins to phenotype..**

3

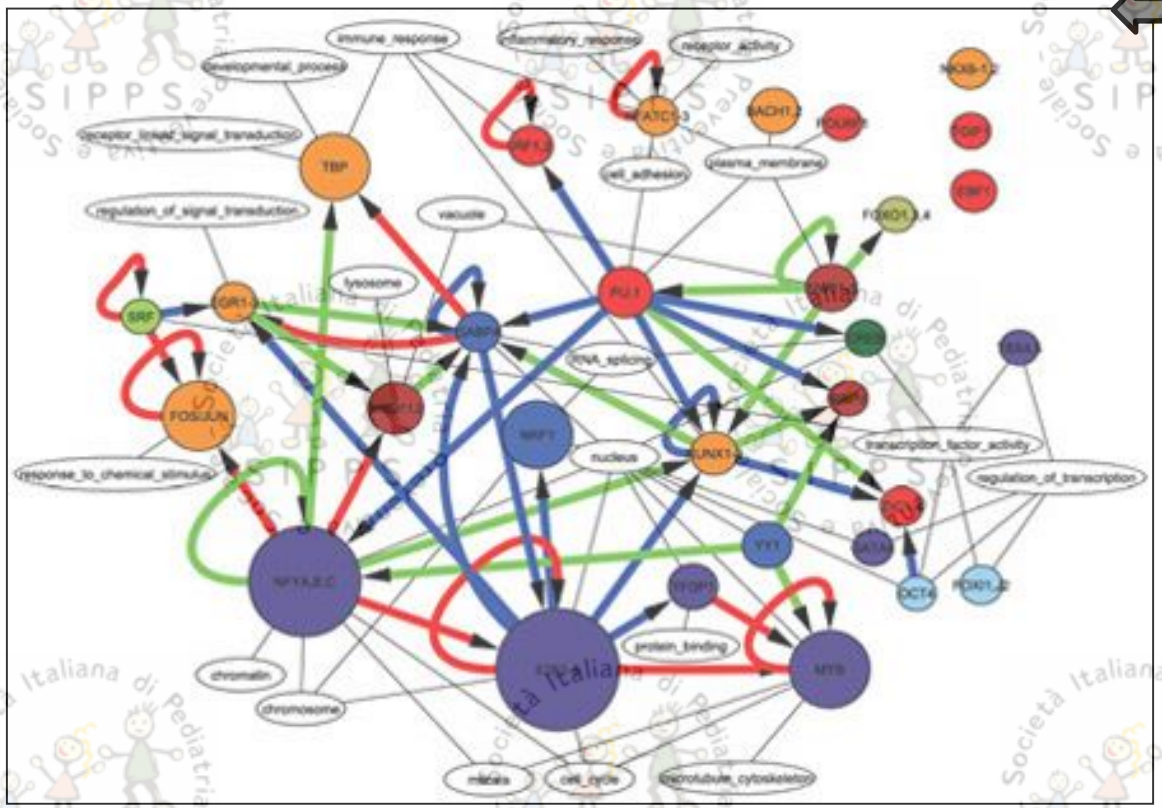
We have **wrongly extended the linear theory of the gene** to the "realm" of the gene management... but the **gene management is an entirely different process,** involving **interactive cellular processes that display an interactive complexity.. which is epigenetic in nature**

Science AAAS

ScienceInsider
Breaking news and analysis from the world of science policy

From directing **the fate of stem cells to determining how.. we grow**, **the genes in our body act in complex networks..** the whole ***Genome*** is a Complex and **highly dynamic molecular Network** of ***interacting Genes*** and ***non-codifying sequences.***. and ***proteins***

***….Genes Know How to Network…BUT…***



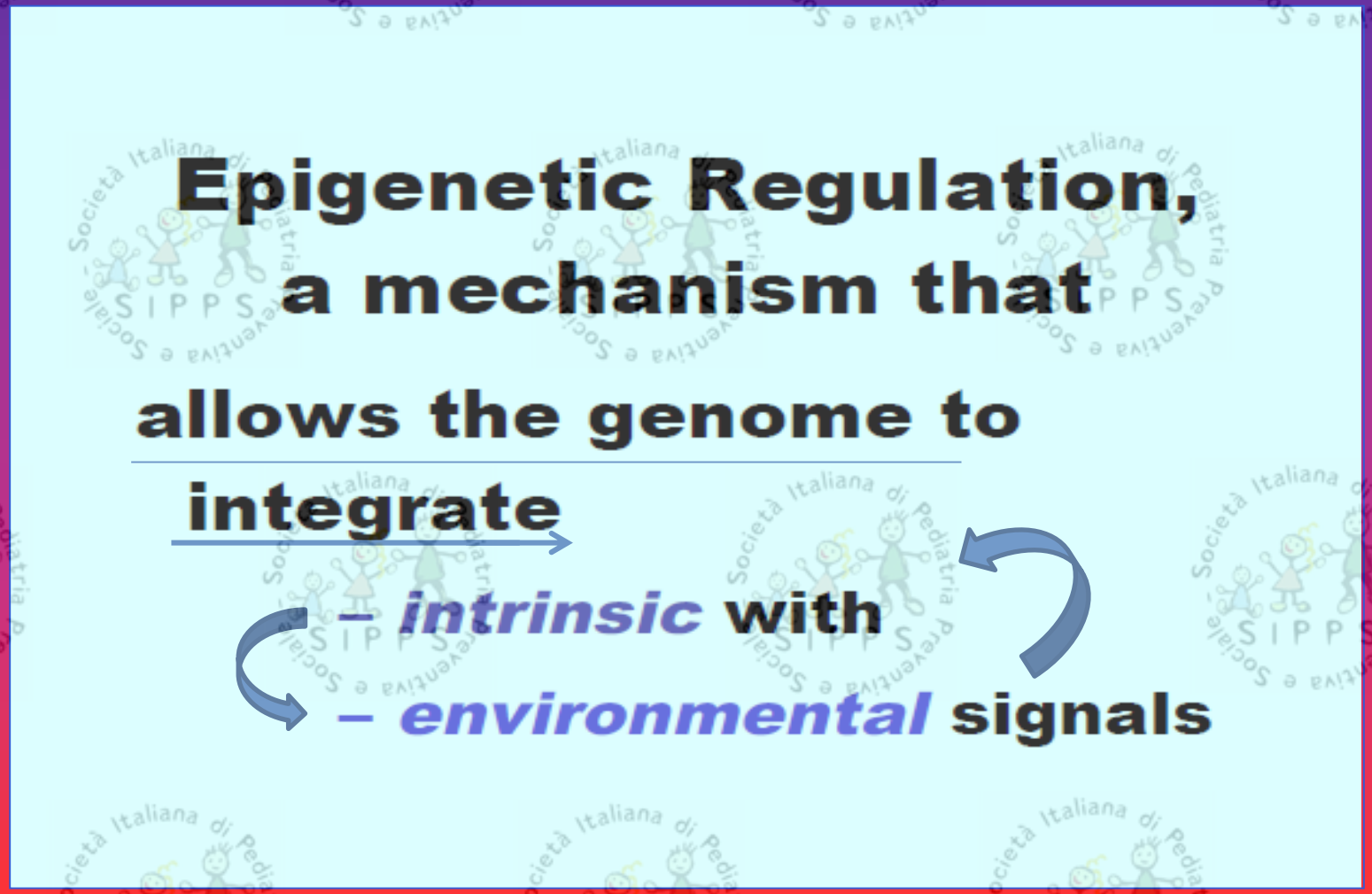
http://news.sciencemag.org/sciencenow/2009/04/21-03.html

**IN FACT Genes need to be told to switch "off" and "on":**

- **Genes need to be told** how much **expression (protein) is required** and where.
- **Genes need to be regulated** – this **regulation is not performed by DNA** but by many other controls arranged in a **complex network**
- DNA has been called the *Book of Life* by the *Human Genome Project* scientists, but many other biologists consider **DNA to be simply a random collection of words from which a meaningful story of life may be assembled…**
- **In order to assemble that meaningful story, a living cell uses a second informational system. (…) The key concept here is that these dynamic-epigenetic networks have a life of their own —they follow network-rules not specified by DNA**

Strohman R. , April 2001 Beyond genetic determinism

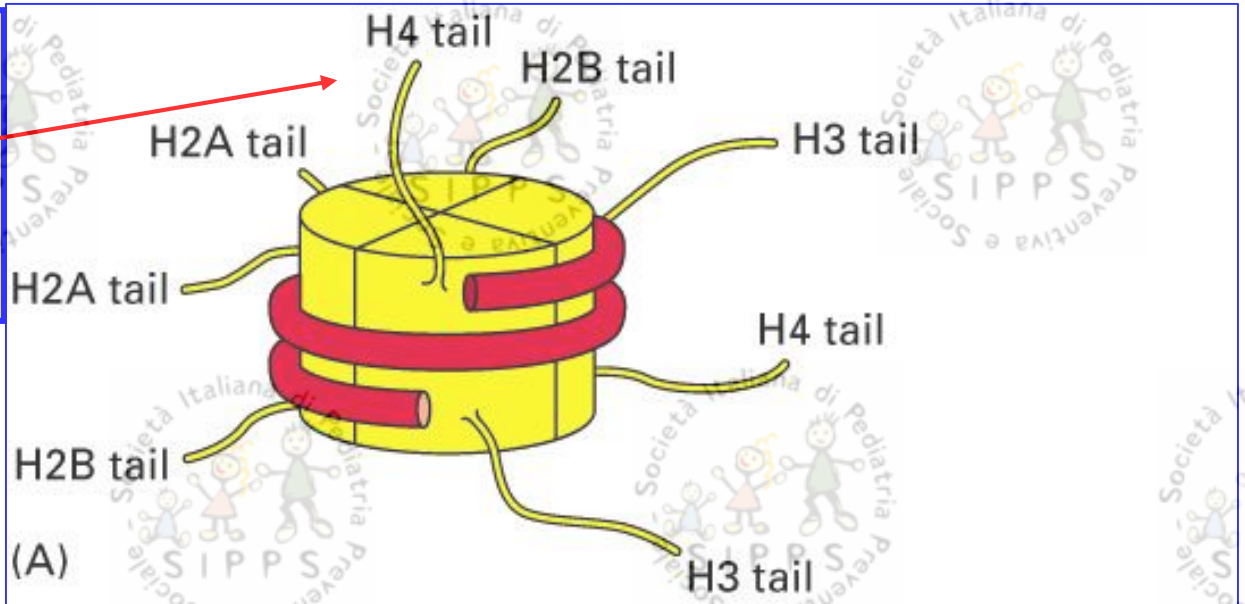
In such a **fluid and systemic model** the ***epigenome*** (also defined by some scientists as **the controlling *software*** of the genome) behaves as a sort of *compensation chamber* - the specific place where the flow of **information** that comes from outside (*environment* and *microenvironment*) meets and interacts with the **information encoded in the genes** for millions years (the ***hardware***)




Rudolf Jaenisch- Whitehead Institute and Dept. of Biology, MIT, Cambridge, MA

The **Histone tails** are a **critical determinant** of chromatin structure

They could be regarded as the **sensory / receptive component** of the genome



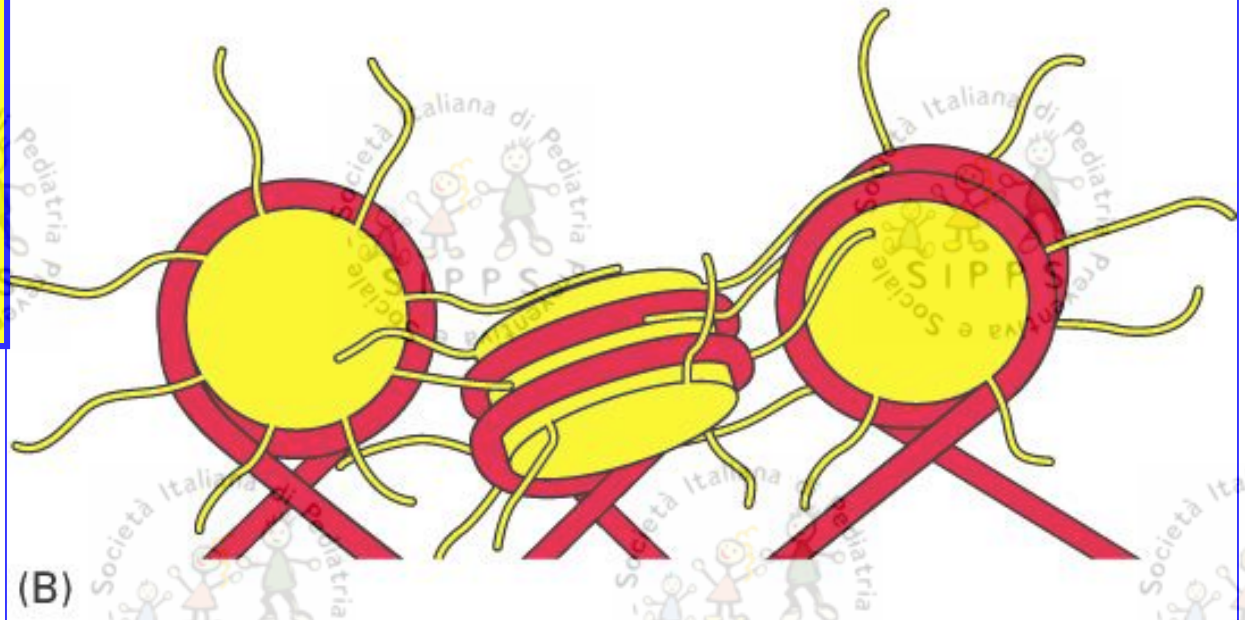




Figure 4–32. Molecular Biology of the Cell, 4th Edition.

**Histone Tails** are subject to a variety of **covalent modifications**

**The Histone Code"** hypothesis: **modifications of the Histone tails** act as marks **read by other proteins** to control the **expression** or **replication** of chromosomal regions

E.g. generally, ***Histone Acetylation*** *is associated with* ***transcriptionally active genes***

***Deacetylation*** is associated with **inactive genes (= gene silencing)**

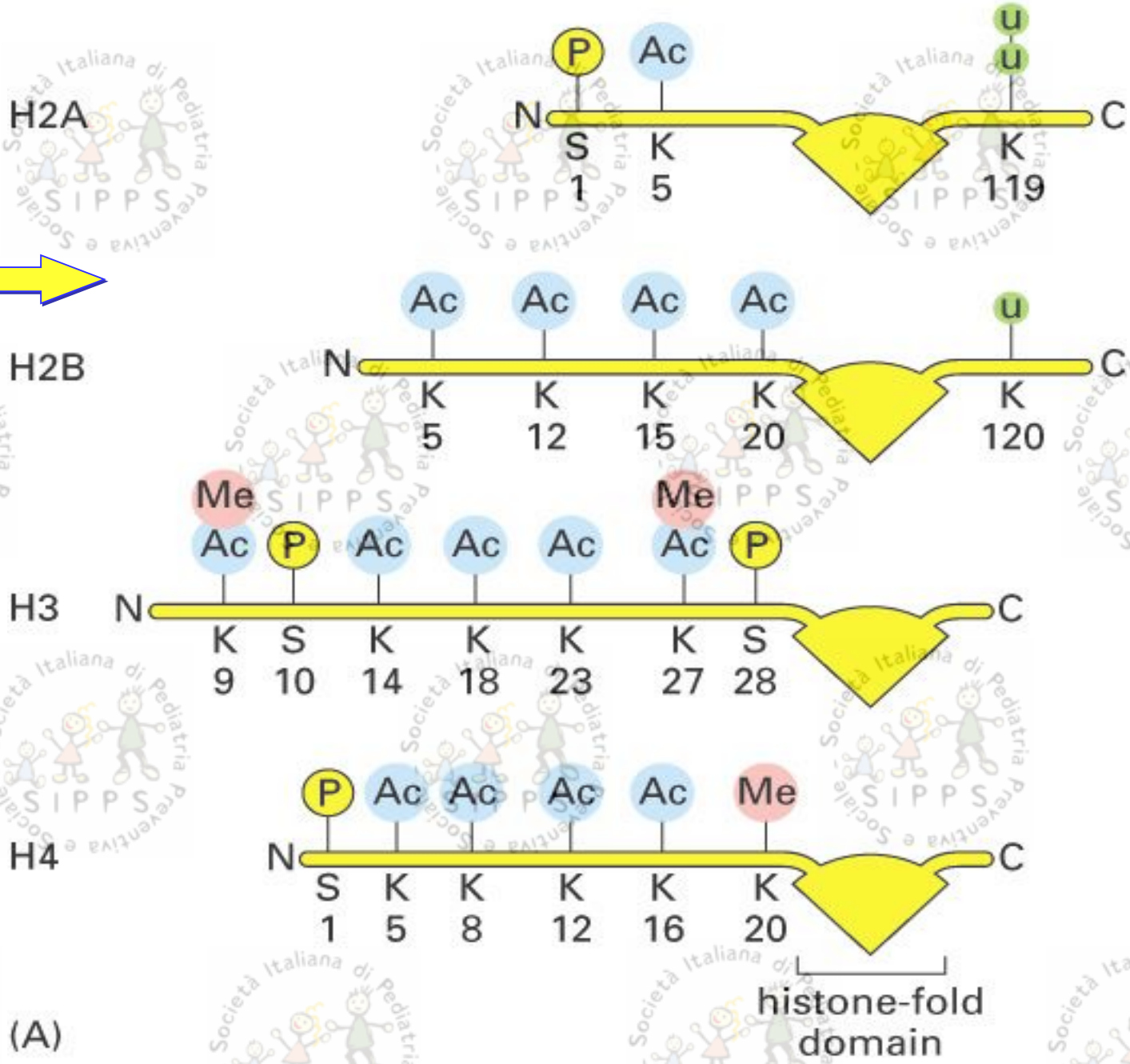
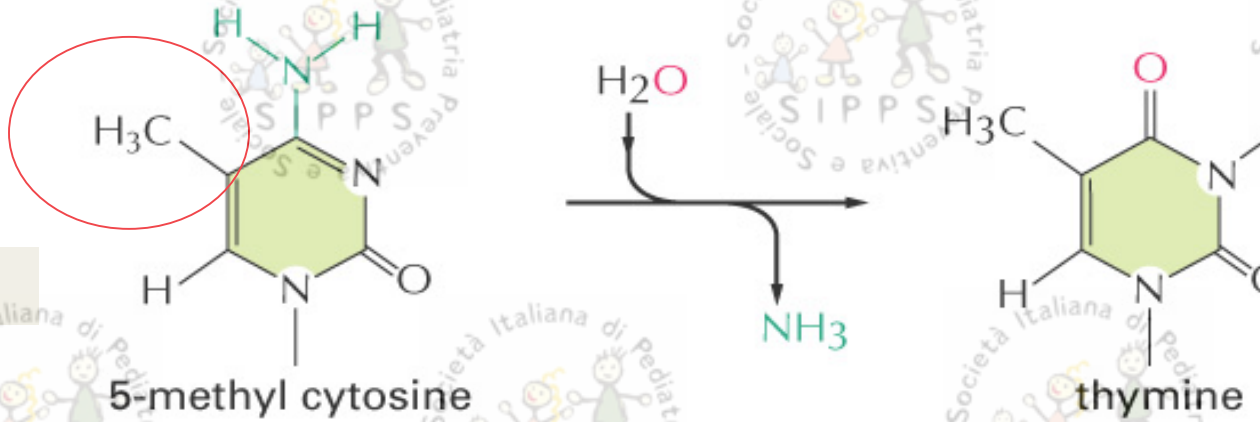


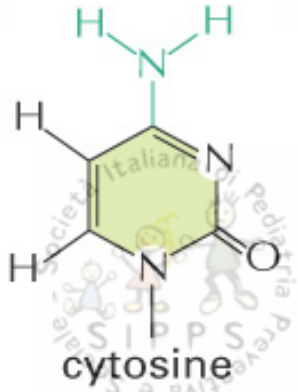

Figure 4–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

# DNA methylation

DNA methylation is a very **stable/covalent modification** of the DNA, very important for ***gene silencing*** in human cells. Most genes have **GC rich areas of DNA in their promoter regions,** that are also referred to as ***CpG islands***. **Methylation of the C residues within the CpG islands leads to gene silencing.**

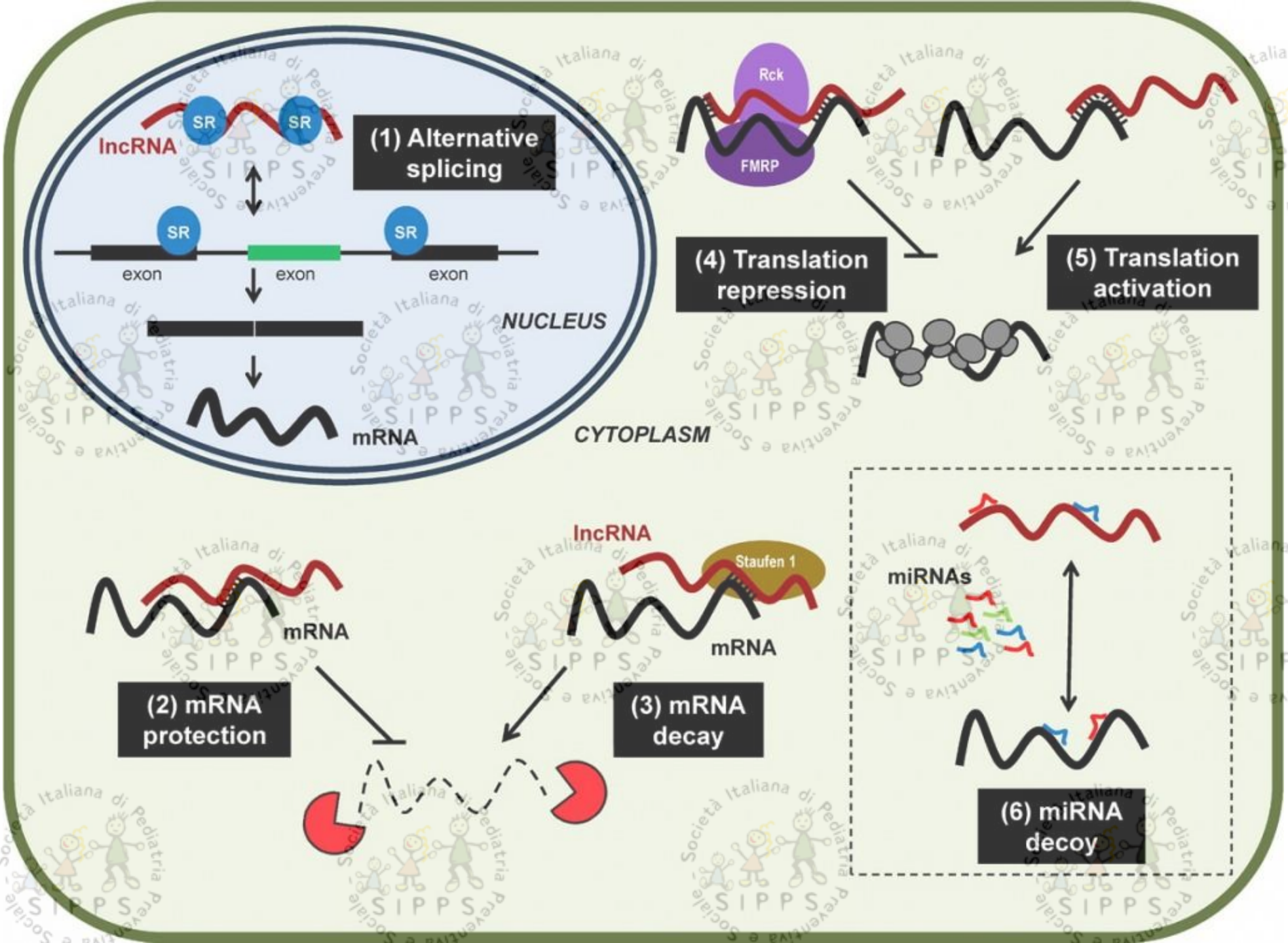
(highly *unstable* base)



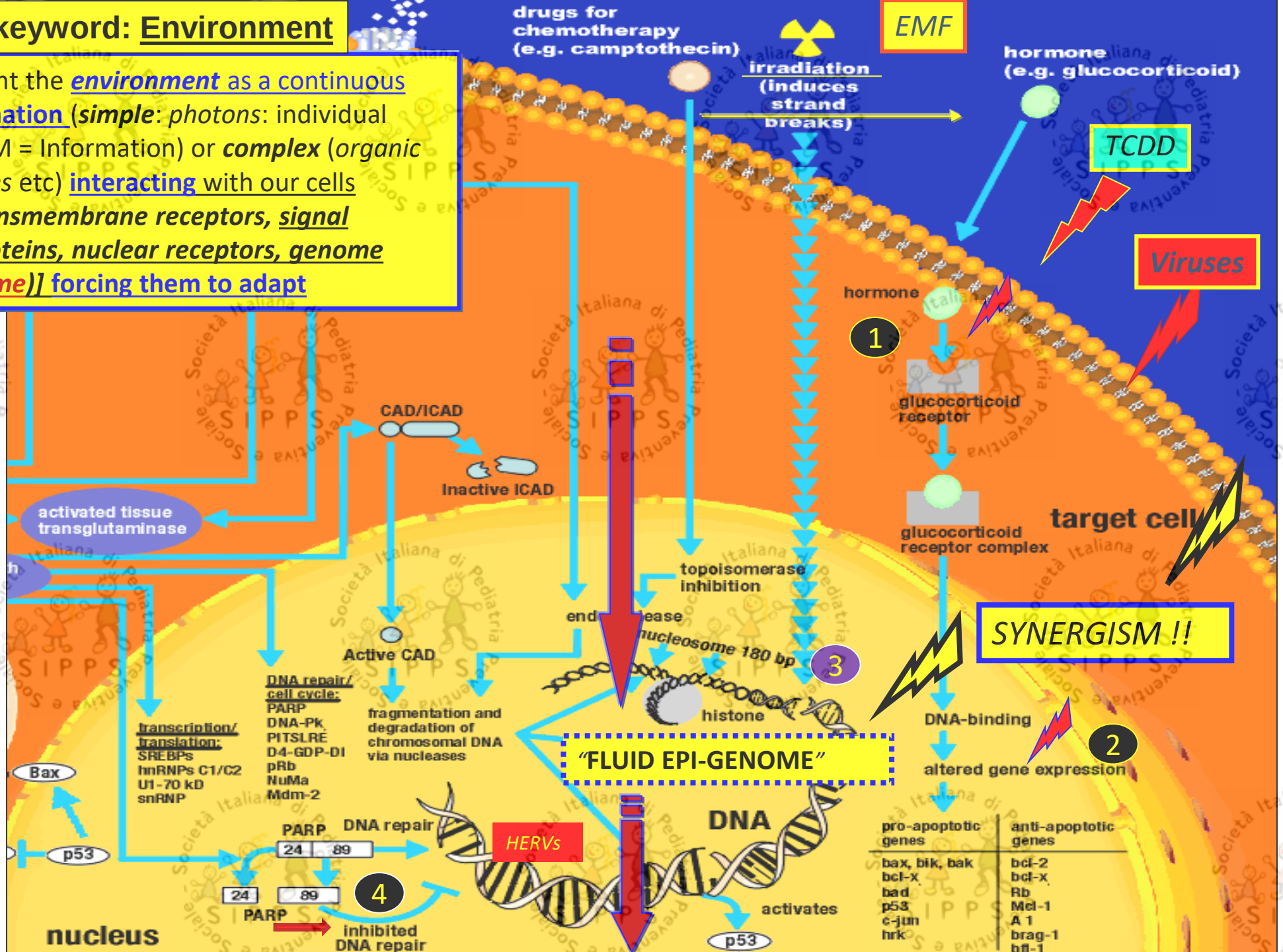
3

The **vast majority of human DNA does not encode proteins**, but ***microRNAs:*** hundreds of these ***ncRNAs*** have already been discovered that play roles of ***natural genetic engineering***

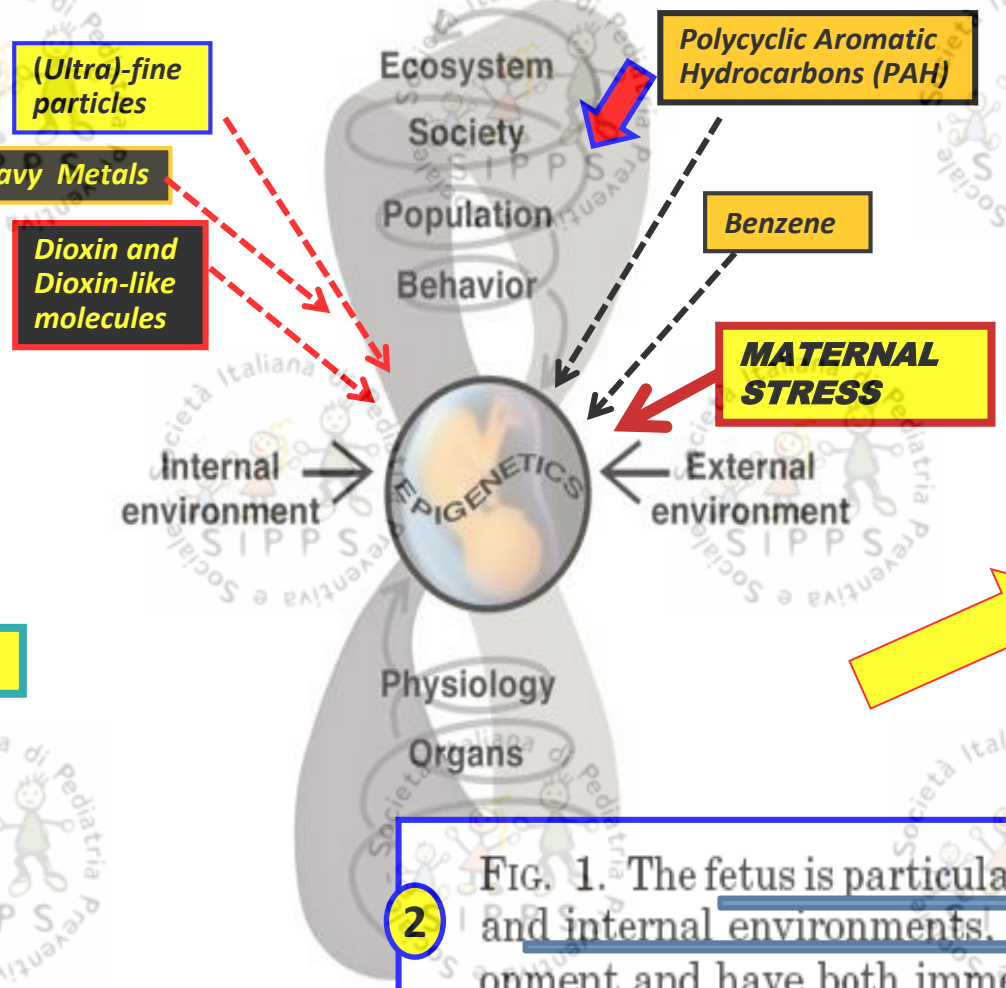


# The **second keyword: Environment**

We may represent the ***environment*** as a continuous stream of **information** (***simple***: *photons*: individual packages of E = M = Information) or ***complex*** (*organic molecules, viruses* etc) **interacting** with our cells [***membrane /transmembrane receptors, signal transduction proteins, nuclear receptors, genome (DNA + Epigenome)]*** **forcing them to adapt**



The **third** key word is ***fetal programming …***

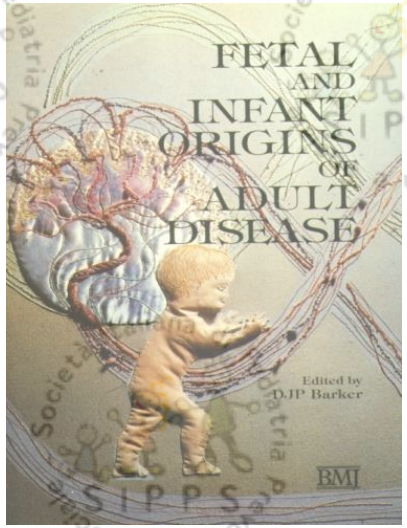



**ONTOGENY**

1

… a technical term that refers to the ***capability*** and, at the same time, the ***requirement***, for **embryo-foetal cells to define their epigenetic setting in a predictive and adaptive way** , in relation to the information coming from the mother and, through her, from the outer world ..

A ***predictive adaptive response (PAR)*** is a developmental trajectory taken by an organism during a period of ***developmental plasticity*** in response to perceived environmental cues..




2

FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular to the organism's behavior and place in society, and tend to be amplified in their consequences as they ascend through these levels. Ultimately, these influences may be epigenetic in nature, inducing mitotically heritable alterations in gene expression without changing the DNA.

3

The **fourth** keyword is ***developmental plasticity***

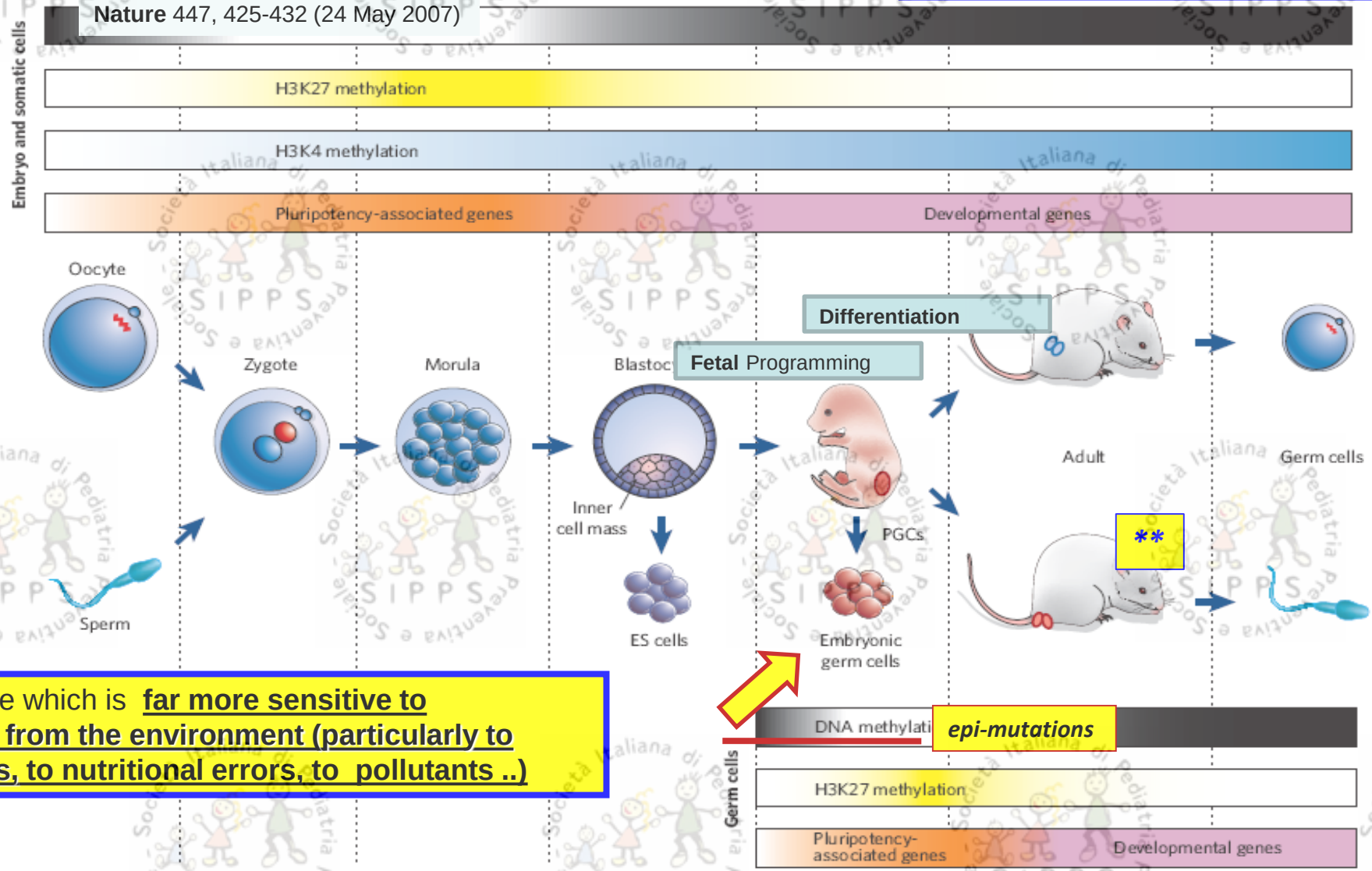
***Cellular Differentiation*: an *epigentic process***

**The actual genetic program of a single multicellular organism is the product of nine months of epigenetic adaptive-predictive "formatting" of trillions of cells)**

1 ⇩ 2

# Stability and flexibility of epigenetic gene regulation in mammalian development

**Nature** 447, 425-432 (24 May 2007)




methylation. During the early development of PGCs, DNA methylation and

**Developmental PLASTICITY**

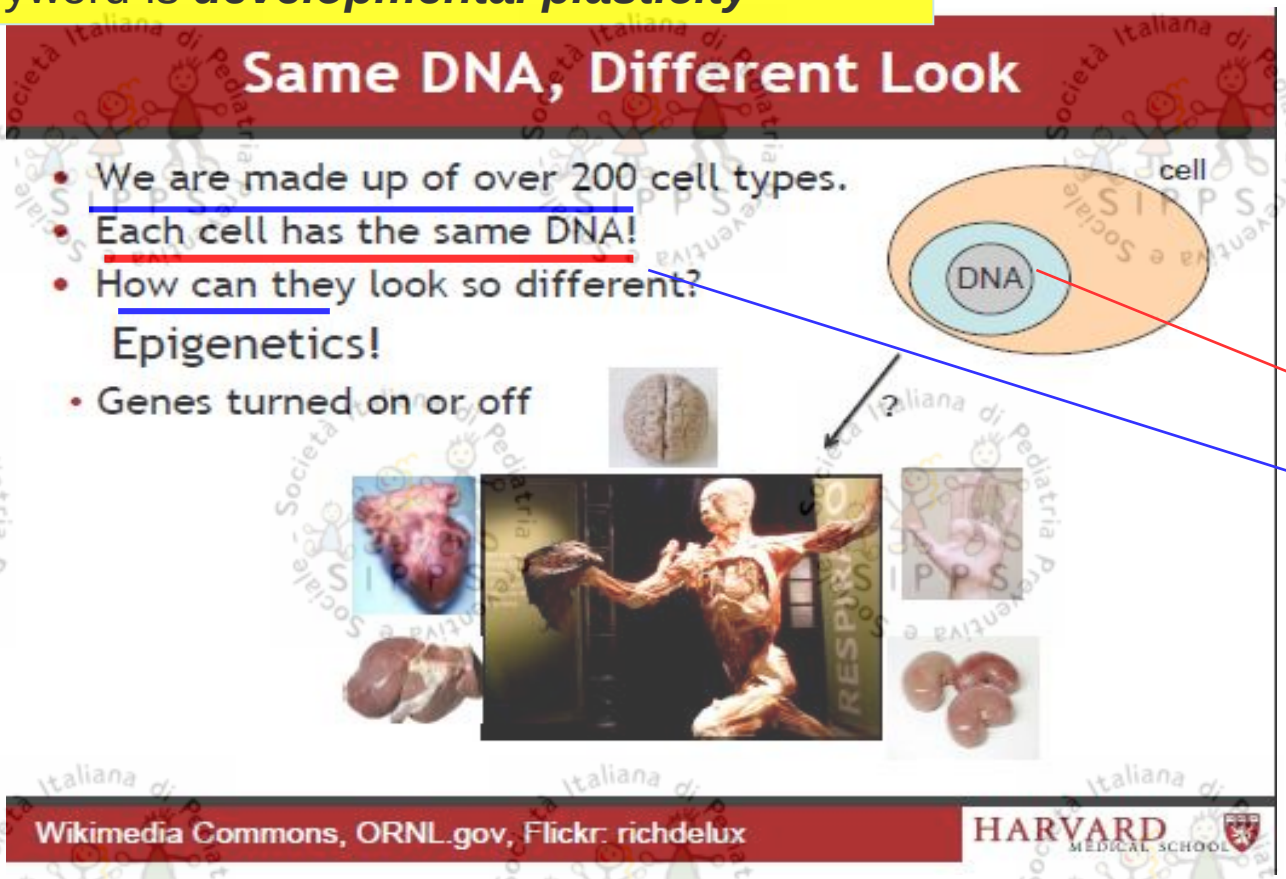
**Differentiation is the process through wich** the organism changes **from a zygote to a complex system** of **tissues** and **200 cell types (genetically identical.. each with its own epigenetic and morpho-functional characteristics)..**

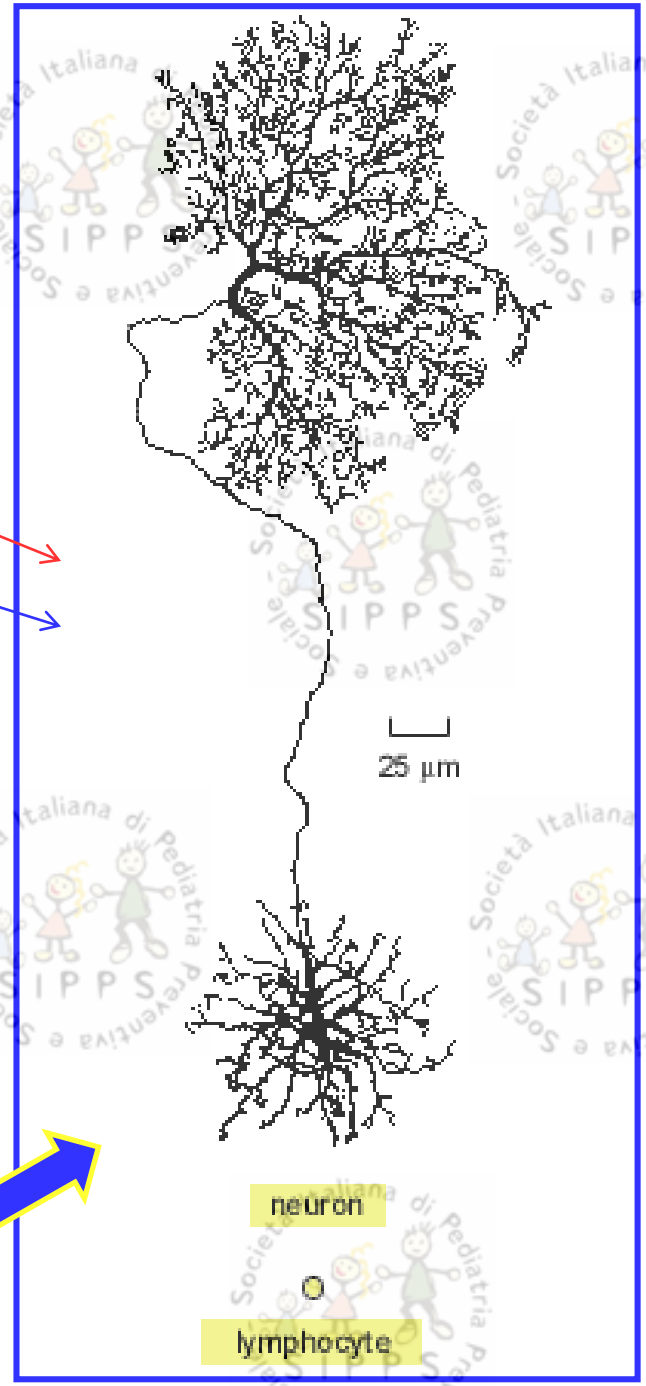
3

This is the stage of life which is **far more sensitive to information coming from the environment (particularly to maternal-fetal stress, to nutritional errors, to pollutants ..)**

The ***brain**** is by far the ***most plastic organ*** during all (human) life

The **fourth** keyword is ***developmental plasticity***



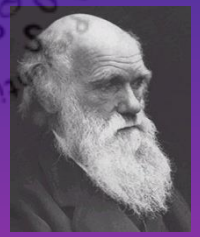




This image clearly shows the **"power" of the epigenome** and the **predominant role of environmental information in the phenotypic shaping of cells, tissues , organisms** .. the **huge phenotypic (morpho- functional) difference** between a *lymphocyte* and a *neuron* **is not due to DNA, which is virtually identical in the two cells** , but to the manner in which **the same genome has been utilized by the two cells**, on the basis of the **information (positional and environmental) received during the first months of life (for neuron in the first 2 years)** and **processed by the epigenetic networks**

The **fifth** key word is **phylogeny**

**The chimpanzee DNA is for 98.77% identical to the human .**
**On average, a gene encoding a protein in a man differs from its chimpanzee ortholog by only two aa substitutions**
**.. almost one third of human genes**
has exactly the **same protein translation** as their orthologs in chimpanzee

**We are quite stable (for millions of years) both genetically and phenotypically**



# Species ***phylogeny***

*From the Tree of the Life Website, University of Arizona*

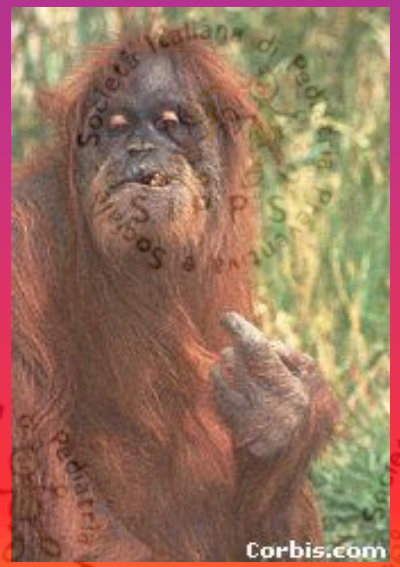
***Evo***

*Orangutan*

*Gorilla*

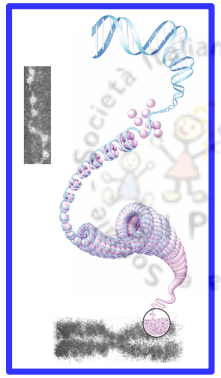
***Chimpanzee***

***Human***

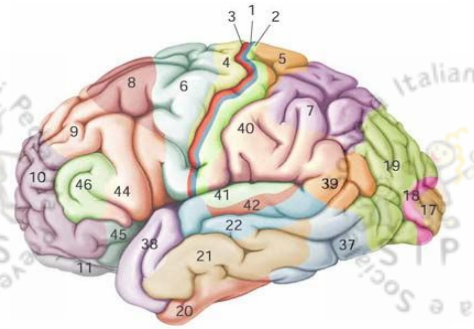





***Sanger Institute***

**of 4 billion years of molecular coevolution** * (in particular, our **DNA** is the **product** of this long journey) ..



We should never forget that **we are at the same time the product**

***Mismatch***

and of **9 months of an individual development**

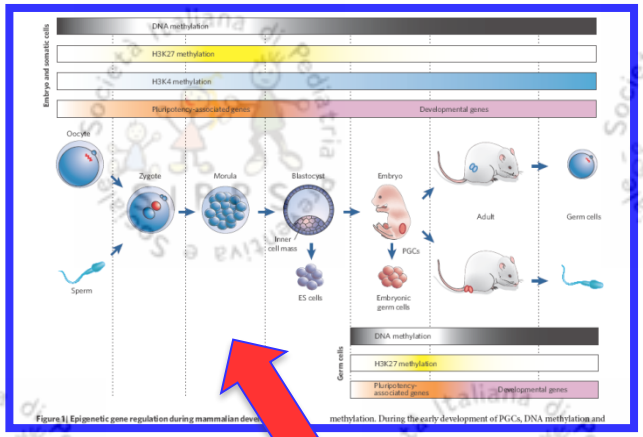
The **epigenome** being the product of nine months of ***cellular and tissue programming*** (**adaptive** to an environment that is rapidly changing)..

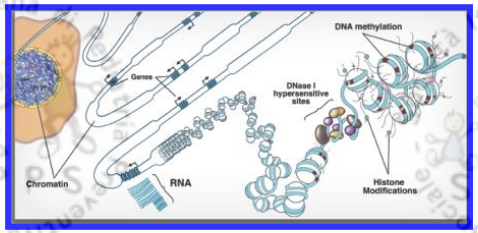
***Ontogeny***

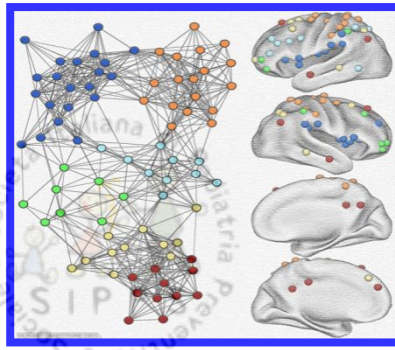
***Devo-Evo***

***Phylogeny***

***Ontogeny*** Recapitulates (***anticipates***) ***Phylogeny***



A ***major risk***: the **EDCs** and other ***xenobiotics*** (***not*** being the product of ***molecular coevolution***) can interfere at this level, acting as ***pseudo-morphogens***

www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2015;4(2):e040237
doi: 10.7363/040237
Received: 2015 Sept 21; accepted: 2015 Oct 10; published online: 2015 Oct 26

Editorial

# Environment and fetal programming: the origins of some current "pandemics"

**Ernesto Burgio**

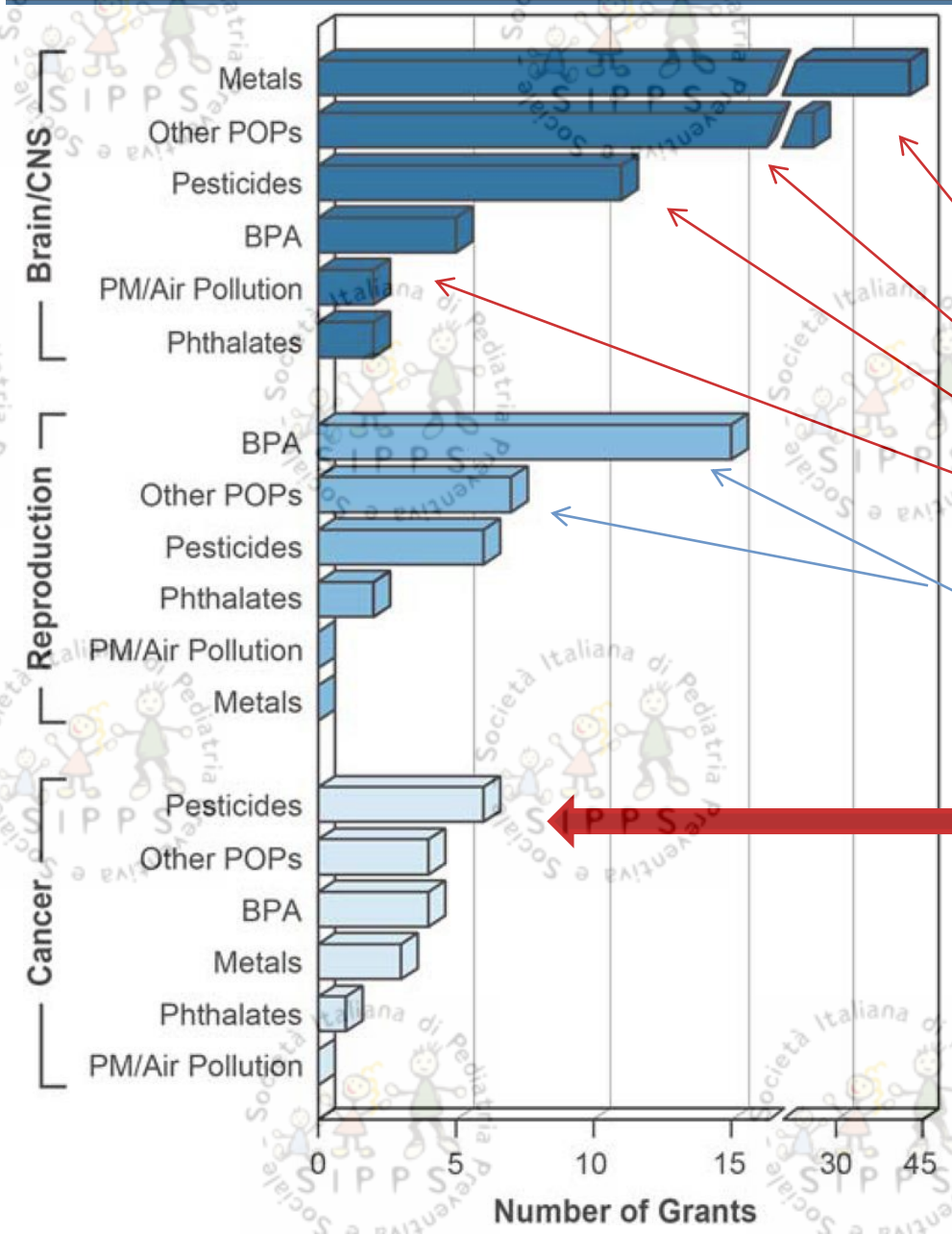
ECERI – European Cancer and Environment Institute, Bruxelles, Belgium

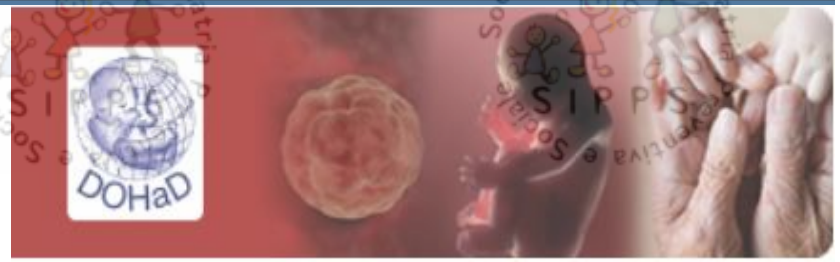
ISDE – International Society of Doctors for Environment (Scientific Office), Arezzo, Italy

*"The womb may be more important than the home"*
David Barker

This new paradigm is important not only to explain in a more exhaustive way the embryo-foetal origins of all the above mentioned disorders and their dramatic increase over the last decades, but also to try to effectively face this epidemiological transition. The key-term in this context is certainly primary prevention: only by reducing the maternal-foetal factors of distress and the exposure of the foetus (and of its gametes) to pollutants, it would be possible to protect the correct programming of cells, tissues and organs.

The key-term in this context is certainly ***primary prevention***

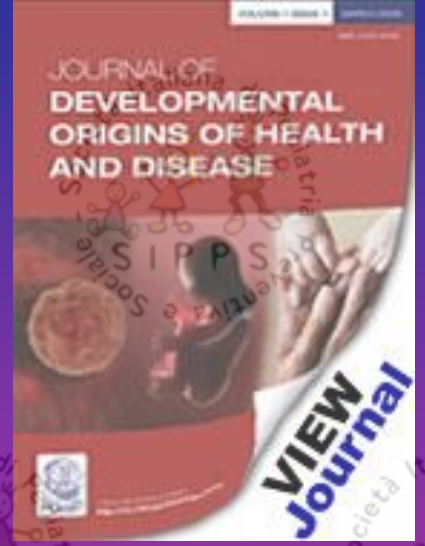



Most studied **disease/organ endpoints** and associated **toxicity endpoints**.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4393755/figure/F3/

Eventually, during the last years, the ***fetal programming mismatch theory*** has been transformed **from a theory essentially useful to explain the pathogenic mechanisms causing certain diseases of adulthood, into the key-model theory of the embryo-fetal origins of adult diseases (DOHA-Developmental Origins of Health and Diseases)**




*Obesogens*

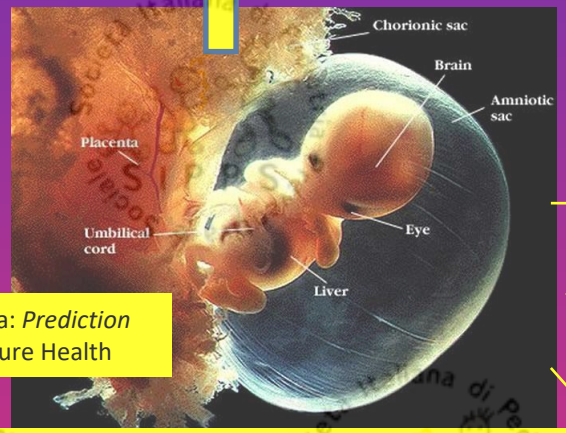
*Multiorgan Effects of Endocrine Disruptors*

*Pesticides*

*In Vitro Fertilization*

*Materno Fetal Stress*

**Obesity/Metabolic Syndrome/Diabetes 2**




Placenta: *Prediction* of Future Health

**Developmental Time Windows of Vulnerability**

**Cardiovascular Diseases**

**Ipertension**

**Asthma and allergies**

Lung Development ⇓

**Reproductive Diseases/Dysfunctions**

**Semen Abnormalities**

**CANCER**

**DOHAD**

**Neurobehavioral Deficits and Diseases**

**Psychiatric Diseases**

# Relative frequency of articles with *epigenetic* or *epigenetics* in their title

International Journal of Epidemiology

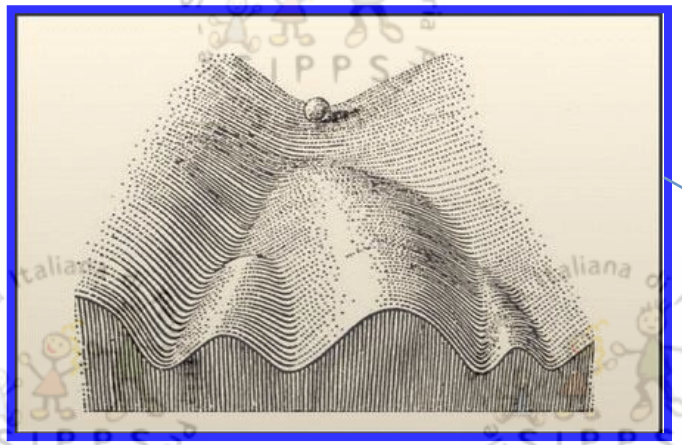
David Haig Int. J. Epidemiol. 2012;41:13-16

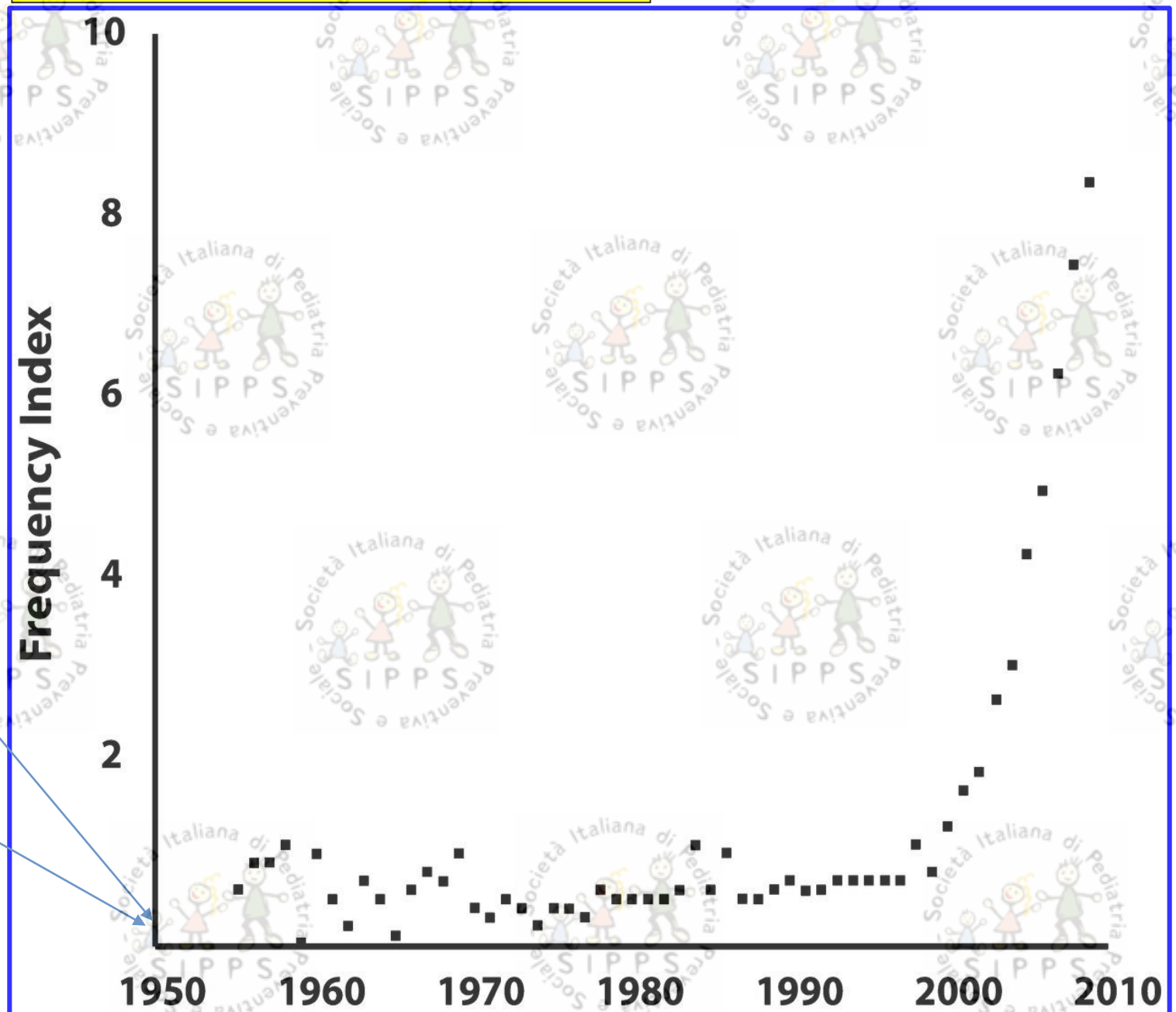
## Foreword 1

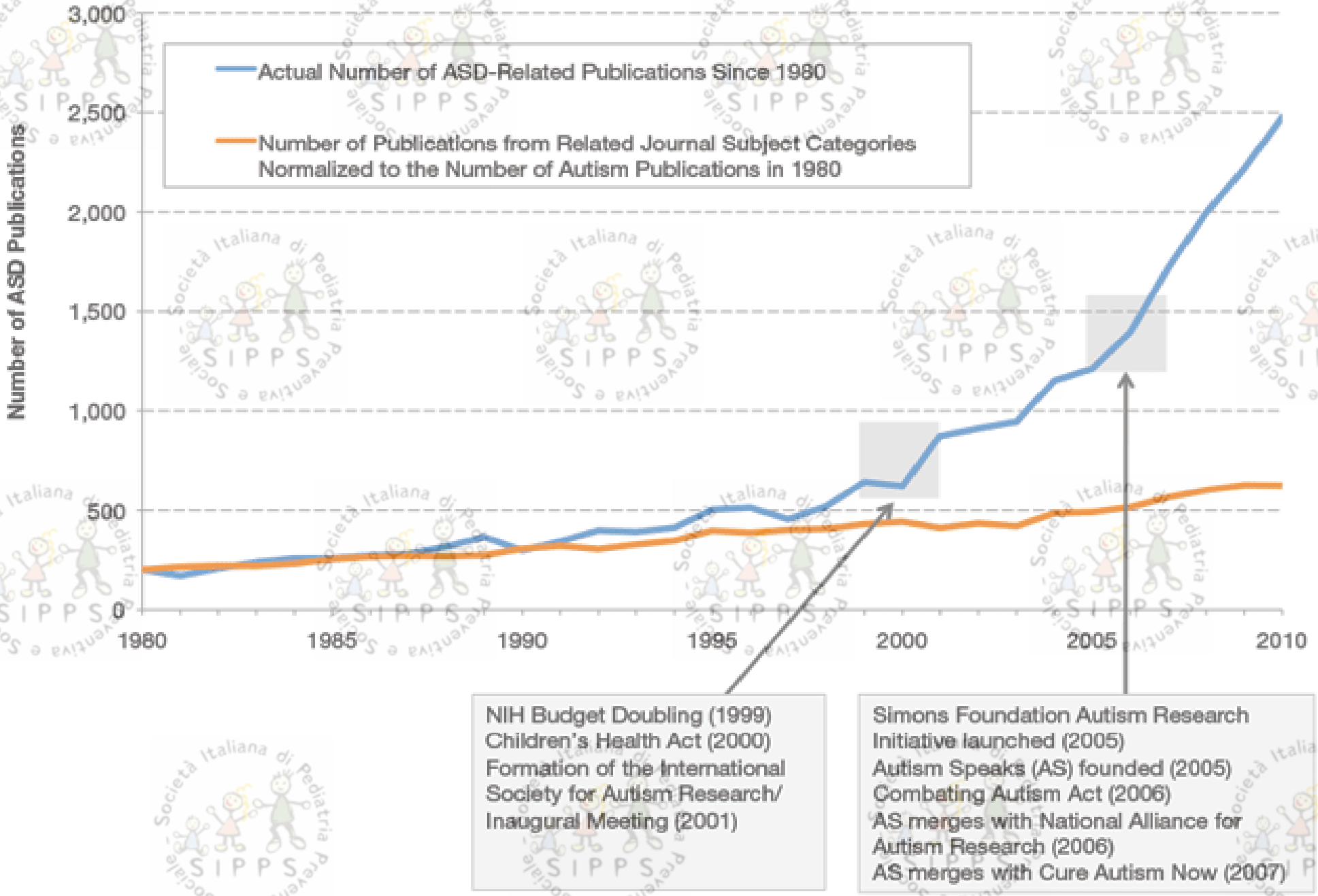
Photo: Ramsey & Muspratt

THE AUTHOR

C. H. Waddington, Sc.D., Fellow of Christ's College, Cambridge. Born 1905. Childhood spent in India and on a farm in Worcestershire. Educated Clifton and Cambridge. Became a research scientist, interested in the changes undergone by living things; first in evolution in fossils, then in inheritance in plants, then in the development of animals. Has held the Gerstenberg Studentship for philosophy, and was awarded the first Brachet Prize for embryology by the Royal Academy of Belgium. Lived mainly in Cambridge, except for two summers in Germany, and a year in the United States. "My ideas about the world have been, I hope, broadened by work in collaboration with scientists of many foreign countries: America, Germany, Hungary, Czechoslovakia, Switzerland, Russia (Red and White), Holland, Belgium, France, Sweden, China, Japan." Married, one son. Author of *How Animals Develop*, *Introduction to Modern Genetics*, *Organisers and Genes*, and about fifty papers in technical journals.






Number of ASD Publications
3,000
2,500
2,000
1,500
1,000
500
0
1980
1985
1990
1995
2000
2005
2010
Actual Number of ASD-Related Publications Since 1980
Number of Publications from Related Journal Subject Categories Normalized to the Number of Autism Publications in 1980
NIH Budget Doubling (1999)
Children's Health Act (2000)
Formation of the International Society for Autism Research/ Inaugural Meeting (2001)
Simons Foundation Autism Research Initiative launched (2005)
Autism Speaks (AS) founded (2005)
Combating Autism Act (2006)
AS merges with National Alliance for Autism Research (2006)
AS merges with Cure Autism Now (2007)

How many **research papers about the brain** are published each year?

For **2013**, a PubMed search using the term "brain" shows that **76,945 papers** were published

For **2012**, a PubMed search using the term "brain" shows that **74,303 papers** were published

For 2011, a PubMed search using the term "brain" shows that **69,927 papers** were published

For 2010, a PubMed search using the term "brain" shows that **64,929 papers** were published

For 2009, a PubMed search using the term "brain" shows that **58,459 papers** were published.

For 2008, a PubMed search using the term "brain" shows that **55,874 p**apers were published.

For 2007, a PubMed search using the term "brain" shows that **53,258** papers were published.

For 2006, a PubMed search using the term "brain" shows that **51,163** papers were published.

For 2005, a PubMed search using the term "brain" shows that 47,383 papers were published.

For 2004, a PubMed search using the term "brain" shows that 42,849 papers were published.

For 2003, a PubMed search using the term "brain" shows that 39,964 papers were published.

For 2002, a PubMed search using the term "brain" shows that 37,304 papers were published.

For 2001, a PubMed search using the term "brain" shows that 36,884 papers were published.

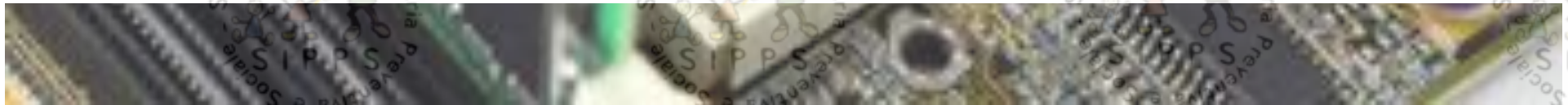
For 2000, a PubMed search using the term "brain" shows that 37,000 papers were published.

For 1999, a PubMed search using the term "brain" shows that 34,828 papers were published.

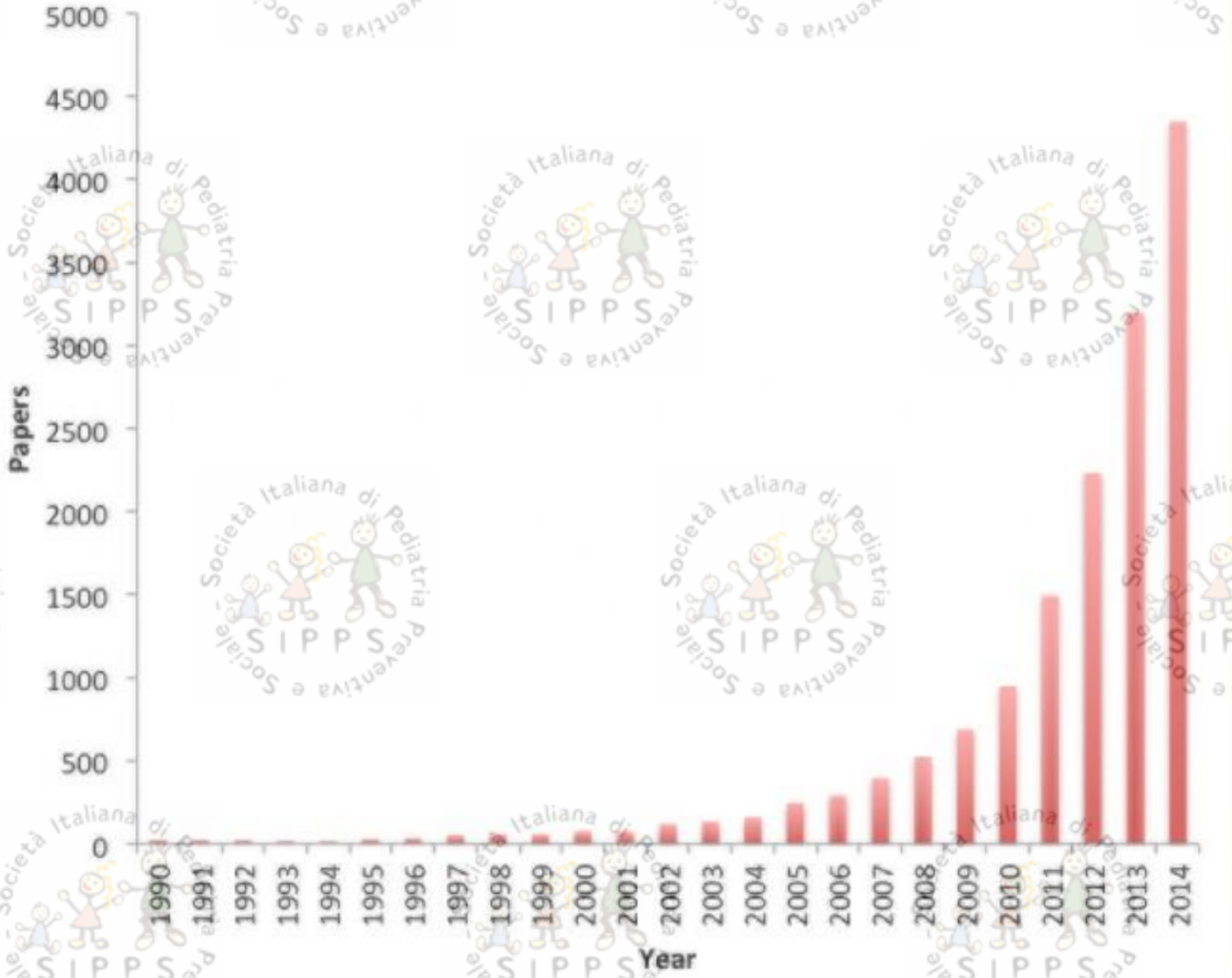
For 1998, a PubMed search using the term "brain" shows that 33,027 papers were published.

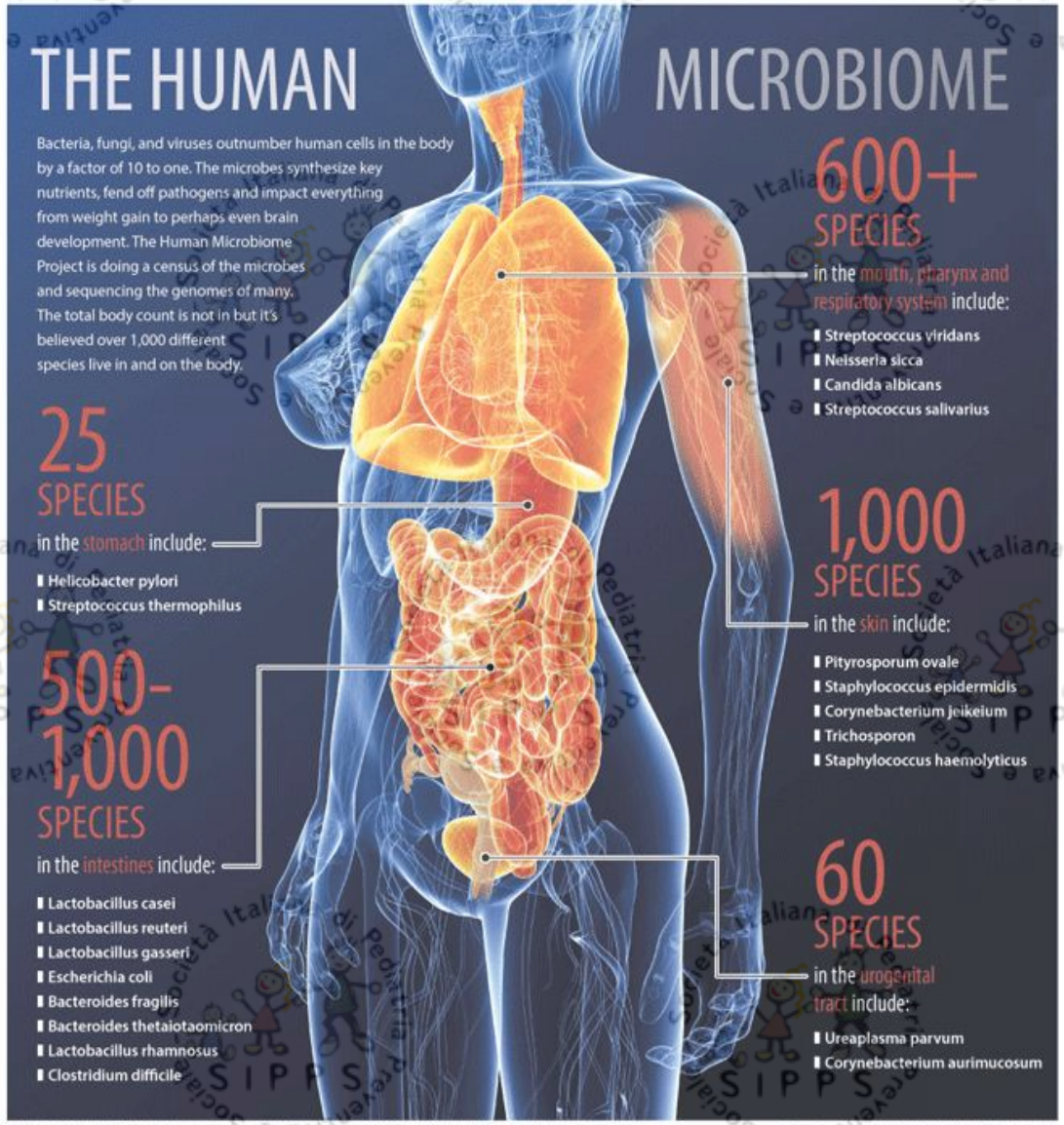
For 1997, a PubMed search using the term "brain" shows that 32,112 papers were published.

For **1996**, a PubMed search using the term "brain" shows that 31,040 papers were published



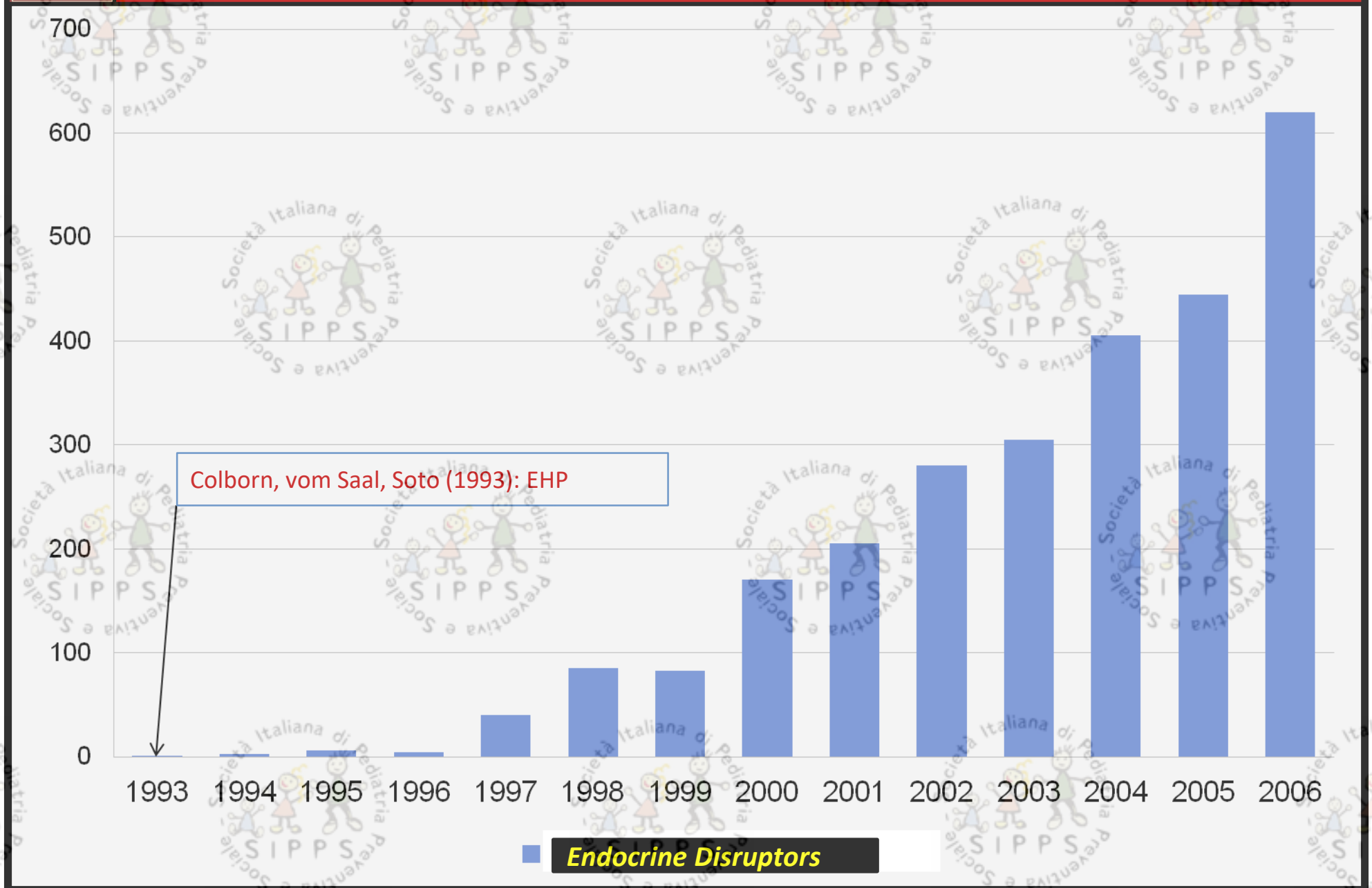
*A quick search for "**Microbiome**" in **scienctific journals online** demonstrates how significantly this field of research has been **growing over the past ten years***



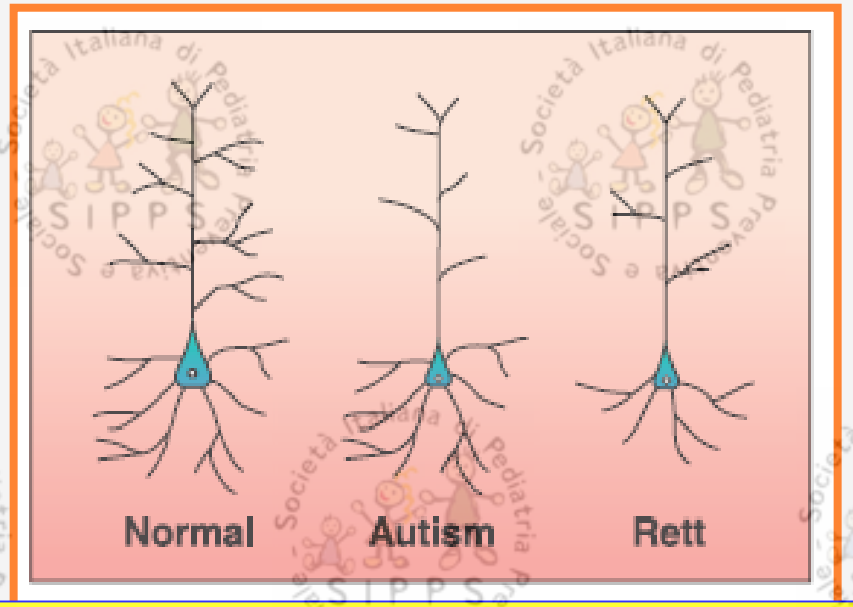



ACADEMY FOR ENVIRONMENTAL MEDICINE

# Published papers about *Endocrine Disruptors* between 1993 and november 2006 (Gies)



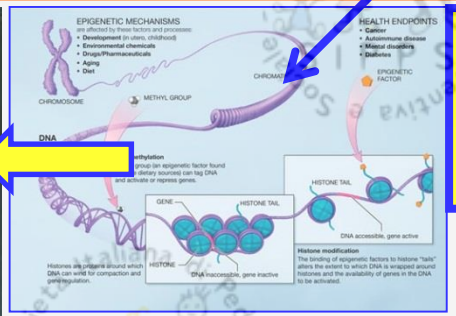
Léo Kanner




Hans Asperger

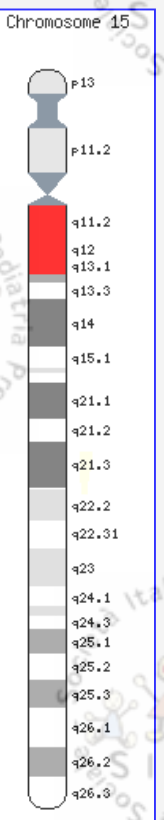
# ASD: from *genetics* to *epigenetics* (and *metagenomics*)

Angelman syndrome




ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee

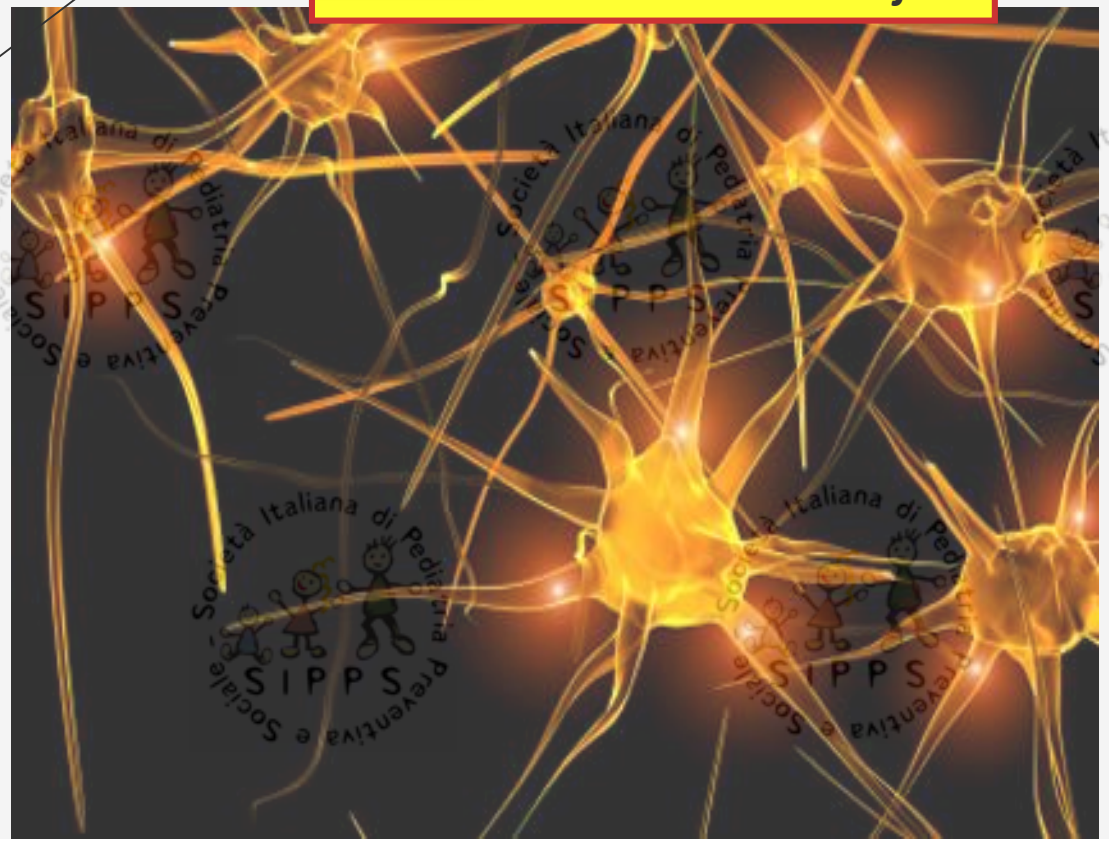




# Autism

- **Autism and autism spectrum disorders (ADS)** are **developmental disorders of neural connections** and, as we will see, of ***synaptogenesis***
- This **affects** the way in which **the brain "processes information"**

*The **Human Connectome Project***



*"We know that synapses are essential for learning, memory, and perception and suspect that imbalances in synapse formation impact disorders of the brain such as autism and schizophrenia," says Elva Diaz, assistant professor of pharmacology at UC Davis. "Our study is the first to identify SynDIG1 as a critical regulator of these important brain connections."*

- The fact that these **problems usually occur after a latency period** (of **normal intellectual and motor development**) shows that
- **the brain basic structures** (cerebral neuronal basic differentiation and migration: definition of the **functional areas of the brain**), **are generally well constructed:**
- It is, so to speak, **the *software (connectome)***
  - ***synaptic*** connections ..
  - ***neuronal circuits*** ..

  **to be damaged.**

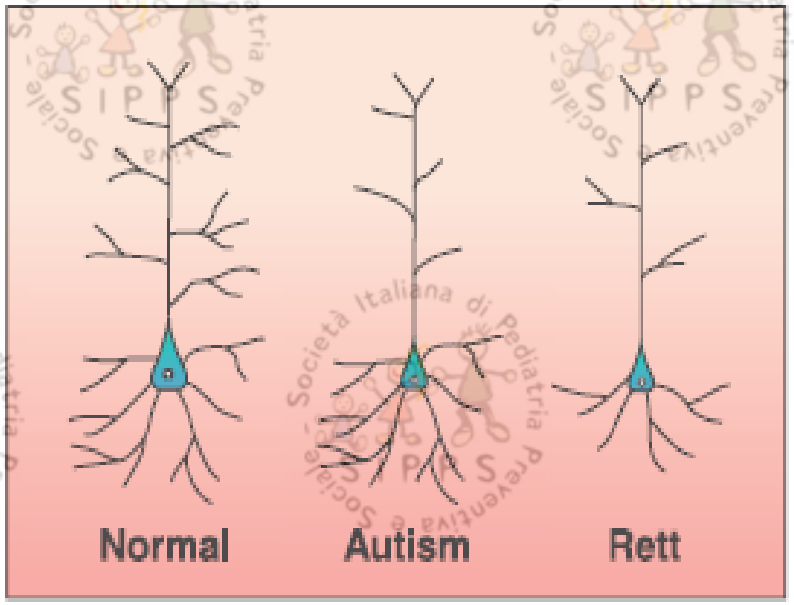



**Fig. 2.** Schematic representation of pyramidal neurons from control, autism, and Rett brains. In autism, the cell body is small and there is reduced dendritic branching. Similar changes occur in Rett, along with reduction in basilar dendritic branching. The reported changes are subtle and apply to a few neurons in selected brain regions in each disorder (*50*, *81*).

**Postnatal Neurodevelopmental Disorders: Meeting at the Synapse?**
Huda Y. Zoghbi, *et al.*
*Science* **302**, 826 (2003);

As for the **causes of autism**

many hypotheses have been advanced:

at present these disorders are ***usually considered as essentially 'genetic' ..***

while the ***environmental causes*** (including ***mercury, EDCs, heavy metals, pesticides***) have been ***considered as highly improbable***

Which is ***in contrast with the dramatic increase of the autism spectrum disorders*** ( generally explained with the **changing of the diagnostic criteria**).

# Autism Spectrum Disorders and Autistic Traits: A Decade of New Twin Studies

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

**Angelica Ronald[1]* and Rosa A. Hoekstra[2]**

[1]Centre for Brain and Cognitive Development, Department of Psychological Sciences, Birkbeck, University of London, London, UK

[2]Department of Life Sciences, Faculty of Science, The Open University, Milton Keynes, UK

Am. J. Med. Genet. Neuropsychiatr. Genet. 156B, 255–274 (2011).

Researchers continue to pursue a better understanding of the symptoms, comorbidities, and causes of autism spectrum disorders. In this article we review more than 30 twin studies of autism spectrum disorders (ASDs) and autistic traits published in the last decade that have contributed to this endeavor. These twin studies have reported on the heritability of autism spectrum disorders and autistic traits in different populations and using different measurement and age groups. These studies have also stimulated debate and new hypotheses regarding why ASDs show substantial symptom heterogeneity, and what causes their comorbidity with intellectual disability, language delay, and other psychiatric disorders such as ADHD. These studies also reveal that the etiology of autism and autistic traits
general population is more similar than differ
tributes to the question of where the bounda
autism and typical development. Recent find
molecular genetic and environmental causes of
cussed in the relation to these twin studies. Lastl
cal assumptions of the twin design are given c
well as issues of measurement. Future researcl
suggested to ensure that this decade is as produ
in attempting to disentangle the causes of autism spectrum disorders. 

Between **1977 and the late 1990s autism was considered highly heritable**: findings from twin studies hushed the "***nurture***" proponents and **heralded the start of a multi-million dollar genetics research area**

Recent findings regarding molecular genetic and environmental causes of autism are discussed: in recent studies, **the correlation estimates between dizygotic twins are increasing, while the correlation between identical twins is considerably fading**

ONLINE FIRST

# Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism

*Joachim Hallmayer, MD; Sue Cleveland, BS; Andrea Torres, MA; Jennifer Phillips, PhD; Brianne Cohen, BA; Tiffany Torigoe, BA; Janet Miller, PhD; Angie Fedele, BA; Jack Collins, MBA; Karen Smith, BS; Linda Lotspeich, MD; Lisa A. Croen, PhD; Sally Ozonoff, PhD; Clara Lajonchere, PhD; Judith K. Grether, PhD; Neil Risch, PhD*

**Context:** Autism is considered the most heritable of neurodevelopmental disorders, mainly because of the large difference in concordance rates between monozygotic and dizygotic twins.

**Objective:** To provide rigorous quantitative estimates of genetic heritability of autism and the effects of shared environment.

**Design, Setting, and Participants:** Twin pairs with ...er (ASD) ...rough the ...ices. ...nostic assessments (Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule) were completed on 192 twin pairs. Concordance rates were calculated and parametric models were fitted for 2 definitions, 1 narrow (strict autism) and 1 broad (ASD).

**Results:** For strict autism, probandwise concordance for male twins was 0.58 for 40 monozygotic pairs (95% confidence interval [CI], 0.42-0.74) and 0.21 for 31 dizygotic pairs (95% CI, 0.09-0.43); for female twins, the concordance was 0.60 for 7 monozygotic pairs (95% CI, 0.28-0.90) and 0.27 for 10 dizygotic pairs (95% CI, 0.09-0.69). For ASD, the probandwise concordance for male twins was 0.77 for 45 monozygotic pairs (95% CI, 0.65-0.86) and 0.31 for 45 dizygotic pairs (95% CI, 0.16-0.46); for female twins, the concordance was 0.50 for 9 monozygotic pairs (95% CI, 0.16-0.84) and 0.36 for 13 dizygotic pairs (95% CI, 0.11-0.60). A large proportion of the variance in liability can be explained by shared environmental factors (55%; 95% CI, 9%-81% for autism and 58%; 95% CI, 30%-80% for ASD) in addition to moderate genetic heritability (37%; 95% CI, 8%-84% for autism and 38%; 95% CI, 14%-67% for ASD).

**Conclusion:** Susceptibility to ASD has moderate genetic heritability and a substantial shared twin environmental component.

*Arch Gen Psychiatry. 2011;68(11):1095-1102.*
*Published online July 4, 2011.*
*doi:10.1001/archgenpsychiatry.2011.76*

A recent **large cohort study of twins** found an **"estimated risk for ASD" of 30-80% for a shared uterine environment** (while the **genetic risk** was estimated at **14-67%**)

ONLINE FIRST

# Is Autism, at Least in Part, a Disorder of Fetal Programming?

ARCH GEN PSYCHIATRY/VOL 68 (NO. 11), NOV 2011 WWW.ARCHGENPSYCHIATRY.COM

The recent switch from an almost exclusive focus on inherited genes controlling neurotransmitters to rare de novo copy number variants that might affect genes regulating synaptic and axonal development has been an extremely important advance. However, it is true that the field will have to reassess the extent to which these rare de novo variants can explain a large proportion of cases because such models would predict much higher MZ and much lower DZ concordance rates than are reported by Hallmayer and colleagues.

The exciting news is that research on shared environmental mechanisms for the etiology of ASD has received renewed impetus. Perhaps ASD can be considered, at least in part, a disorder of fetal programming.[11]

The recent switch from an almost exclusive focus on **inherited genes controlling neurotransmitters** to **rare *de novo copy number variants* that might affect genes regulating synaptic and axonal development** has been an extremely important advance.

⇩

The exciting news is that **research on shared environmental mechanisms for the etiology of ASD** has received renewed impetus. Perhaps ***ASD can be considered, at least in part, a disorder of fetal programming.***

# Genome-wide Epigenetic Regulation by Early-Life Trauma

**Context:** Our genome adapts to environmental influences, in part through epigenetic mechanisms, including DNA methylation. Variations in the quality of the early environment are associated with alterations in DNA methylation in rodents, and recent data suggest similar processes in humans in response to early-life adversity.

**Objective:** To determine genome-wide DNA methylation alterations induced by early-life trauma.

**Childhood adversities** are associated with **epigenetic changes in the promoters of several genes in hippocampal neurons.**

The **genes involved in *neuronal plasticity*** are among the most significantly ***differentially methylated***

methylation
ldhood.

**Measures:**
ofiled using
owed by mi-
sue from 41
severe child-
ylation pro-
enome-wide
ger RNA mi-
croarrays. Methylation differences between groups were validated on neuronal and nonneuronal DNA fractions isolated by fluorescence-assisted cell sorting. Functional consequences of site-specific
tion were assessed by luciferase ass

**Results:** We identified 362 differentially methylated promoters in individuals with a history of abuse compared with controls. Among these promoters, 248 showed hypermethylation and 114 demonstrated hypomethylation. Validation and site-specific quantification of DNA methylation in the 5 most hypermethylated gene promoters indicated that methylation differences occurred mainly in the neuronal cellular fraction. Genes involved in cellular/neuronal plasticity were among the most significantly differentially methylated, and, among these, Alsin (*ALS2*) was the most significant finding. Methylated *ALS2* constructs mimicking the methylation state in samples from abused suicide completers showed decreased promoter transcriptional activity associated with decreased hippocampal expression of *ALS2* variants.

**Conclusion:** Childhood adversity is associated with epigenetic alterations in the promoters of several genes in hippocampal neurons.

*Arch Gen Psychiatry*. 2012;69(7):722-731

# Abuse Leaves Its Mark on the Brain

http://news.sciencemag.org/biology/2009/02/abuse-leaves-its-mark-brain

Francisco_de_Goya,_Saturno_devorando_a_su_hijo_(1819-1823)

**Child abuse** is an environmental factor that **leaves an epigenetic mark on the brain**

In a comparison of **suicide victims** who were abused or not, **only the abused victims had an epigenetic tag on the GR gene**

Interestingly, **the GR gene receives a similar epigenetic tag in rat pups who receive low quality care** from their mothers.


http://learn.genetics.utah.edu/content/epigenetics/brain/

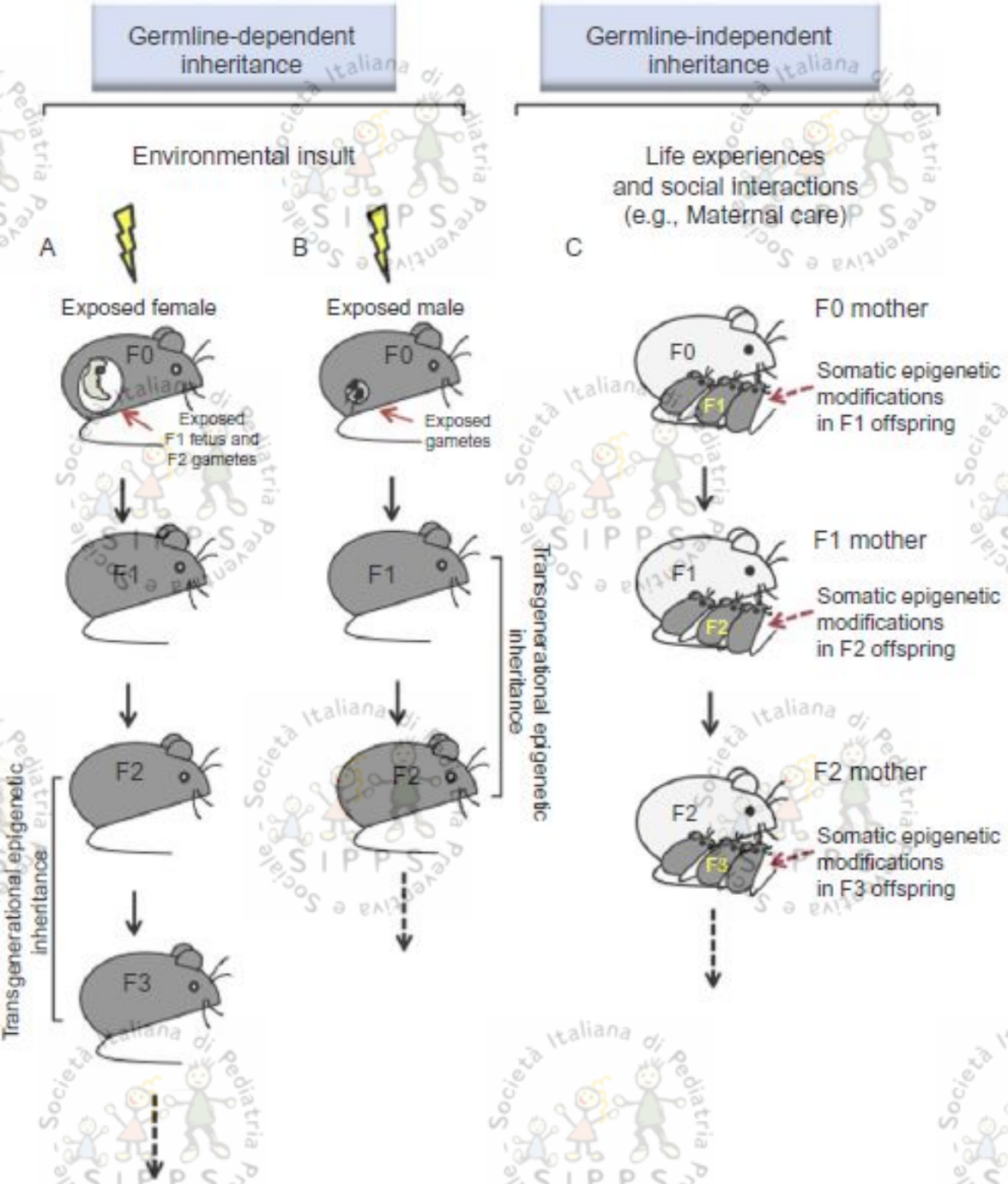



Figure 2.1 Germline-dependent versus germline-independent epigenetic inheritance.

In the **germline-dependent route of inheritance**, two mechanisms have been suggested:

(A) **exposure of a gestating mother (F0) to an environmental stressor** leads to the **direct exposure of three consecutive generations** to the same environmental factor, the mother (F0), the fetus (F1), and the F1 germline from which originates the F2 generation. The **transgenerational effect in this case is only observed at the F3 generation** since the latter was never directly exposed to the environmental factor.

(B) In **the case of an F0 male exposure to an environmental factor**, the transgenerational effect is seen at the **F2 generation**.

One of the mechanisms implicated in this epigenetic inheritance involves **epigenetic modifications in sperm cells (e.g., DNA methylation, HPTMs, and sncRNA interference)**.

The other well-known mechanism of epigenetic inheritance does **not involve the transmission of epigenetic changes through the germline**; the multigenerational transmission in this case is mediated **through social interactions and early-life experiences**.

(C) For example, low maternal **licking and grooming of pups**, during the early postnatal period, lead to an **increased DNA methylation of the promoter region of the GR and GR gene silencing**. These epigenetic changes were associated with **stress intolerance and were maintained in the adult female offspring (F1 mother) which in turn perpetuated the phenotype of low licking and grooming to the next generation of mothers (F2).**

# Association of Maternal Exposure to Childhood Abuse With Elevated Risk for Autism in Offspring

*Andrea L. Roberts, PhD; Kristen Lyall, ScD; Janet W. Rich-Edwards, ScD; Alberto Ascherio, DrPH; Marc G. Weisskopf, PhD, ScD*

*JAMA Psychiatry. 2013;70(5):508-515.*
*Published online March 20, 2013.*
*doi:10.1001/jamapsychiatry.2013.447*

**Importance:** Adverse perinatal circumstances have been associated with increased risk for autism in offspring. Women exposed to childhood abuse experience more adverse perinatal circumstances than women unexposed, but whether maternal abuse is associated with autism in offspring is unknown.

**Design and Setting:** Nurses' Health Study II, a population-based longitudinal cohort of 116 430 women.

**Conclusions and Relevance:** We identify an intergenerational association between maternal exposure to childhood abuse and risk for autism in the subsequent generation. Adverse perinatal circumstances accounted for only a small portion of this increased risk.

Another **transgenerational effect**, is based **on a broad longitudinal cohort study *(Nurses' Health Study II*)** which **identified maternal exposure to abuse in early childhood (!!)** as a risk factor for having a child with autism **e (Nurses 'Health Study II)**

# Autism Risk Across Generations

## *A Population-Based Study of Advancing Grandpaternal and Paternal Age*

*Emma M. Frans, MSc; Sven Sandin, MSc; Abraham Reichenberg, PhD; Niklas Långström, MD, PhD; Paul Lichtenstein, PhD; John J. McGrath, MD, PhD; Christina M. Hultman, PhD*

**Importance:** Advancing paternal age has been linked to autism.

**Objective:** To further expand knowledge about the association between paternal age and autism by studying the effect of grandfathers' age on childhood autism.

**Design:** Population-based, multigenerational, case-

tained for more than 90% of the cohort. Grandparental age at the time of birth of the parent was obtained for a smaller subset (5936 cases and 30 923 controls).

**Main Outcome and Measure:** *International Classification of Diseases* diagnosis of childhood autism in the patient registry.

**Results:** A statistically significant monotonic association was found between advancing grandpaternal age at the time of birth of the parent and risk of autism in grand-

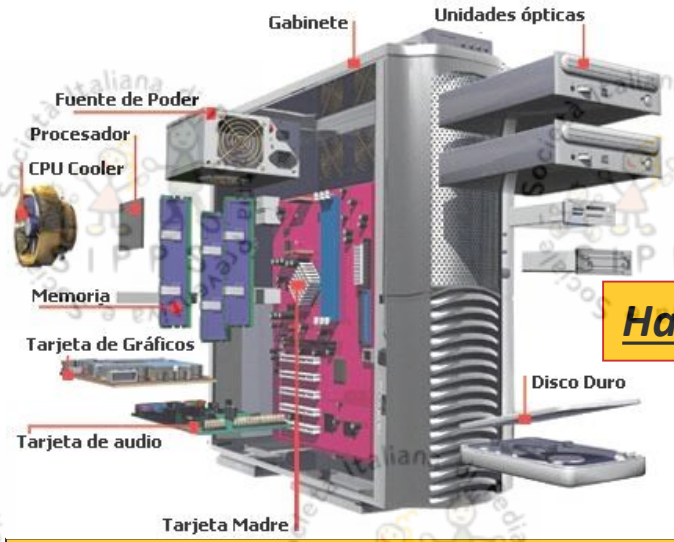
children. Men who had fathered a daughter when they were 50 years or older were 1.79 times (95% CI, 1.35-2.37; $P < .001$) more likely to have a grandchild with autism, and men who had fathered a son when they were 50 years or older were 1.67 times (95% CI, 1.35-2.37; $P < .001$) more likely to have a grandchild with autism, compared with men who had fathered children when they were 20 to 24 years old, after controlling for birth year of the spouse, family history of ghest family educational level, A statistically significant mono- o found between advancing pa- ism in the offspring. Sensitivity hese findings were not the re- g data on grandparental age.

**Conclusions and Relevance:** Advanced grandparental age was associated with increased risk of autism, suggesting that risk of autism could develop over generations. The results are consistent with mutations and/or epigenetic alterations associated with advancing paternal age.

*JAMA Psychiatry. 2013;70(5):516-521. Published online March 20, 2013. doi:10.1001/jamapsychiatry.2013.1180*

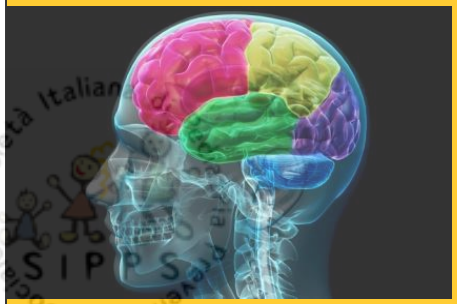
Recently, several epidemiological studies have emphasized the potential importance of the **environmental transgenerational effects** as a risk for ASD. In particular, **a study revealed a significant association between grandparents advanced age (!!)** and **risk of autism in grandchildren**: suggesting that the risk of **autism could increase over the generations.**

# Key *words*



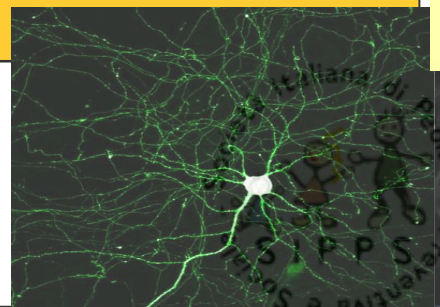

## *Hardware*

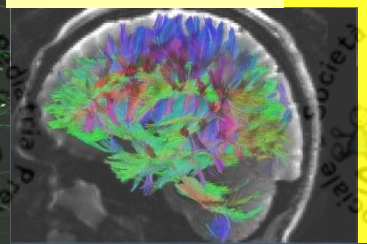
***Hardware*: Devices** that are required to store and execute (or run) the ***software***.



## *Ancestral Cablage*

**Input,storage,processing, control, and output devices. CD-ROM, monitor, printer, video card, scanners , label makers, routers , and modems**





## *Phenotype*

## *Software*

***Software*: Collection of instructions** that enables a user to interact with the computer. Software is **a program that enables a computer to perform a specific task,** as **opposed** to the **physical components of the system (*hardware*).**

## *Mind/Soul*

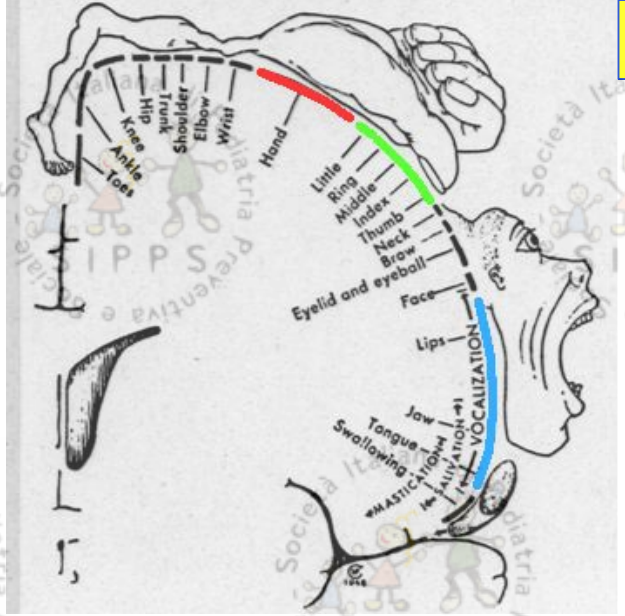
DNA *Genome* *Epigenome*
*Genotype*

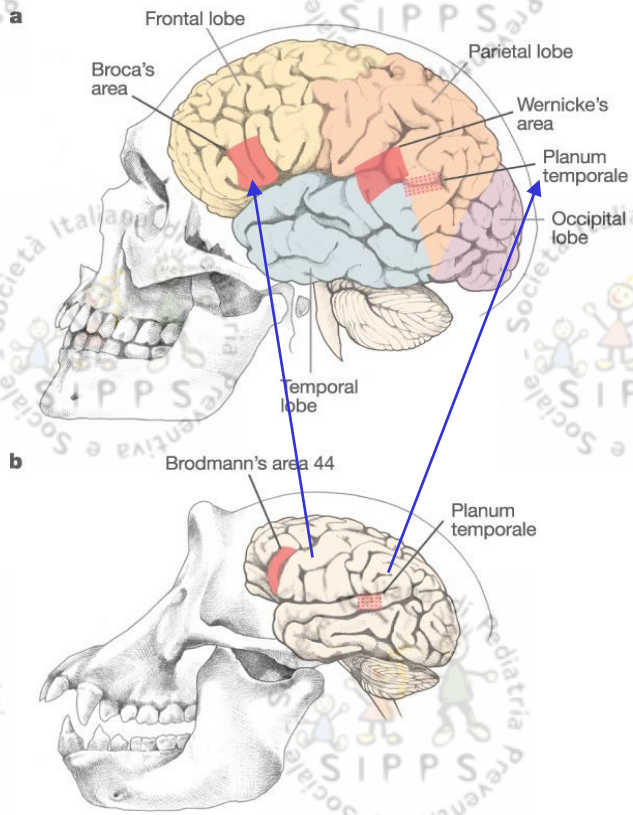
## Individual Cablage - *Connectome*

**Quickbooks, Adobe Acrobat, Winoms-Cs, Internet Explorer , Microsoft Word , Microsoft Excel..**

# The ***ancestral*** wiring

## Le ***câblage*** ancestral



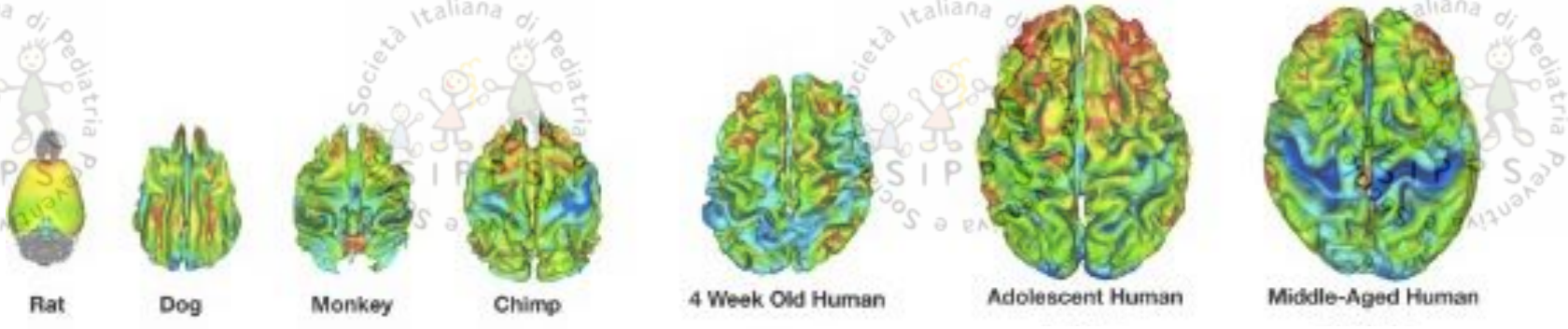



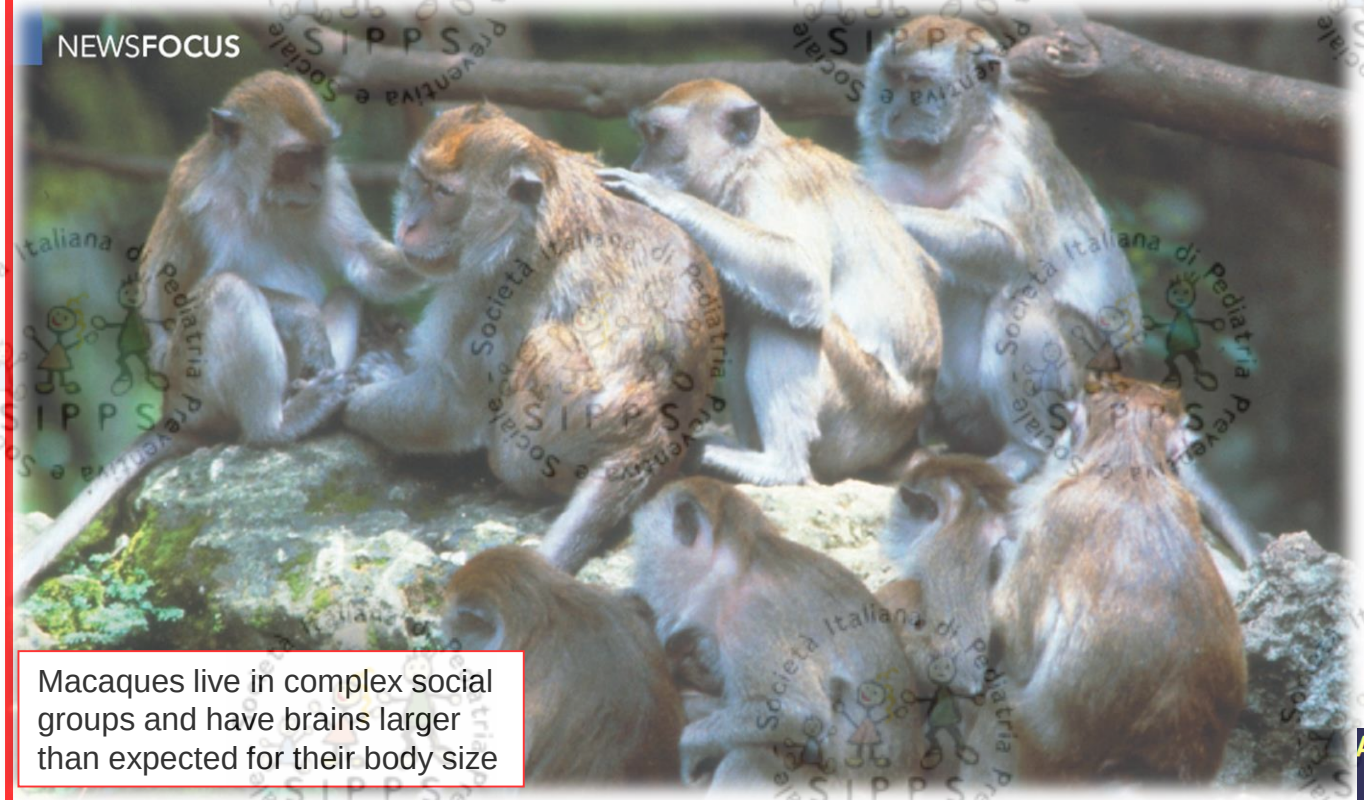

As with the **sensory cortex**, **Wilder Penfield** was responsible for **mapping the motor cortex…**

**Chimps** also have a motor cortex, but the **area of cortex devoted to vocal control is restricted** relative to what you see in the human animal.

**Their brains are just not built for the detailed vocalizations** you need to **in order to pronounce all the phonemes** that comprise linguistic verbal communication. Neurologists knew this, and **had the chimp trainers consulted a neurologist before starting, they would have saved themselves years of wasted effort**, and moved directly to the more realistic goal of seeing whether chimps could learn sign language

Carroll SB ***Genetics and the making of Homo sapiens*** Nature (2003) 422, 849-857



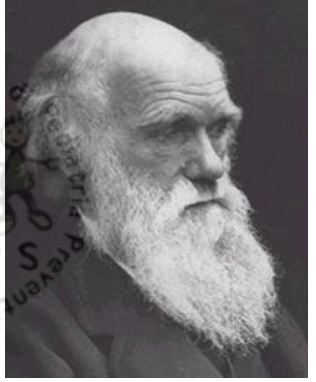




Macaques live in complex social groups and have brains larger than expected for their body size

# Why Are Our Brains So Big?

Science, 2012

# Chimpanzee-human divergence



**Evo**

**Brain:**
**a *rapidly evolving Organ ?***

***6-8 million years***

The ***ancestral*** **wiring**

***Hominids or hominins***

The ***Individual*** wiring !!

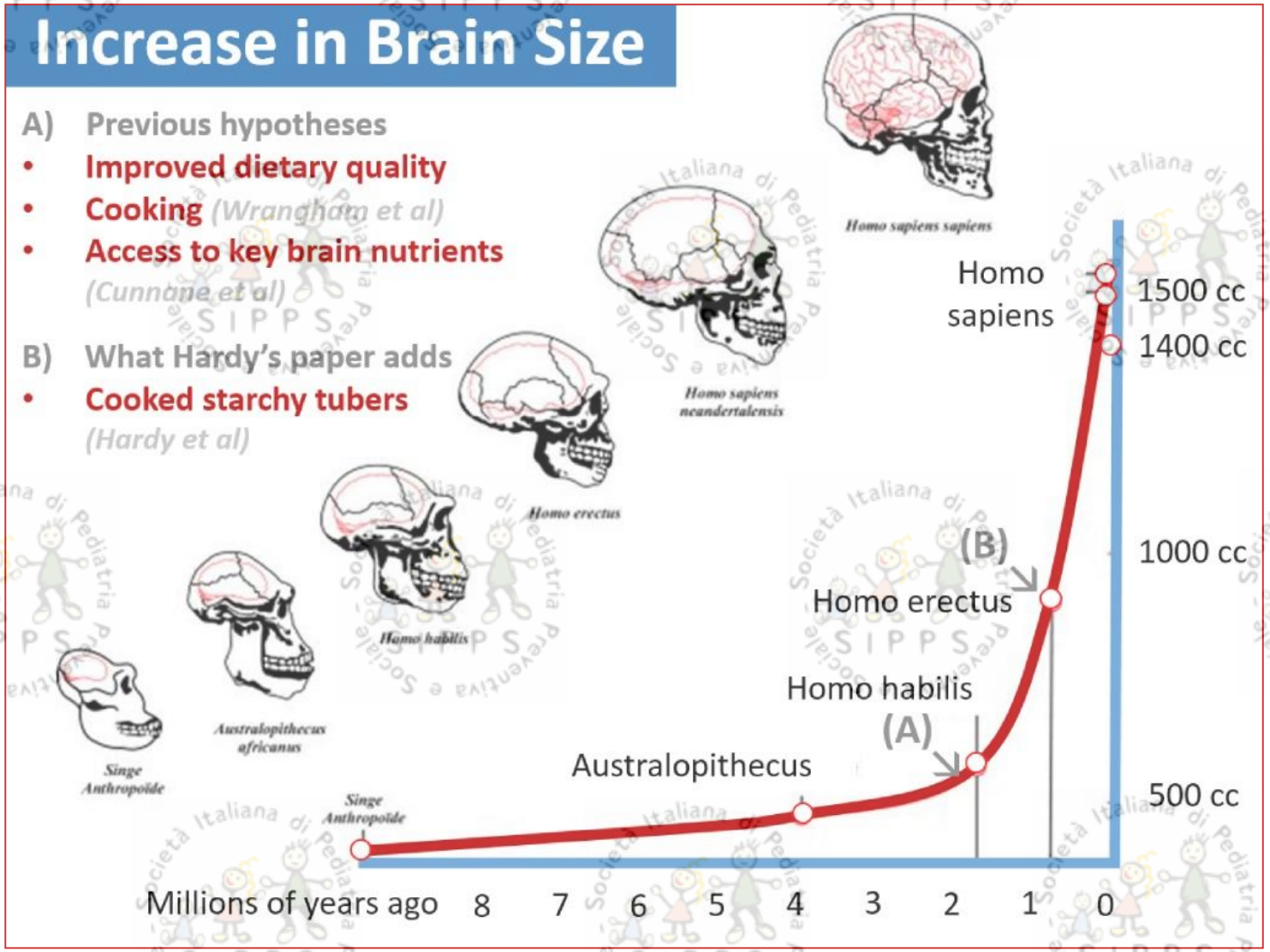
***+ Soft Wired-memory***

***Chimpanzees***

***Humans***

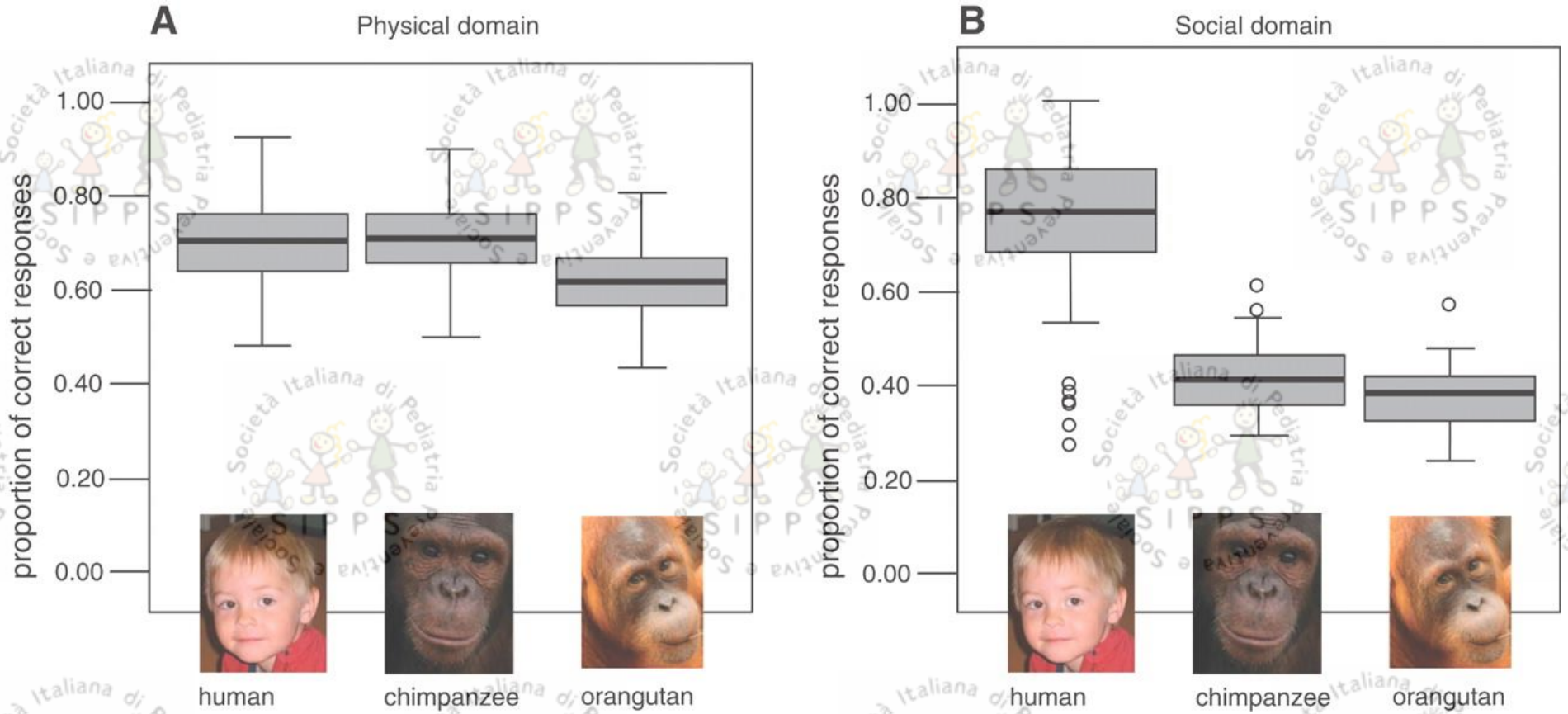
**Brain Size and Intellectual Capabilities**

The absolute brain size of hominids has tripled since the Pliocene age (from an average of 450 $cm^3$ in *Australopithecus* to 1,345 $cm^3$ in *H. sapiens*: Holloway, 1996)



# Adolescenza, Stili di Vita, Psicopatologia

*Giovanni Biggio*
*Centro di Eccellenza per la "Neurobiologia delle Dipendenze", Università degli Studi di Cagliari*




**In the social domain, a very different pattern emerged**.
Averaging across all of the tasks in the social domain, the human children were correct on ~74% of the trials, whereas the two ape species were correct about half as often (33 to 36% of the trials). **Statistically, the humans were more skillful than either of the two ape species ($P < 0.001$ in both cases), which did not differ from one another.**

# Five-Year Olds, but Not Chimpanzees, Attempt to Manage Their Reputations

**Jan M. Engelmann*, Esther Herrmann, Michael Tomasello**

Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

Non-human primates lack of the ***Theory of mind***

## Abstract

Virtually all theories of the evolution of cooperation require that cooperators find ways to interact with one another selectively, to the exclusion of cheaters. This means that individuals must make reputational judgments about others as cooperators, based on either direct or indirect evidence. Humans, and possibly other species, add another component to the process: they know that they are being judged by others, and so they adjust their behavior in order to affect those judgments – so-called impression management. Here, we show for the first time that already preschool children engage in such behavior. In an experimental study, 5-year-old human children share more and steal less when they are being watched by a peer than when they are alone. In contrast, chimpanzees behave the same whether they are being watched by a groupmate or not. This species difference suggests that humans' concern for their own self-reputation, and their tendency to manage the impression they are making on others, may be unique to humans among primates.

**Citation:** Engelmann JM, Herrmann E, Tomasello M (2012) Five-Year Olds, but Not Chimpanzees, Attempt to Manage Their Reputations. PLoS ONE 7(10): e48433. doi:10.1371/journal.pone.0048433

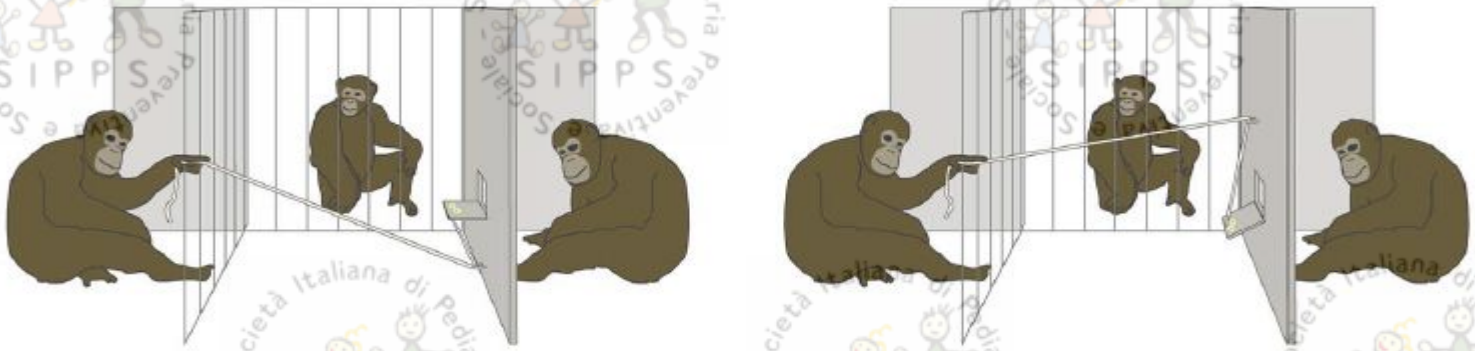


**Figure. 3. Setup of the chimpanzee study.** Illustration of the experimental setup for chimpanzees, viewed from the experimenter's point of view. The observed condition (pictured here) consisted of three different roles, subject (left), observer (middle) and receiver (right). In the stealing task (left), subjects could steal food from the receiver by collapsing the food platform. In the helping task (left), subjects could give food to the recipient, which they couldn't obtain otherwise.
doi:10.1371/journal.pone.0048433.g003

# Extraordinary intelligence and the care of infants

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May 23, 2016, doi:
10.1073/pnas.1506752113
PNAS May 23, 2016

Steven T. Piantadosi[a,1] and Celeste Kidd[a,1]

[a]Department of Brain and Cognitive Sciences, University of Rochester, Rochester, NY 14627

We present evidence that pressures for early childcare may have been one of the driving factors of human evolution. We show through an evolutionary model that runaway selection for high intelligence may occur when (*i*) altricial neonates require intelligent parents, (*ii*) intelligent parents must have large brains, and (*iii*) large brains necessitate having even more altricial offspring. We test a prediction of this account by showing across primate genera that the helplessness of infants is a particularly strong predictor of the adults' intelligence. We discuss related implications, including this account's ability to explain why human-level intelligence evolved specifically in mammals. This theory complements prior hypotheses that link human intelligence to social reasoning and reproductive pressures and explains how human intelligence may have become so distinctive compared with our closest evolutionary relatives.

"**Our theory is that there is a kind of self-reinforcing cycle where big brains lead to very premature offspring and premature offspring lead to parents having to have big brains.** What our formal modeling work shows is that those dynamics can result in **runaway pressure for extremely intelligent parents and extremely premature offspring.**"

"**Humans have a unique kind of intelligence**. We are good at social reasoning and something called ***'theory of mind***'--**the ability to anticipate the needs of others, and to recognize that those needs may not be the same as our own**.. This is especially helpful when taking care of an infant who is not able talk for a couple of years."

https://www.sciencedaily.com/releases/2016/05/160523160445.htm


Who is really
nurturing who?

# Sex differences in the structural connectome of the human brain

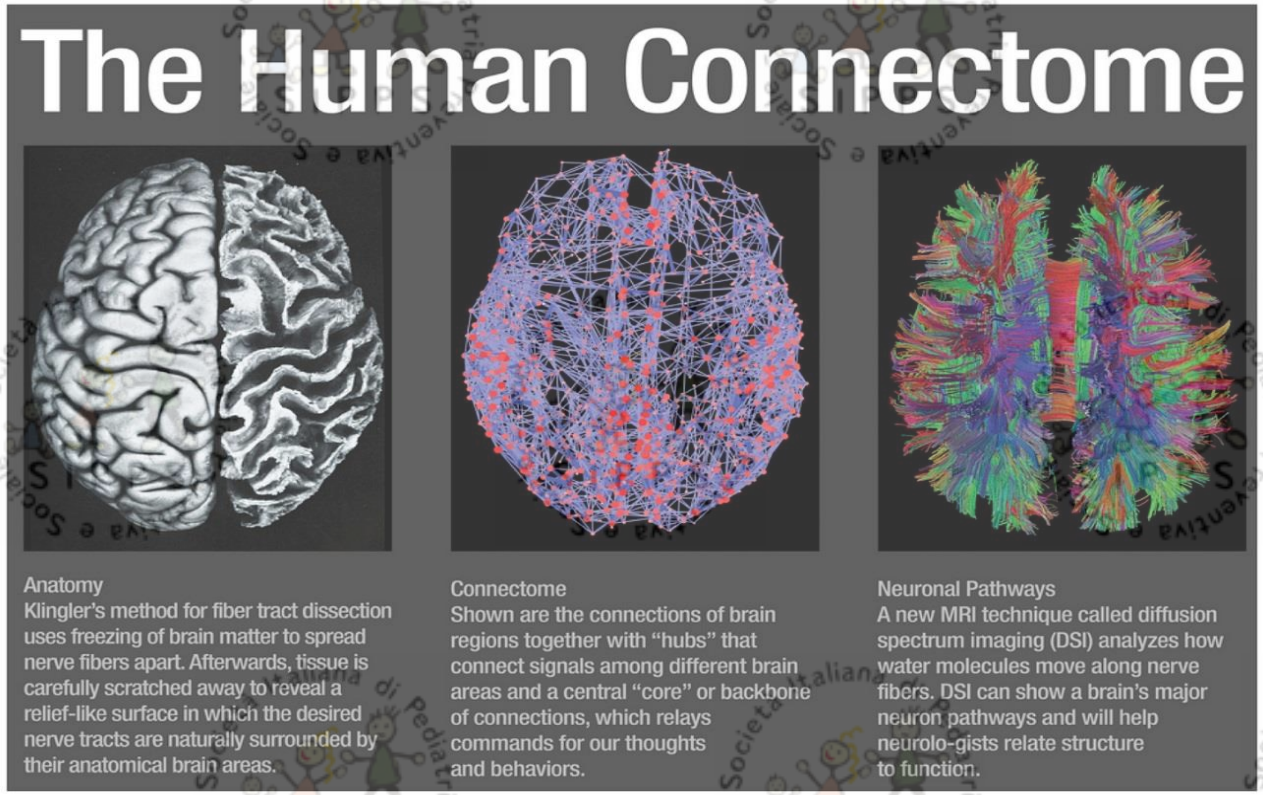
Madhura Ingalhalikar[a,1], Alex Smith[a,1], Drew Parker[a], Theodore D. Satterthwaite[b], Mark A. Elliott[c], Kosha Ruparel[b], Hakon Hakonarson[d], Raquel E. Gur[b], Ruben C. Gur[b], and Ragini Verma[a,2]

Sex differences in human behavior show adaptive complementarity: Males have better motor and spatial abilities, whereas females have superior memory and social cognition skills. Studies also show sex differences in human brains but do not explain this complementarity. In this work, we modeled the structural connectome using diffusion tensor imaging in a sample of 949 youths (aged 8–22 y, 428 males and 521 females) and discovered unique sex differences in brain connectivity during the course of development. Connection-wise statistical analysis, as well as analysis of regional and global network measures, presented a comprehensive description of network characteristics. In all supratentorial regions, males had greater within-hemispheric connectivity, as well as enhanced modularity and transitivity, whereas between-hemispheric connectivity and cross-module participation predominated in females. However, this effect was reversed in the cerebellar connections. Analysis of these changes developmentally demonstrated differences in trajectory between males and females mainly in adolescence and in adulthood. Overall, the results suggest that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes.

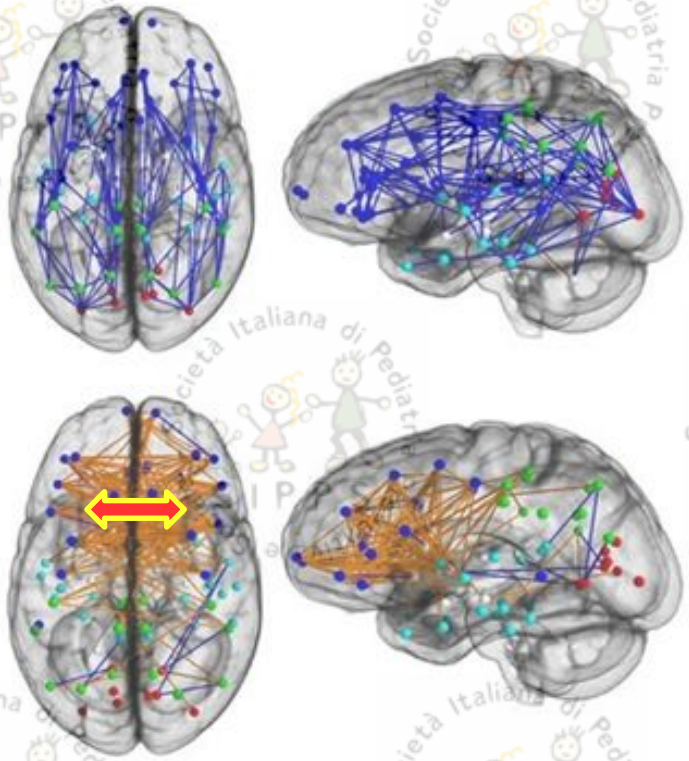
**Sex differences are of high scientific and societal interes**
because of their **prominence in behavior of humans and nonhuman species**. This work is highly significant because it studies **a very large population of 949 youths** (8–22 y, 428 males and 521 females) **using the diffusion-based structural connectome of the brain, identifying novel sex differences**. The results establish that **male brains are optimized for intrahemispheric** and **female brains for interhemispheric communication.**

**The developmental trajectories of males and females separate at a young age, demonstrating wide differences during adolescence** and **adulthood**. The observations suggest that **male brains are structured to facilitate connectivity between perception and coordinated action**, whereas **female brains are designed to facilitate communication between analytical and intuitive processing modes.**

http://www.humanconnectomeproject.org/




*The Human Connectome* - Eugen Ludwig, Josef Klingler, Patric Hagmann & Olaf Sporns - 1956, 2008



♂

♀

**Male brains during development are structured to facilitate within-lobe and within-hemisphere connectivity**, with networks that are transitive, modular, and **discrete** whereas **female brains have greater interhemispheric connectivity and greater cross-hemispheric participation.**

♂

♀

Le ***connectome*** est un **plan complet des *connexions neuronales*** dans un cerveau

# The *ancestral* wiring 2: emotions

THE

# EXPRESSION OF THE EMOTIONS

IN

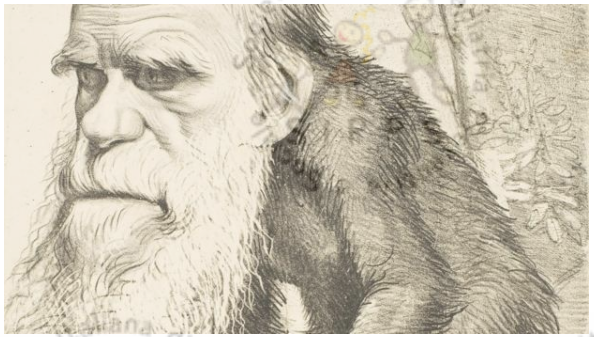
# MAN AND ANIMALS.

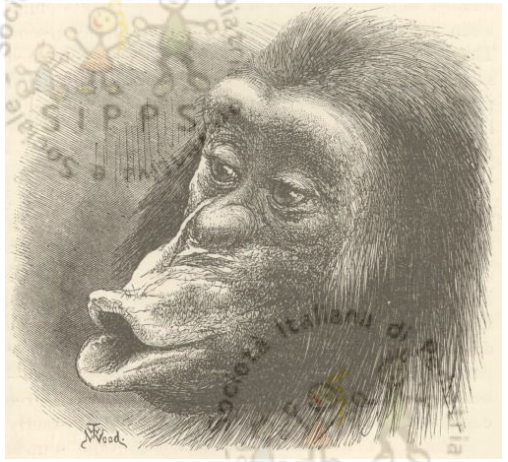
By CHARLES DARWIN, M.A., F.R.S., &c.

WITH PHOTOGRAPHIC AND OTHER ILLUSTRATIONS.

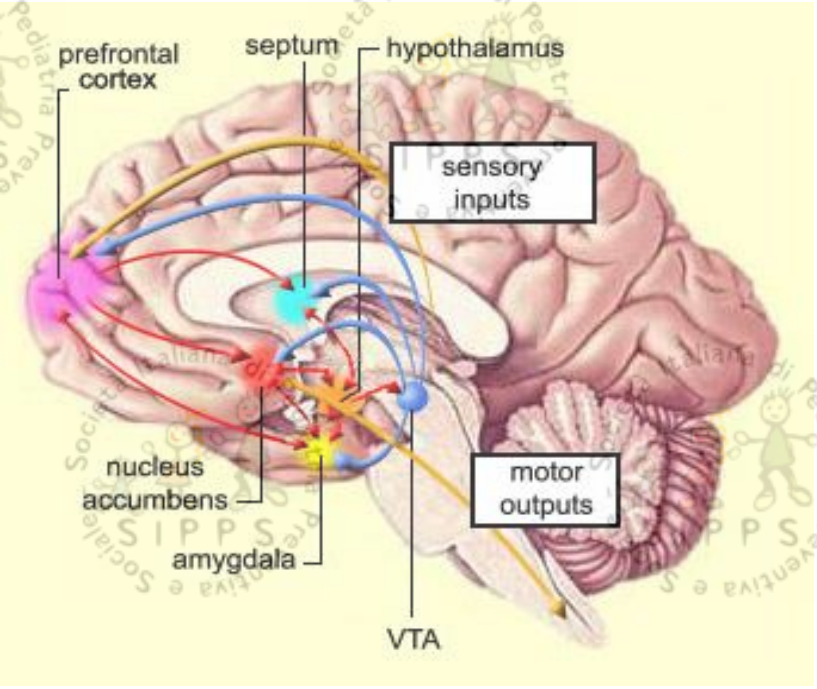
LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1872.





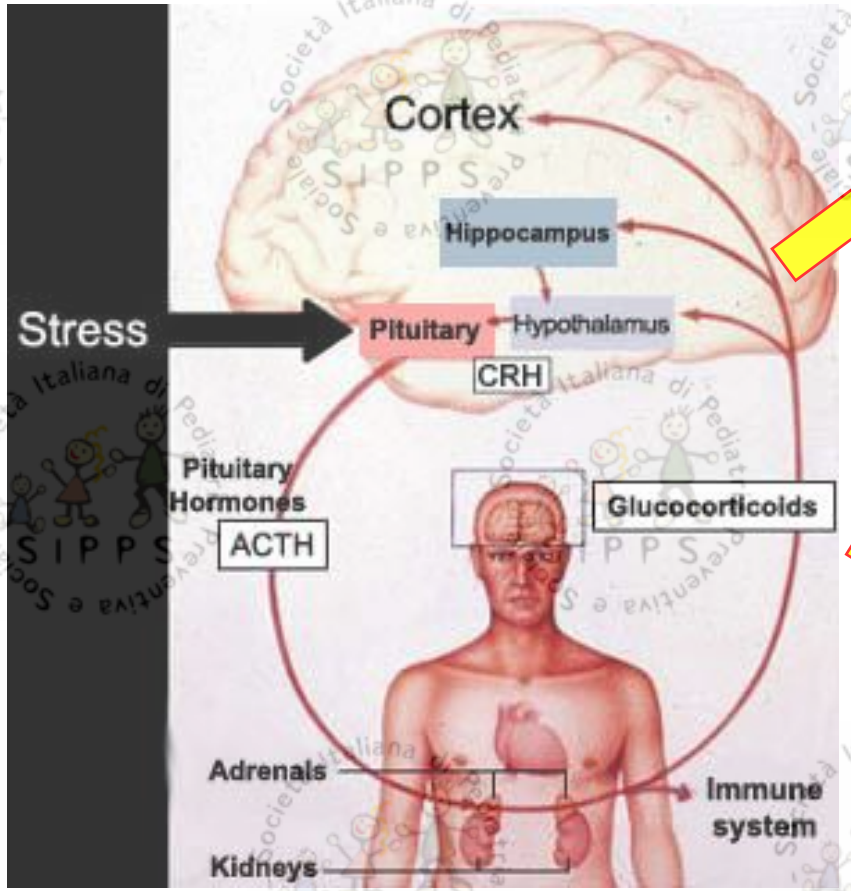


## THE PLEASURE CENTRES

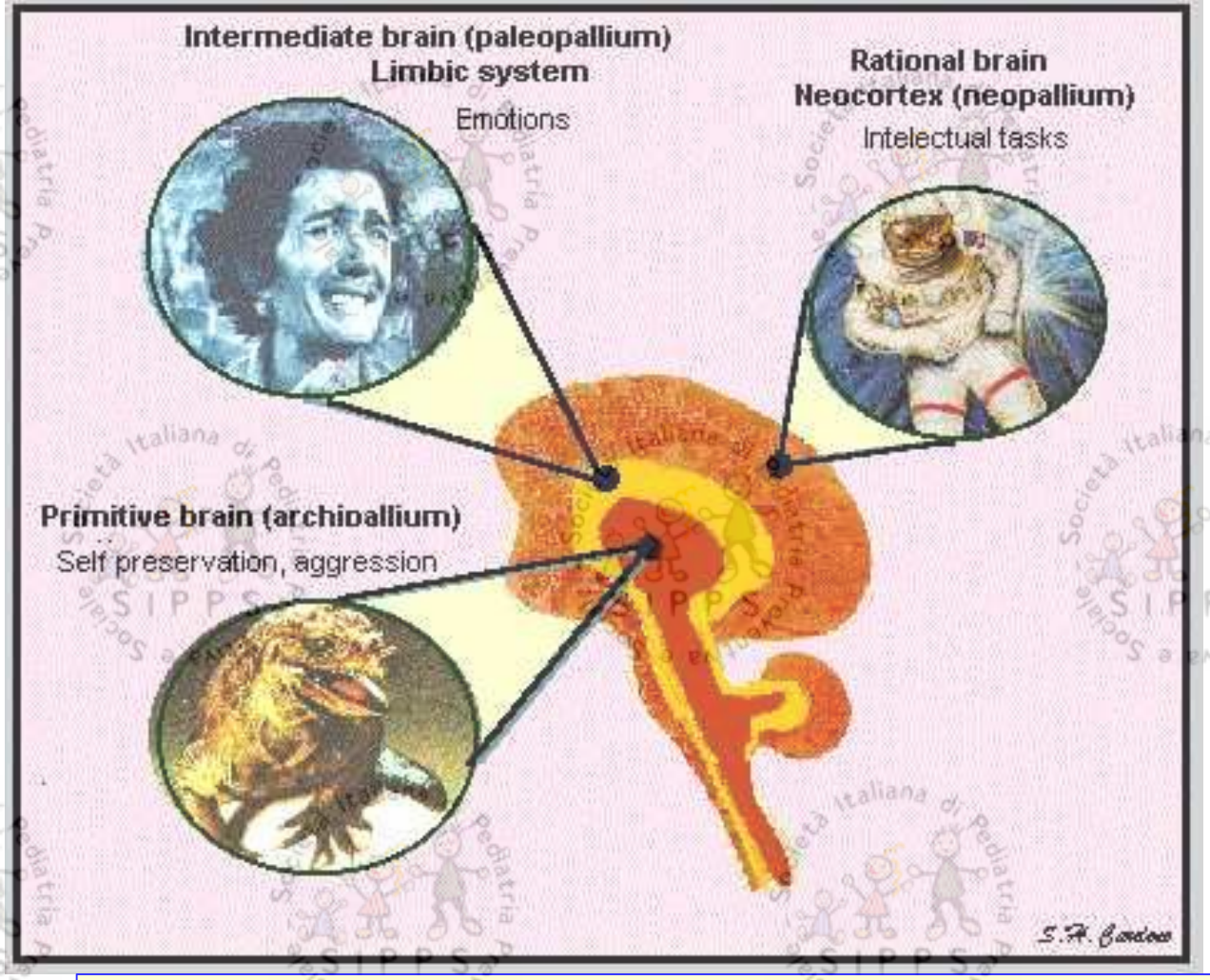



**Ventral Tegmental Area**

## WHEN FEAR TAKES THE CONTROLS




## DEPRESSION

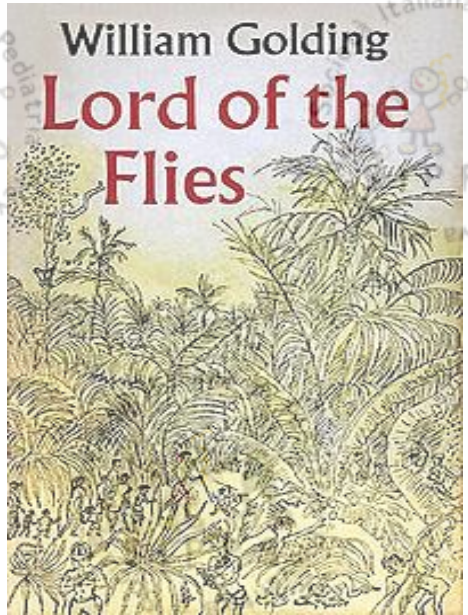



***Nurture***
Culture

***WAR***
***HOLOCAUST***

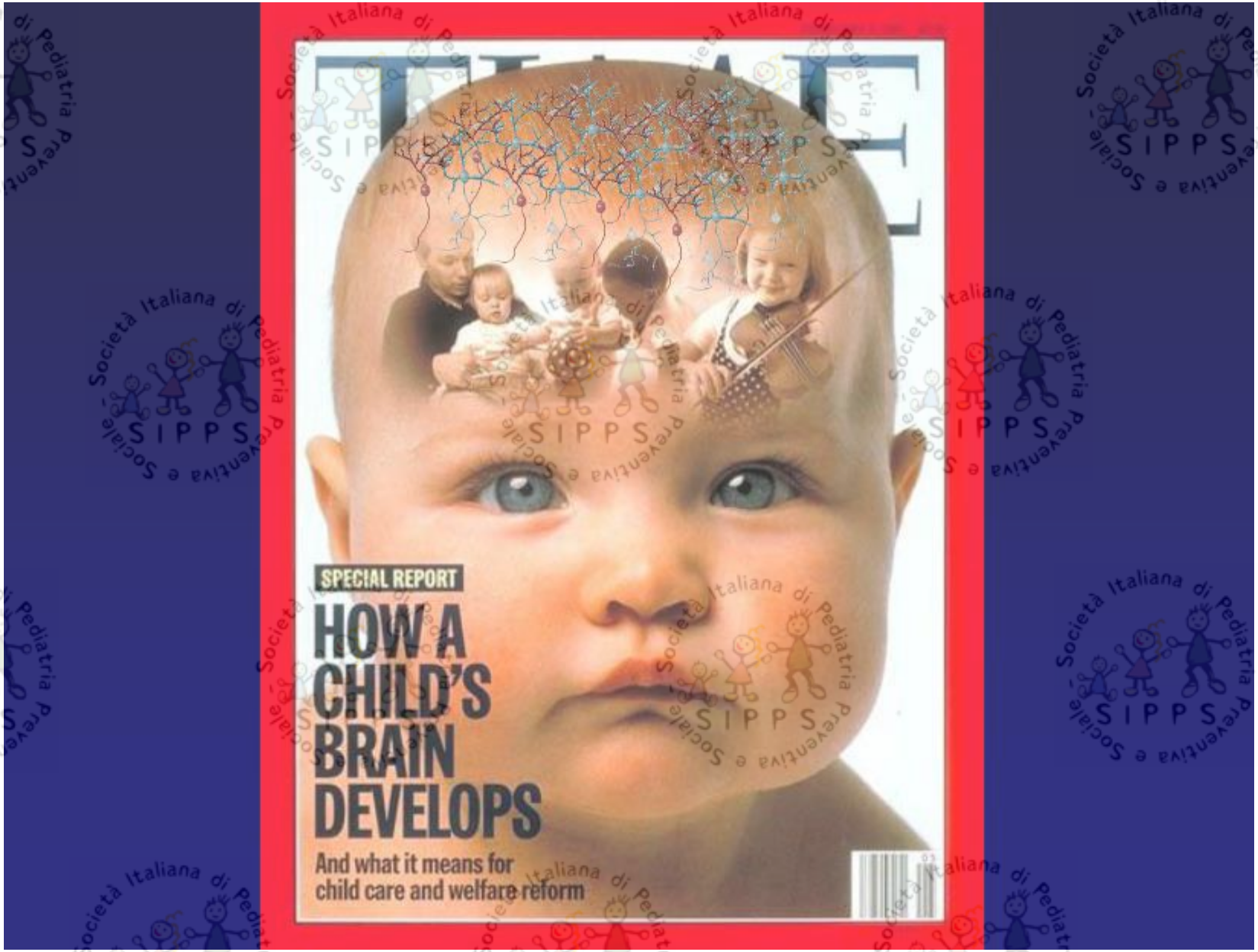
***The Ghost in the Machine*** is a book written by Arthur Koestler and published in 1967. One of the book's central concepts is that
- as the human triune brain has evolved, it has retained and **built upon earlier, more primitive brain structures**.
- The **head portion** of the "ghost in the machine" has, as a consequence of **poor, inadequate connections, a rich potential for conflict**

***The Lucifer Principle*** is a book by Howard Bloom.
It sees a **social group, not an individual, as a main subject of human evolution**. It "explores the **intricate relationships among genetics, human behavior, and culture**" and argues that **"evil is a by-product of nature's strategies for creation and that it is woven into our most basic biological fabric**





1961




**Adolescenza, Stili di Vita, Psicopatologia**

***Giovanni Biggio***

*Centro di Eccellenza per la "Neurobiologia delle Dipendenze", Università degli Studi di Cagliari*

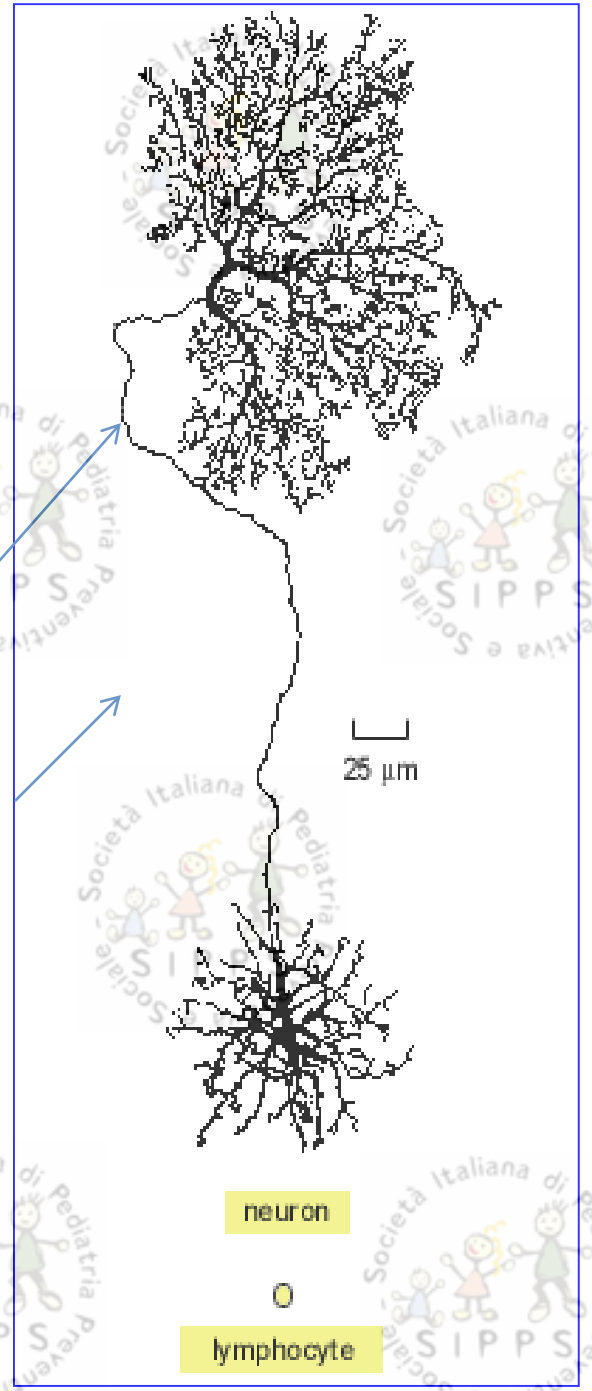
# The ***Individual*** wiring

.. what really interests us here is the ***software***
(which is essentially constituted by ***neuronal circuits***
and thus by the ***synaptic connections*** **)**

and the way in which - in the course of ***ontogenesis***, mainly
during the **fetal life*** and the **first two years of life**
( ie in the period of maximal ***developmental plasticity***)

**billion of dendritic tree structures are connecting with each other in response to information coming from the environment**
and **from the rest of the "network " under construction**

[what is really hard to understand is why so many scientists prefer,
even in this context , **a selective (neo-Darwinian) evolutionary model** rather than **an instructive and constructive one**
(***Lamarckian*** and Darwinian)]



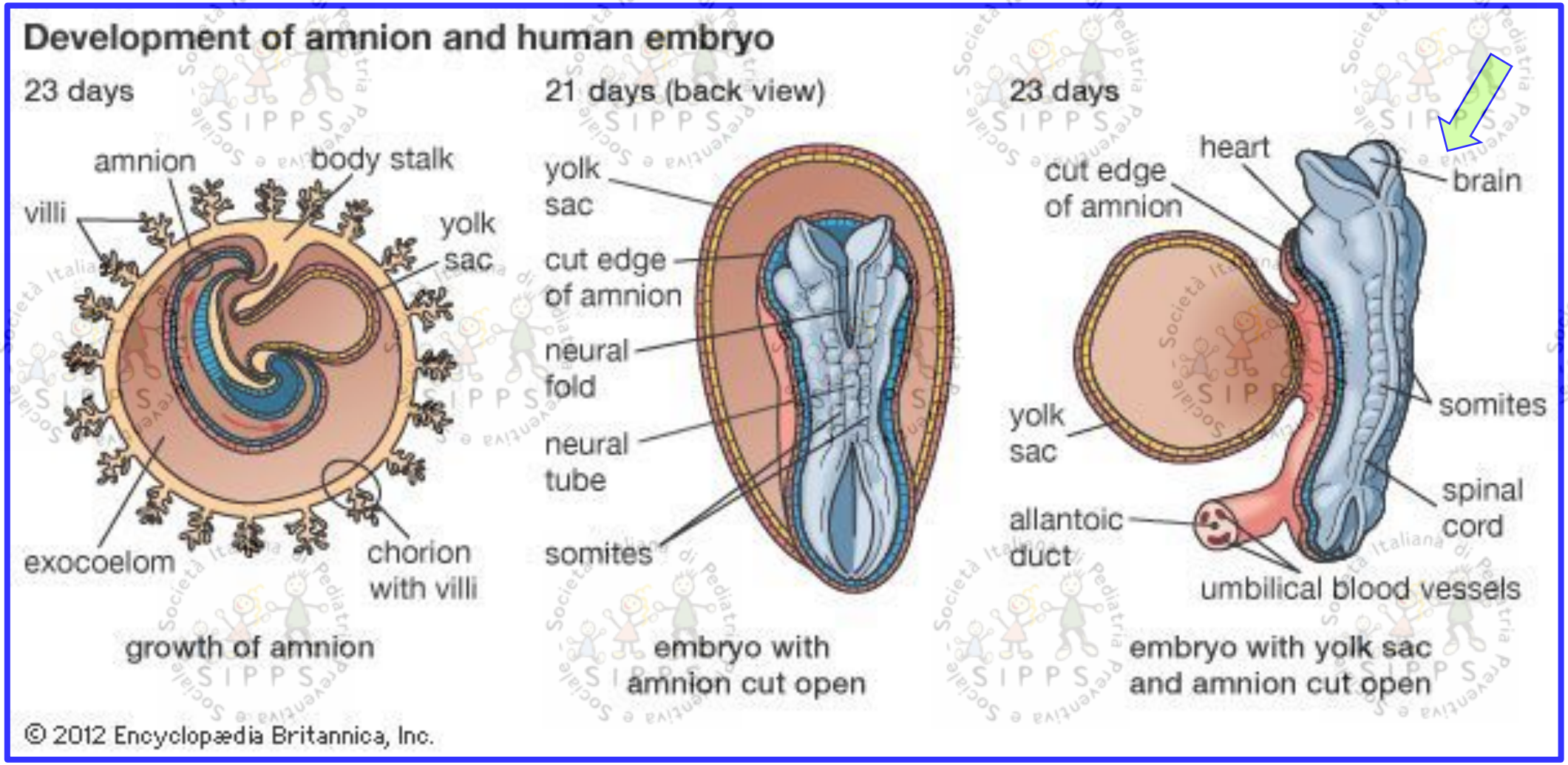

* In our species ***synaptogenesis*** begins as early as the **second month of fetal life** (in ***other mammals*** **only a few synapses are in place at birth** )

.. *unlike your **genome**, which is **fixed from the moment of conception*** **(…)**
your **connectome* changes throughout your life**.

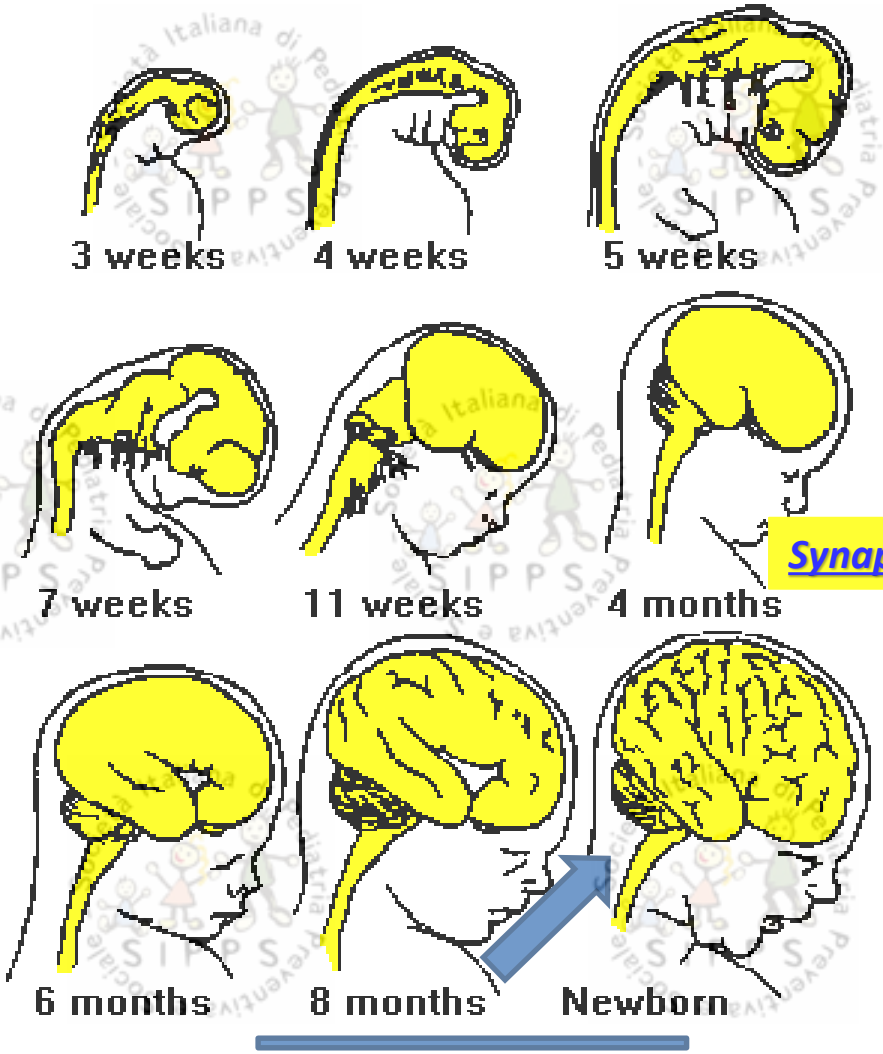
**Neurons adjust…their connections** (to one another) by ***strengthening*** or ***weakening*** them.

Neurons **reconnect by creating and eliminating synapses**, and **they rewire by growing and retracting branches**. ***You are more than your genes. You are your connectome (Sebastian Seung, MIT)***

Seung S. ***Connectome: How the brain's wiring makes us who we are*** (2012)




Embryo of 23 days showing (K) growth of the amnion, (L) amnion cut open, and (M) yolk sac and amnion cut open.




***Synaptogenesis***

The brain grows at an amazing rate during development.
At times during brain development, **250,000 neurons are added every minute!**
**At birth, almost all the neurons** that the brain will ever have are present.

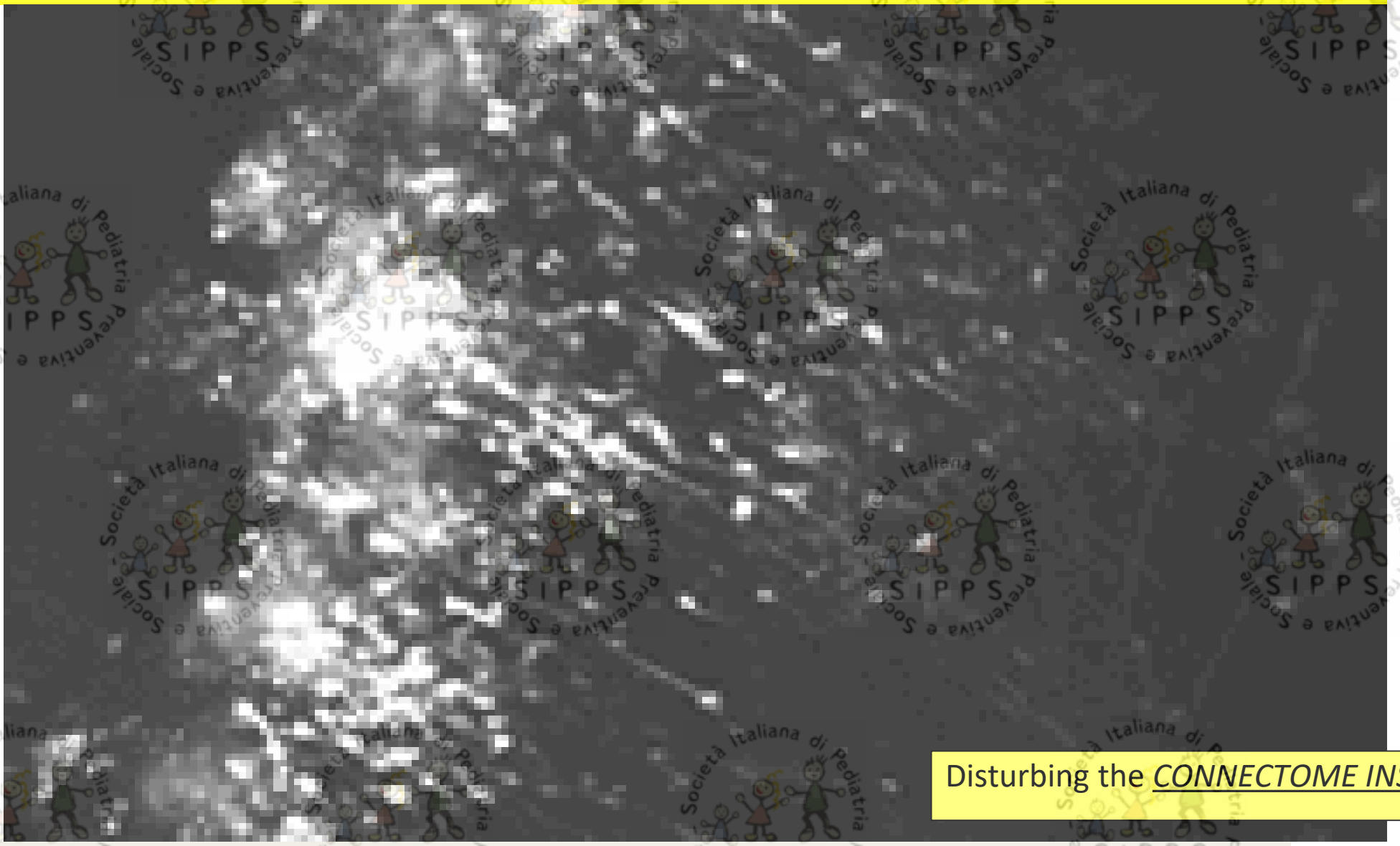
However, the brain continues to grow for many years after birth.

**By the age of 2 years** old, the brain is about **80% of the adult size**

A **stegosaurus dinosaur weighed approximately 1,600 kg but had a brain that weighed only approximately 70 grams (0.07 kg).** Therefore, **the brain was only 0.004% of its total body** weight. In contrast, an adult human weighs approximately 70 kg and has a brain that weighs approximately 1.4 kg. Therefore, **the human brain is about 2% of the total body weight**. This makes the brain to body ratio of the human **500 times greater than that of the stegosaurus**

# **Brain plasticity** and modulation of its structure and its functions

The ***Individual*** wiring



**Motility of neurons** and in particular the **formation of new connections (synapses) can be modified (perturbed) by exposure** to ***environmental stressors***

Disturbing the *CONNECTOME INSTRUCTION*

Wingate ***Imagining the brain cell: the neuron in visual culture***. Nature Rev Neuroscience 2006; 7: 745-752.

The ***Individual*** wiring

# Early critical periods in the development of SYNAPTOGENESIS and brain functions

## Formation of new synapses following stimulation..

Disturbing the *CONNECTOME INSTRUCTION*

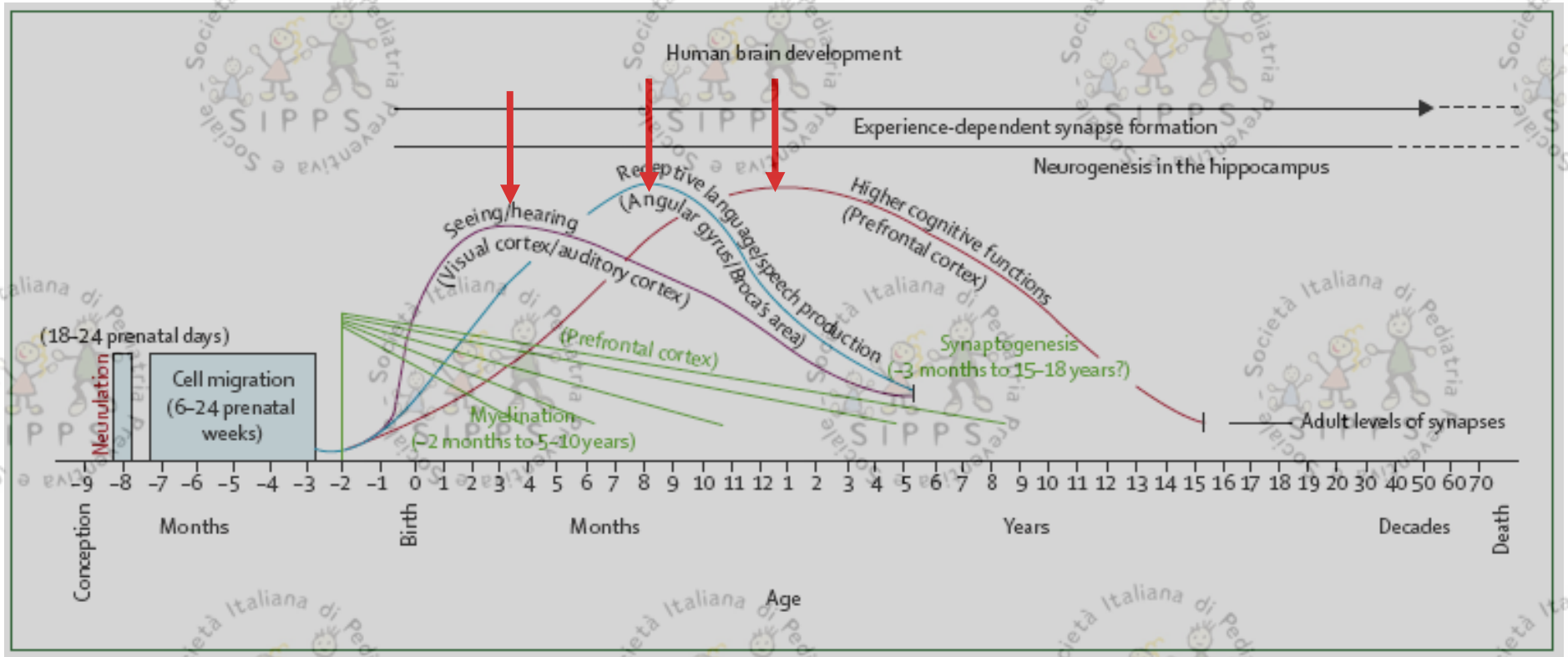



***Figure 1:*** **Human brain development**
Reproduced with permission of authors and American Psychological Association[37] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; 56: 5–15).

NEUROSCIENCE

# WHAT MAKES EACH BRAIN UNIQUE

How can identical twins grow up with different personalities? "Jumping genes" move around in neurons and alter the way they work

*By Fred H. Gage and Alysson R. Muotri*

IN BRIEF

**Genes we inherit** and environmental factors both influence human behaviors. Scientists have recently discovered other underlying processes at work.

**So-called jumping genes**, segments of DNA that can copy and paste themselves into new places in the genome, can alter the activity of full-length genes. Occasionally they will turn on neighboring genes in these locations. That activity occurs more in the brain than other areas, resulting in different traits and behaviors, even in closely related individuals.

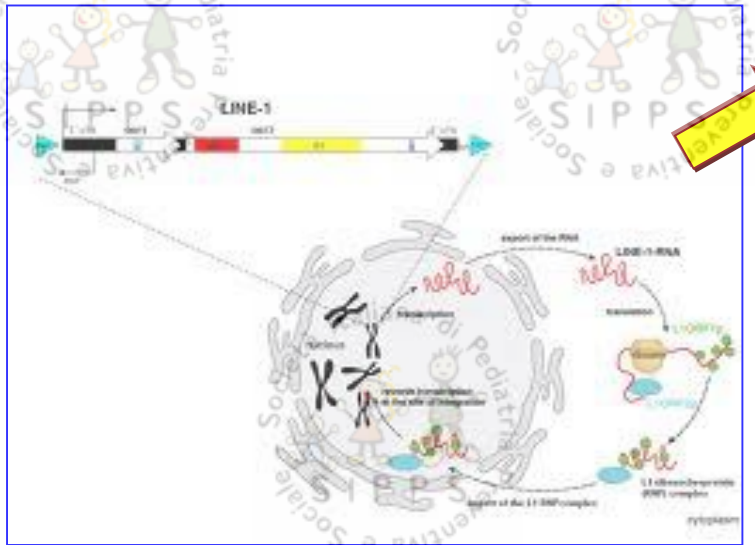
**These mobile genetic elements** may also turn out to play a role in people's disposition to psychiatric disorders. **Researchers are now** beginning to investigate whether jumping genes help us adapt to rapidly changing environmental conditions.

However, claiming that **the genome remains fairly stable throughout life** is **not only a simplification, but a big mistake**

in fact the **genome changes constantly , not only in its *software* ( the *epigenome* )** assigned to respond physiologically to ***stress*** and to ***information*** coming from outside, **but also, and with amazing frequency – mainly in the human brain - within the DNA sequence,** thanks to the continuous transfer of mobile sequences..

If we are right, and **the activity of the L1 jump really increases as the nervous system learns and adapts to the outside world** ,

this would indicate that the **individual brains and neural networks** of which they are made change and **are constantly changing at every new experience , even in genetically identical twins (which affects the assumption that identical twins are really genetically identical)**




Gage FH, Muotri AR. ***What makes each brain unique***.Sci Am. (2012);306(3):26-31

Leading Edge
Previews

Cell 164, February 11, 2016 ª2016 Elsevier Inc. 593

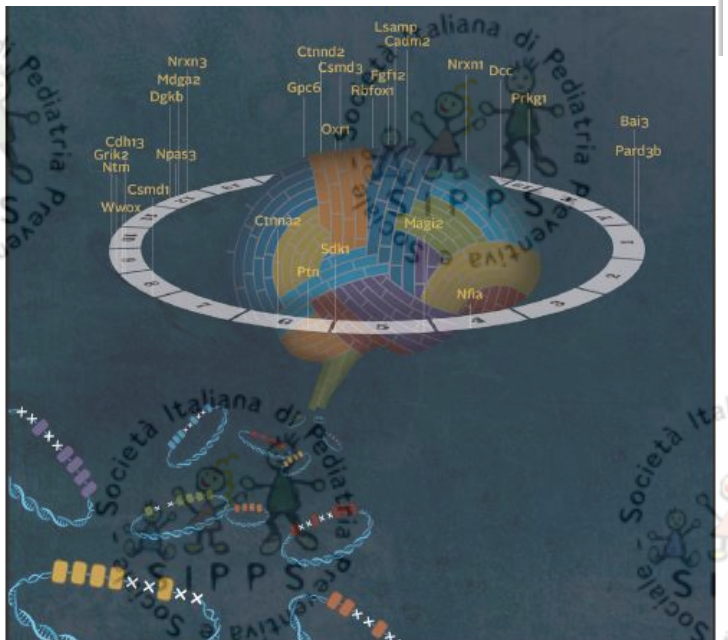
Cell

# A Mechanism for Somatic Brain Mosaicism

Irving L. Weissman[1,*] and Fred H. Gage[2,*]
[1]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford University, Palo Alto, CA 94305, USA
[2]The Salk Institute for Biological Studies, Laboratory of Genetics, La Jolla, CA 92037, USA
*Correspondence: irv@stanford.edu (I.L.W.), gage@salk.edu (F.H.G.)
http://dx.doi.org/10.1016/j.cell.2016.01.048

Double-strand break repair is required for neural development, and brain cells contain somatic genomic variations. Now, Wei et al. demonstrate that neural stem and progenitor cells undergo very frequent DNA breaks in a very restricted set of genes involved in neural cell adhesion and synapse function.

Many of the identified genes are **expressed in NSPCs located in the brain regions responsible for higher functions such as short-term learning,** and mutations in these genes in humans are associated with (and maybe predispose to) **psychiatric and neurological disorders manifested in mind functions—autism, manic depressive and depressive disorders, schizophrenia**, and others



SCIENCE sciencemag.org
2 OCTOBER 2015 • VOL 350 ISSUE 6256

NEURODEVELOPMENT

# Somatic mutation in single human neurons tracks developmental and transcriptional history

Michael A. Lodato,[1*] Mollie B. Woodworth,[1*] Semin Lee,[2*] Gilad D. Evrony,[1] Bhaven K. Mehta,[1] Amir Karger,[3] Soohyun Lee,[2] Thomas W. Chittenden,[3,4†] Alissa M. D'Gama,[1] Xuyu Cai,[1‡] Lovelace J. Luquette,[2] Eunjung Lee,[2,5] Peter J. Park,[2,5§] Christopher A. Walsh[1§]

Neurons live for decades in a postmitotic state, their genomes susceptible to DNA damage. Here we survey the landscape of somatic single-nucleotide variants (SNVs) in the human brain. We identified thousands of somatic SNVs by single-cell sequencing of 36 neurons from the cerebral cortex of three normal individuals. Unlike germline and cancer SNVs, which are often caused by errors in DNA replication, neuronal mutations appear to reflect damage during active transcription. Somatic mutations create nested lineage trees, allowing them to be dated relative to developmental landmarks and revealing a polyclonal architecture of the human cerebral cortex. Thus, somatic mutations in the brain represent a durable and ongoing record of neuronal life history, from development through postmitotic function.

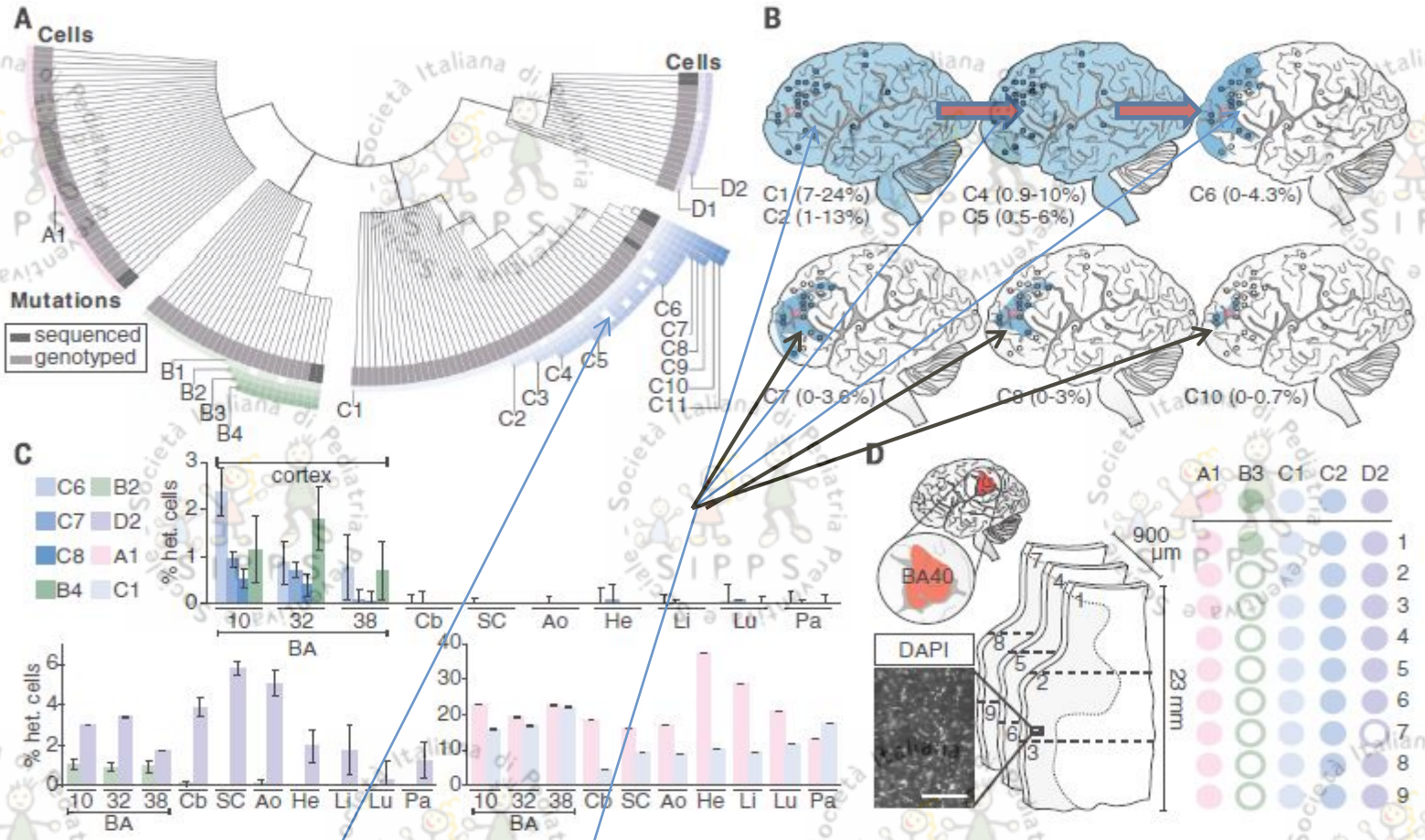



**Fig. 3. Somatic mutations are shared between multiple neurons and demonstrate lineage relationships.** (**A**) Lineage map of 136 human cortical neurons from brain B derived from 13 clonal somatic mutations, including SNVs, long interspersed nuclear element (LINE) insertions, and a TG-dinucleotide expansion. Neurons are placed into four distinct nested clades (pink, green, blue, purple) defined by one or more independent mutations. Cells are ordered within clades according to the presence of multiple somatic mutations. A few cells in each clade fail to manifest individual SNVs shared by other cells of the same clade (indicated by open squares), likely representing incomplete amplification (fig. S2). Dark gray boxes represent cells analyzed by WGS; light gray represents cells analyzed by Sanger-based genotyping. Genomic locations of somatic mutations are given in fig. S11. (**B**) Ultradeep sequencing of mutated loci across the cortex of brain B. Clonal SNVs from a single clade are progressively regionally restricted to frontal cortex and become progressively rarer in bulk tissue, reflecting their later origin during development and neurogenesis. Blue circle, mutation present; empty circle, mutation absent; blue shading, likely spatial distribution of mutation. Percentage range of heterozygous cells is indicated for each SNV. (**C**) Ultradeep sequencing of mutated loci across the brain and body. Some variants are brain-specific (top) and others are shared across germ layers (bottom). Samples sequenced are prefrontal cortex [Brodmann area (BA) 10/BA46], cingulate cortex (BA32/BA8), temporal cortex (BA38), cerebellum (Cb), spinal cord (SC), aorta (Ao), heart (He), liver (Li), lung (Lu), and pancreas (Pa). (**D**) Genotyping shared variants in small sections of human cortex. Left: 4′,6-diamidino-2-phenylindole (DAPI) stain of segment of representative section; scale bar, 200 µm. Center: Three consecutive 300-µm coronal sections from BA40 (red, upper left) were dissected into three axial regions each (1 to 9). Right: Genotyping results for dissected sections. Solid circles denote presence of mutation in indicated sample; open circles denote absence. Mutations with high allele fractions are present in all or virtually all regions, whereas only the least prevalent somatic variant (present in <0.5% of cells) is present in one region but not most regions.

# Developmental Plasticity: Synaptic Pruning

**At birth, each neuron** in the cerebral cortex has approximately **2,500** synapses.

By the time an infant is **two or three years old**, the number of synapses is approximately **15,000 synapses per neuron** (Gopnick, et al., 1999). This amount is **about twice that of the average adult brain**.

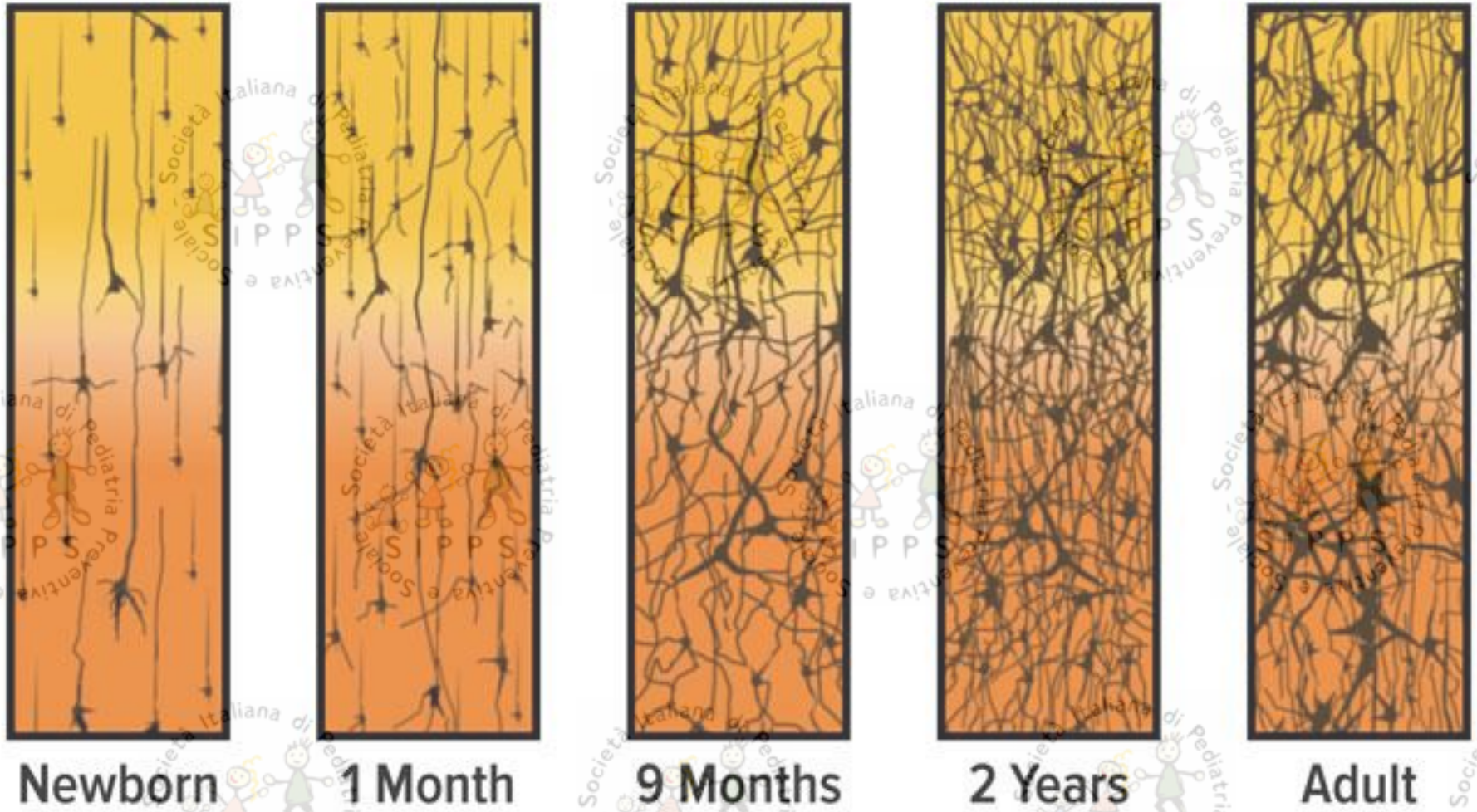
**As we age**, old connections are deleted through a process called ***synaptic pruning***

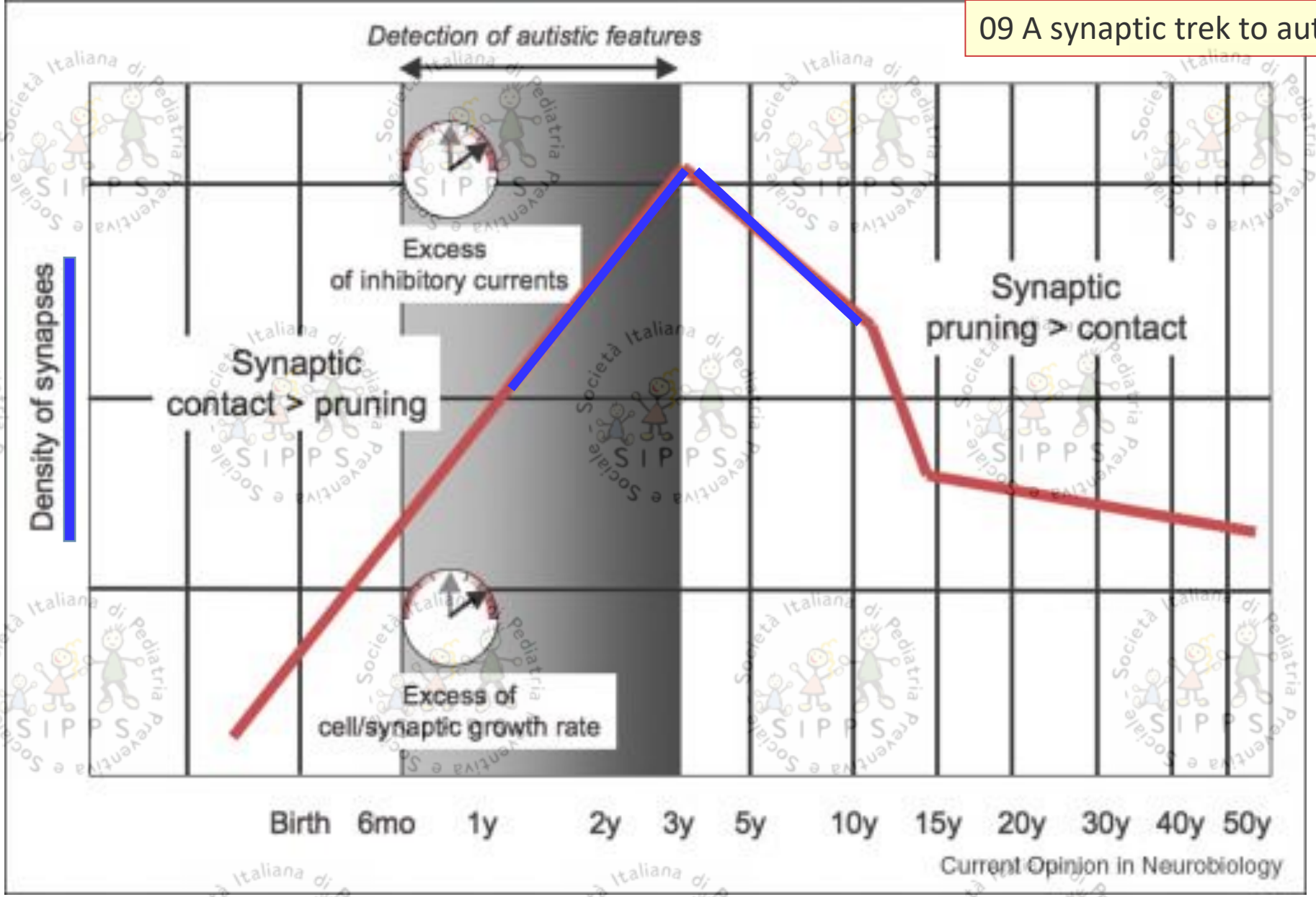
**Ineffective or weak connections are "pruned" in much the same way a gardener would prune a tree or bush**, giving the plant the desired shape.

It is ***plasticity*** that **enables the process of developing and pruning connections, allowing the brain to adapt itself to its environment**

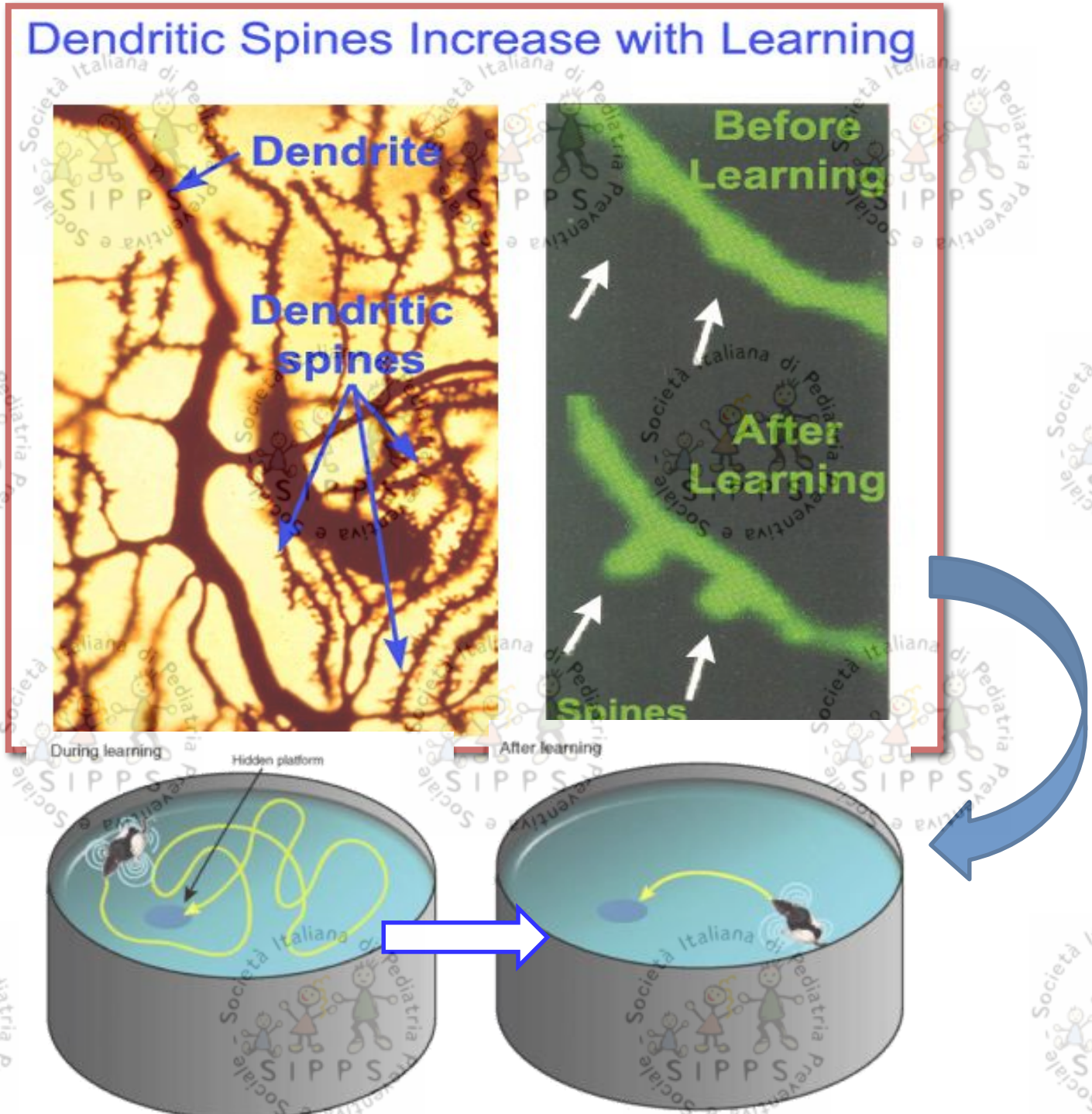
https://faculty.washington.edu/chudler/plast.html

# Connessioni interneurali dall'infante all'adulto umano



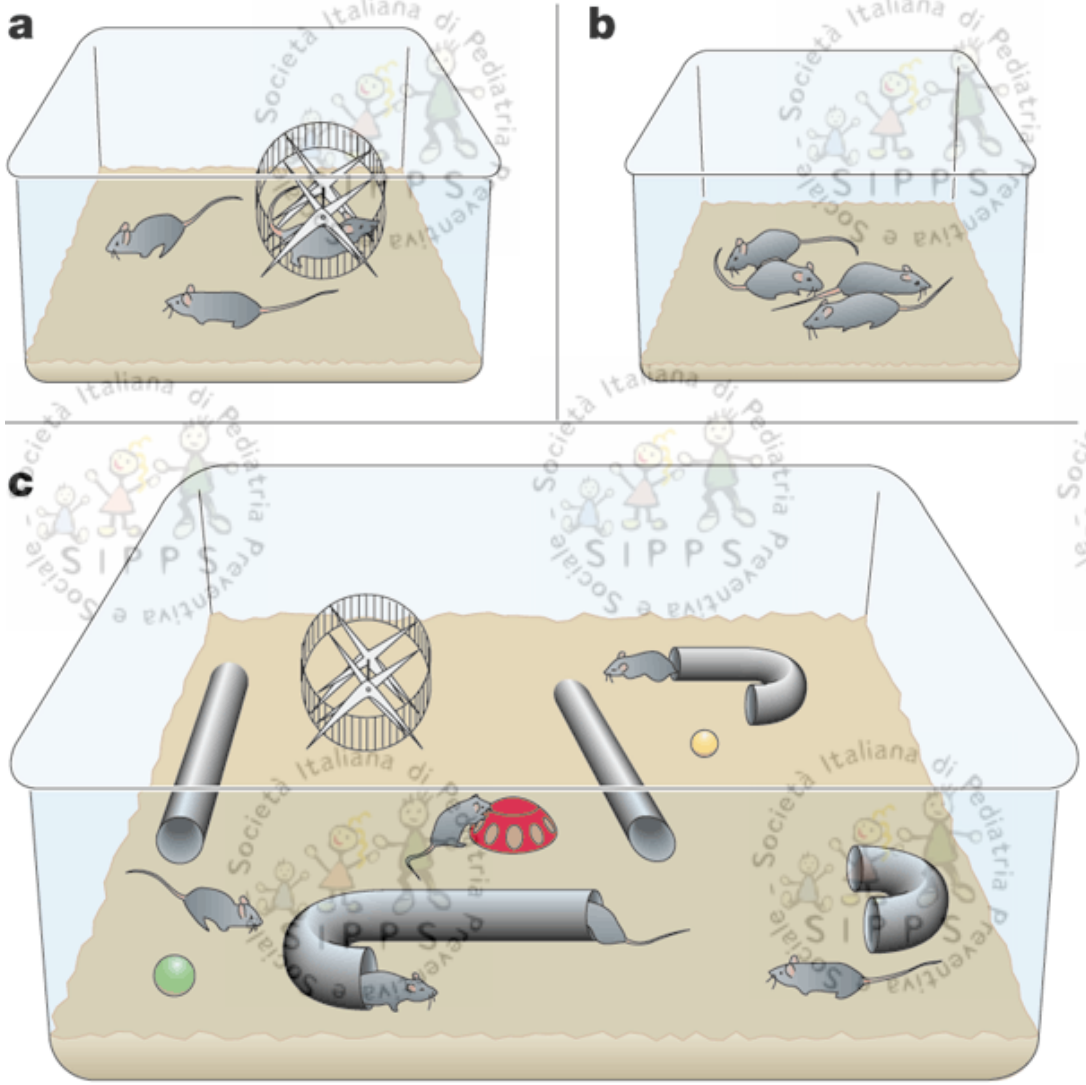



Schematic representation of the **different phases of synaptogenesis** in the human brain.
**During the first three years of life, an excess of cell/synaptic growth rate and inhibitory currents could increase the risk of ASD.**




**Spine plasticity** is implicated in **motivation, learning** and **memory**. In particular **long-term memory** is mediated by the **growth of new dendritic spines** (or the enlargement of pre-existing spines) **to reinforce a particular neural pathway**.

- A questo proposito si possono ricordare gli studi che hanno dimostrato come un **ambiente arricchito** permetta un
- **maggior sviluppo cerebrale (e in particolare un grande incremento di sinapsi/circuiti)**
- **negli animali di laboratorio**
- **e che gli animali che vivono in Natura hanno cervelli più grandi, complessi, attivi, efficienti**

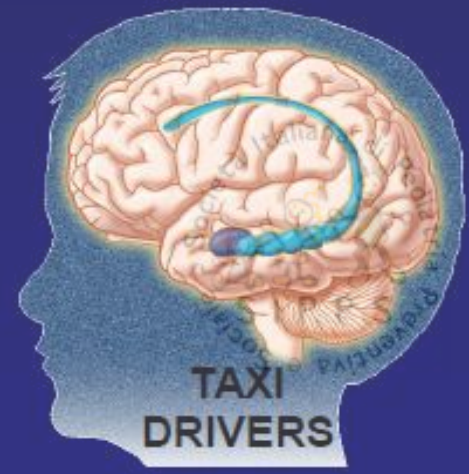



Nature Reviews | Neuroscience

# Navigation-related structural change in the hippocampi of taxi drivers

*Maguire EA,. Gadian DG., Johnsrude IS., Good CD., Ashburner J-, Frackowiak RSJ., Frith CD.*

*PNAS, 2000*

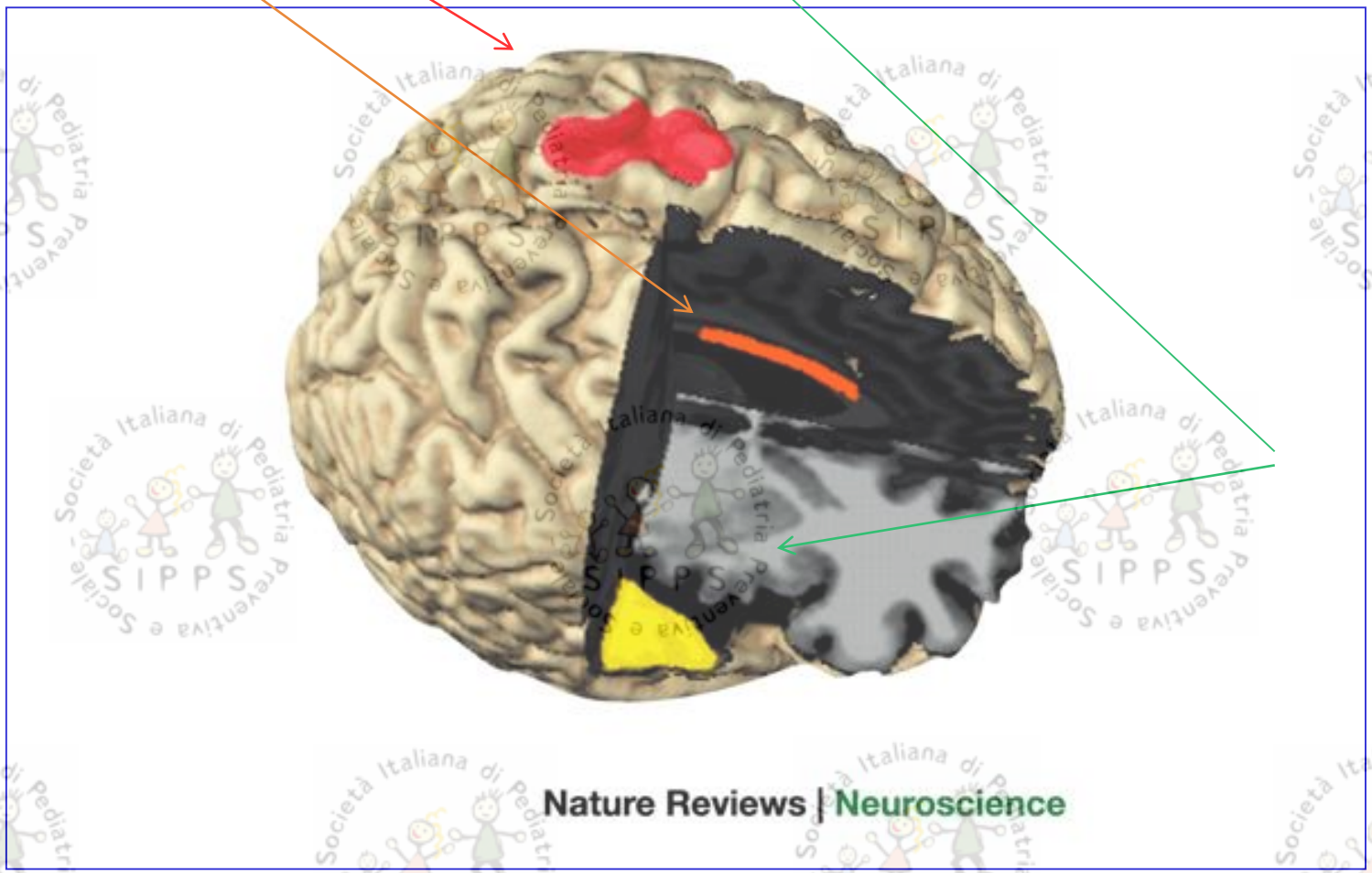

The **posterior hippocampi of taxi drivers were significantly larger relative to those of control subjects**.. volume correlated with the **amount of time spent** as a taxi driver (→ local **plastic change** in the structure of adult human brain in response to the environment)


# How Music shapes our Brain

Un caso estremamente interessante è quello del **cervello del musicista** che presenta una **struttura alquanto particolare, almeno nei casi in cui lo studio della musica ha avuto inizio nelle primissime fasi della vita..**

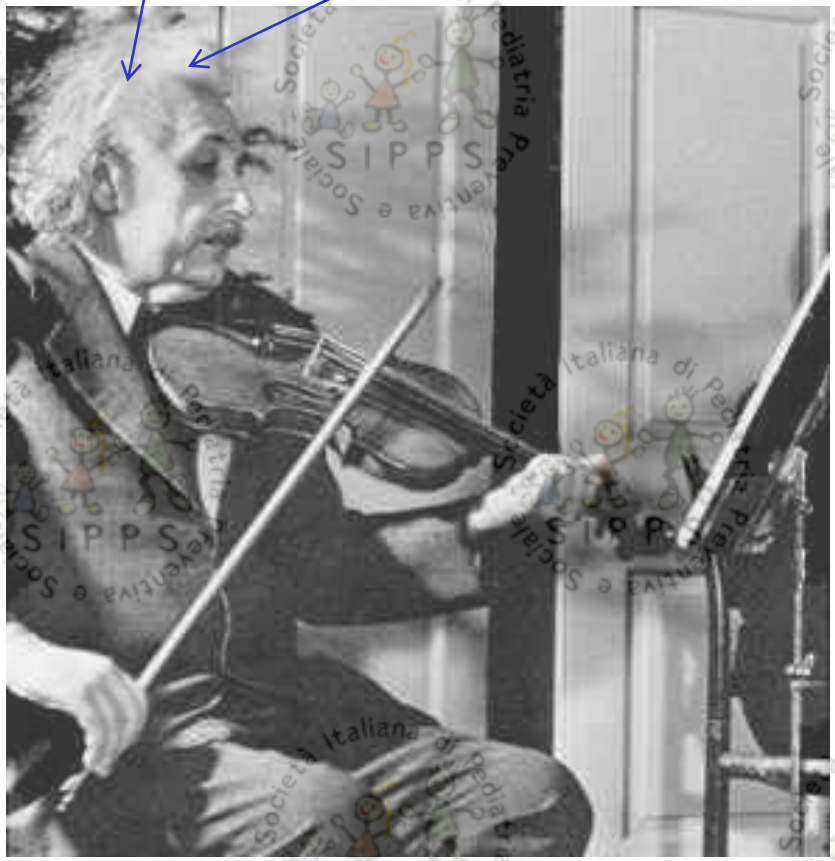
"You are your synapses. They are who you are."
--- Joseph LeDoux, 2002 (in *Synaptic Self*)

Some of **the brain areas that have been found to be enlarged in musicians** in morphometric studies based on **structural magnetic resonance imaging**. *Red*, **primary motor cortex**; yellow, **planum temporale**; orange, **anterior part of the corpus callosum**.




http://www.nature.com/nrn/journal/v3/n6/fig_tab/nrn843_F2.html#figure-title

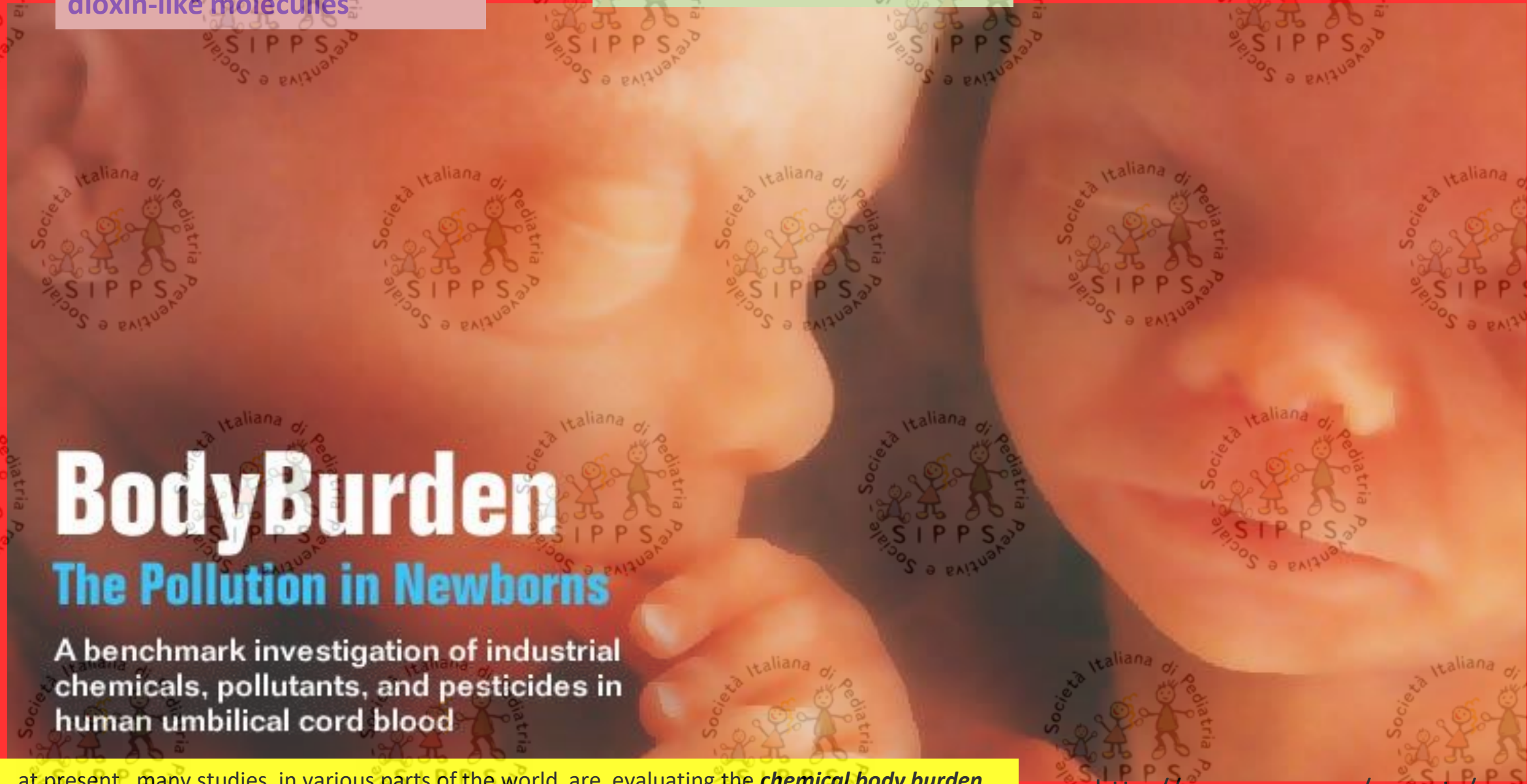
Everybody know that **Albert Einstein**, when he was young, **did extremely poor in school…** and that his grade school teachers told his parents to take him out of school because **he was "too stupid to learn"** and it would be a waste of resources for the school to invest time and energy in his education. **The school suggested that his parents get Albert an easy, manual labor job as soon as they could**. His mother did not think that Albert was "stupid". **Instead of following the school's advice, Albert's parents bought him a violin.** Albert became good at the violin. **Music was the key that helped Albert Einstein become one of the smartest men who has ever lived**. Einstein himself says that the reason he was so smart is because he played the violin and **loved the music of both Mozart and Bach** ..



# CHEMICAL FALL OUT

1. ENDOCRINE DISRUPTORS
   dioxin-like moleculles
2. HEAVY METALS
3. ULTRAFINE PARTICLES

## The gift our mothers never wanted to give us

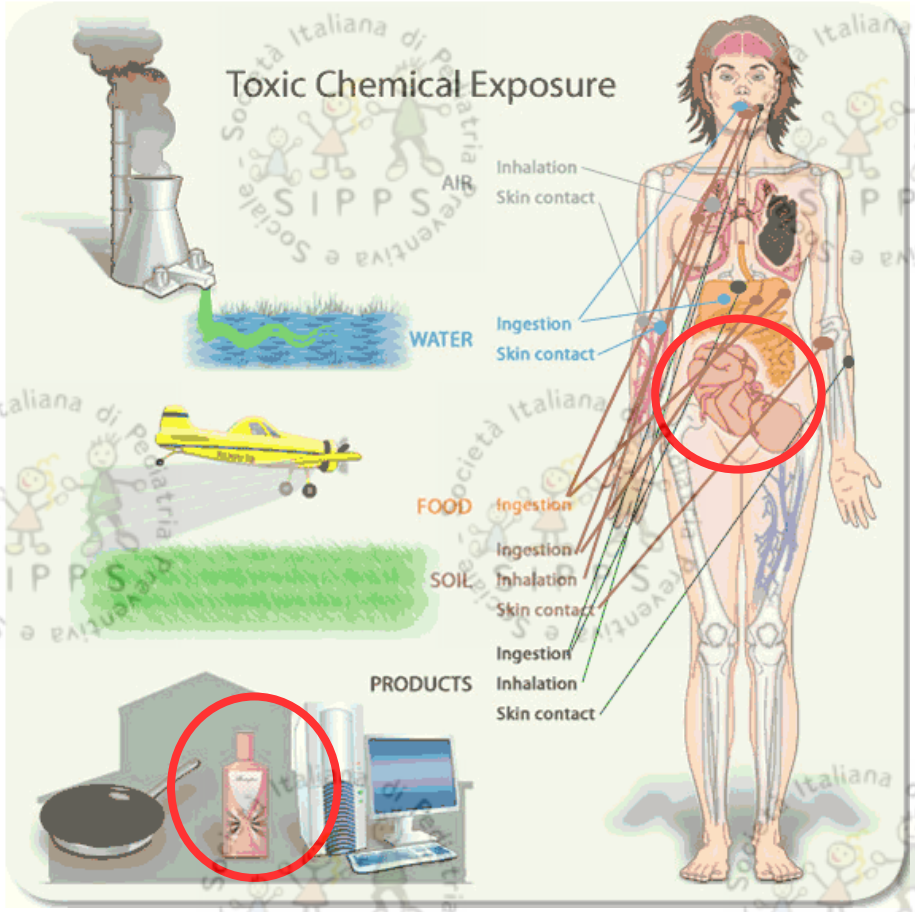


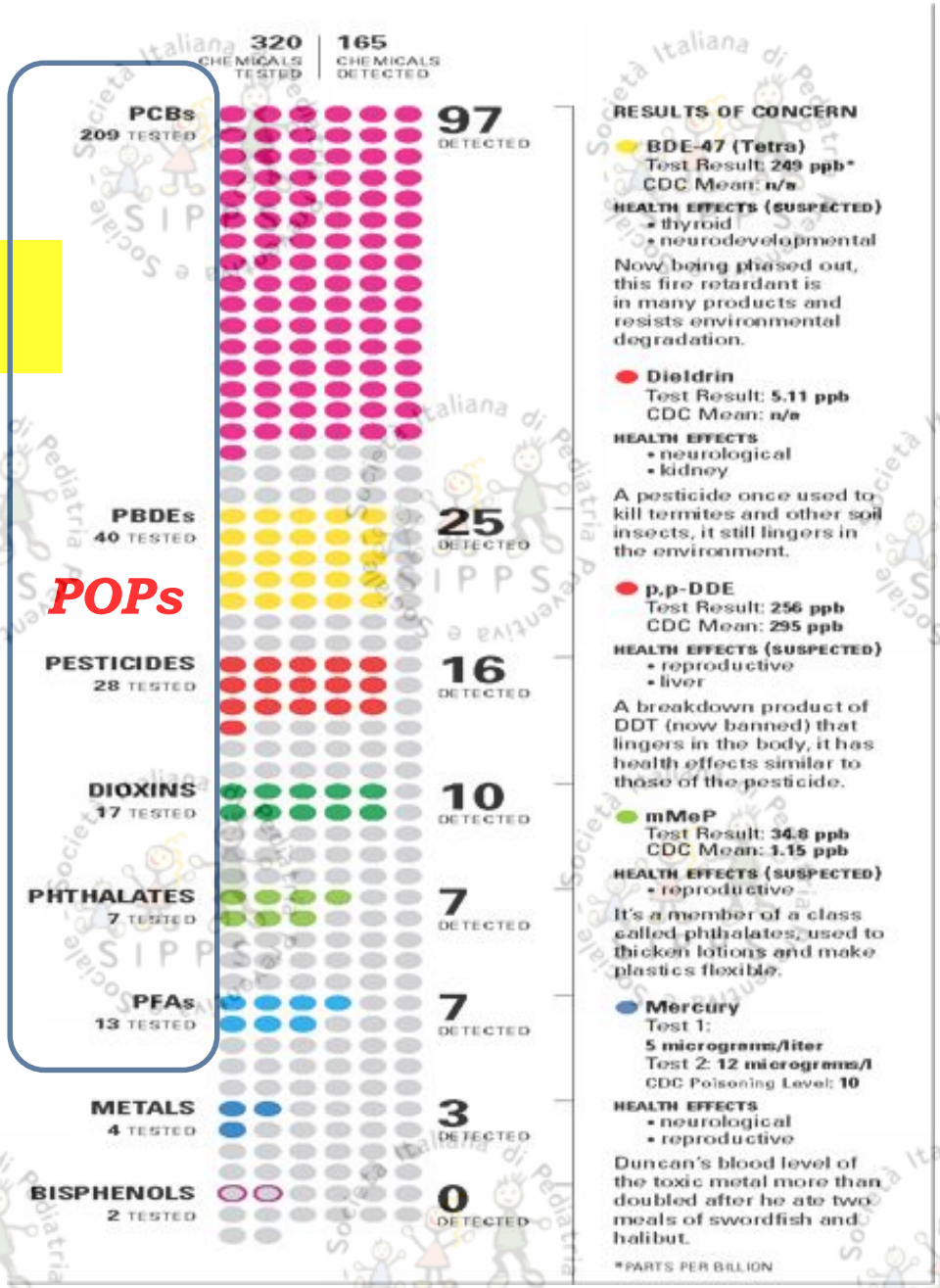

.. at present many studies in various parts of the world are evaluating the ***chemical body burden*** .. especially in women, children, embryos / fetuses **providing dramatic results**

http://www.ewg.org/reports/generations/

# Monitoring Body-Burdens

700 different synthetic chemicals or heavy metals found in human blood,



# Pre or postnatal exposure ?

## *Dioxines & Furans*

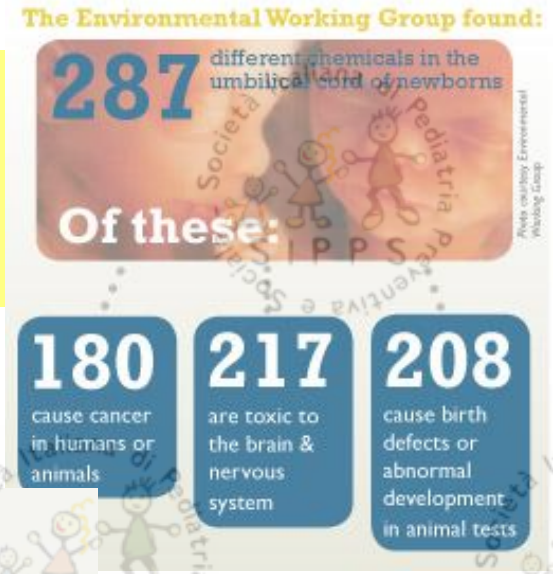

**Incinerators, landfills.. primitive waste recycle, etc.**

**Higher PCDD/F levels were found in placenta (10.3 TEq-pg/g lipid) and venous serum (9.1 TEq-pg/g lipid), compared to those in breast milk (7.6 TEq-pg/g lipid).**

Chemosphere. 2004 Mar;54(10):1459-73. ***Infant exposure to polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls (PCDD/Fs, PCBs)--correlation between prenatal and postnatal exposure***. Wang SL, Lin CY, Guo YL, Lin LY, Chou WL, Chang LW.

# Pre or postnatal exposure ?

**PCBs**




on a lipid basis, the highest concentration of **PCB** in **placenta** (5027 ng/g fat) was **2.8 times higher** than the highest concentration of PCB in **breast milk** (1770 ng/g fat)

**J Expo Anal Environ Epidemiol. 2000 May-Jun;10(3):285-93. PCB exposure in utero and via breast milk. A review. DeKoning EP, Karmaus W. Et al.**

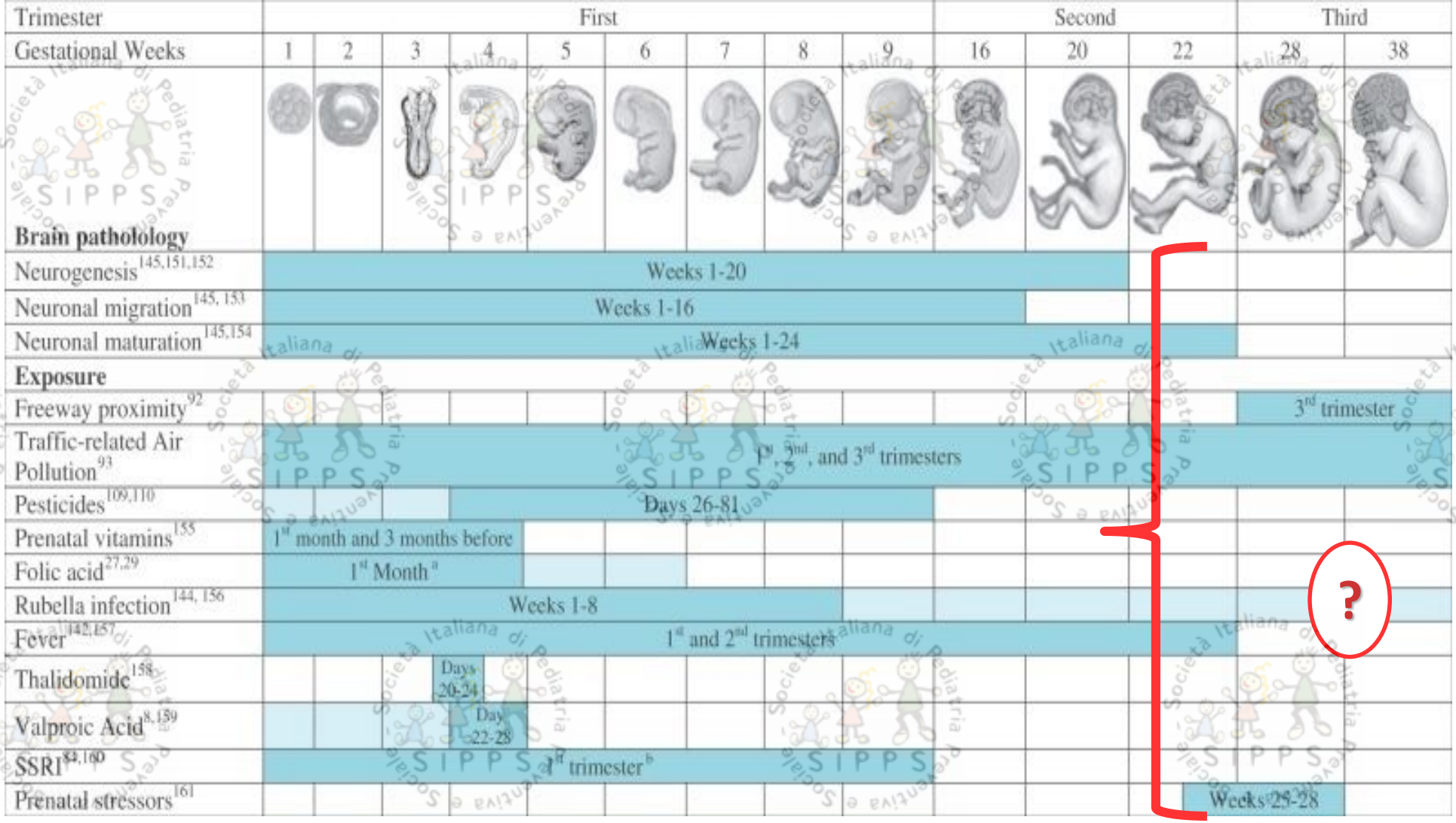
# Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study

Janie F. Shelton,[1] Estella M. Geraghty *Environ Health Perspect*; DOI:10.1289/ehp.1307044: 23 June 2014

970 participants, **California Pesticide Use Report** (1997-2008) linked to the ***addresses during pregnancy***. *Pounds of active ingredient …*
aggregated within 1.25km, 1.5km, and 1.75km buffer distances from the home



- **Organophosphates** higher 3rd trimester expos: **60% increased risk ASD**
- **Pyrethroid insecticide** just prior to conception or for 3rd trimester at **greater risk for both ASD and DD** (developmental delay)
- **Carbamate**: risk for **DD** increased (Arprocarb : Undene, **Propoxur = Baygon**).




**Neuropathology (autopsy and imaging) studies** of brains of individuals with autism found evidence of **dysregulated neurogenesis, neuronal migration and neuronal maturation** .. processes that generally occur **in the first half of pregnancy**. Figure shows **windows of critical periods indicated by evidence from epidemiological studies of environmental factors demonstrating an association with ASDs**.
Int J Epidemiol. 2014 Apr; 43(2): 443–464.

Research | Children's Health

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1408133.

VOLUME 123 | NUMBER 3 | March 2015 · Environmental Health Perspectives

# Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case–Control Analysis within the Nurses' Health Study II Cohort

*Raanan Raz,[1] Andrea L. Roberts,[2] Kristen Lyall,[3,4] Jaime E. Hart,[1,5] Allan C. Just,[1] Francine Laden,[1,5,6] and Marc G. Weisskopf[1,6]*

BACKGROUND: Autism spectrum disorder (ASD) is a developmental disorder with increasing prevalence worldwide, yet has unclear etiology.

OBJECTIVE: We explored the association between maternal exposure to particulate matter (PM) air pollution and odds of ASD in her child.

METHODS: We conducted a nested case–control study of participants in the Nurses' Health Study II (NHS II), a prospective cohort of 116,430 U.S. female nurses recruited in 1989, followed by biennial mailed questionnaires. Subjects were NHS II participants' children born 1990–2002 with ASD ($n$ = 245), and children without ASD ($n$ = 1,522) randomly selected using frequency matching for birth years. Diagnosis of ASD was based on maternal report, which was validated against the Autism Diagnostic Interview-Revised in a subset. Monthly averages of PM with diameters ≤ 2.5 μm ($PM_{2.5}$) and 2.5–10 μm ($PM_{10-2.5}$) were predicted from a spatiotemporal model for the continental United States and linked to residential addresses.

RESULTS: $PM_{2.5}$ exposure during pregnancy was associated with increased odds of ASD, with an adjusted odds ratio (OR) for ASD per interquartile range (IQR) higher $PM_{2.5}$ (4.42 μg/m$^3$) of 1.57 (95% CI: 1.22, 2.03) among women with the same address before and after pregnancy (160 cases, 986 controls). Associations with $PM_{2.5}$ exposure 9 months before or after the pregnancy were weaker in independent models and null when all three time periods were included, whereas the association with the 9 months of pregnancy remained (OR = 1.63; 95% CI: 1.08, 2.47). The association between ASD and $PM_{2.5}$ was stronger for exposure during the third trimester (OR = 1.42 per IQR increase in $PM_{2.5}$; 95% CI: 1.09, 1.86) than during the first two trimesters (ORs = 1.06 and 1.00) when mutually adjusted. There was little association between $PM_{10-2.5}$ and ASD.

CONCLUSIONS: Higher maternal exposure to $PM_{2.5}$ during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD.

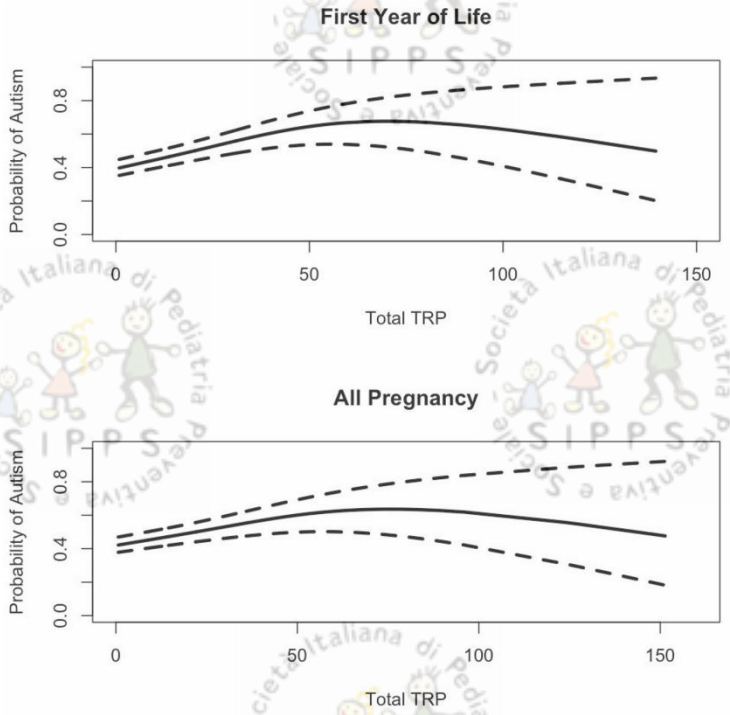
**ASDs risk (OR> 50%) increased significantly among mothers exposed to fine particles (PM 2.5)** and not to PM 2.5-10 especially during the **third trimester of pregnancy (Synaptogenesis!)**

**Two large case-control studies had already shown this correlation**
**JAMA Psy** 2013;70(1):71-7;
**EHP** 2013;121(3):380-6

# Living near a freeway, based on the location of the birth, and third trimester address, and **autism**

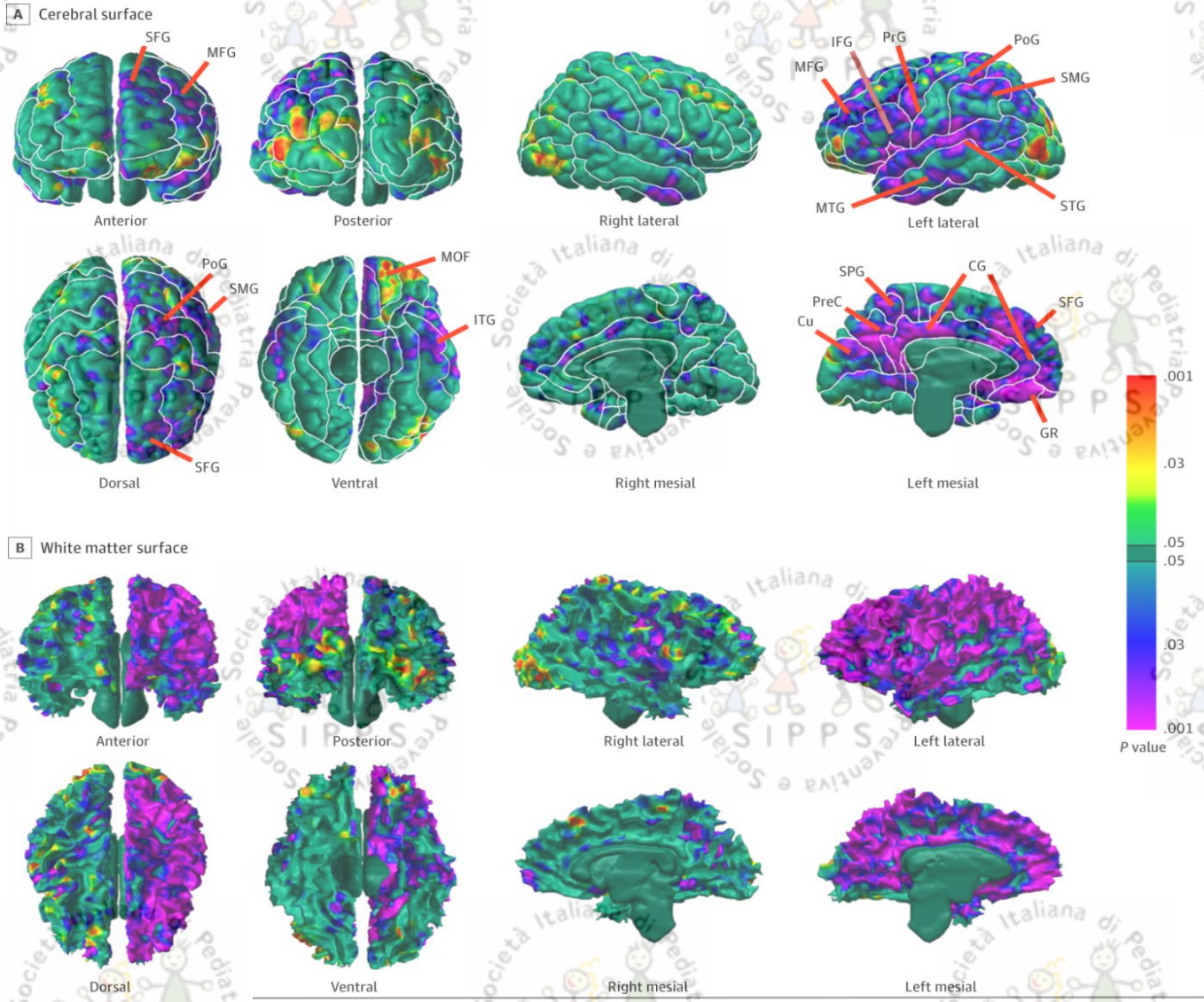
PM2.5, PM10, and NO2 at residences were higher in children with autism.

The magnitude of these **associations** appear to be **most pronounced during late gestation** (OR=1.98, 95%CI 1.20–3.31) **and early life / first year of life** (OR=1.98, 95%CI 1.20–3.31)




*JAMA Psychiatry. 2013 January ; 70(1): 71–77. doi:10.1001/jamapsychiatry.2013.266*

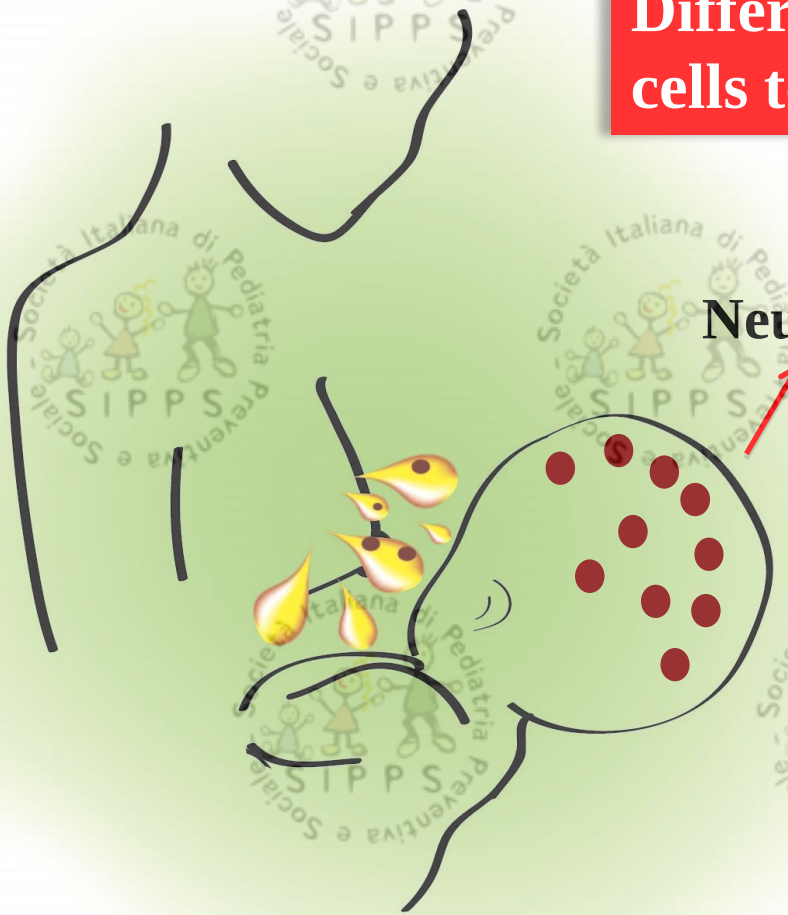
**JAMA Psychiatry**. **Published online March 25, 2015**. doi:10.1001/jamapsychiatry.2015.57




We detected a **dose-response relationship between increased prenatal PAH exposure** (measured in the **third trimester** but thought to index **exposure for all of gestation**) and **reductions of the white matter surface in later childhood** that were confined almost exclusively to the **left hemisphere of the brain** and that involved almost its entire surface

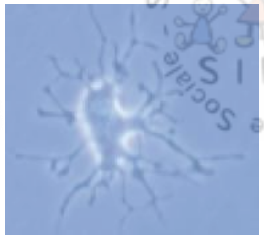
# FROM BREAST MILK TO BRAIN

**Differentiation of breast-milk stem cells to neural stem cells and neurons**



Neurons

Oligodendrocytes



Astrocytes

Metabolomica liquido cellule staminali

*Hosseini SM Neurol Res Int 2014*

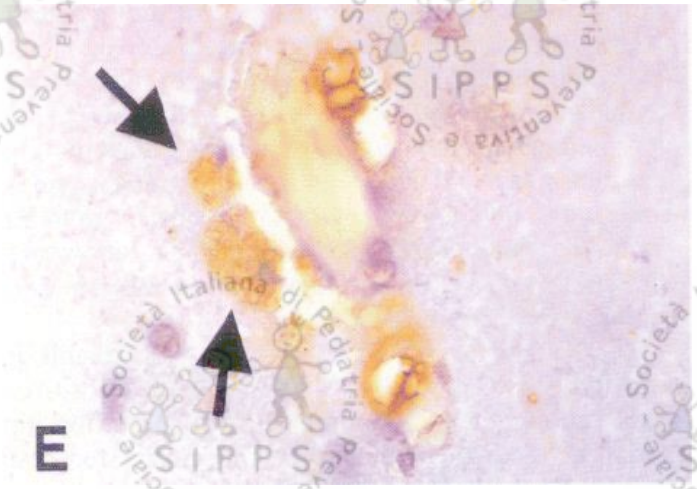
Toxicologic Pathology
http://tpx.sagepub.com

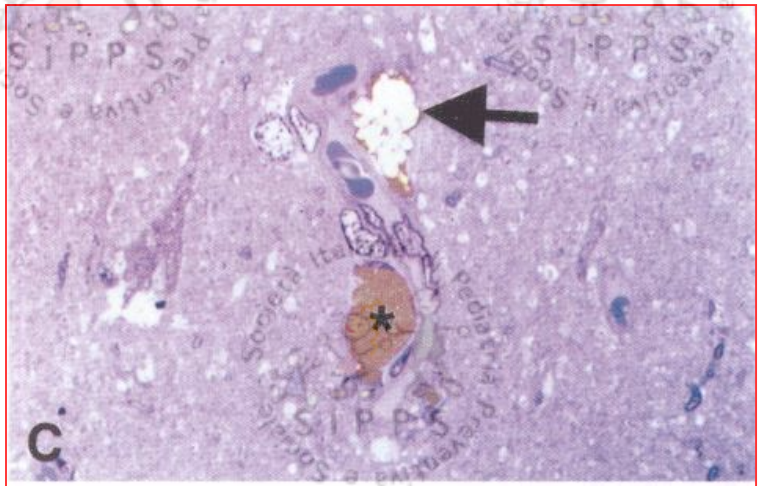
# Air Pollution and Brain Damage

Lilian Calderón-Garcidueñas, Biagio Azzarelli, Hilda Acuna, Raquel Garcia, Todd M. Gambling, Norma Osnaya, Sylvia Monroy, Maria Del Rosario Tizapantzi, Johnny L. Carson, Anna Villarreal-Calderon and Barry Rewcastle

*Toxicol Pathol* 2002; 30; 373
DOI: 10.1080/01926230252929954

Exposure to complex mixtures of air pollutants produces inflammation in the upper and lower respiratory tract. Because the nasal cavity is a common portal of entry, respiratory and olfactory epithelia are vulnerable targets for toxicological damage. This study has evaluated, by light and electron microscopy and immunohistochemical expression of nuclear factor-kappa beta (NF-$\kappa B$) and inducible nitric oxide synthase (iNOS), the olfactory and respiratory nasal mucosae, olfactory bulb, and cortical and subcortical structures from 32 healthy mongrel canine residents in Southwest Metropolitan Mexico City (SWMMC), a highly polluted urban region. Findings were compared to those in 8 dogs from Tlaxcala, a less polluted, control city. In SWMMC dogs, expression of nuclear neuronal NF-$\kappa B$ and iNOS in cortical endothelial cells occurred at ages 2 and 4 weeks; subsequent damage included alterations of the blood–brain barrier (BBB), degenerating cortical neurons, apoptotic glial white matter cells, deposition of apolipoprotein E (apoE)-positive lipid droplets in smooth muscle cells and pericytes, nonneuritic plaques, and neurofibrillary tangles. Persistent pulmonary inflammation and deteriorating olfactory and respiratory barriers may play a role in the neuropathology observed in the brains of these highly exposed canines. Neurodegenerative disorders such as Alzheimer's may begin early in life with air pollutants playing a crucial role.



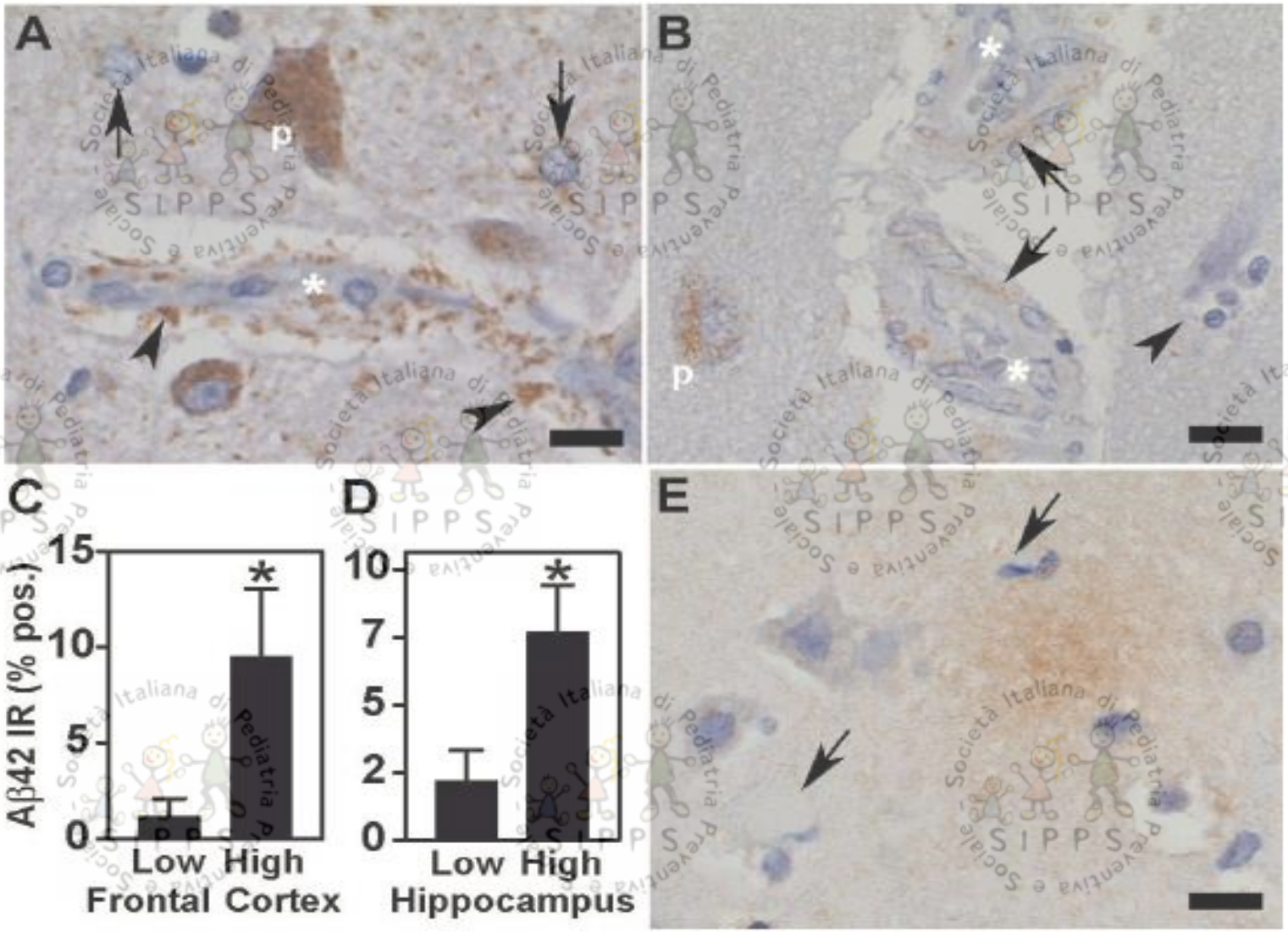



**Figure 3**

Aβ42 accumulation in frontal cortex and hippocampus. Aβ42 was localized in sections of paraffin-embedded tissues by IHC. (A) Aβ42 IHC stained pyramidal neurons (p), astrocytes (arrows) and astrocytic processes (arrowheads) around blood vessels (*). (B) In addition to accumulation in pyramidal neurons (p) Aβ42 was deposited in smooth muscle cells (arrows) in cortical arterioles (*). A dead neuron surrounded by glial cells is indicated (arrowhead). (C and D) Quantitative image analysis of Aβ42 IHC showed a significant increase in Aβ42 immunoreactivity (Aβ42 IR) in both frontal cortex (C, * $p = 0.04$) and hippocampus (D, * $p = 0.001$) in the high exposure group. (E) Aβ42 IHC of frontal cortex from a 38 year old subject from Mexico City showing diffuse plaque-like staining with surrounding reactive astrocytes (arrows). Scale = 20 μm.

Toxicologic Pathology
http://tpx.sagepub.com

# Pediatric Respiratory and Systemic Effects of Chronic Air Pollution Exposure: Nose, Lung, Heart, and Brain Pathology

Lilian Calderón-Garcidueñas, Maricela Franco-Lira, Ricardo Torres-Jardón, Carlos Henriquez-Roldán, Gerardo Barragán-Mejía, Gildardo Valencia-Salazar, Angelica González-Maciel, Rafael Reynoso-Robles, Rafael Villarreal-Calderón and William Reed

*Toxicol Pathol* 2007; 35; 154

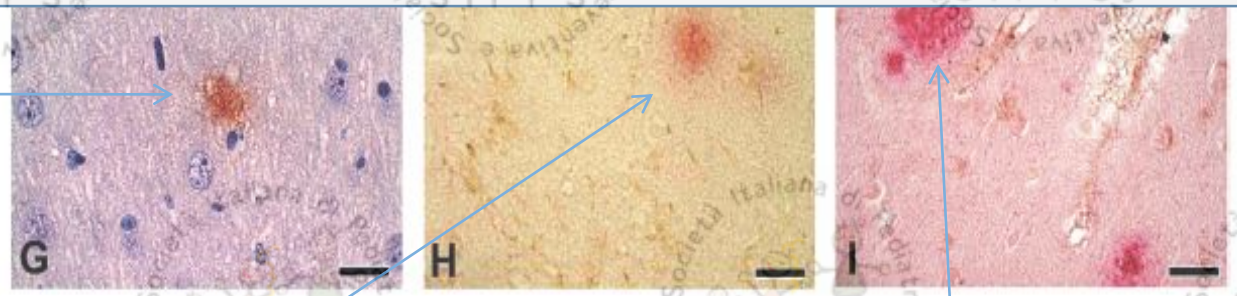
Exposures to **particulate matter and gaseous air pollutants** have been associated with **respiratory tract inflammation**, disruption of the nasal respiratory and olfactory barriers, **systemic inflammation**, production of mediators of inflammation capable of **reaching the brain and systemic circulation of particulate matter**. Mexico City (MC) residents are exposed to significant amounts of ***ozone, particulate matter*** and associated *lipopolysaccharides*. **MC dogs** exhibit brain inflammation and an acceleration of **Alzheimer's-like pathology, suggesting that the brain is adversely affected by air pollutants**.

**MC children, adolescents and adults** have a significant **upregulation of cyclooxygenase-2 (COX2) and interleukin-1*β* (IL-1*β*) in olfactory bulb and frontal cortex**, as well as **neuronal and astrocytic accumulation of the 42 amino acid form of *β*-amyloid peptide (A*β*42), including diffuse amyloid plaques in frontal cortex**.

The pathogenesis of Alzheimer's disease (AD) is characterized by brain inflammation and the accumulation of A*β*42, which precede the appearance of neuritic plaques and neurofibrillary tangles, the pathological hallmarks of AD.

**Our findings of nasal barrier disruption, systemic inflammation, and the upregulation of COX2 and IL-1*β* expression and A*β*42 accumulation in brain suggests that sustained exposures to significant concentrations of air pollutants such as particulate matter could be a risk factor for AD and other neurodegenerative diseases.**

The frontal cortex of an 11-month-old healthy MC dog exhibits **A*β*42** *staining of a* ***diffuse plaque****, surrounded by a microglia-like nucleus*




The frontal cortex of a **17-year-old MC boy**… shows **a diffuse A*β*42 *plaque*** *(red product) and GFAP-negative astrocytes*

The **frontal cortex of a 36-year-old MC male** with an E3/E4 ApoE genotype .. shows **abundant mature and diffuse A*β*42 *plaques*** *(red stain) along* with GFAP-positive reactive astrocytosis

Review

Trends in Neurosciences

Cell PRESS

# Air pollution: mechanisms of neuroinflammation and CNS disease

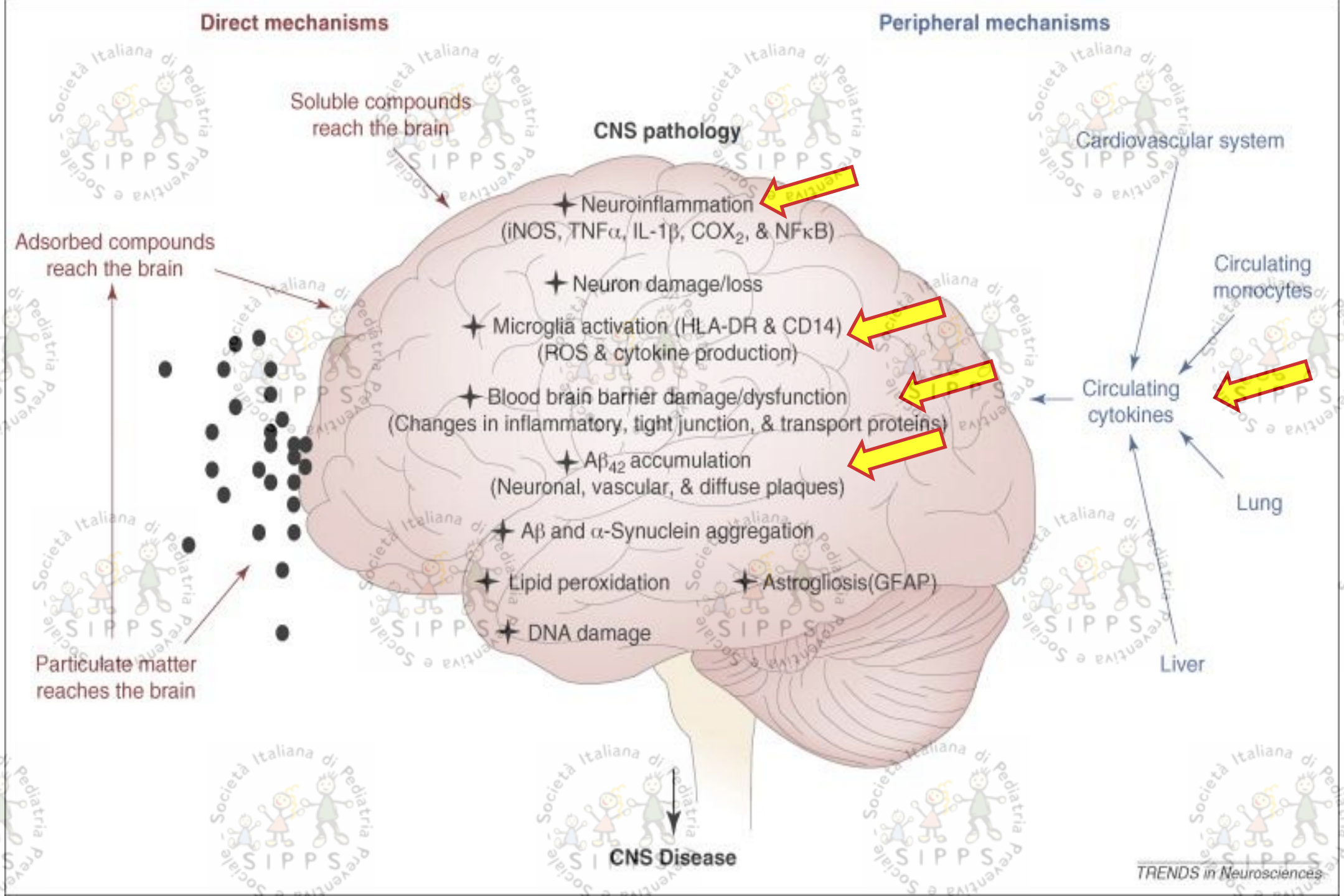
Michelle L. Block[1] and Lilian Calderón-Garcidueñas[2,3]

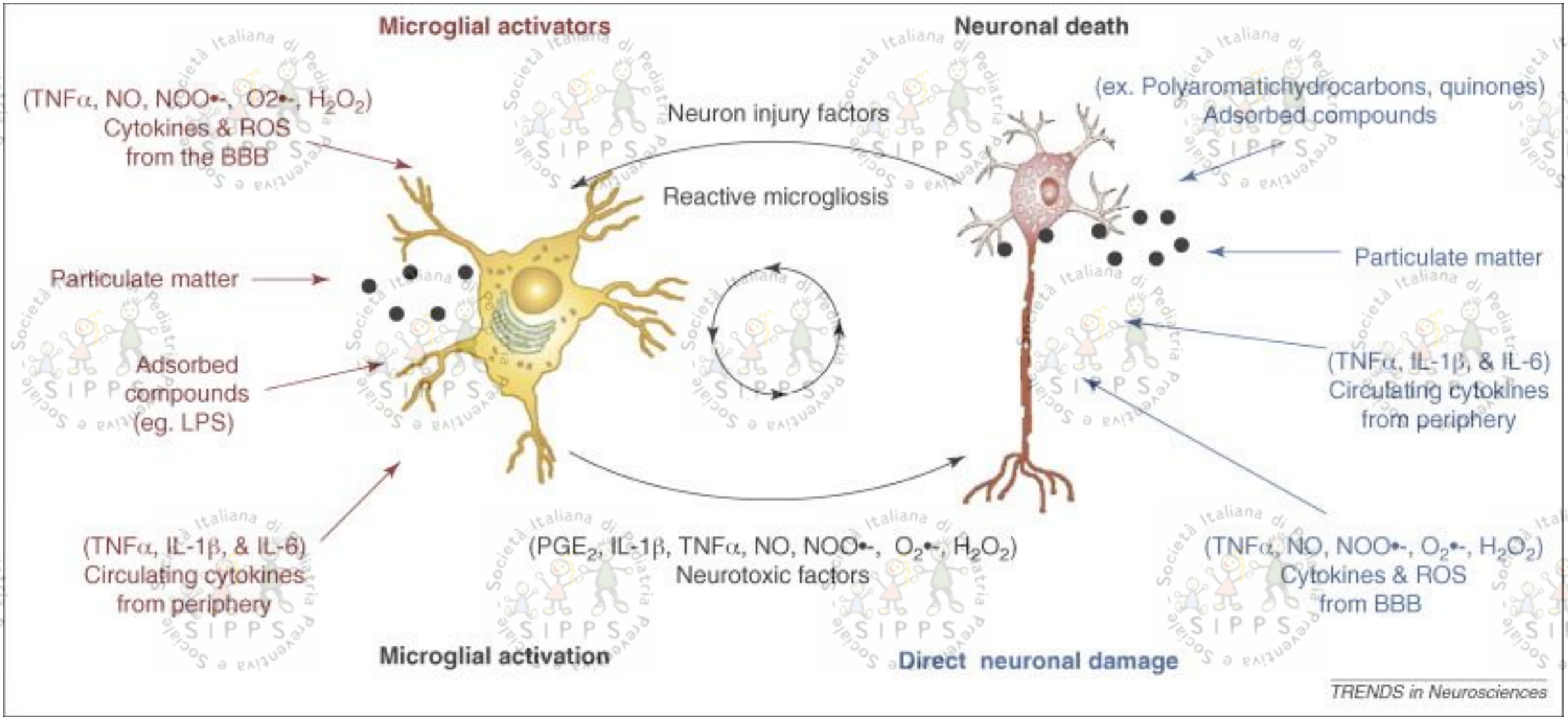
Volume 32, Issue 9, September 2009, Pages 506–516

Air pollution has been implicated as a chronic source of neuroinflammation and reactive oxygen species (ROS) that produce neuropathology and central nervous system (CNS) disease. Stroke incidence and Alzheimer's and Parkinson's disease pathology are linked to air pollution. Recent reports reveal that air pollution components reach the brain; systemic effects that impact lung and cardiovascular disease also impinge upon CNS health. While mechanisms driving air pollution-induced CNS pathology are poorly understood, new evidence suggests that microglial activation and changes in the blood–brain barrier are key components. Here we summarize recent findings detailing the mechanisms through which air pollution reaches the brain and activates the resident innate immune response to become a chronic source of pro-inflammatory factors and ROS, culminating in CNS disease.

While mechanisms driving air pollution-induced CNS pathology are poorly understood, new evidence suggests that **microglial activation and changes in the blood–brain barrier** are key components. Here we summarize recent findings detailing the **mechanisms through which air pollution reaches the brain and activates the resident innate immune response to become a chronic source of pro-inflammatory factors and ROS, culminating in CNS disease.**

Fig 1: It is likely that CNS pathology is due to the **synergistic interactions of the multiple pathways listed here**, making air pollution a potent, biologically relevant environmental exposure and a significant challenge for mechanistic inquiry.


Direct mechanisms
Peripheral mechanisms
Soluble compounds reach the brain
CNS pathology
Cardiovascular system
Neuroinflammation (iNOS, TNFα, IL-1β, COX2, & NFκB)
Adsorbed compounds reach the brain
Circulating monocytes
Neuron damage/loss
Microglia activation (HLA-DR & CD14) (ROS & cytokine production)
Circulating cytokines
Blood brain barrier damage/dysfunction (Changes in inflammatory, tight junction, & transport proteins)
Aβ42 accumulation (Neuronal, vascular, & diffuse plaques)
Lung
Aβ and α-Synuclein aggregation
Lipid peroxidation
Astrogliosis(GFAP)
DNA damage
Liver
Particulate matter reaches the brain
CNS Disease
TRENDS in Neurosciences

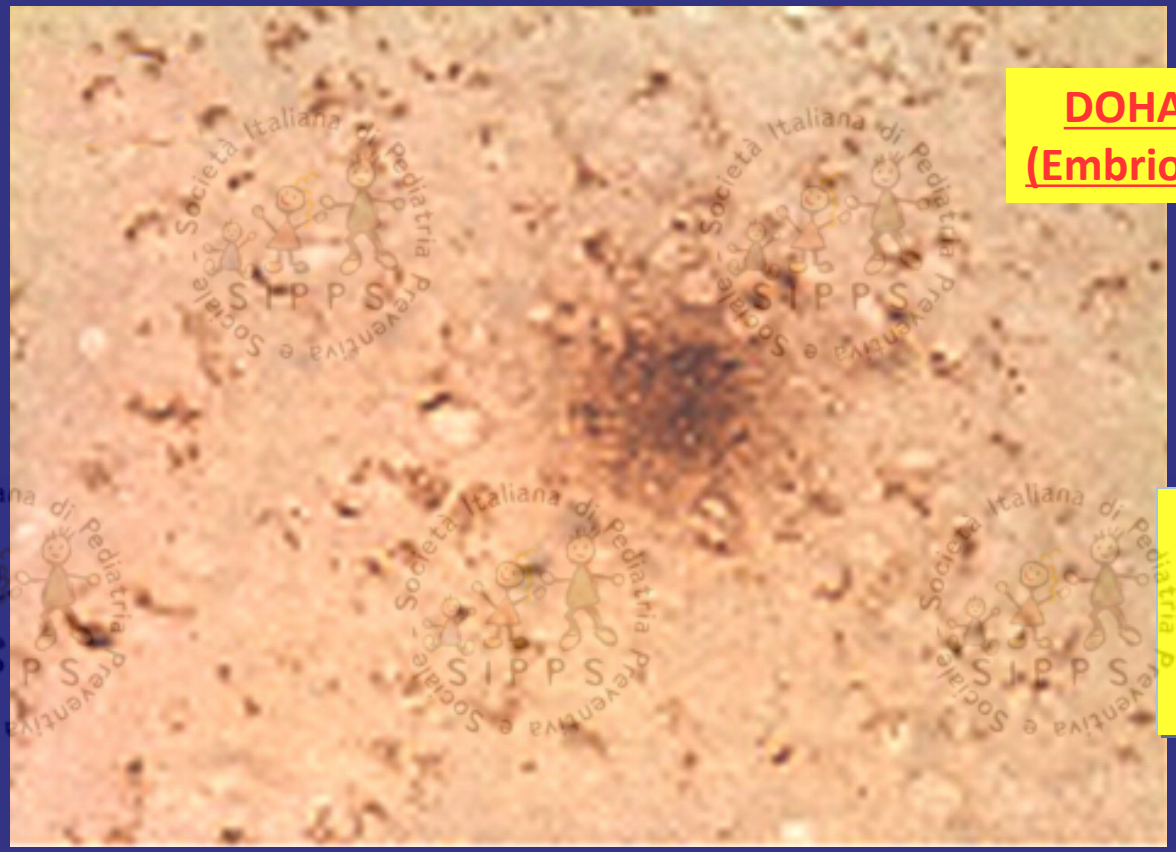



**Air pollution can contribute to toxic microglial activation** by triggering the cycle of ***reactive microgliosis*** through three mechanisms: (i) components of **air pollution may directly activate microglia**; (ii) ***cytokines*** from the peripheral systemic inflammatory response **may activate microglia**; (iii) **particles, adsorbed compounds, or cytokines derived from the periphery may directly damage neurons to activate *reactive microgliosis***.

# Alzheimer's Disease (AD)-Like Pathology in Aged Monkeys after Infantile Exposure to Environmental Metal Lead (Pb): Evidence for a Developmental Origin and Environmental Link for AD

The Journal of Neuroscience, 2008 • 28(1):3–9 • 3

**Environmental Trigger**



**DOHA -Developmental (Embrio-Fetal) Origin of AD.**

**Early life exposures**

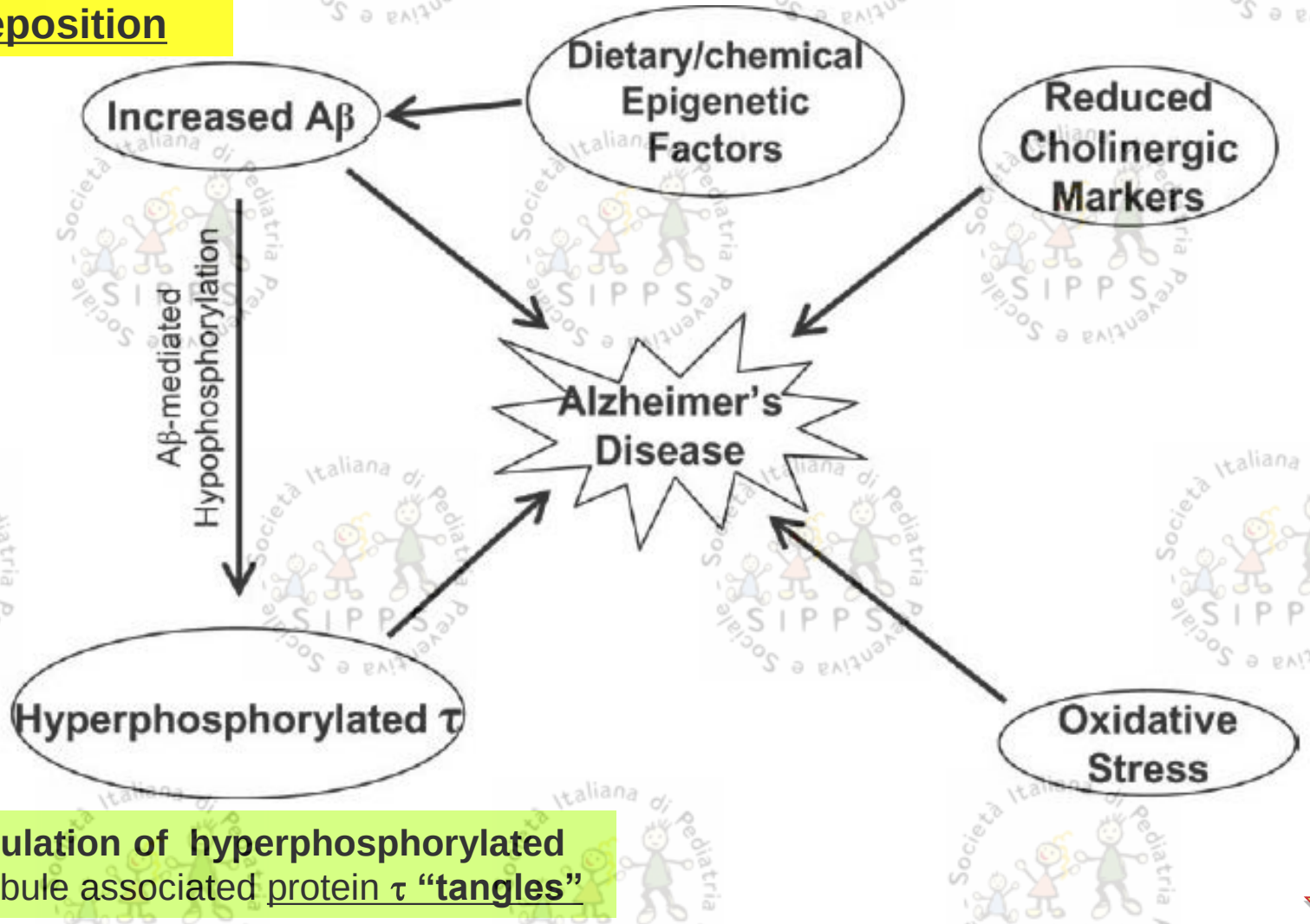
The **cause for most Alzheimer's cases is still *essentially unknown*** (except for 1**% to 5% of cases where genetic differences** have been identified)……..



SOCIETY FOR NEUROSCIENCE The Journal of Neuroscience

**(LEARn) model : early environmental factors** such as exposure to **Pb, nutritional deficiencies** (e.g., folate or B12), or **oxidative stress** alter DNA ***epigenetically***, by **reducing the activity of enzymes as DNMTs…**

**Increased amyloid Aβ-deposition**




**Accumulation of hyperphosphorylated** microtubule associated protein τ **"tangles"**

SCIENTIFIC REPORTS

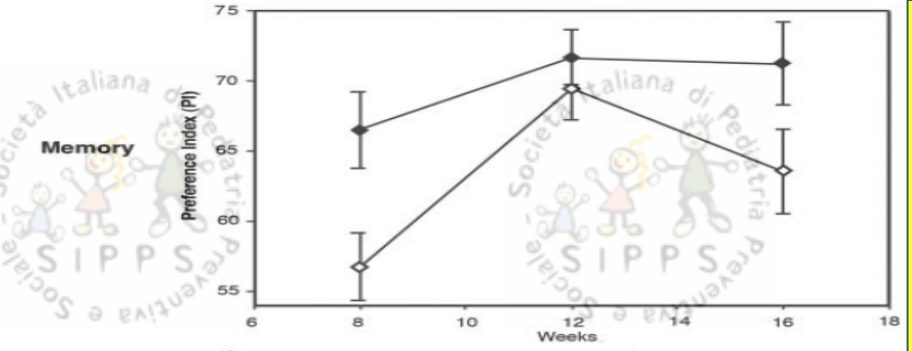
www.nature.com

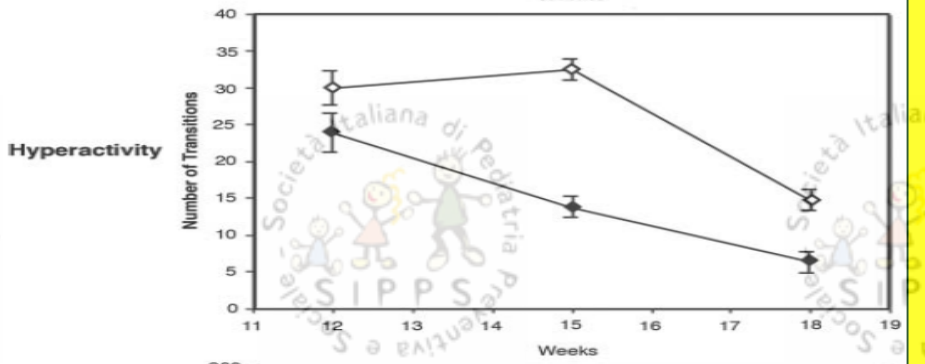
SCIENTIFIC REPORTS | 2 : 312 | DOI: 10.1038/srep00312

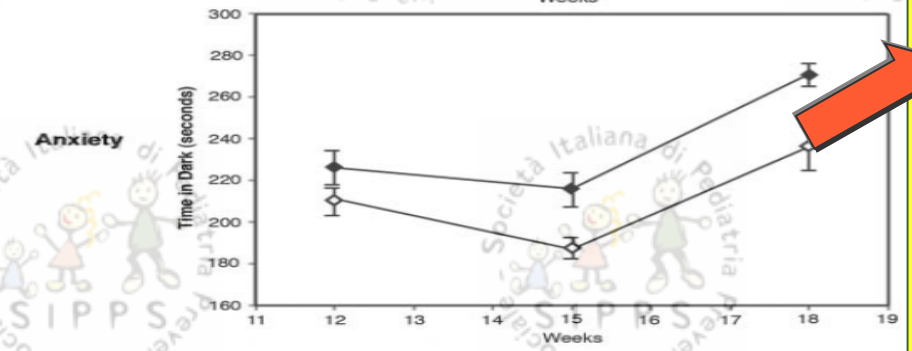
# Fetal Radiofrequency Radiation Exposure From 800-1900 Mhz-Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice

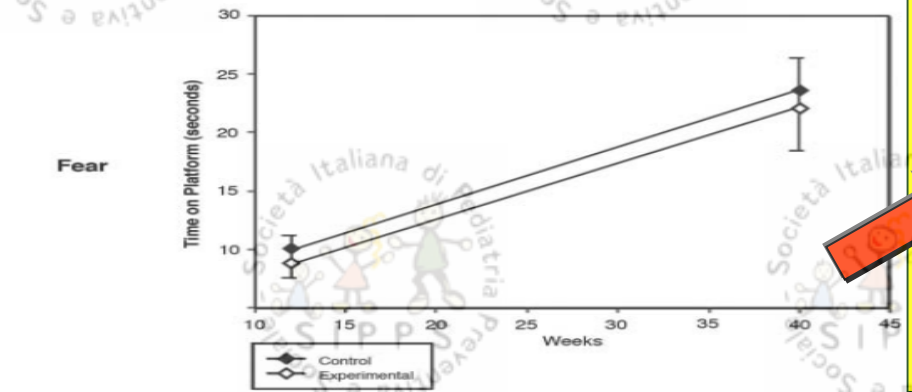
Tamir S. Aldad[1,2], Geliang Gan[2], Xiao-Bing Gao[2,3] & Hugh S. Taylor[1,2,4]

..a **growing overload of electromagnetic radiations** is adding to chemical toxic burden: here we demonstrate that the **fetal exposure** to **800–1900 Mhz-rated radio-frequency radiation from cellular telephones** leads to **behavioral and neurophysiological alterations that persist into adulthood**.




Mice exposed during pregnancy had **impaired memory, were *hyperactive*,** and had increasing **anxiety, indicating that *in-utero* exposure to radiofrequency is a potential cause of *neurobehavioral disorders.***

- **We further demonstrated *impairment of glutamatergic synaptic transmission* onto pyramidal cells *in the prefrontal cortex* associated with these behavioral changes**

- **suggesting *a mechanism by which in-utero cellular telephone radiation exposure*** may lead to the ***increased prevalence of neurobehavioral disorders.***

**Many studies indicate a relationship between NT MW exposure and permeability of the brain–blood barrier** (Nittby et al. 2008), **cerebral blood flow** (Huber et al. 2005), **stress response** (Blank and Goodman 2004), and **neuronal damage** (Salford et al. 2003).


Nittby H, et al. ***Radiofrequency and extremely low-frequency electromagnetic field effects on the blood-brain barrier***. Electromagn Biol Med. 2008;27(2):103–126

Huber R, et al. ***Exposure to pulse-modulated radio frequency electromagnetic fields affects regional cerebral blood flow***. Eur J Neurosci. 2005;21(4):1000–1006

Blank M, Goodman R. ***Comment: a biological guide for electromagnetic safety: the stress response.*** Bioelectromagnetics. 2004;25(8):642–646

Salford LG, et al. ***Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones***. Environ Health Perspect. 2003;111:881–883

Belyaev et al [2010] reported that **915 MHz microwave exposure** significantly affects human **stem cells**

"**The strongest microwave effects were always observed in stem cells**. This result may suggest both significant **misbalance in DSB repair, and severe stress response**.

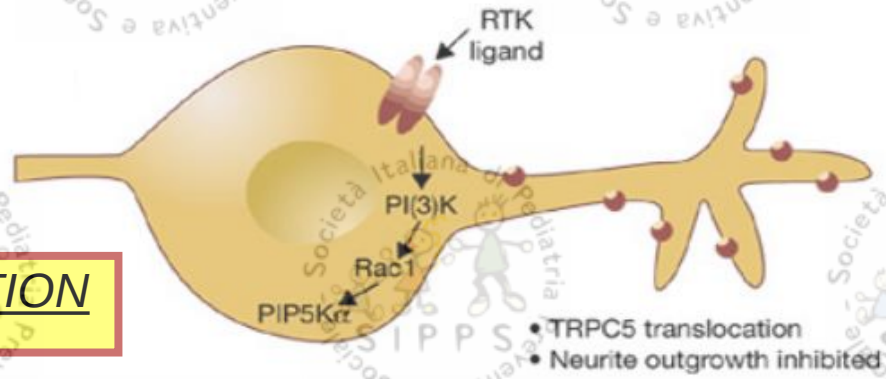
Our findings that **stem cells are the most sensitive to microwave exposure,** and **react to more frequencies than do differentiated cells may be important for cancer risk assessment and indicate that**

**stem cells are the most relevant cellular model for validating safe mobile communication signals."**

Belyaev I, Markova E, Malmgren L. [2010] ***Microwaves from Mobile Phones Inhibit 53BP1 Focus Formation in Human Stem Cells Stronger than in Differentiated Cells: Possible Mechanistic Link to Cancer Risk***. Environ Health Perspect. 118(3): 394–399

Chen C, Ma Q, Liu C, Deng P, Zhu G, Zhang L, He M, Lu Y, Duan W, Pei L, Li M, Yu Z, Zhou Z ***Exposure to 1800 MHz radiofrequency radiation impairs neurite outgrowth of Embryonic neural stem cells***. Sci Rep. 2014 May 29;4:5103

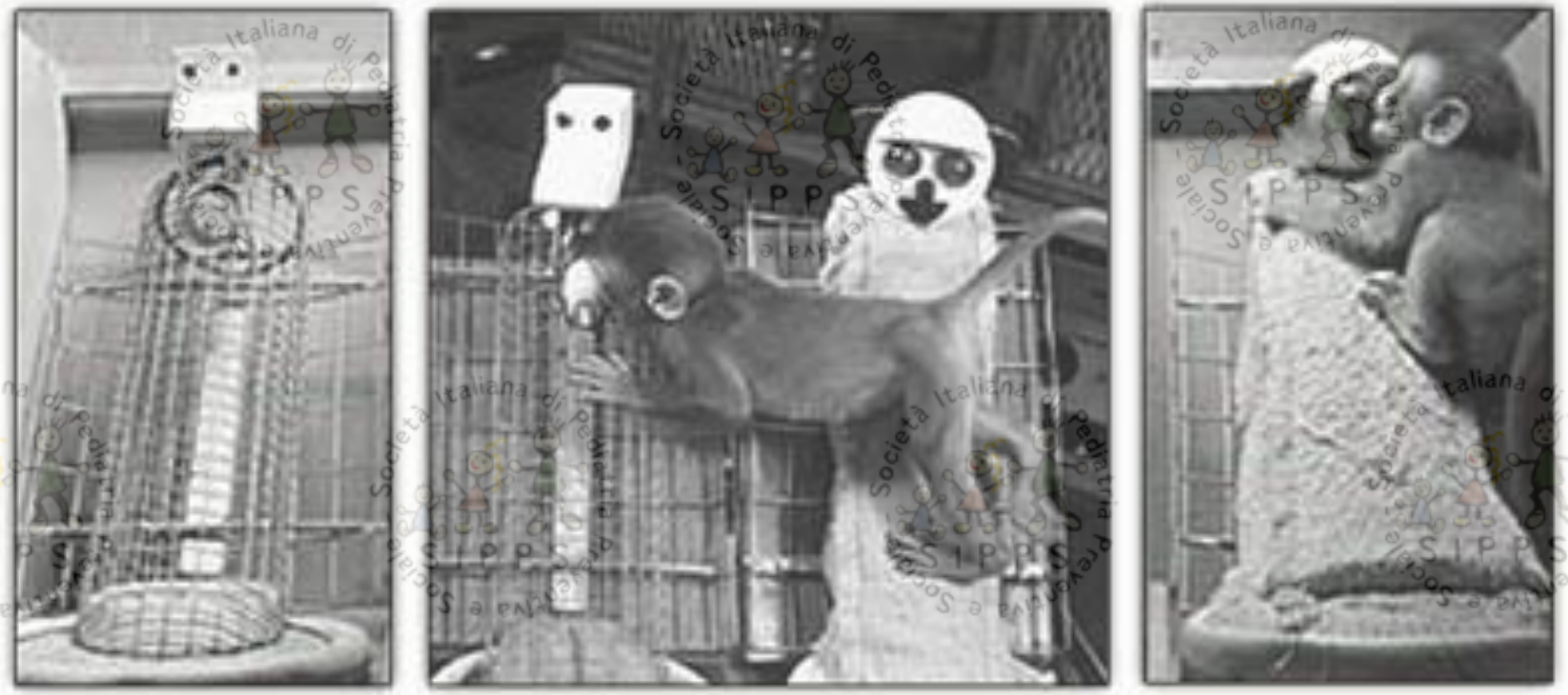
**A radiofrequency electromagnetic field (RF-EMF) of 1800 MHz is widely used in mobile communications. However, the effects of RF-EMFs on cell biology are unclear. Embryonic neural stem cells (eNSCs) play a critical role in brain development**. **Thus, detecting the effects of RF-EMF on eNSCs is important for exploring the effects of RF-EMF on brain development**. We exposed eNSCs to 1800 MHz RF-EMF at specific absorption rate (SAR) values of 1, 2, and 4 W/kg for 1, 2, and 3 days. We found that 1800 MHz RF-EMF exposure did not influence eNSC apoptosis, proliferation, cell cycle or the mRNA expressions of related genes. RF-EMF exposure also did not alter the ratio of eNSC differentiated neurons and astrocytes. However, **neurite outgrowth of eNSC differentiated neurons was inhibited after 4 W/kg RF-EMF exposure for 3 days. Additionally, the mRNA and protein expression of the proneural genes Ngn1 and NeuroD, which are crucial for neurite outgrowth, were decreased after RF-EMF exposure.** The **expression of their inhibitor Hes1 was upregulated by RF-EMF exposure**. These results together suggested that **1800 MHz RF-EMF exposure impairs neurite outgrowth of eNSCs. More attention should be given to the potential adverse effects of RF-EMF exposure on brain development.**




Disturbing the *CONNECTOME INSTRUCTION*

# Harlow and 50 years of cruelty

## A History of Primate Experimentation at the University of Wisconsin, Madison



http://www.madisonmonkeys.com/history_30-81.htm

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# PRENATAL STRESS AND RISK FOR AUTISM

Dennis K. Kinney, Ph.D.[a,b,*], Kerim M. Munir, M.D., M.P.H., D.Sc.[b,c], David J. Crowley[a], and Andrea M. Miller[a]

This paper reviews several converging lines of research that suggest that prenatal exposure to environmental stress may increase risk for Autistic Disorder (AD). We first discuss studies finding that prenatal exposure to stressful life events is associated with significantly increased risk of AD, as well as other disorders, such as schizophrenia and depression. We then review evidence from animal and human
resemble the defi
such as learning
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role for prenatal s
fetal brain develo
AD, including po
prevention progra

**Prenatal exposure to stressful life events is associated with significantly increased risk of Autistic Disorders (AD),** as well as other disorders, such as **schizophrenia** and **depression**..

**Prenatal stress** can produce both

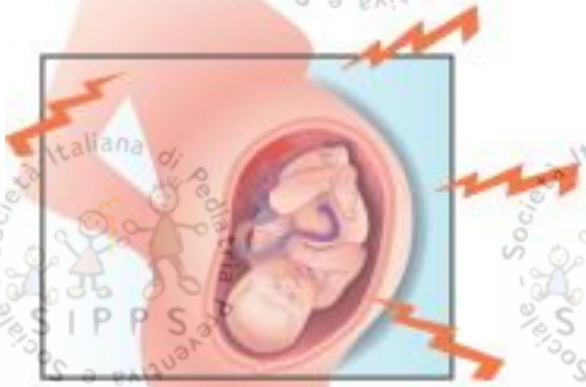
(a) abnormal postnatal behaviors that resemble the defining **symptoms of AD**, and

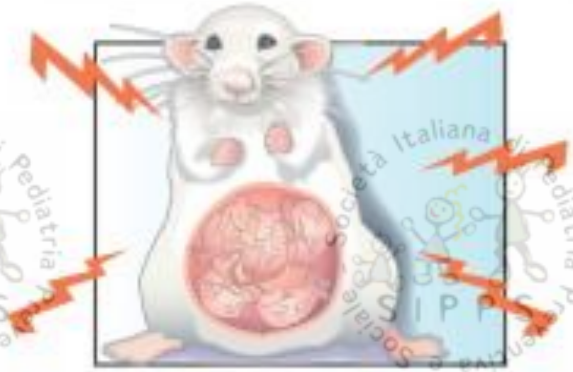
(b) other abnormalities that have elevated rates in AD, such as **learning deficits, seizure disorders, perinatal complications, immunologic and neuroinflammatory anomalies, and low postnatal tolerance for stress**

# Prenatal Stress

Traumatic war experiences, natural disasters, death of husband

Repeated experimental stressors





Human evidence

Animal studies

Elevated risk of schizophrenia in children

Schizophrenia-like phenotype in the offspring (cognitive deficits, disrupted social behaviour, hyperactivity)

Molecular changes in the brain

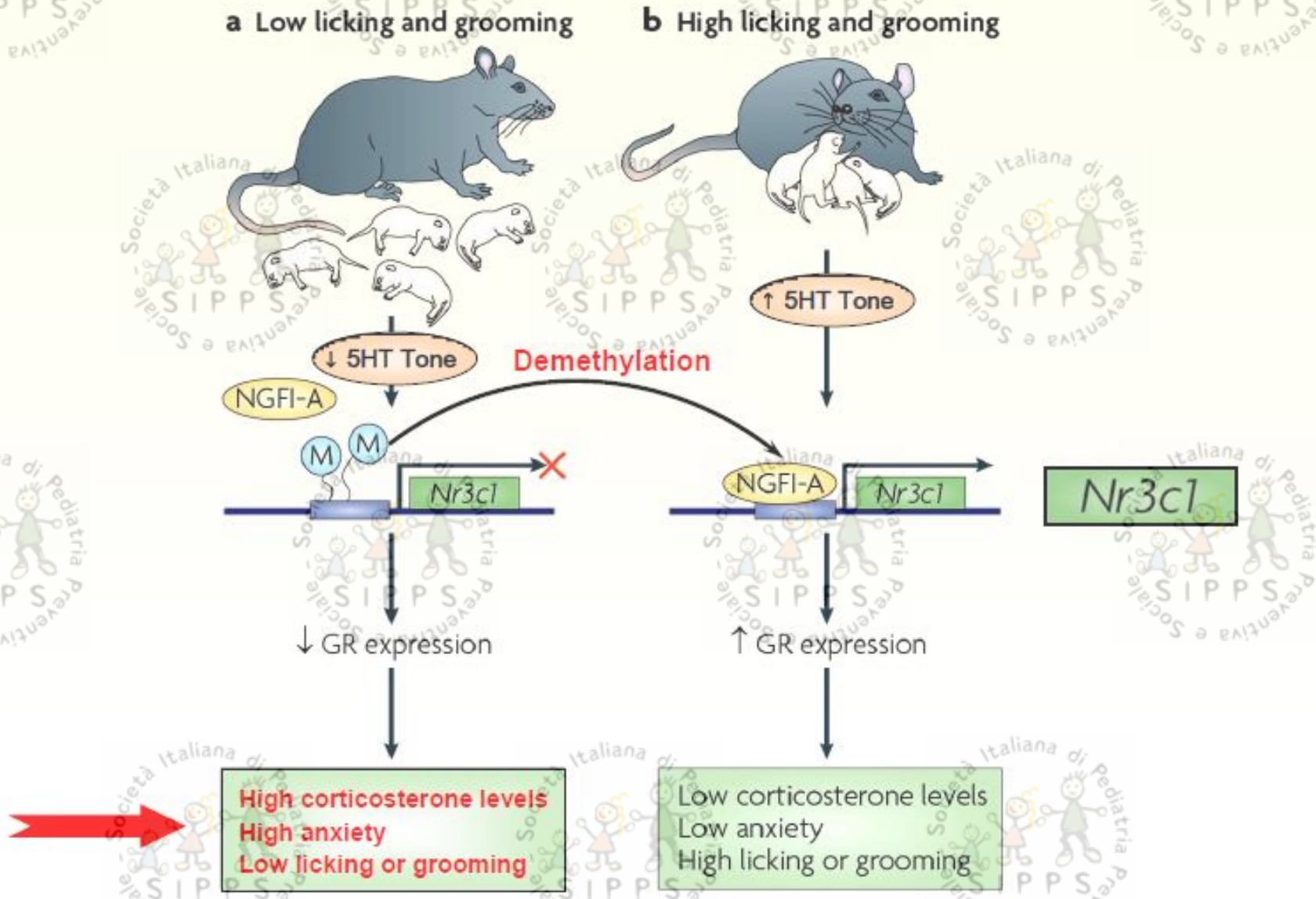
- Altered DNA methylation in prefrontal cortex
- Disrupted maturation of prefrontal cortex
- Impaired HPA axis regulation
- Impaired synaptic plasticity

Altered miRNA expression? Other epigenetic changes?

Are molecular changes regulated by epigenetic mechanisms that were disrupted during prenatal life?

# Epigenetic mechanisms of stress responsiveness

Nature, June 14 2009



# Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse

nature neuroscience

Patrick O McGowan[1,2], Aya Sasaki[1,2], Ana C D'Alessio[3], Sergiy Dymov[3], Benoit Labonté[1,4], Moshe Szyf[2,3], Gustavo Turecki[1,4] & Michael J Meaney[1,2,5]

VOLUME 12 | NUMBER 3 | MARCH 2009 NATURE NEUROSCIENCE

Maternal care influences hypothalamic-pituitary-adrenal (HPA) function in the rat through epigenetic programming
glucocorticoid receptor expression. In humans, childhood abuse alters HPA stress responses and increases the risk
We examined epigenetic differences in a neuron-specific glucocorticoid receptor (*NR3C1*) promoter between postr
hippocampus obtained from suicide victims with a history of childhood abuse and those from either suicide victim
childhood abuse or controls. We found decreased levels of glucocorticoid receptor mRNA, as well as mRNA transc
glucocorticoid receptor $1_F$ splice variant and increased cytosine methylation of an *NR3C1* promoter. Patch-methyl
promoter constructs that mimicked the methylation state in samples from abused suicide victims showed decrease
transcription factor binding and NGFI-A–inducible gene transcription. These findings translate previous results fro
and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor

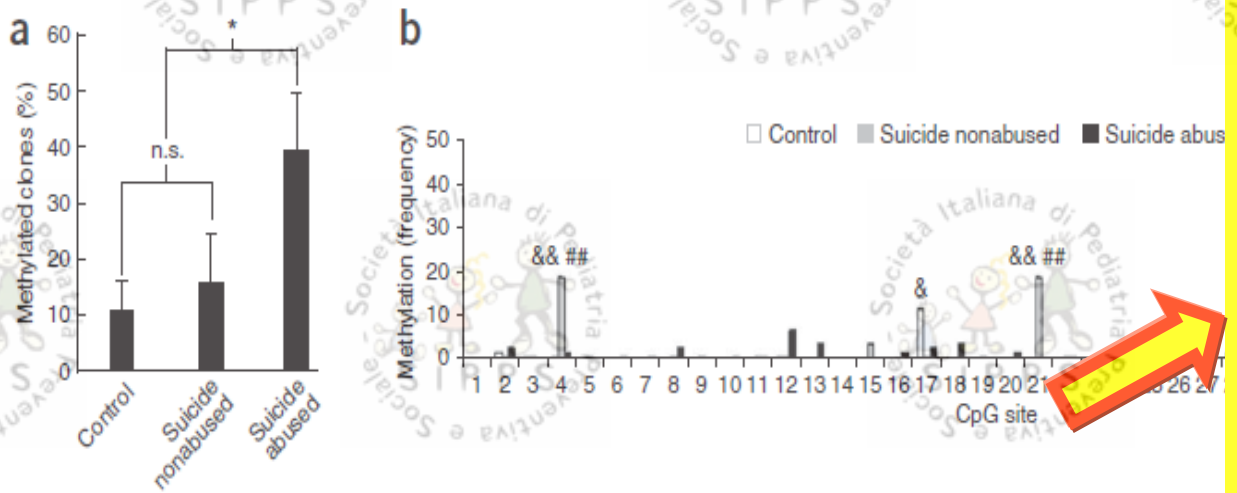


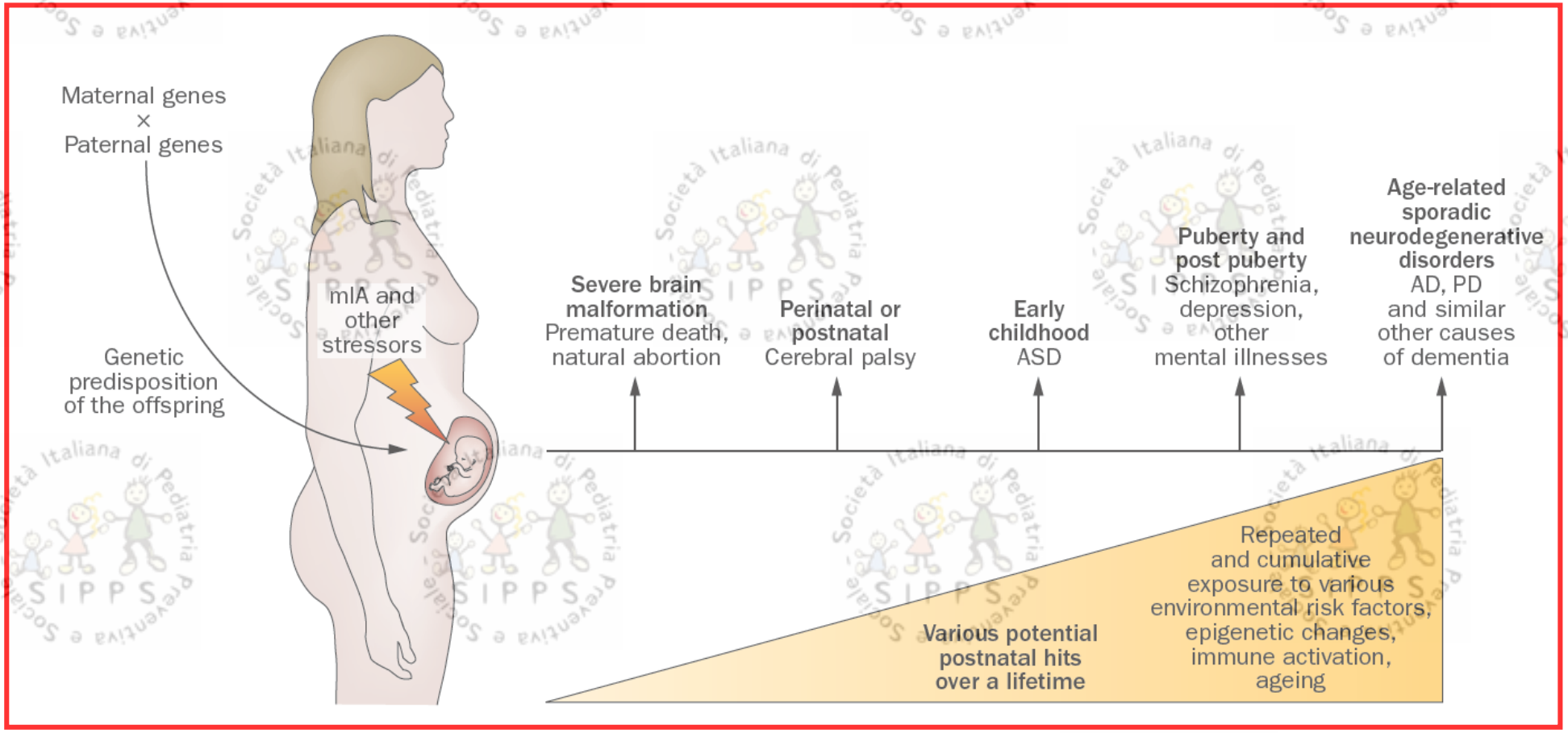

Figure 2 Methylation of the *NR3C1* promoter in the hippocampus. Twenty clones were sequenced for each subject for m
percentage of methylated clones for suicide victims with a history of childhood abuse ($n = 12$), suicide victims without a
and controls ($n = 12$). The methylation percentage was calculated as the number of clones with at least one methylated
number of clones (* indicates $P \leq 0.05$; n.s. indicates not statistically significant). (b) Methylation of the *NR3C1* promo
of methylation observed at each CpG site for suicide victims with a history of childhood abuse, suicide victims with no h
control subjects (*$P < 0.05$, **$P < 0.001$, abused suicides versus controls; $^{\&}P < 0.05$, $^{\&\&}P < 0.001$, non-abused su
$^{\#\#}P < 0.001$, abused suicides versus non-abused suicides; Bonferroni *post hoc* comparisons).

**Maternal care influences the programming** of the hypothalamic-pituitary-adrenal Axis (**HPA**) through epigenetic programming of ***glucocorticoid receptors expression***...

We found a **greatly increased methylation of cytosine in the promoter of a gene** codifying for a Glucocorticoids-Neuro-Receptor (NR3C1) **in the hippocampus of suicide victims with a history of childhood abuse** .. (post-mortem examinations)

# Maternal immune activation and abnormal brain development across CNS disorders

Nature Reviews Neurology 10, 643–660 (2014)




**Epidemiological studies** have shown a clear association between **maternal infection and schizophrenia or autism** in the progeny. **Animal models** have revealed **maternal immune activation (mIA) to be a profound risk factor for neurochemical and behavioural abnormalities in the offspring**.

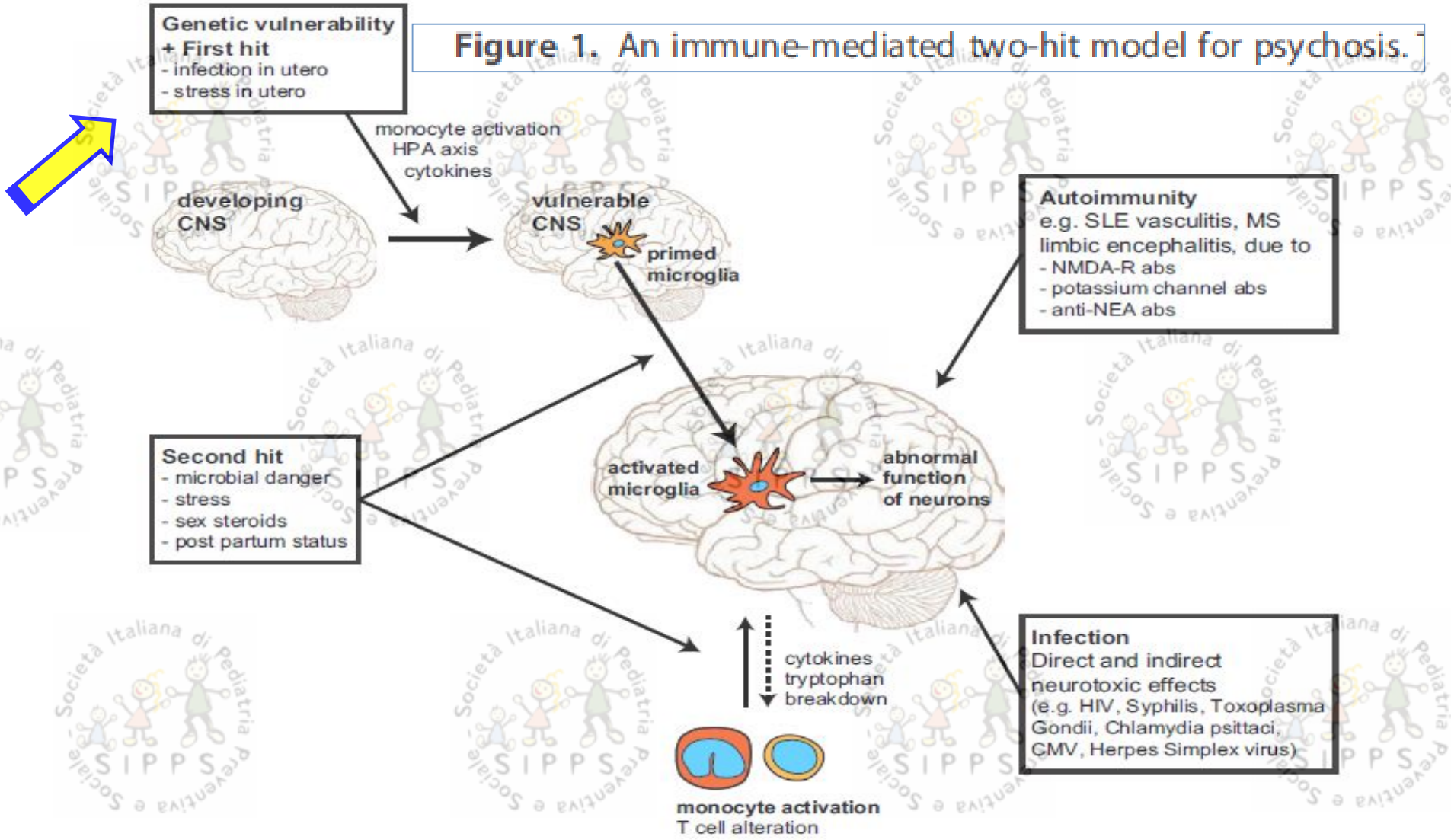



**Figure 1.** An immune-mediated two-hit model for psychosis.

Infection **but also environmental stressors during gestation/early life activate microglia, perturbing neuronal development, thereby setting the stage for vulnerability for later psychotic disorders.**
A **second hit, such as endocrine changes, stress, or infection, could further activate microglia, leading to functional abnormalities of the neuronal circuitry in the brain and psychosis**

Clinical Therapeutics

Volume 35, Issue 5, May 2013, Pages 584–591

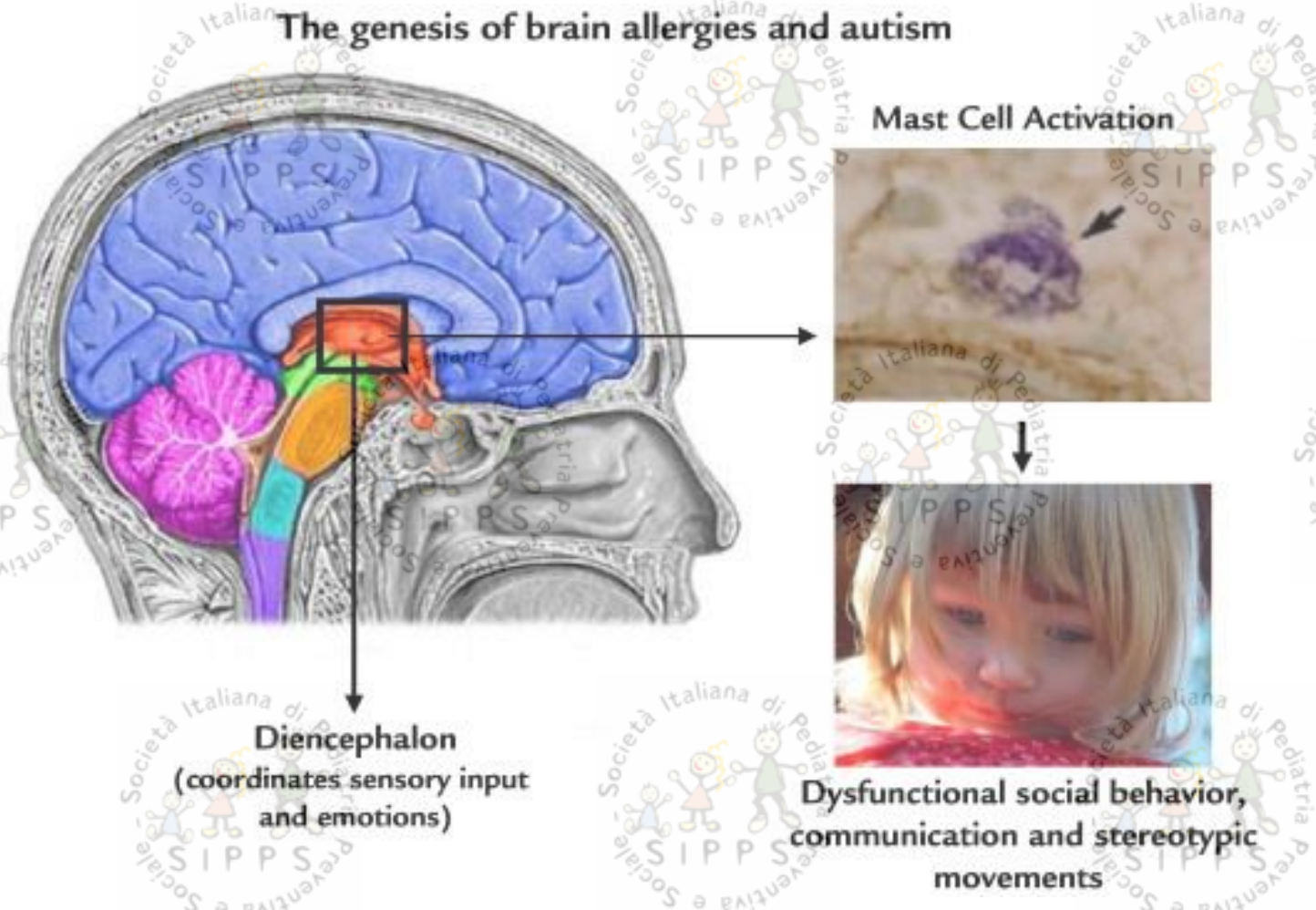
New "atopic" clinical entities in search of pathogenesis and treatment

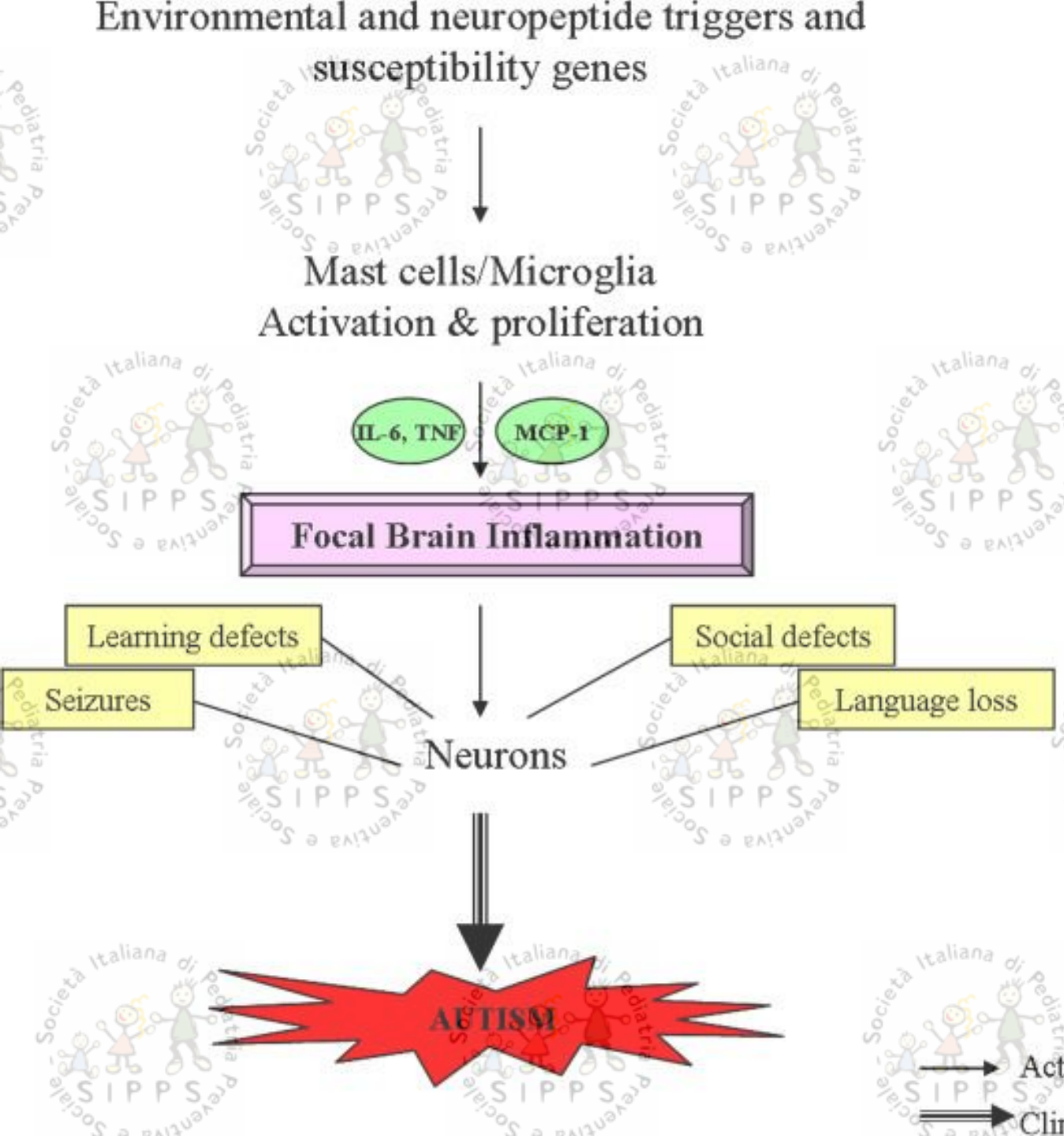
# Is a Subtype of Autism an Allergy of the Brain?

Theoharis C. Theoharides, MS, MPhil, PhD, MD

Show more

doi:10.1016/j.clinthera.2013.04.009





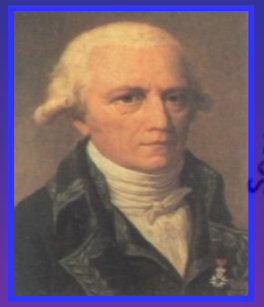

Diagrammatic representation of **how stimulation of mast cells and microglia could lead to multiple effects that contribute brain inflammation** and the **pathogenesis and symptoms of autism**.

MCP, monocyte chemotactic protein

# THE *SINS* OF THE FATHER

*The roots of inheritance may extend beyond the genome,*

**When Brian Dias became a father last October**, he was, like any new parent, **mindful of the enormous responsibility** that lay before him… But, unlike most new parents, **Dias was also aware of the influence of his past experiences — not to mention those of his parents, his grandparents and beyond, whether they smoked, endured famine or fought in a war.** As a postdoc he had spent much of the two years before studying these kinds of questions in mice: **specifically, he looked at how fear associated with a particular smell affects the animals and leaves an imprint on the brains of their descendants.**

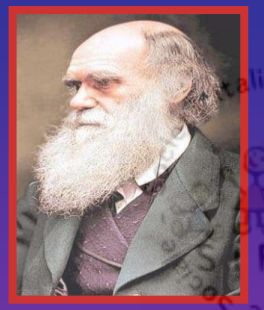


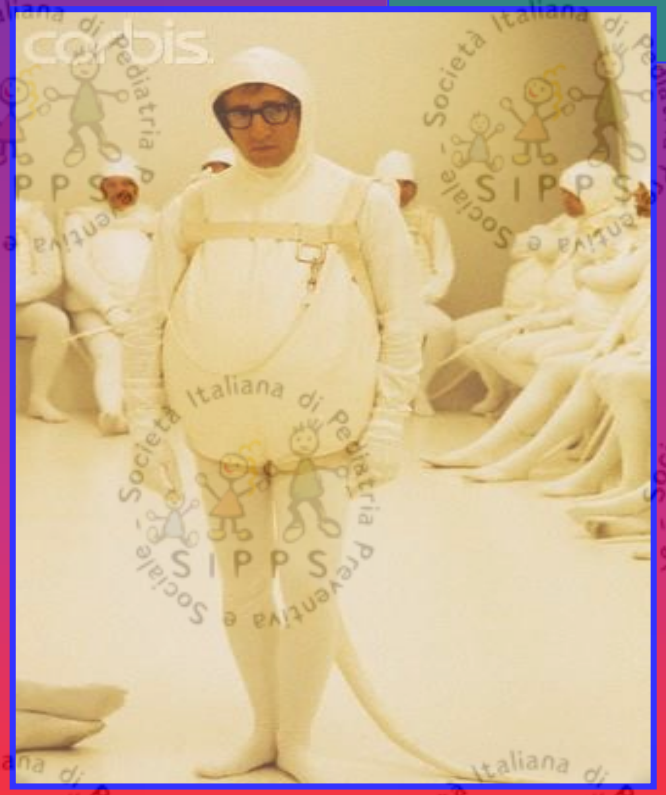
# 5° Journée annuelle de l'Impact de l'environnement sur la santé de la femme, mère & de l'enfant

**30 avril 2015**

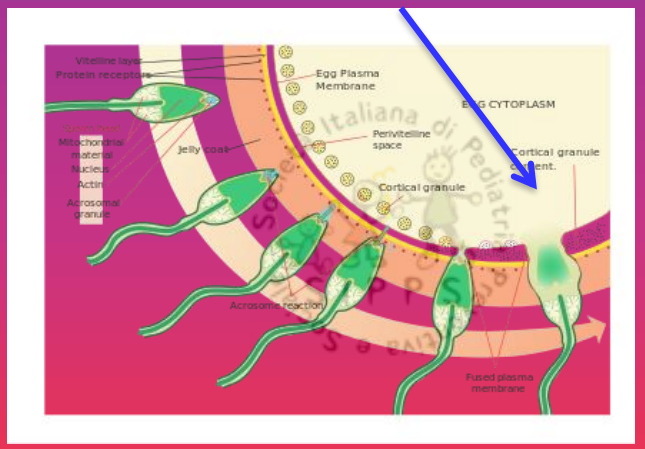
**Focus sur la périconception**

**et la grossesse**






## The overlooked heritage: the genetic transmission by the father




***Everything You Always Wanted to Know About Sex (But Were Afraid to Ask)***
**Woody Allen dressed as a sperm (1972)**


ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee

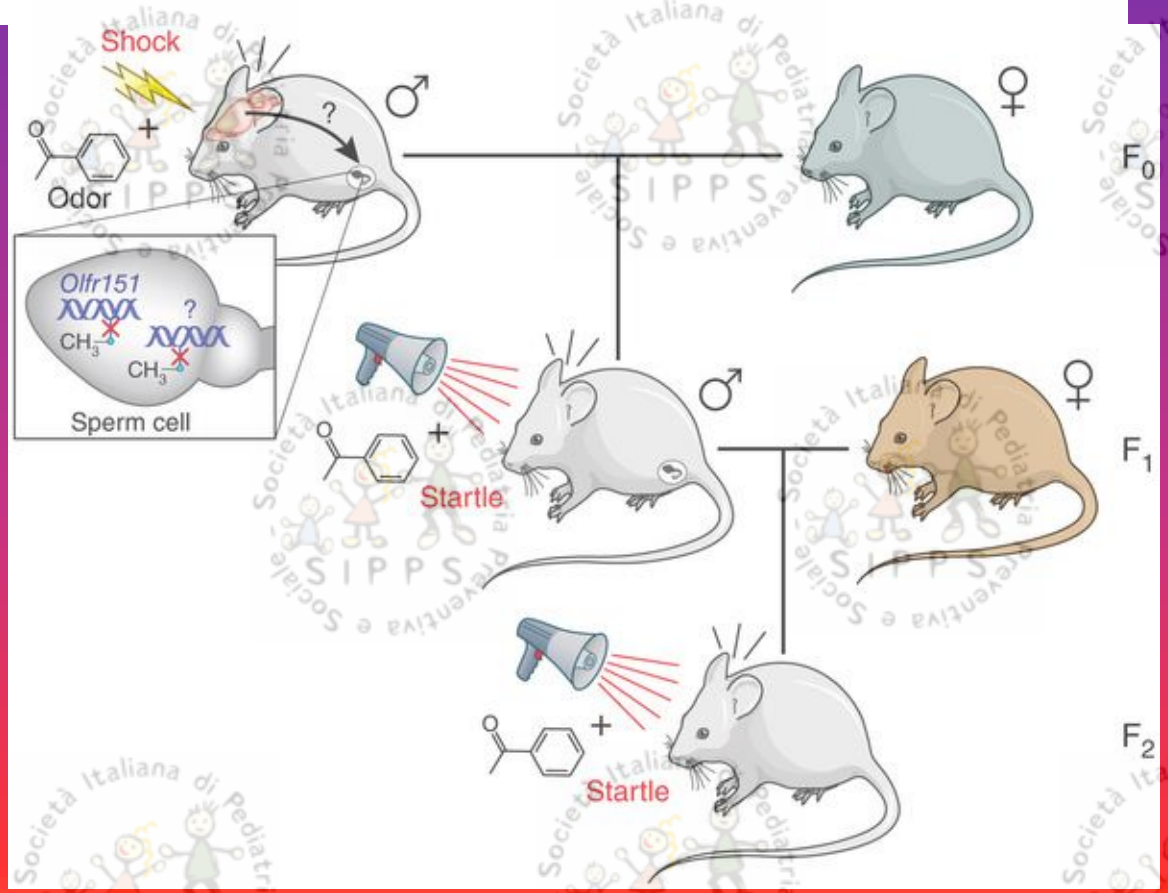
# Lamarck revisited: epigenetic inheritance of ancestral odor fear conditioning

Nature Neuroscience 17, 2–4 (2014)

Moshe Szyf

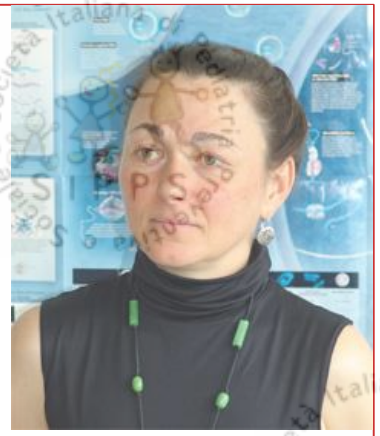
A study shows that when mice are taught to fear an odor, both their offspring and the next generation are born fearing it. The gene for an olfactory receptor activated by the odor is specifically demethylated in the germ line and the olfactory circuits for detecting the odor are enhanced.

A study shows that **when mice are taught to fear an odor, both their offspring and the next generation are born fearing it.**
The **gene for an olfactory receptor activated by the odor is specifically demethylated in the germ line** and **the olfactory circuits for detecting the odor are enhanced**



Remarkably, **offspring from both paternal stress groups displayed significantly reduced HPA stress axis responsivity**…In examining **epigenetic mechanisms of germ cell transmission, we found robust changes in sperm microRNA (miR)..**

nature neuroscience



# Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice

Katharina Gapp[1], Ali Jawaid[1], Peter Sarkies[2], Johannes Bohacek[1], Pawel Pelczar[3], Julien Prados[4,5], Laurent Farinelli[4], Eric Miska[2] & Isabelle M Mansuy[1]

Small non-coding RNAs (sncRNAs) are potential vectors at the interface between genes and environment. We found that traumatic stress in early life altered mouse microRNA (miRNA) expression, and behavioral and metabolic responses in the progeny. Injection of sperm RNAs from traumatized males into fertilized wild-type oocytes reproduced the behavioral and metabolic alterations in the resulting offspring.

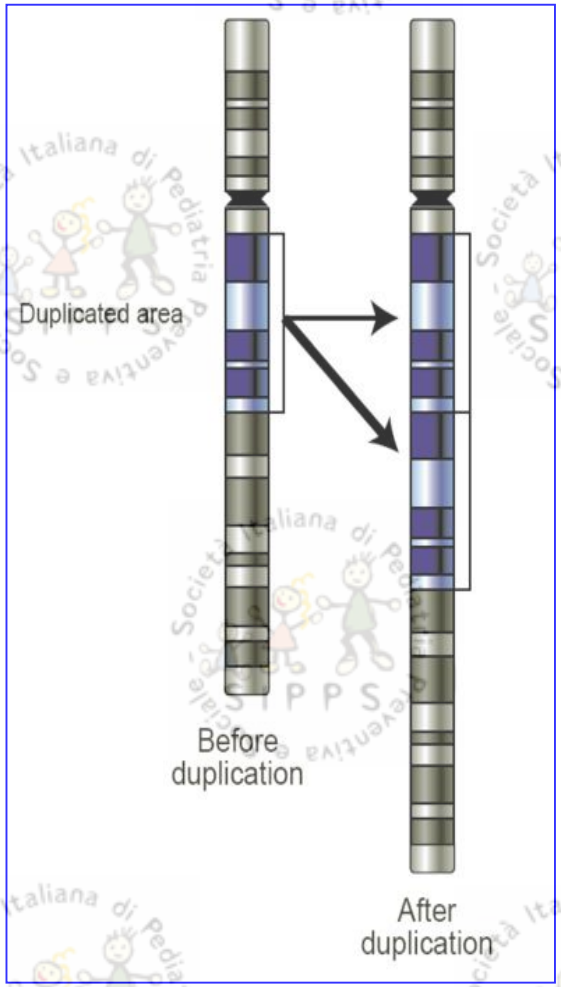
Isabelle Mansuy..**periodically separated mother mice from their young pups and exposed the mothers to stressful situations** — either by placing them in cold water or physically restraining them. These separations occurred every day but at erratic times, **so that the mothers could not comfort their pups**

When raised this way, **male offspring showed depressive behaviours and tended to underestimate risk**, the study found. Their **sperm also showed abnormally high expression of five microRNAs**. One of these, **miR-375, has been linked to stress and regulation of metabolism.**

**The F1 males' offspring, the F2 generation, showed similar depressive behaviours, as well as abnormal sugar metabolism.** The F1 and F2 generations also had **abnormal levels of the five microRNAs in their blood and in the hippocampus**, a brain region involved in stress responses. **Behavioural effects persisted in the F3 generation as well.**

The researchers also collected **RNA from the F1 males' sperm and injected it into freshly fertilized eggs from untraumatized mice**. This resulted in mice with comparable depressive behaviours and metabolic symptoms — and **the depressive behaviours were passed, in turn, to the next generation**.

**What is most striking is that the same CNVs have been found, at least in some cases, in the semen of parents, showing that autism could be the consequence of a parental exposure to pollutants and a transgenerational transmission:** which could provide **an explanation for the unremitting "pandemic" increase of these disorders.**




All that said .. it **is absolutely necessary to reconsider the problem of many early environmental exposures or even gametic, and their possible synergy .. which can induce an epigenetic instability,**

Trends in Molecular Medicine

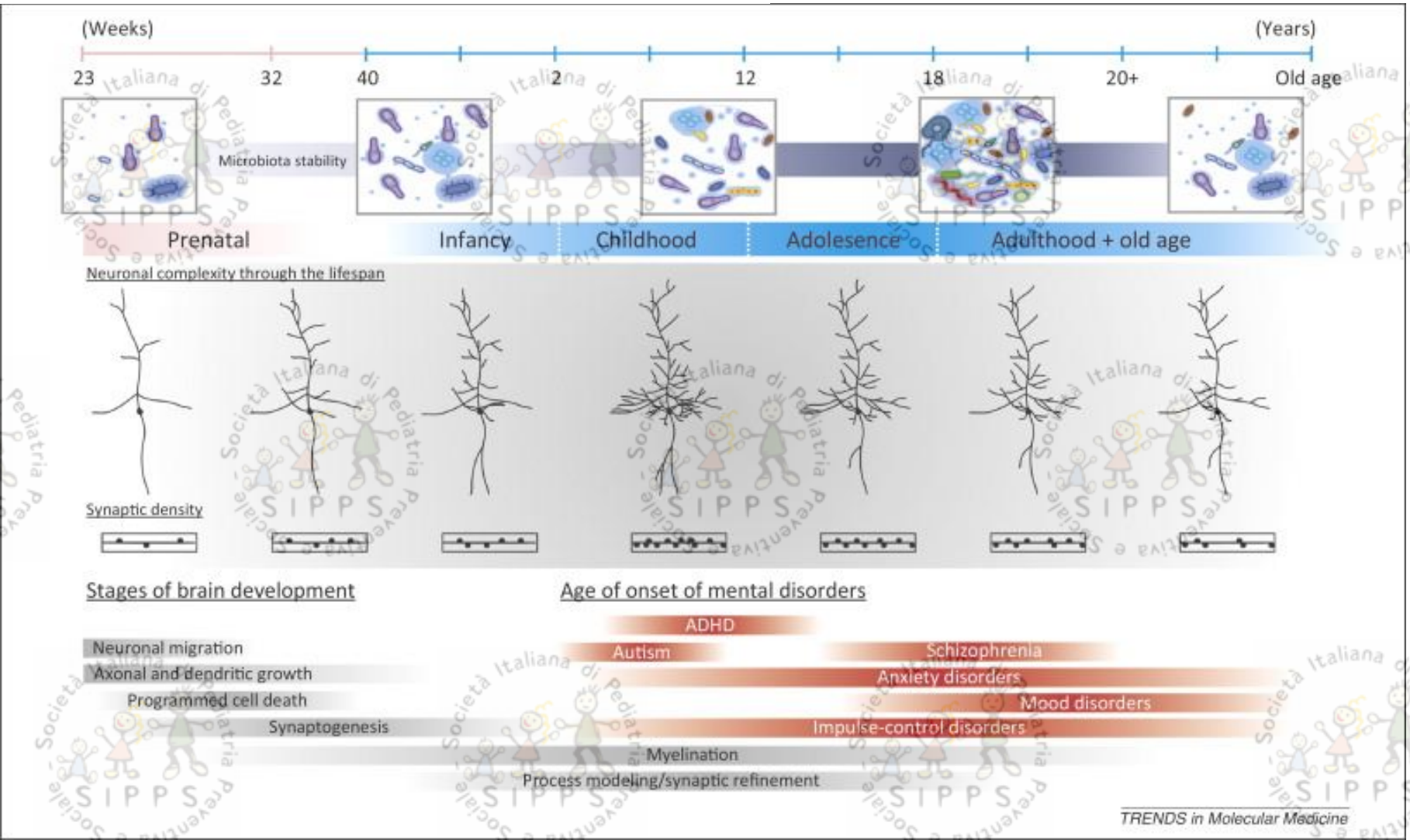
Volume 20, Issue 9, September 2014, Pages 509–518

Review

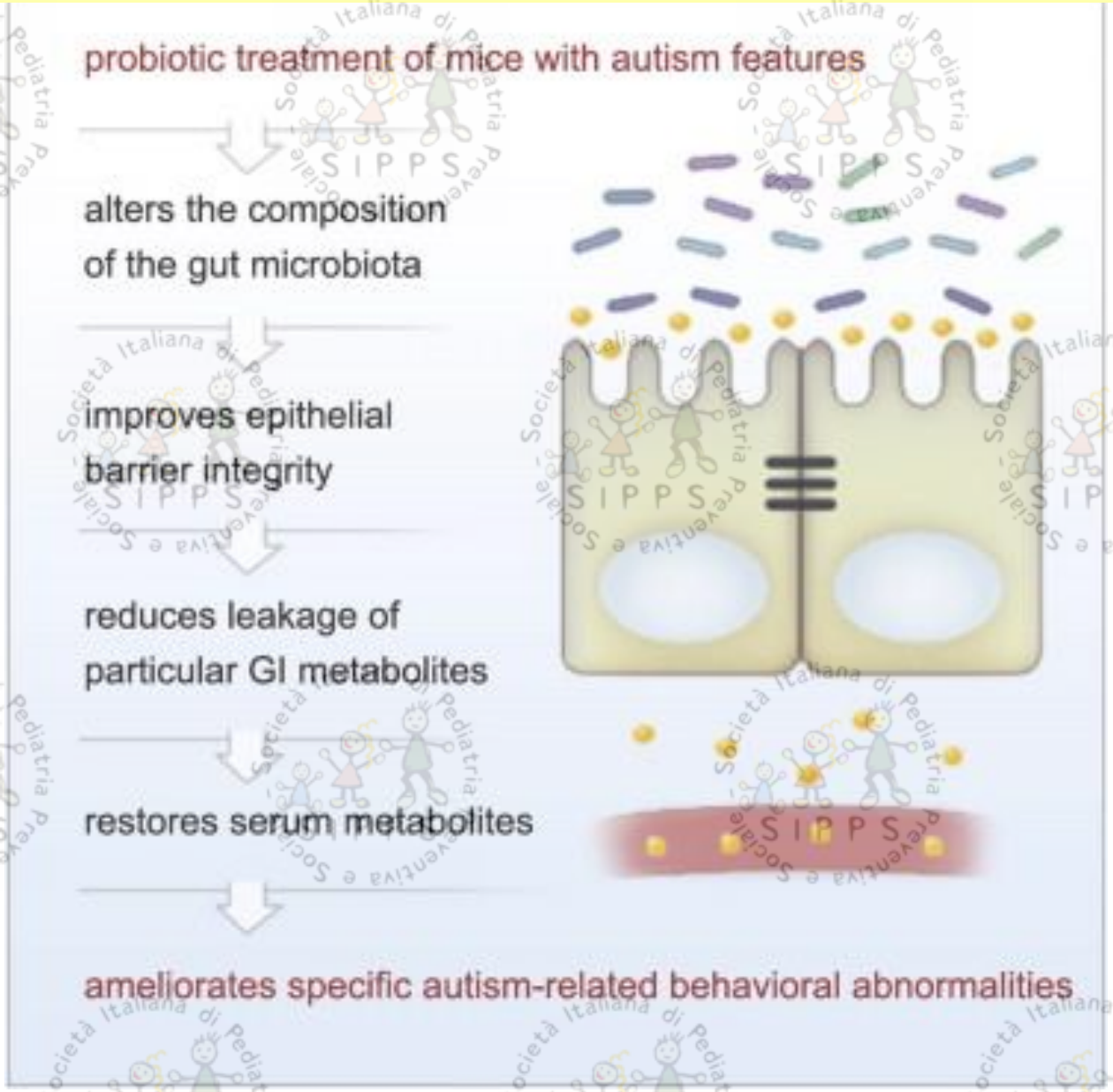
# Microbiota and neurodevelopmental windows: implications for brain disorders

Yuliya E. Borre[1], Gerard W. O'Keeffe[2, 3], Gerard Clarke[1, 4], Catherine Stanton[4, 5], Timothy G. Dinan[1, 4], John F. Cryan[1, 2]

**Early life perturbations of the developing gut microbiota** can **impact neurodevelopment** and potentially lead to **adverse mental health outcomes later in life**



# Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders




**The normal development of the brain may also depend on microorganisms. The gut microbiota produces about 30% of the metabolites in mammalian circulation, including many neurotransmitters such as γ-aminobutyric acid (GABA), serotonin, histamine and dopamine**.

Consistent with this, **in germ-free mice, dopamine and glutamate receptor expression as well as serotonin levels are significantly altered in the circulation during brain development compared with conventional mice**.

This establishes **the gut microbiota–brain axis as an essential regulator of neurodevelopment..** Indeed, **the microbiota may be crucial in shaping host behaviours across many animal taxa, from fruitflies to humans and mice**

**Germ-free mice exhibit behaviours of social avoidance, self-grooming, and other traits similar to those observed in disorders of neurodevelopment such as autism spectrum disorder (ASD)**.

Elaine Y. Hsiao, Sara W. McBride, Sophia Hsien, Gil Sharon, Embriette R. Hyde, Tyler McCue, Julian A. Codelli, Janet Chow, Sarah E. Reisman, Joseph F. Petrosino, Paul H. Patterson, Sarkis K. Mazmanian
**Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders** Cell (2013) 155, 7, 1451–1463
http://dx.doi.org/10.1016/j.cell.2013.11.024

# Autism and nutrition: the role of the gut–brain axis

Nutr Res Rev. 2014 Dec;27(2):199-214. doi: 10.1017/S0954422414000110

Marijke M. H. van De Sande, Vincent J. van Buul and Fred J. P. H. Brouns*

Autism spectrum disorder (ASD) is characterised by deficits in the ability to socialise, communicate and use imagination, and displays of stereotypical behaviour. It is widely accepted that ASD involves a disorder in brain development. However, the real causes of the neurodevelopmental disorders associated with ASD are not clear. In this respect, it has been found that a majority of children with ASD display gastrointestinal symptoms, and an increased intestinal permeability. Moreover, large differences in microbiotic composition between ASD patients and controls have been reported. Therefore, nutrition-related factors have been hypothesised to play a causal role in the aetiology of ASD and its symptoms. Through a review of the literature, it was found that abnormalities in carbohydrate digestion and absorption could explain some of the gastrointestinal problems observed in a subset of ASD patients, although their role in the neurological and behavioural problems remains uncertain. In addition, the relationship between an improved gut health and a reduction of symptoms in some patients was evaluated. Recent trials involving gluten-free diets, casein-free diets, and pre- and probiotic, and multivitamin supplementation show contradictive but promising results. It can be concluded that nutrition and other environmental influences might trigger an unstable base of genetic predisposition, which may lead to the development of autism, at least in a subset of ASD patients. Clear directions for further research to improve diagnosis and treatment for the different subsets of the disorder are provided.

..a **majority of children with ASD display gastrointestinal symptoms**, and an **increased intestinal permeability**. Moreover, **large differences in microbiotic composition** between ASD patients and controls have been reported. Therefore, **nutrition-related factors** have been hypothesised to play a causal role in the aetiology of ASD and its symptoms.. Recent trials involving **gluten-free diets, casein-free diets, and pre- and probiotic, and multivitamin supplementation** show contradictive but promising results

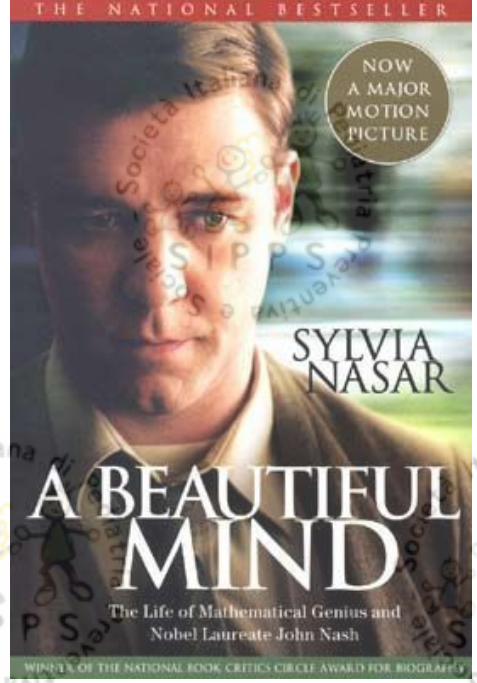
**Bacteriotherapy**

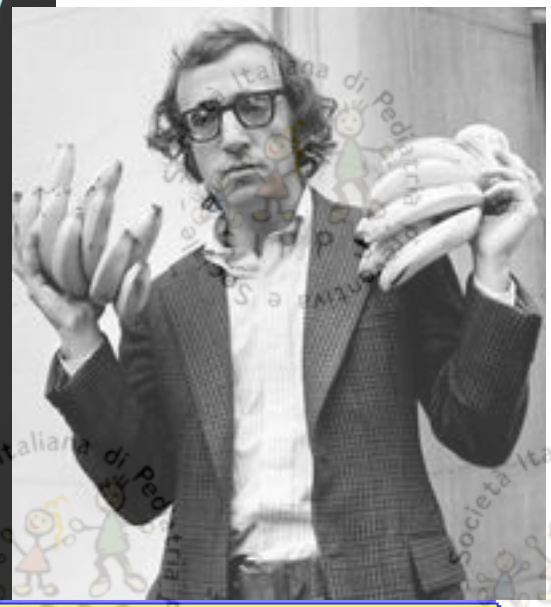
A recent therapy named ***bacteriotherapy*** (based on the transfer of **a certain amount of stool (fecal transplant) from a healthy donor into the gastrointestinal tract of ASD patients**. Usually donors are family members and the stool is transferred as homogenate using a rectal enema, colonoscopy, nasoduodenal tube or stool pills…a pilot study that includes **9 autistic children who were fecal transplanted with 20 gut bacteria and the preliminary results indicates a clear improvement in speaking, listening and task performance**

http://biomeonboardawareness.com/ .http://www.microbiome-autism.com

My **brain**? That's my **second favorite organ**

**Woody Allen**



Allen Stewart Königsberg

# Developmental changes in large-scale network connectivity in autism

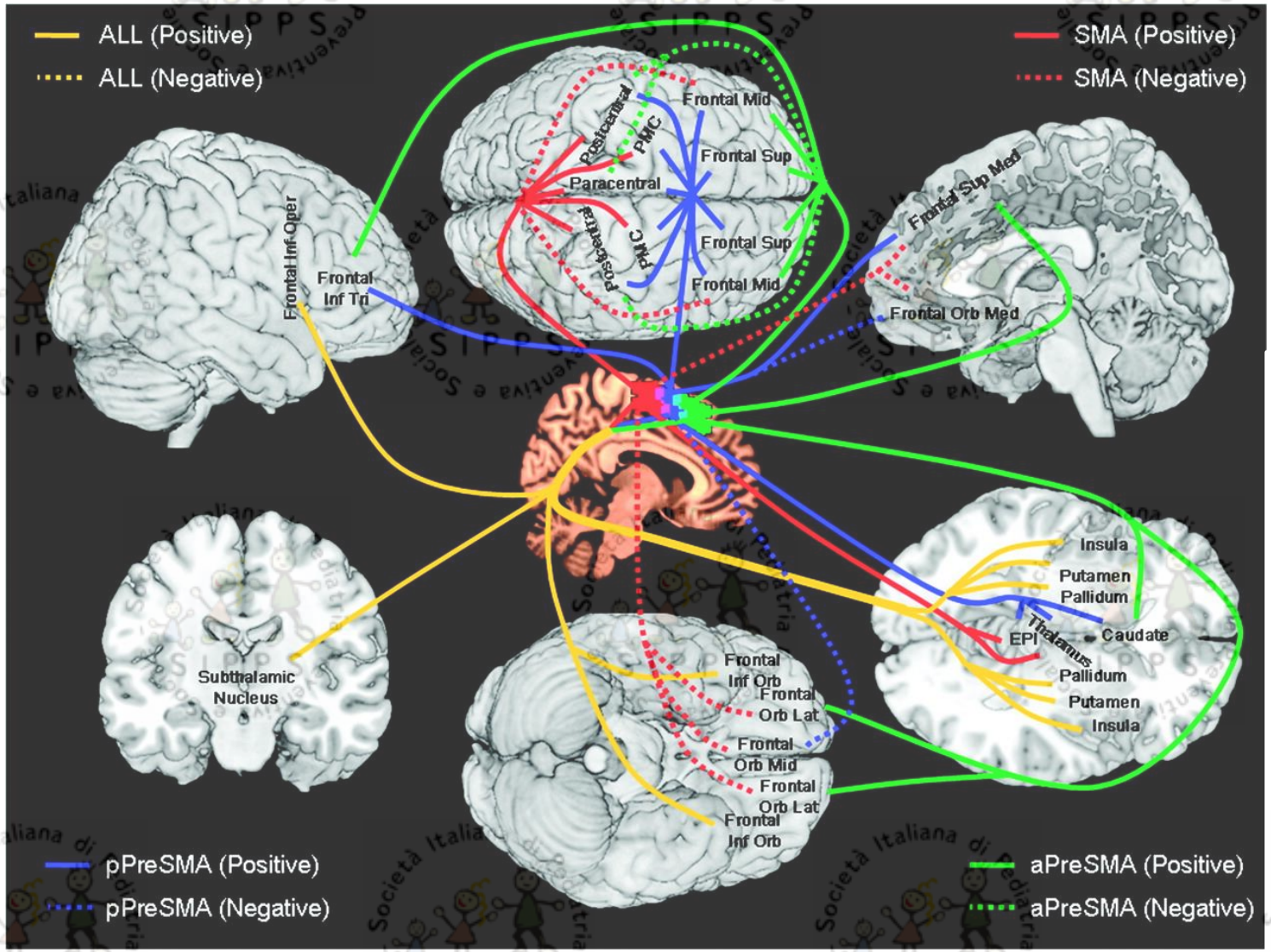
Nomi JS, Uddin LQ. ***Developmental changes in large-scale network connectivity in autism***. Neuroimage Clin. 2015 Mar 6;7:732-41.

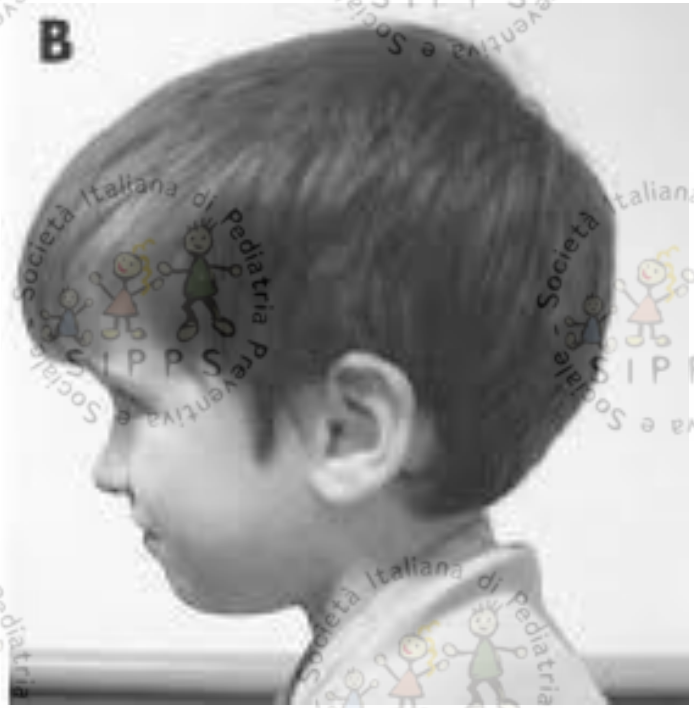
A recent theory attempting to reconcile conflicting results in the literature proposes that **hyper-connectivity of brain networks may be more characteristic of young children with ASD**, while **hypo-connectivity may be more prevalent in adolescents and adults** with the disorder when compared to typical development (TD) 1 2

**Previous work has examined** only **young children**, mixed groups of children and **adolescents**, or **adult cohorts** in **separate studies**, **leaving open the question of developmental influences on functional brain connectivity in ASD**

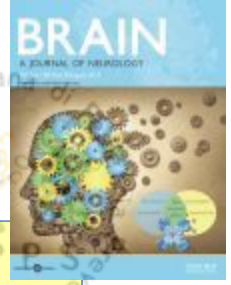
* Uddin etal., ***Reconceptualizing functional brain connectivity in autism from a developmental perspective*** (2013)

K.A. Stigler, B.C. McDonald, A. Anand, A.J. Saykin, C.J. McDougle ***Structural and functional magnetic resonance imaging of autism spectrum disorders*** Brain Res, 1380 (2011), 146–161 **..the frontal cortex, including the orbitofrontal region, has been shown to be a main target area of early brain overgrowth in ASDs**




https://brmlab.cz/project/brain_hacking/tdcs/pfc




# ***Autism reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self***

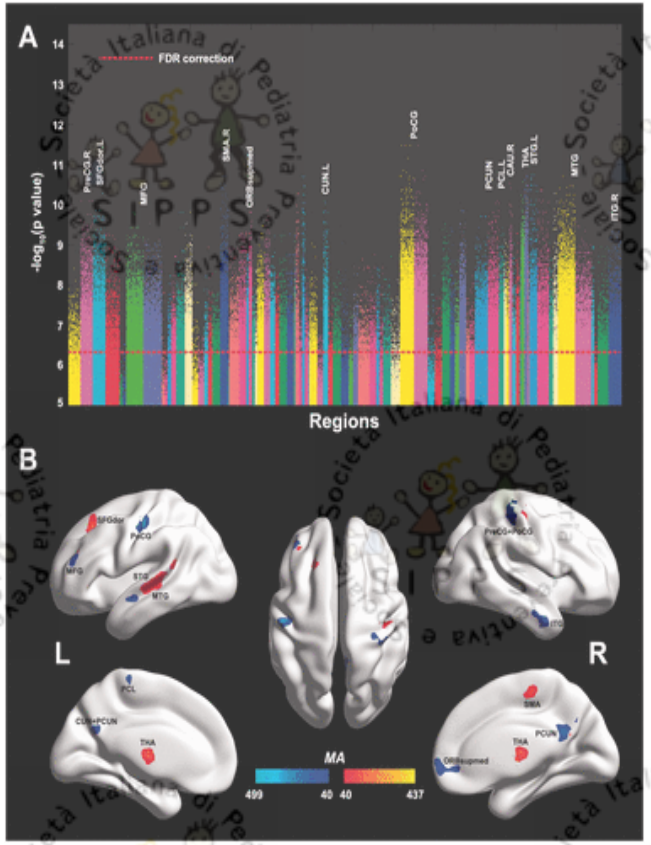
Cheng W, Rolls ET, Gu H, Zhang J, Feng J

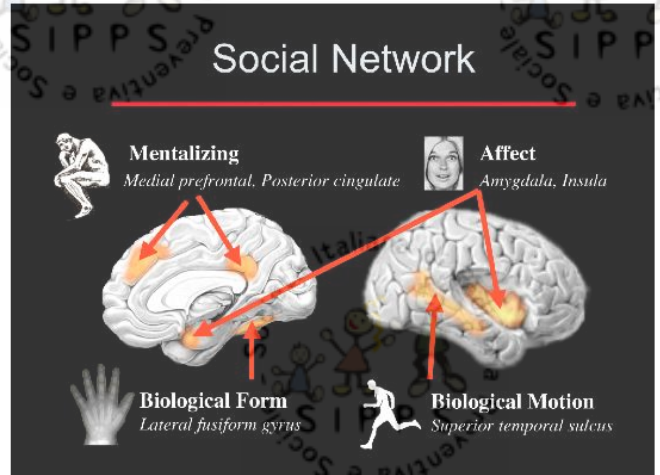
***Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self.*** Brain. 2015 May;138(Pt 5):1382-93.

..we have identified a **key system in the MTG/STS sulcus region that has reduced functional connectivity with other cortical areas** (and **increased connectivity with the medial thalamus**),

which is **implicated in face expression and motion processing involved in social behaviour**, and which has **onward connections to the orbitofrontal cortex/ventromedial prefrontal cortex**.

The same system is **implicated in theory of mind processing,** and in **audio-visual integration for e.g. *speech***, and possibly in further aspects of ***communication using language***.



**Developmental dyslexia is a brain disorder**

**Structural MRI abnormalities**

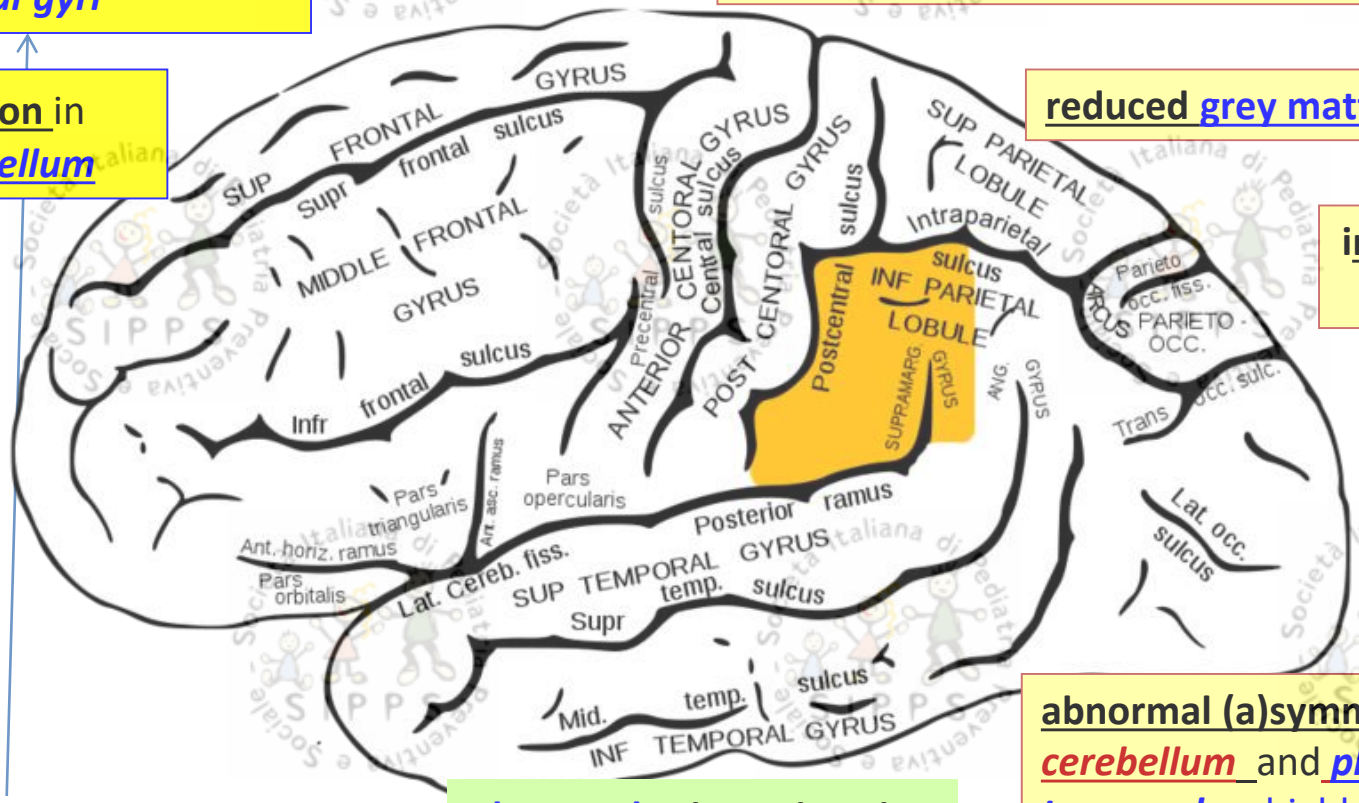
**under-activations** in the **left hemisphere fusiform** and ***supramarginal gyri***

**over-activation** in the ***left cerebellum***

**decreased cerebral white matter gyrifications**

**reduced grey matter volumes**

**increased *corpus callosum* size**




**Functional MRI : abnormal activation patterns in dyslexia during reading operations**

**Abnormal orientations in areas within the *white matter micro-structures* (*diffusion tensor imaging*)**

**abnormal (a)symmetry of the *cerebellum* and *planum temporale*** a highly lateralized structure involved with ***language*** and with ***music***

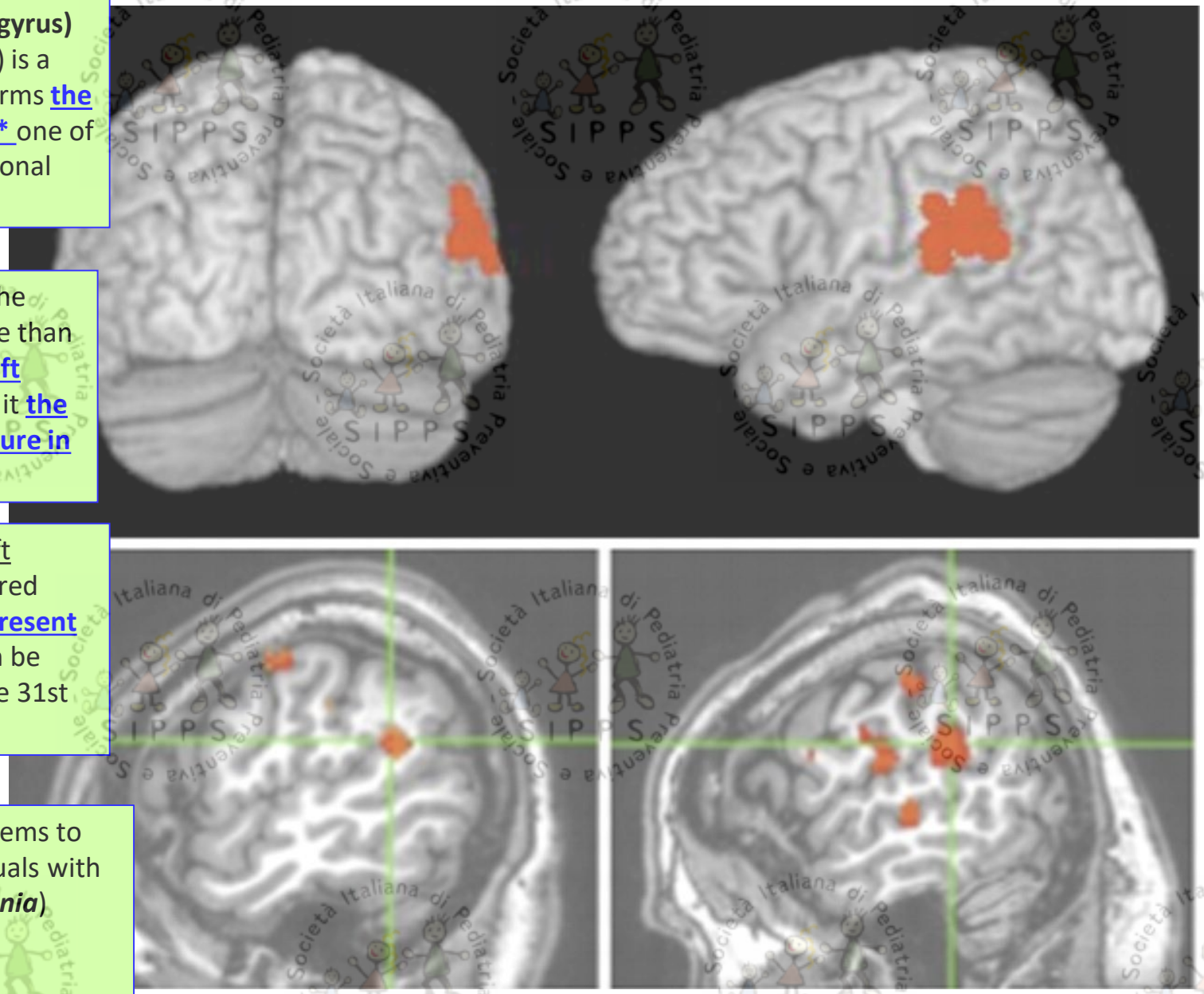

Elnakib A, Soliman A, Nitzken M, Casanova MF, Gimel'farb G, El-Baz A. ***Magnetic resonance imaging findings for dyslexia: a review.*** J Biomed Nanotechnol. **2014** Oct;10(10):2778-805.

The ***planum temporale*** (the cortical area just posterior to the ***auditory cortex*** **(Heschl's gyrus) within the Sylvian fissure**) is a triangular region which forms **the heart of Wernicke's area *** one of the most important functional areas for language

In some people's brains, the ***planum temporale*** is more than **five times larger on the left than on the right**, making it **the most asymmetrical structure in the brain ***

**This greater size** of the left *planum temporale* compared with the right **is already present in the fetus *** where it can be observed starting from the 31st week of gestation.

The ***planum temporale*** seems to be **symmetrical** in individuals with ***dyslexia***, (and ***schizophrenia***) which may indicate a **low specialization in the left hemisphere** as a cause of their disability.




I'M AFRAID MY BRAIN HAS LEFT FOR THE DAY
©PNTS