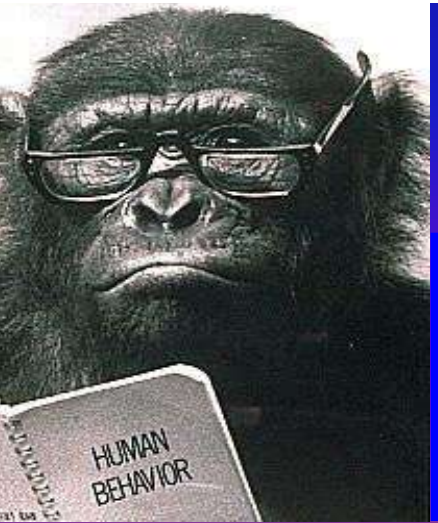
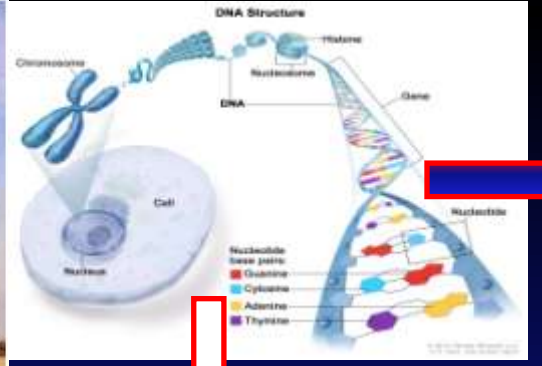
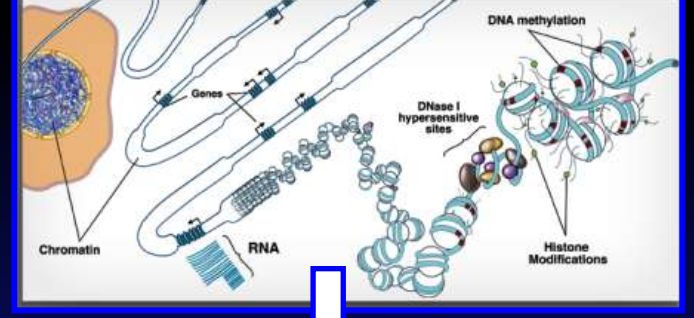
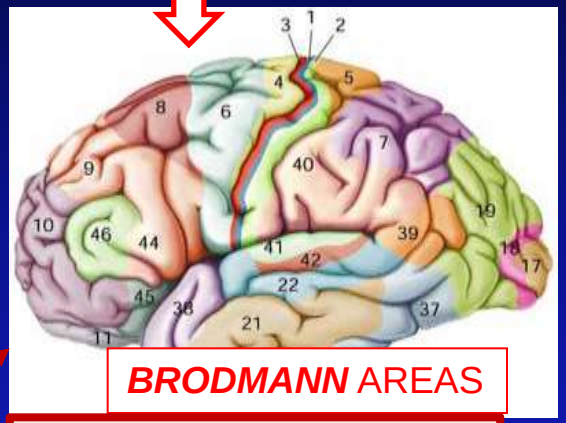
Early/late-life adversities and behavioural phenotypes: insight into metabolomics, genomics and connectomics

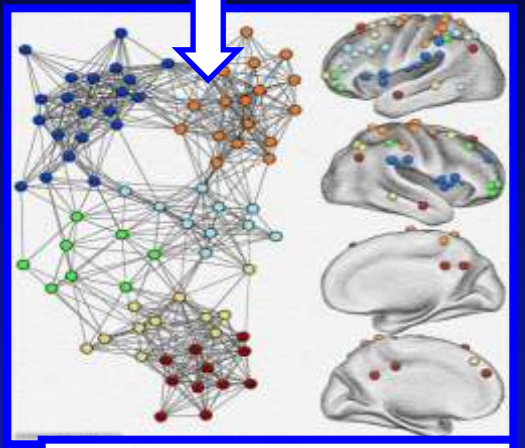








(I) The building of the *hardware* is under ***genetic control***



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

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

EHM Executive Healthcare

autism the great modern health concern

CDC Centers for Disease Control and Prevention

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 ~~meaning~~

2014 1 : 68

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

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

2008 1 : 88

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

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

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/

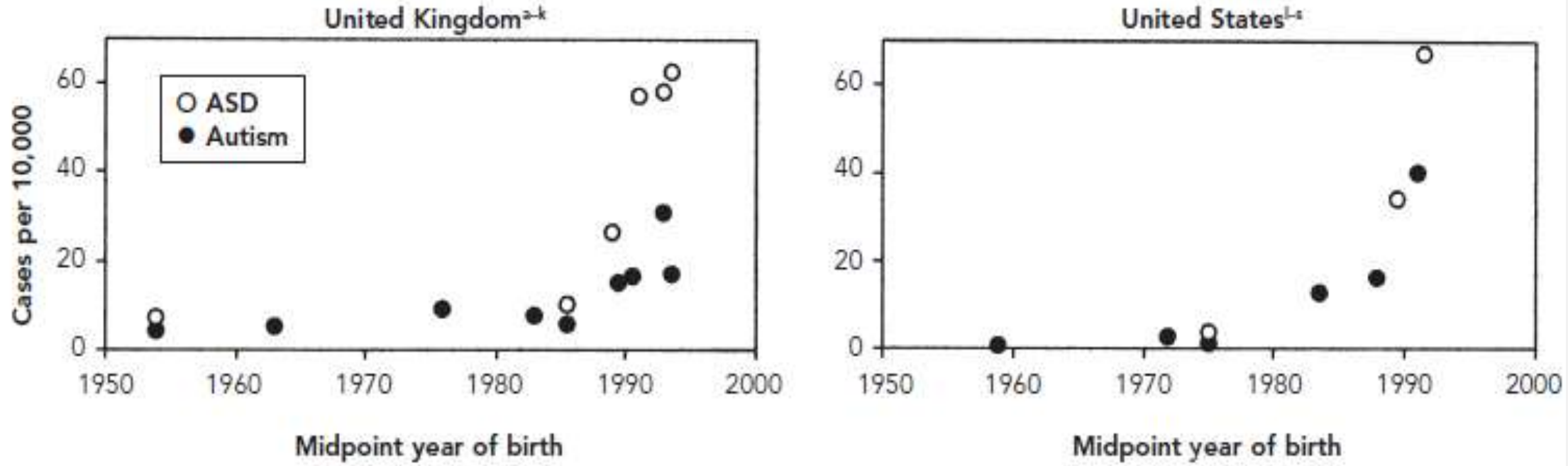
AUTISM
(ASD :Autism Spectrum Disorders)

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

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

The estimated **<u>prevalence</u> 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]

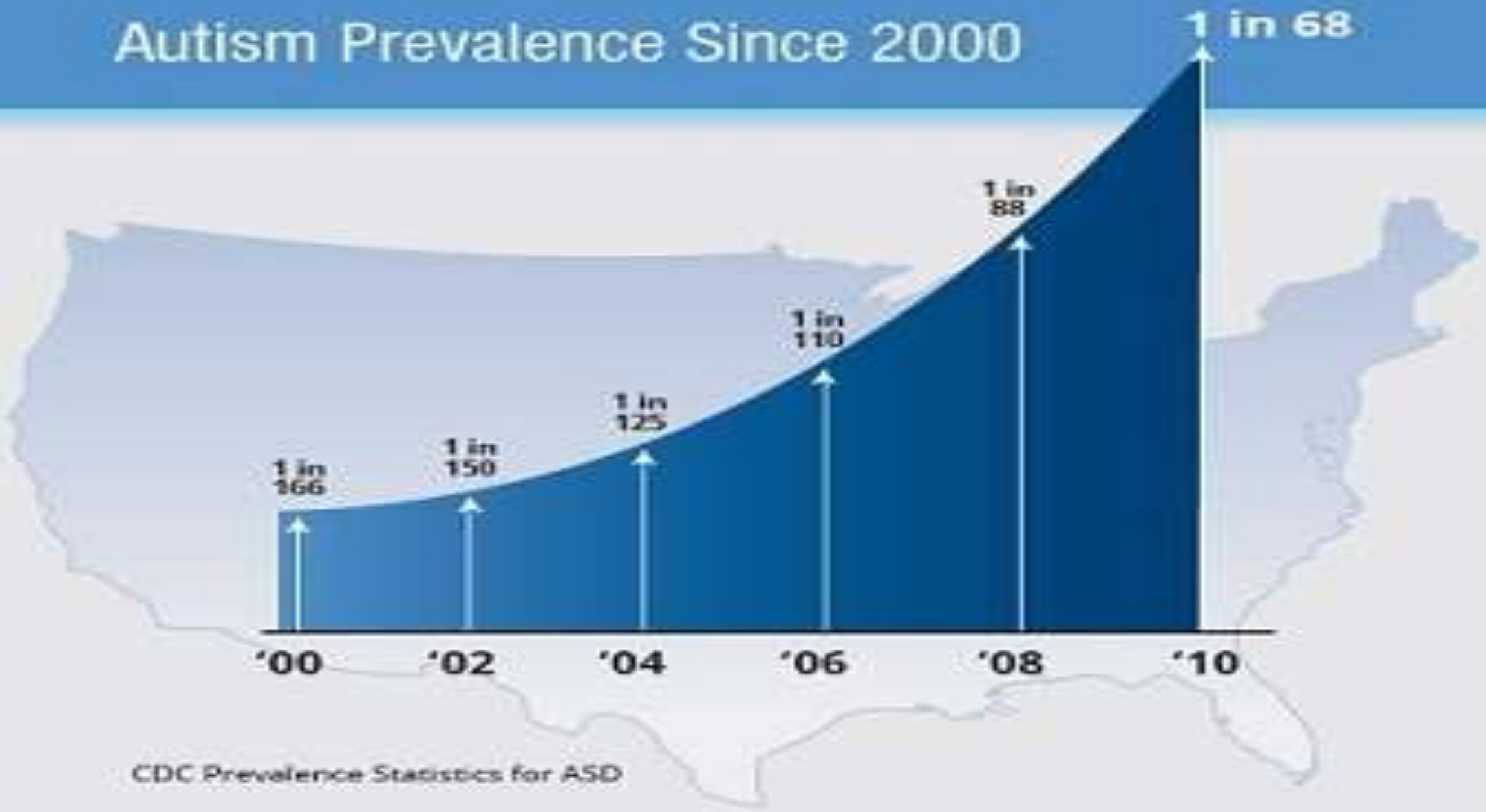
[l]Treffert 1970[36]

[m]Ritvo et al. 1989[53]

[n]Burd et al. 1987[45]

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

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%

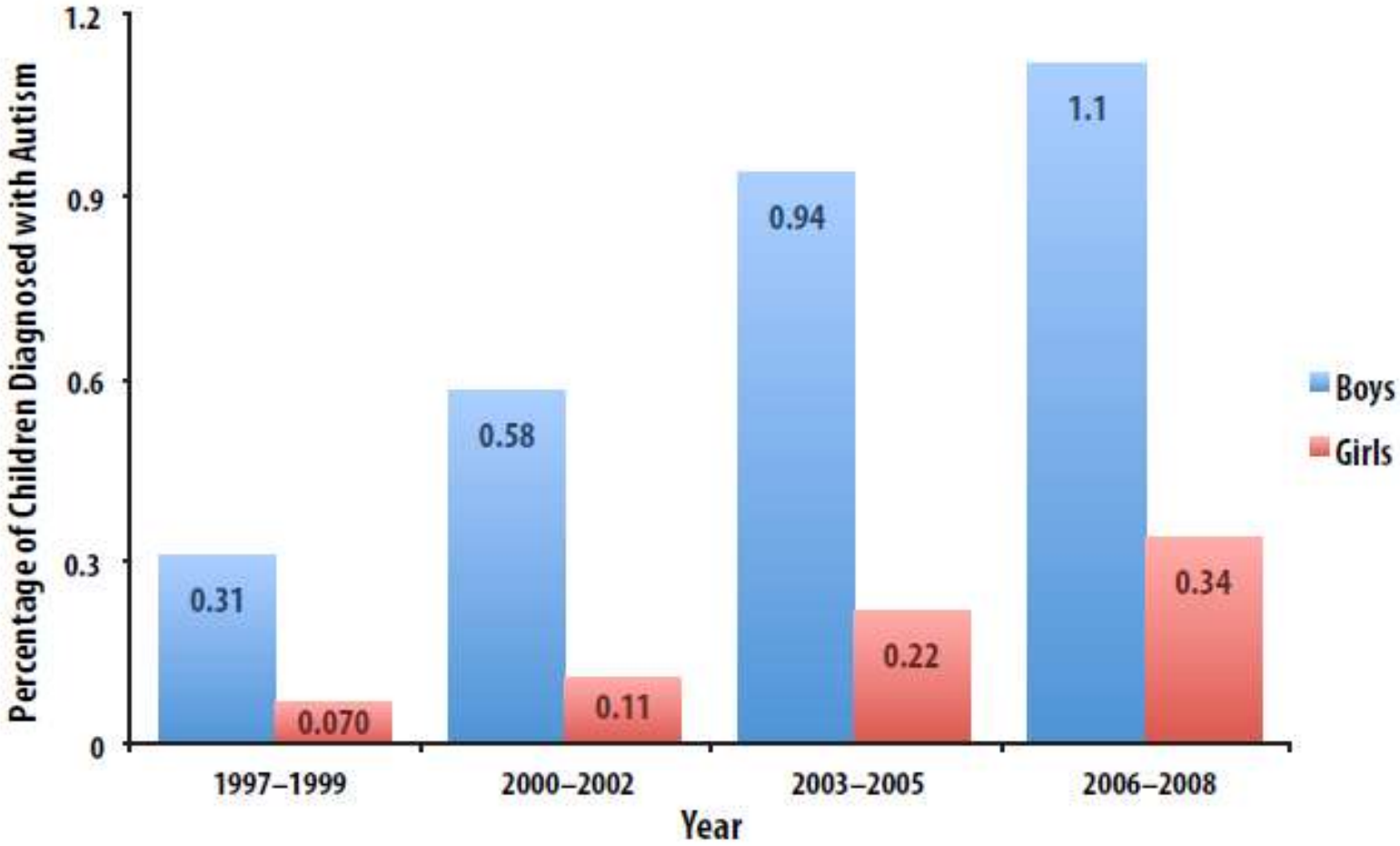
***Autism*. Lai MC, Lombardo MV, Baron-Cohen S. Lancet. 2014 Mar.**

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

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

1:59 Gran Bretagna Russel et al., 2014

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)

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

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

Lancet Neurol 2014; 13: 330–38

Published Online
February 15, 2014
http://dx.doi.org/10.1016/S1474-4422(13)70278-3

Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark (P Grandjean MD); Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA (P Grandjean); and Icahn School of Medicine at Mount Sinai, New York, NY, USA (P J Landrigan MD)

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

Philippe Grandjean, Philip J Landrigan

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.

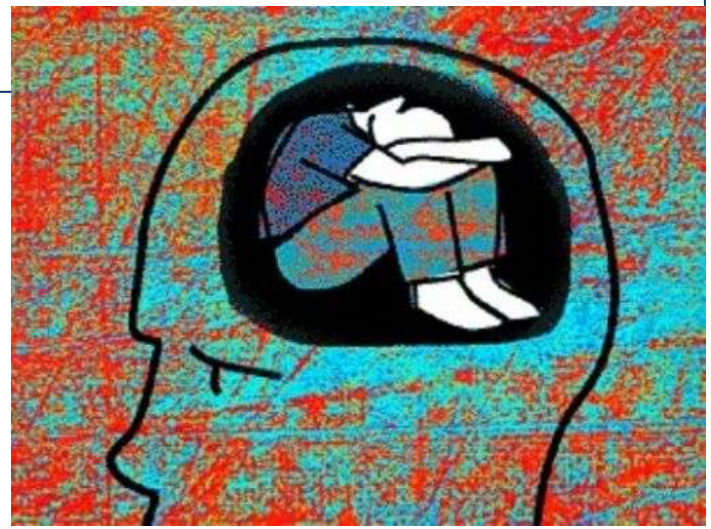
Since 2006, epidemiological studies have documented **six additional developmental neurotoxicants — manganese, fluoride, chlorpyrifos, tetrachloroethylene, dichlorodiphenyltrichloroethane,, and the polybrominated diphenyl ethers.**
We postulate that even more neurotoxicants remain undiscovered

AUTISMO: come si presenta?

- ✓ **Compromissione della comunicazione e dell'interazione** sociale
- ✓ **Interessi ristretti, modelli comportamentali ripetitivi e stereotipati**

Comparsa (diagnosi) nei primi anni di vita

Interferenza con le normali funzioni



cristina.panisi@tin.it

AUTISMO:
quali campanelli d'allarme?

cristina.panisi@tin.it

A 18 mesi il tuo bambino e' in grado di.....

1. Guardarti e indicare quando lui/lei desidera mostrarti qualcosa

2. Guardare quando tu indichi qualcosa

3. Usare l'immaginazione mentre gioca facendo finta di

Se la risposta e' NO, il tuo bambino potrebbe presentare delle difficoltà legate allo spettro dell' AUTISMO.
Per favore allerta il tuo medico o pediatra immediatamente.

Basato su CHAT (Checklist for Autism in Toddlers)

- La **diagnosi precoce e la possibilità di un intervento educativo appropriato** consentono un **significativo miglioramento** dei sintomi core dell' autismo, attenuando la disabilità futura.

- La **SA** viene solitamente diagnosticata più tardi, poiché l'intelligenza e un linguaggio spesso assai sviluppato, possono mascherare le **difficoltà di interazione sociale e i comportamenti stereotipati.**

- Per tale motivo, è importante che le **periodiche valutazioni pediatriche prevedano l'impiego strumenti di screening** per i disturbi dello spettro autistico

cristina.panisi@tin.it

Original Article

autism

Autism
2015, Vol. 19(3) 327–337

DOI: 10.1177/1362361314521329
aut.sagepub.com
SAGE

Identification of infants at risk for autism spectrum disorder and developmental language delay prior to 12 months

Carole A Samango-Sprouse[1,2,3], Emily J Stapleton[3], Farhad Aliabadi[4], Robert Graw[4], Rebecca Vickers[5], Kathryn Haskell[3], Teresa Sadeghin[2], Robert Jameson[3], Charles L Parmele[6] and Andrea L Gropman[1,7]

Abstract

Studies have shown an increased head circumference and the absence of the head tilt reflex as possible risk factors for autism spectrum disorder, allowing for early detection at 12 months in typically developing population of infants. Our aim was to develop a screening tool to identify infants prior to 12 months at risk for autism spectrum disorder and developmental learning delay, not affected by literacy or primary parental language, and provide immediate determination of risk for autism spectrum disorder. An abrupt head circumference acceleration and the absence of head tilt reflex by 9 months were used to identify infants at risk for autism spectrum disorder. Stability of early findings was then investigated when compared to comprehensive standardized neurodevelopmental assessment results and complete neurological and genetics evaluations. A total of 1024 typically developing infants were enrolled by 9 months, with 14 identified as at risk for autism spectrum disorder and 33 for developmental learning delay. There was a good positive predictive value for the identification of autism spectrum disorder prior to 12 months. This study demonstrates an efficient means to identify infants at risk for autism spectrum disorder by 9 months of age and serves to alert primary care providers of infants who are vulnerable for autism spectrum disorder before symptoms are discernible by clinical judgment of primary care providers, parental concerns, or by screening questionnaires.

nature
International weekly journal of science

LETTER

doi:10.1038/nature21369

Early brain development in infants at high risk for autism spectrum disorder

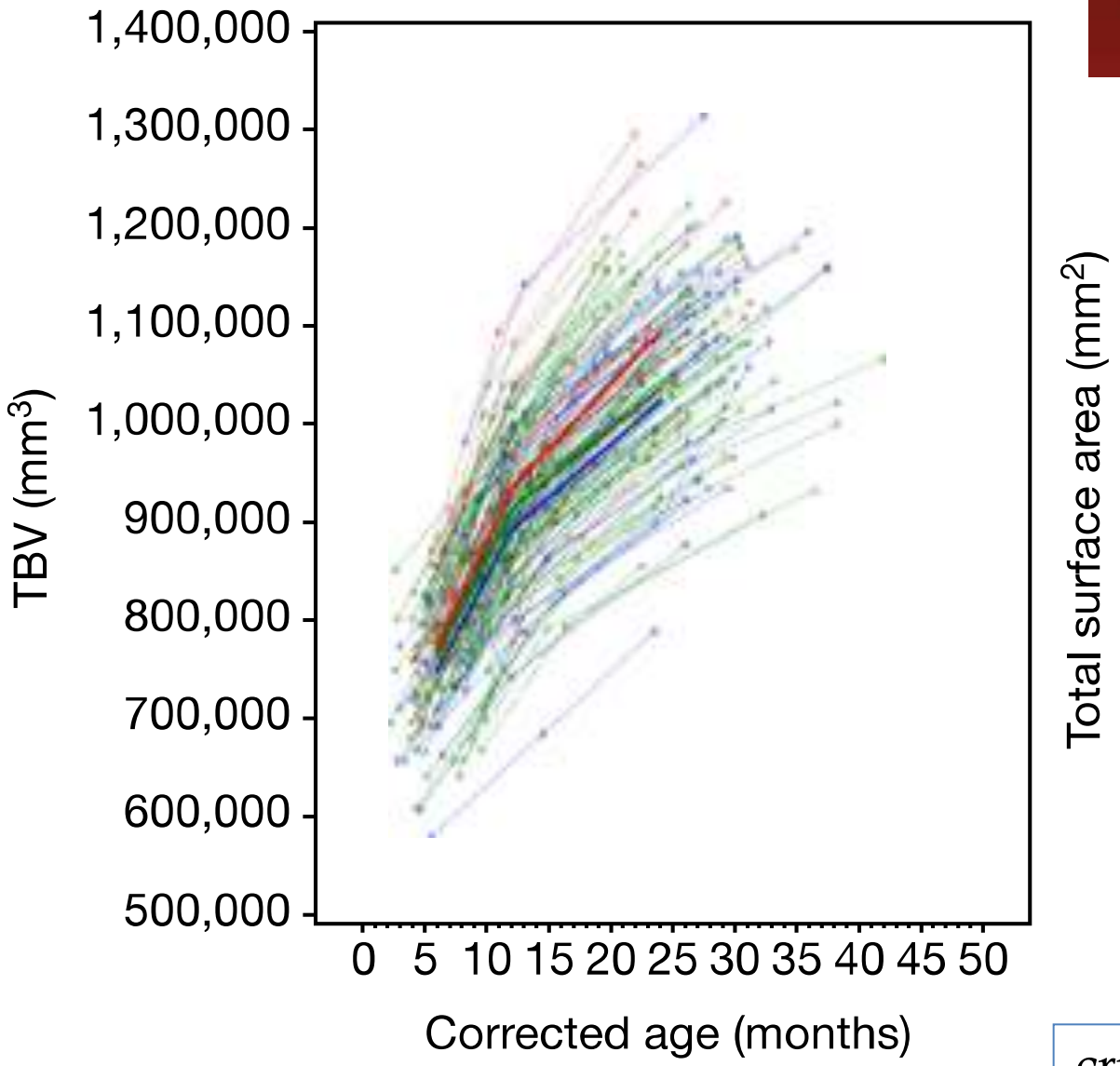
Hazlett HC et al

On the basis of our previous findings at 2–4 years of age[2], we hypothesized that brain overgrowth in ASD begins before 24 months of age; that overgrowth is associated with hyper-expansion of the cortical surface area; and that these early brain changes are temporally linked to the emergence of the defining behaviours of ASD. We also investigated whether differences in the development of brain characteristics might suggest early biomarkers (that is, occurring before the onset of the defining behaviours of ASD) for the detection of ASD.

cristina.panisi@tin.it

nature
International weekly journal of science

Hazlett HC et al



cristina.panisi@tin.it

Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis

AUTHORS: Barbara O. McElhanon, MD,[a] Courtney McCracken, PhD,[a] Saul Karpen, MD, PhD,[a] and William G. Sharp, PhD[a,b]

[a]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; and [b]Marcus Autism Center, Atlanta, Georgia

KEY WORDS

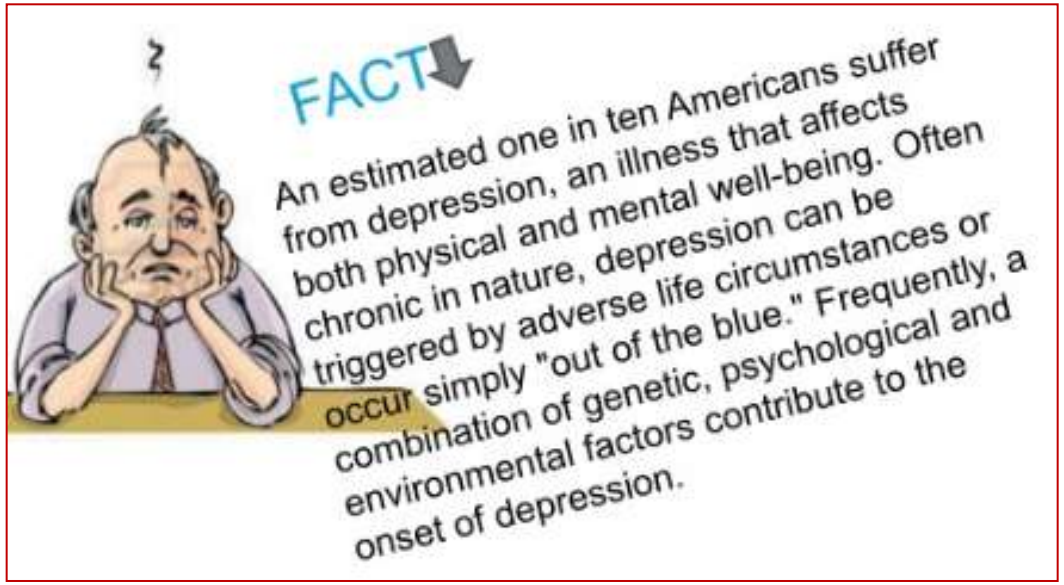
autism spectrum disorder, constipation, digestive disorders, GI

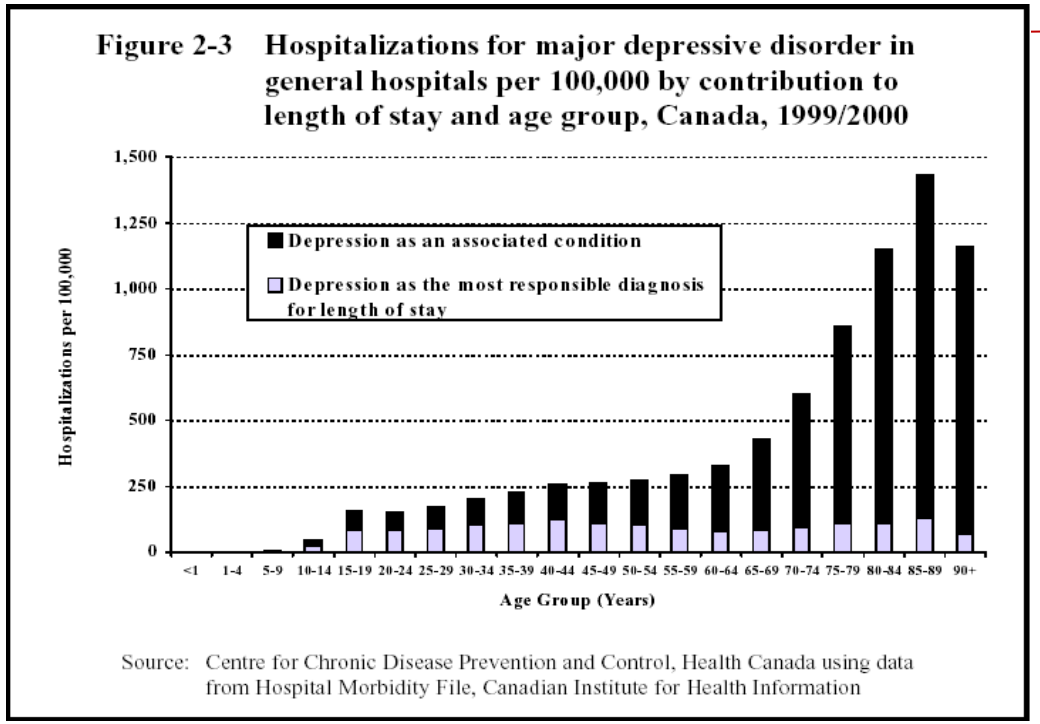
PEDIATRICS Volume 133, Number 5, May 2014

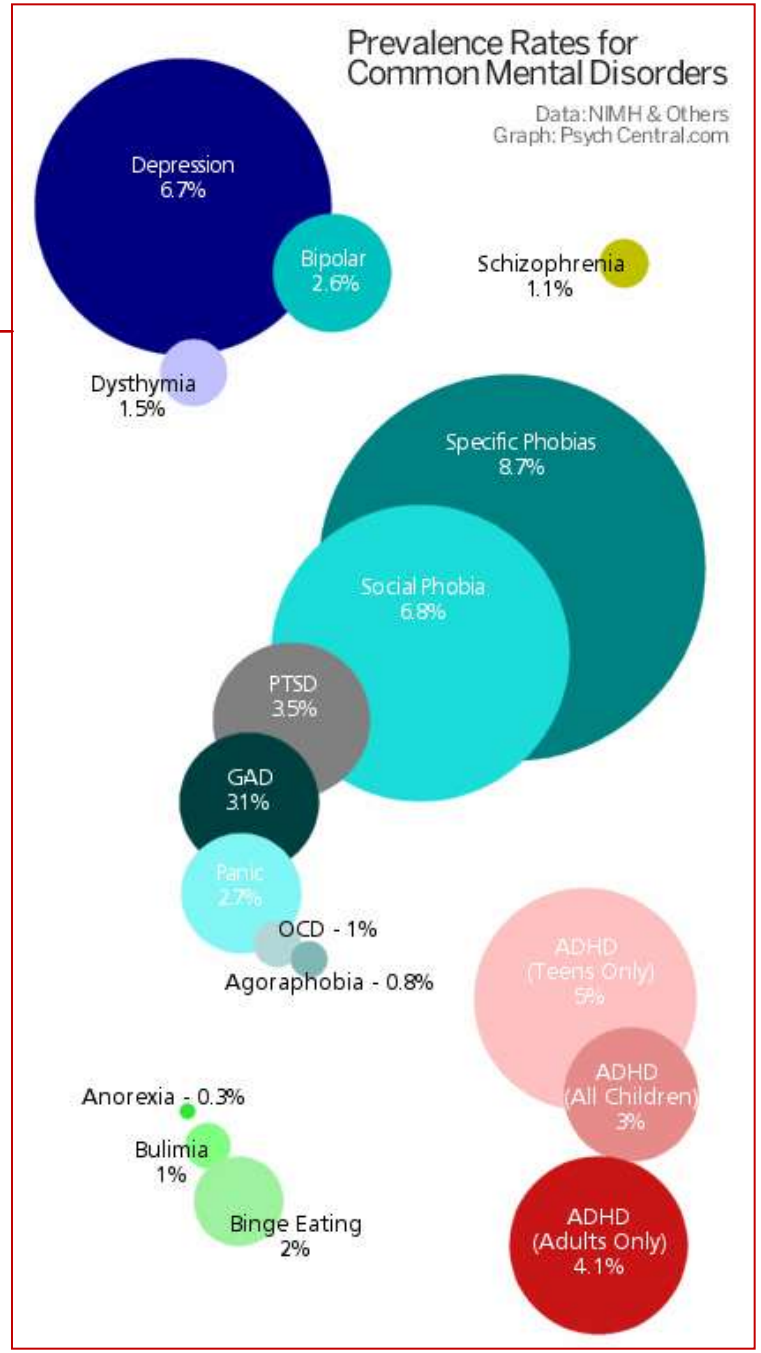
- Sintomi gastroenterici: **4X**
- Diarrea: **>3X**
- Stipsi**: >3X**
- Dolori addominali: **>2X**

cristina.panisi@tin.it

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







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

Depressione Major
Major depressive disorder

Fattori
psicologici,
psicosociali,
ambientali,
ereditari,
evolutivi

Biologici
(genetici-epigenetici metagenomici)
(psico-neuro-immuno-endocrini)

Persistente tristezza, ansia, o **senso di "*vuoto*"**

Senso di **disperazione**, **pessimismo**

Sensi di colpa, ***inutilità***, ***bassa autostima***

Anedonia (**perdita di interesse o piacere** nelle attività **normalmente piacevoli**)

Calo di energia, affaticabilità

Irritabilità, nervosismo

Movimenti e linguaggio **rallentati**

Senso di ***irrequietezza***, difficoltà a rimanere seduti

Difficoltà a ***concentrarsi, ricordare***, ***prendere decisioni***

Disturbi del sonno, di **risveglio**, **ipersonnia**

Cambiamenti nell'***appetito, alimentazione/peso***

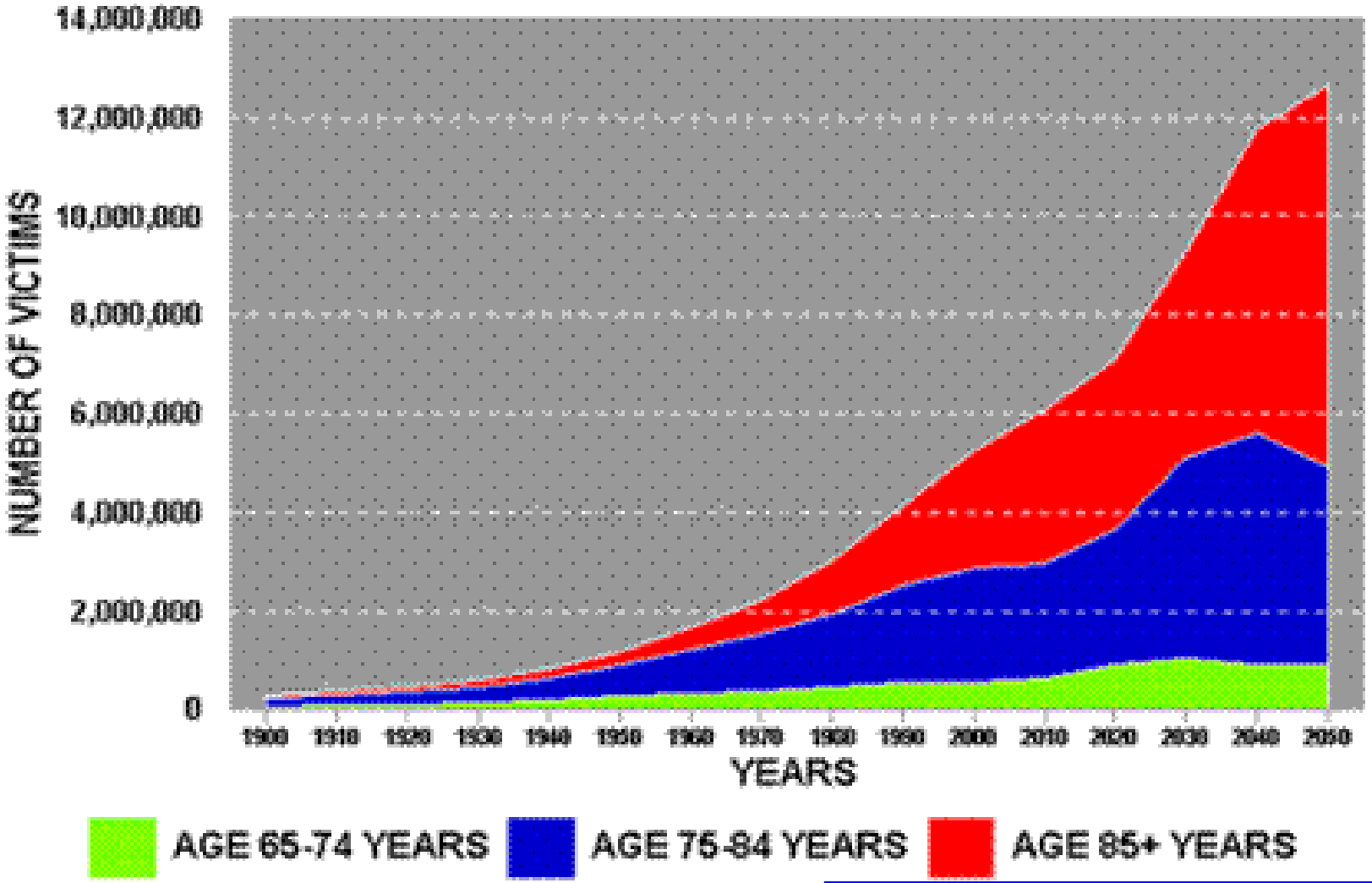
Pensieri di ***morte*** o ***suicidio***, o tentativi di suicidio

Dolori, mal di testa, crampi, problemi digestivi o senza una chiara causa fisica e senza sollievo con il trattamento

Il **decorso è molto variabile**: da un **episodio unico della durata di alcune settimane**
fino ad un **disordine perdurante per tutta la vita con ricorrenti episodi di depressione maggiore**.

PREVALENCE OF ALZHEIMER'S DISEASE

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

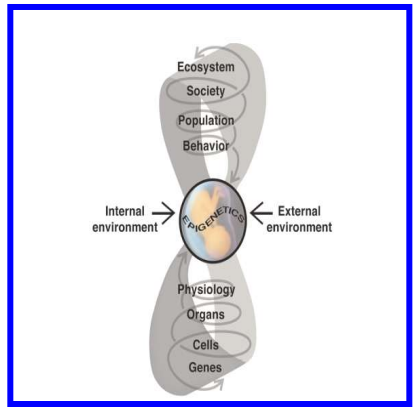


An equally dramatic trend show **neurodegenerative diseases** and in particular **Alzheimer's disease**

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

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

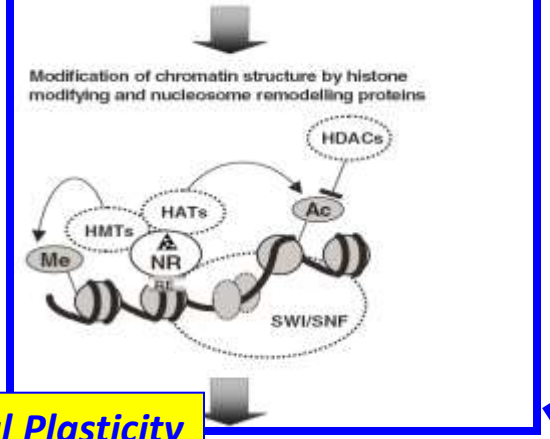
The 7 keywords: from genetics to *epigenetics*



3

Ontogeny*

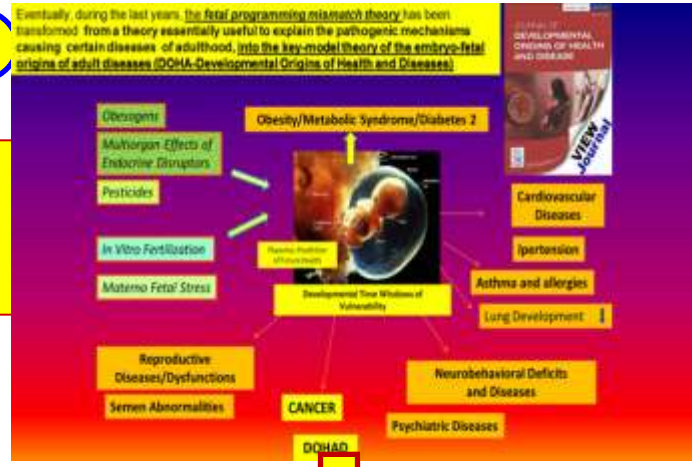
4



Developmental Plasticity

Epi-genetic Mismatch DOHA

6

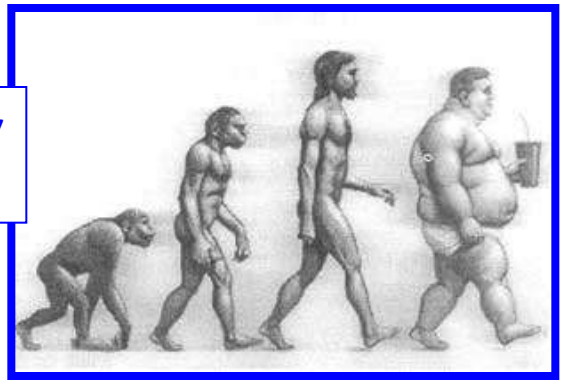


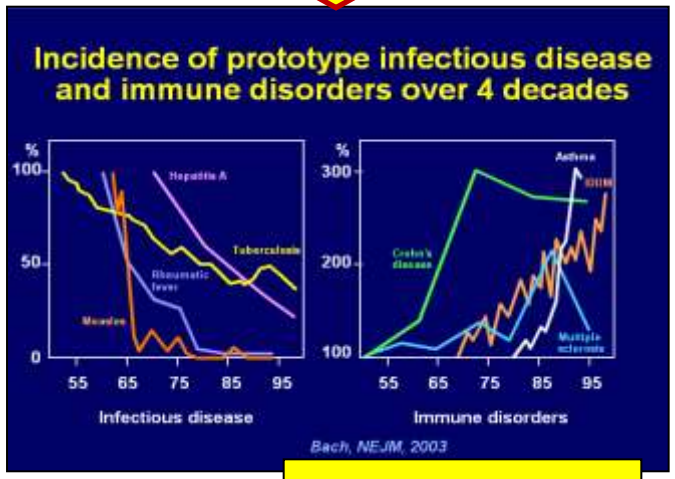
Devo → Evo

Fetal programming

Phylogeny*

Evolutionary Medicine





2

Environment

5

1

From Genetics to *Epigenetics*

7

XXI Century Epidemiological Transition

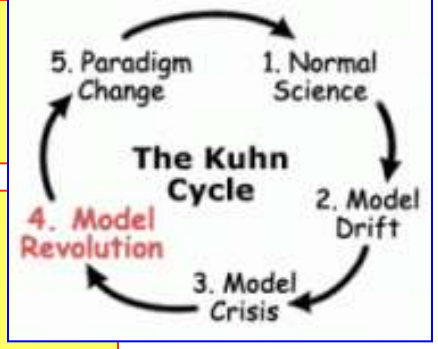
Towards a paradigm shift in biomedicine.
Environmental interference with the human (epi)genome

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

ECERI
European Cancer and Environment Research Institute

Foreword 2

We are currently facing a *paradigm shift* in biomedicine

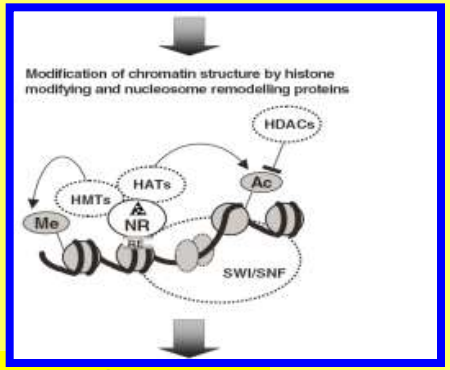


For the last 50 years it was agreed to consider **DNA as the code and the key project for the assembly of our phenotype**.

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**

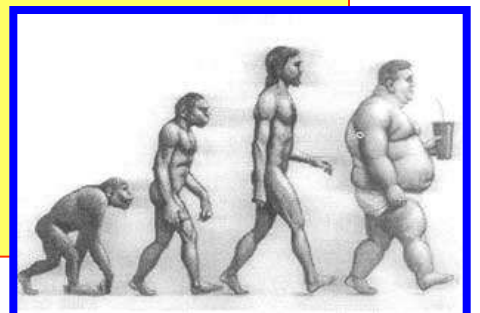
and the **information** deeply inscribed **inside the DNA**



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

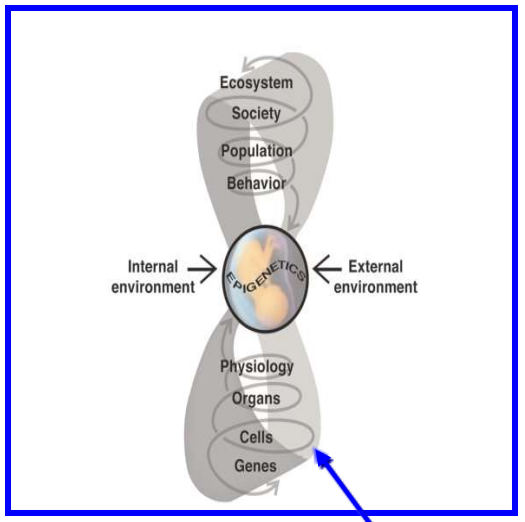


The other **key concepts** (obviously interdependent) are:

- ***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

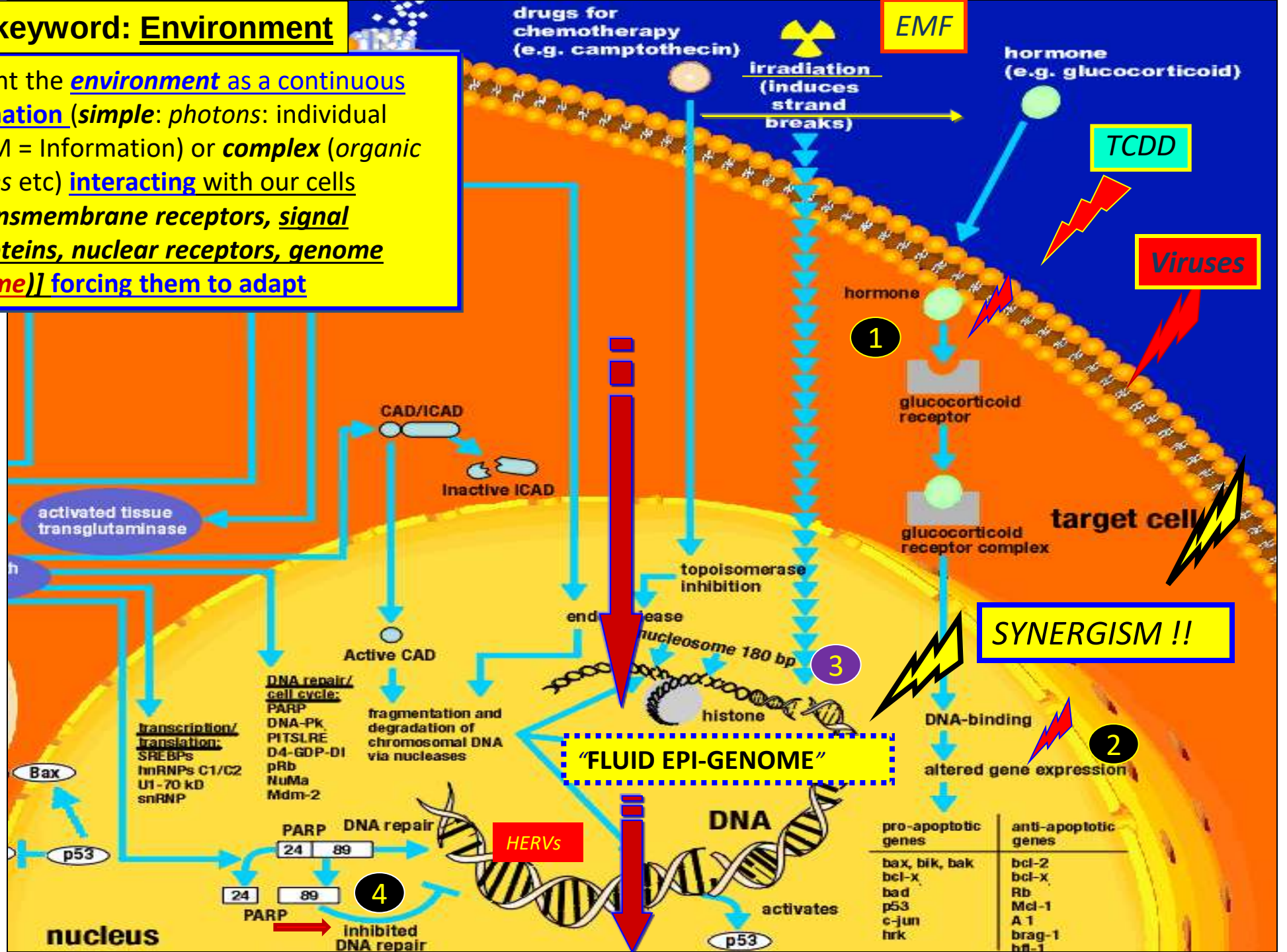
discrepancies between the **information** that the baby receives before and after birth **(*mismatch*)**

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

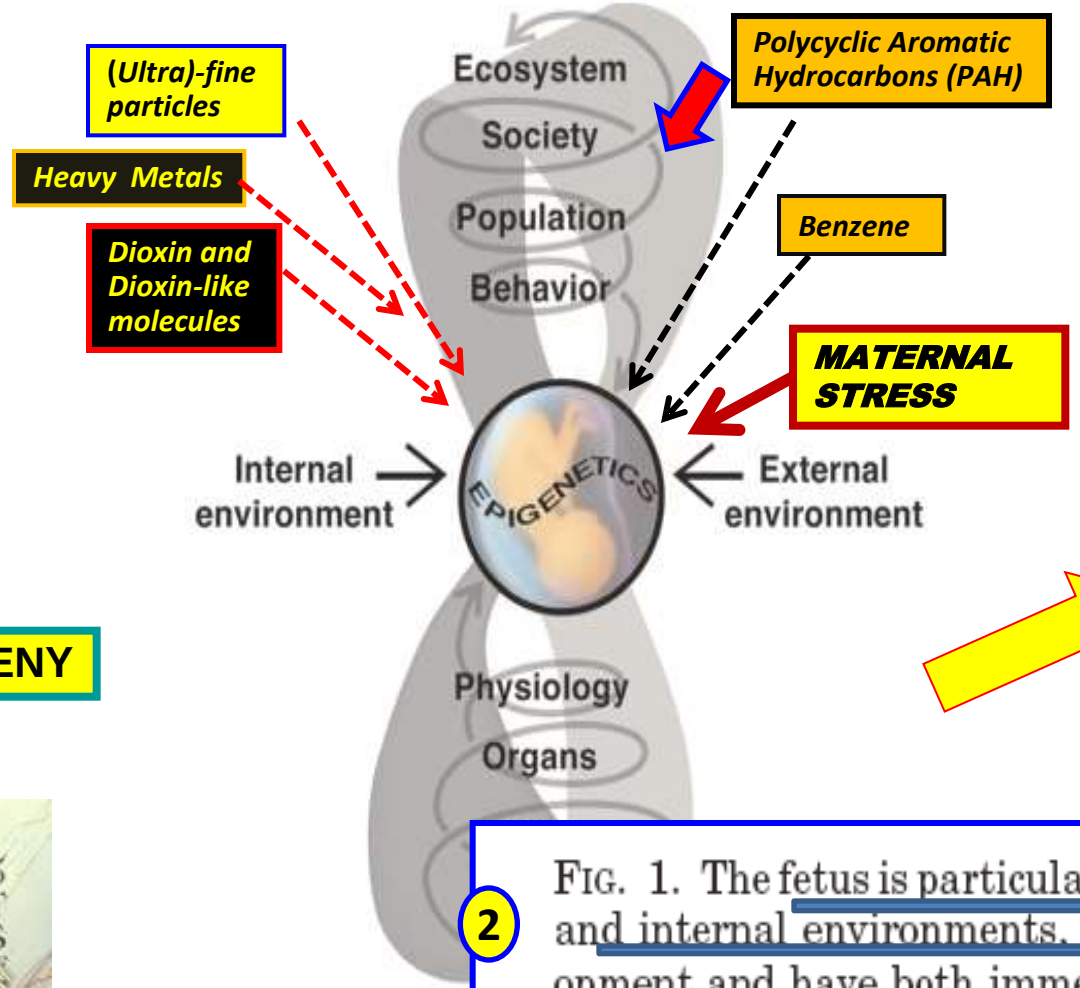
This theory (***DOHaD Developmental Origins of Health and Disease***) could help us to **explain the current epidemiological transition** ..

The **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 …***

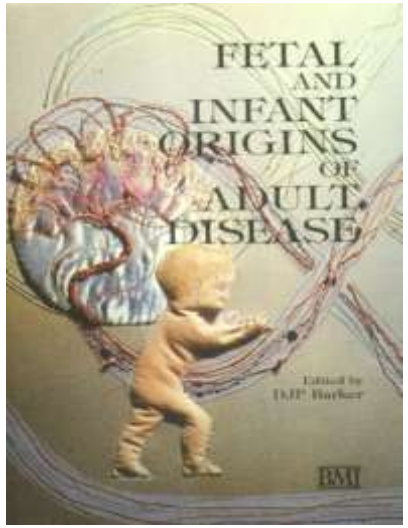


ONTOGENY

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

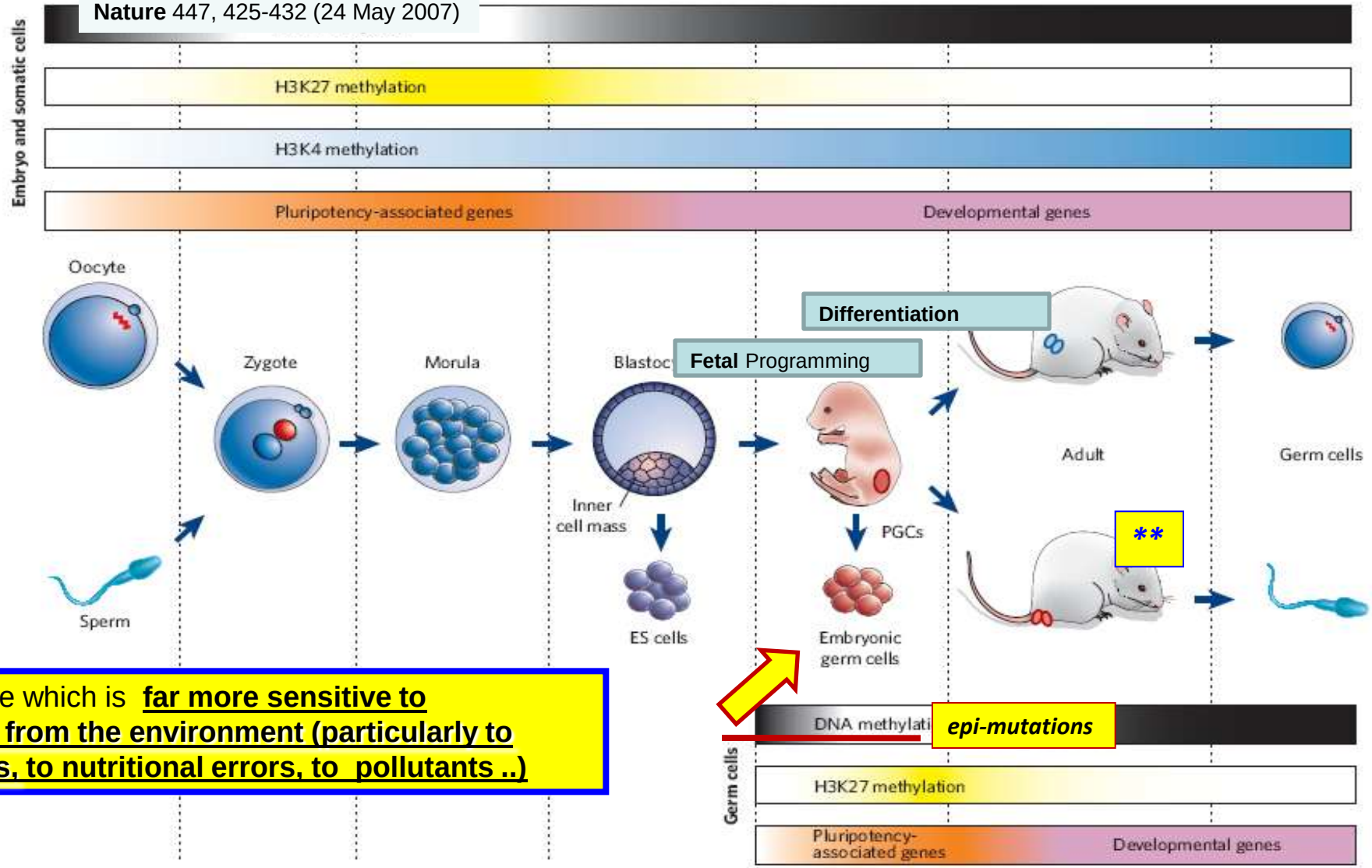
The **fourth** keyword is ***developmental plasticity***

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



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

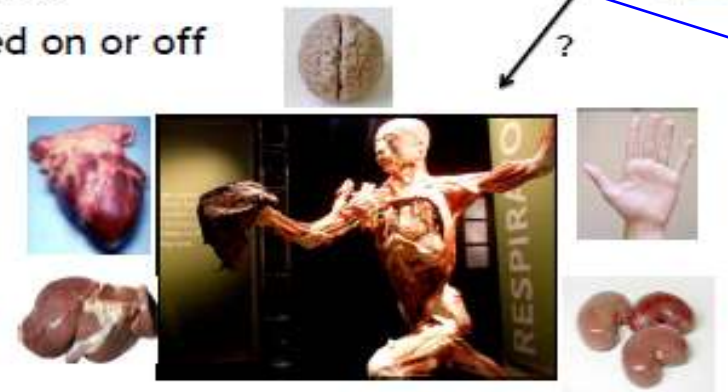
The **fourth** keyword is ***developmental plasticity***

Same DNA, Different Look

- We are made up of over 200 cell types.
- Each cell has the same DNA!
- How can they look so different?

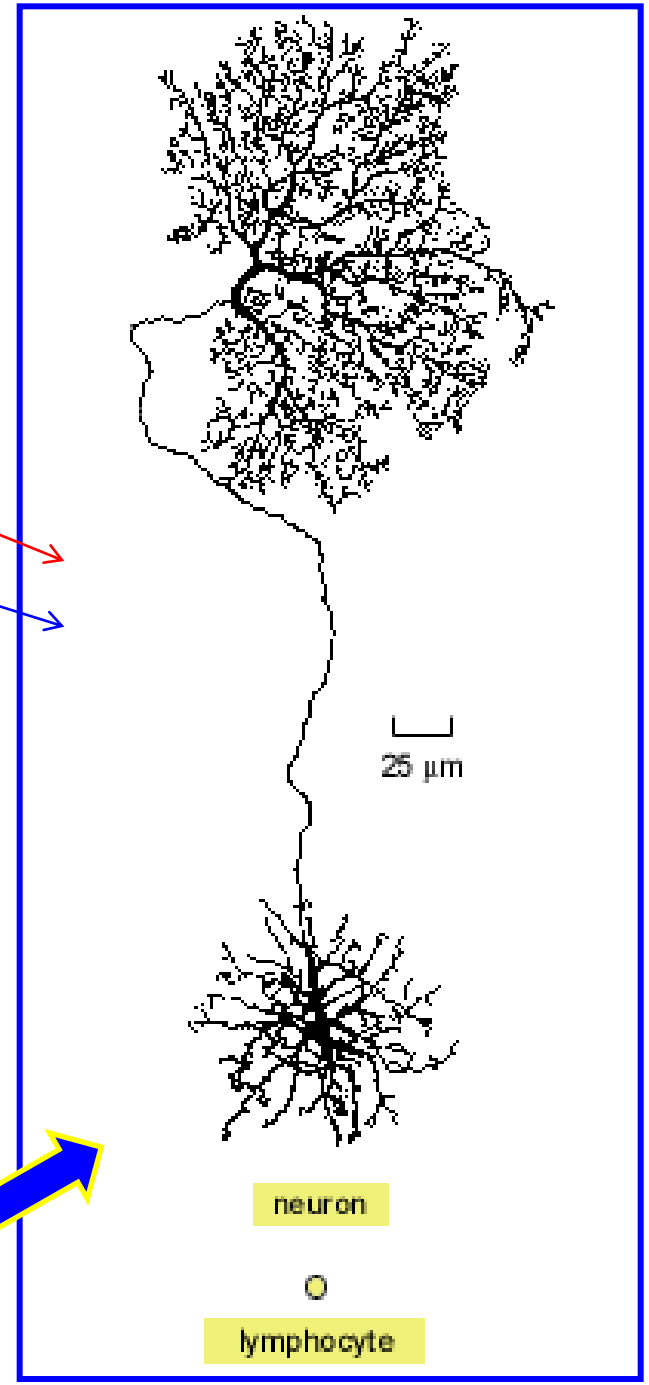
Epigenetics!

- Genes turned on or off



Wikimedia Commons, ORNL.gov, Flickr: richdelux

HARVARD MEDICAL SCHOOL



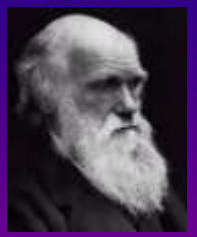
This image clearly shows the **"power" of the epigenome** and the **predominant role of environmental information in the phenotypic shaping of cells, tissues , organisms** .. the **huge phenotypic (morpho- functional) difference** between a *lymphocyte* and a *neuron* **is not due to DNA, which is virtually 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

Phylogeny

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**

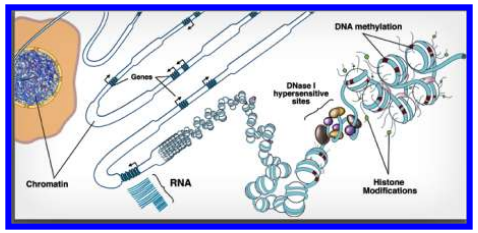
Mismatch

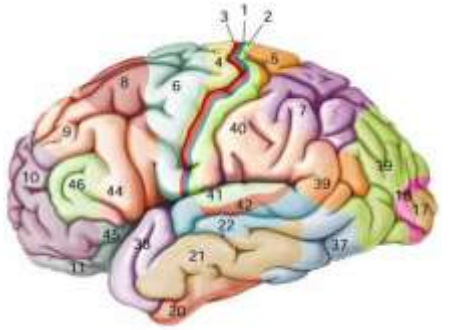
and of **9 months of an individual development**

Devo-Evo

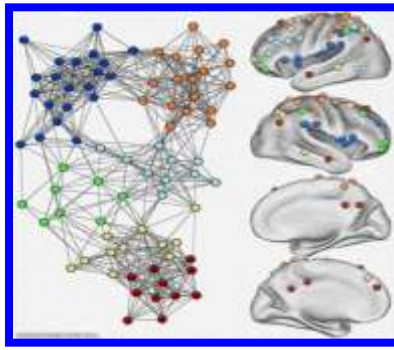
Ontogeny

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





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



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"

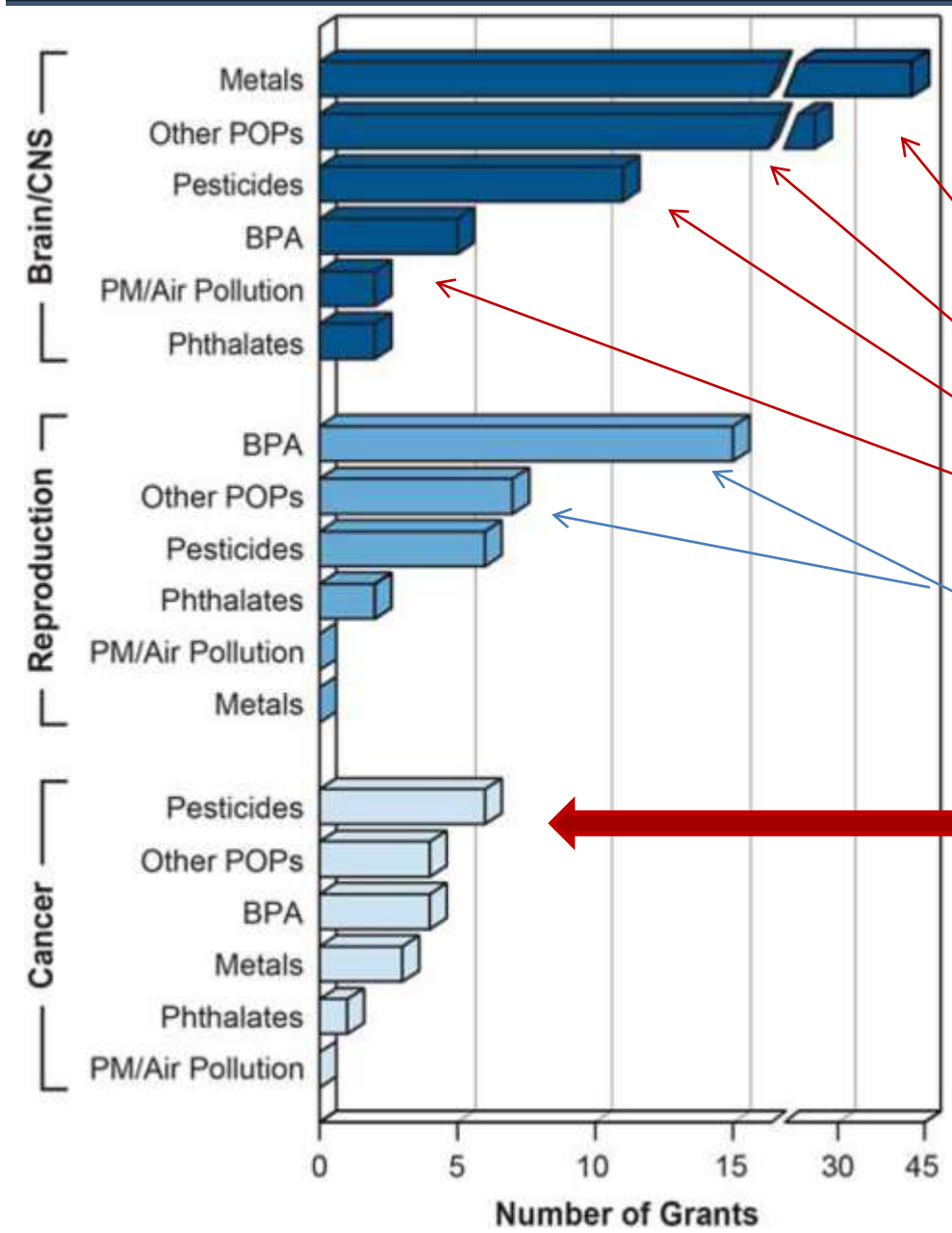
Ernesto Burgio

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

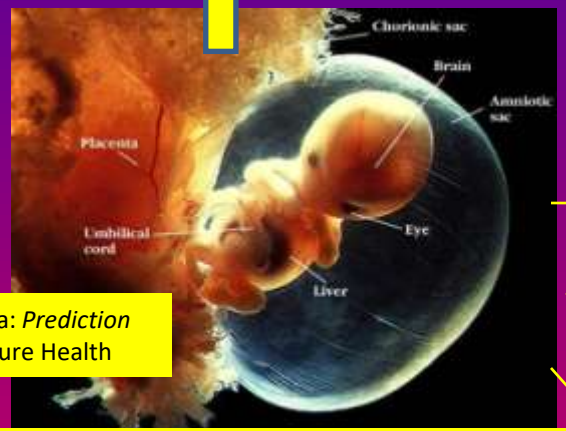
Multiorgan Effects of Endocrine Disruptors

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

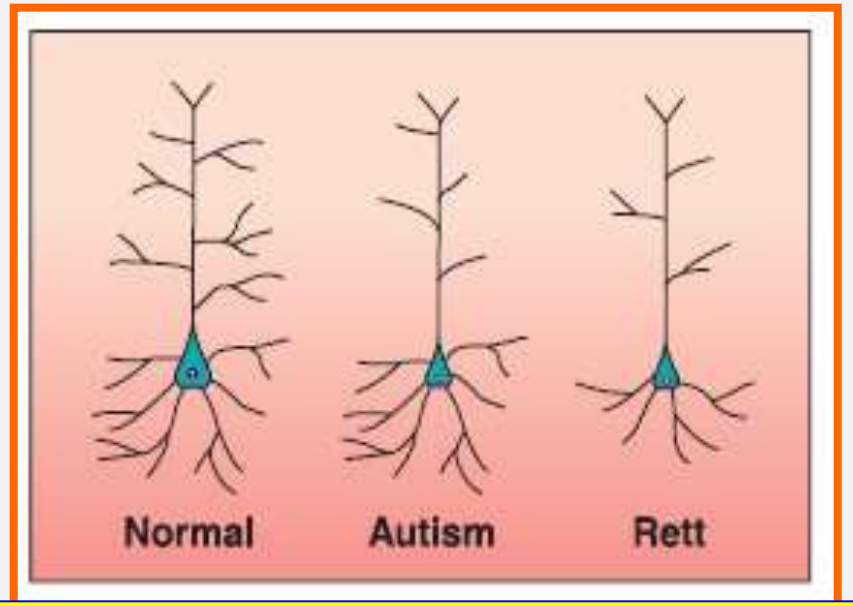
CANCER

Neurobehavioral Deficits and Diseases

Psychiatric Diseases

DOHAD

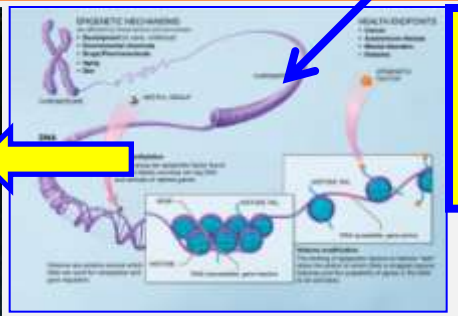
Léo Kanner



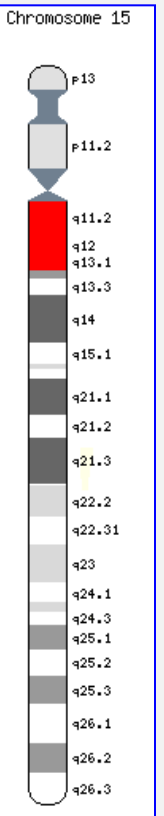
Hans Asperger

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

Angelman syndrome



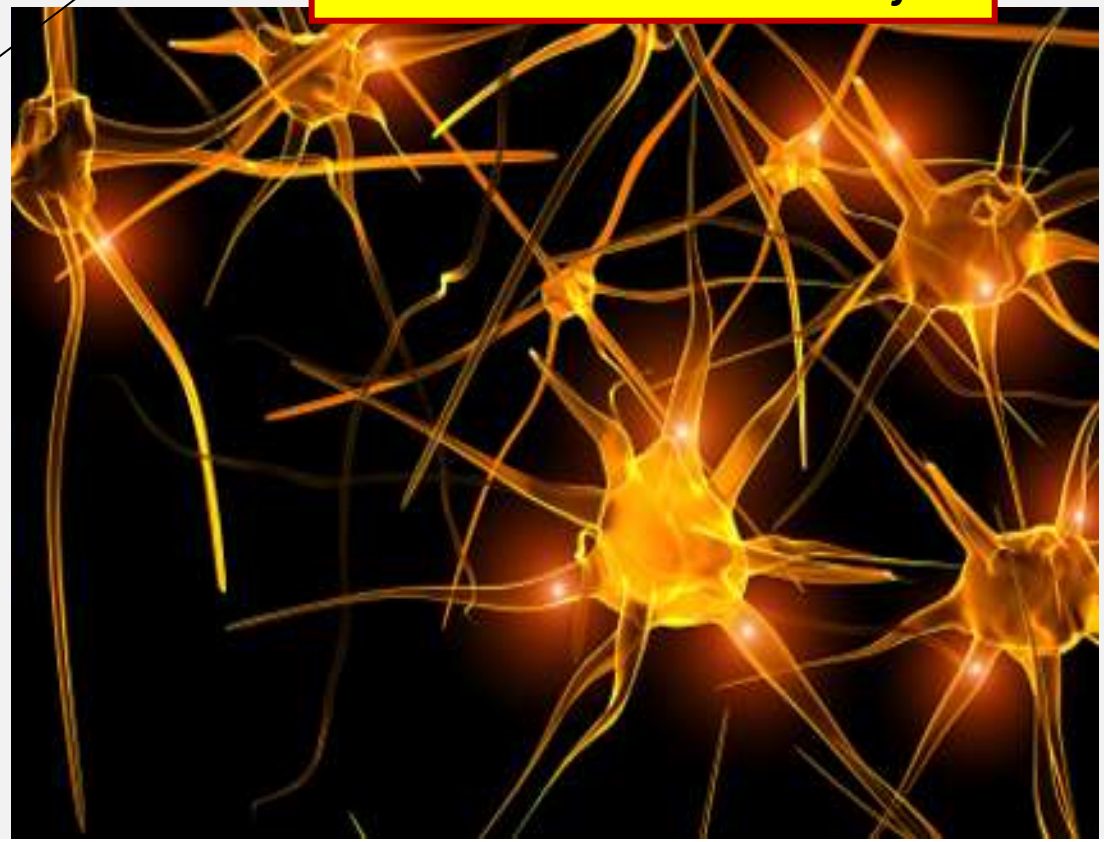
ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee



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.

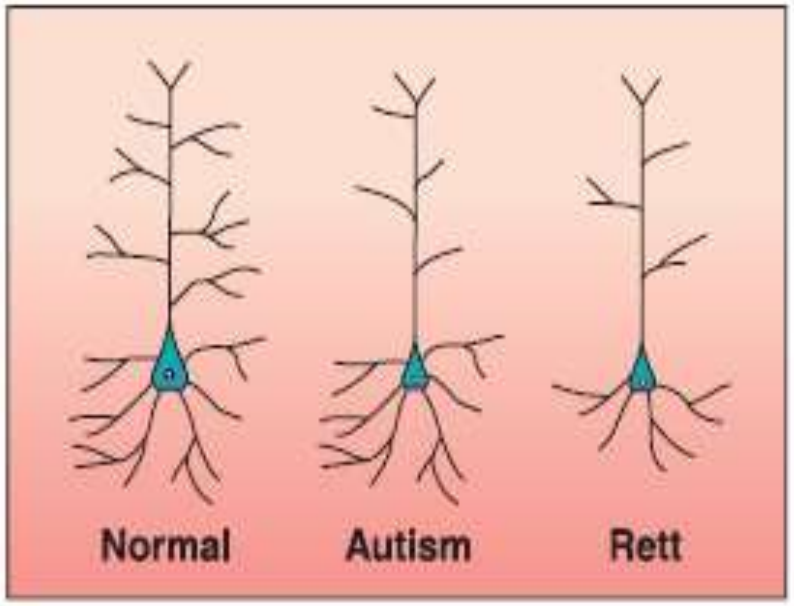


Fig. 2. Schematic representation of pyramidal neurons from control, autism, and Rett brains. In autism, the cell body is small and there is reduced dendritic branching. Similar changes occur in Rett, along with reduction in basilar dendritic branching. The reported changes are subtle and apply to a few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

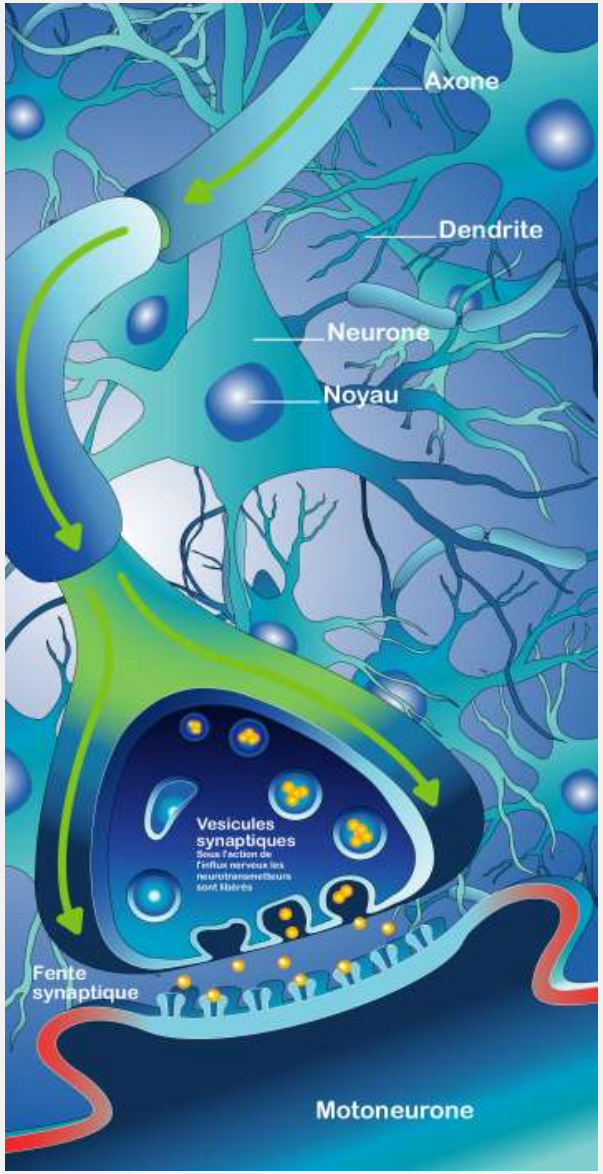
As for the **causes of autism**

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**).



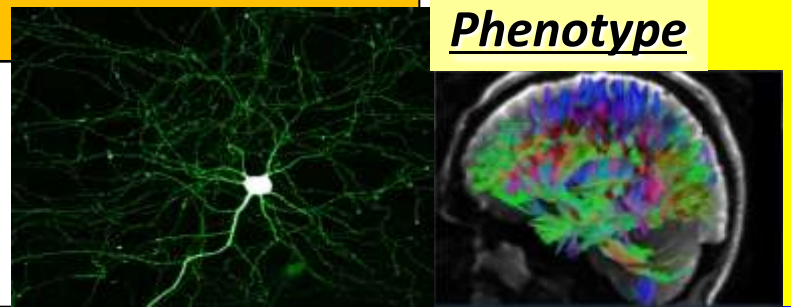
Key *words*

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



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

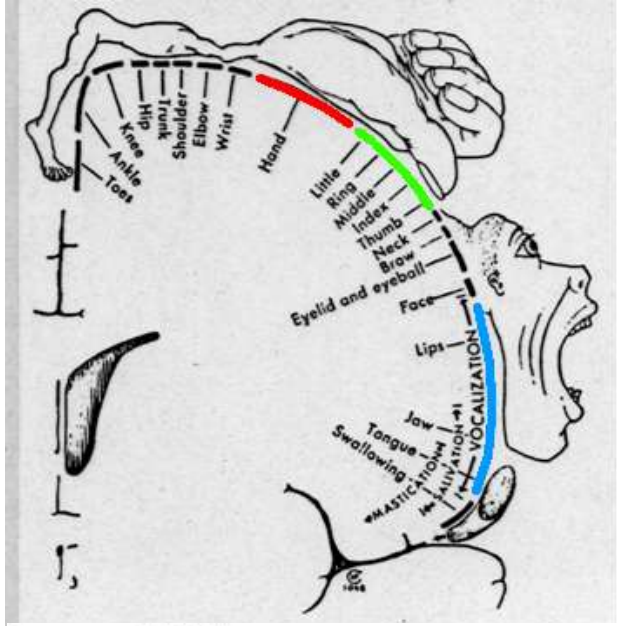
Individual Cablage - *Connectome*

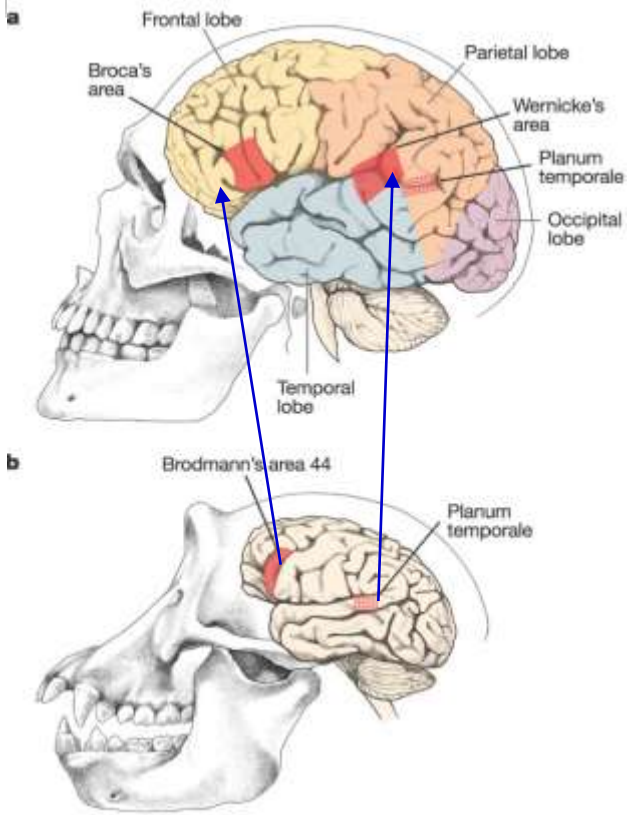
Phenotype

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

The ***ancestral*** wiring

Le ***câblage*** ancestral

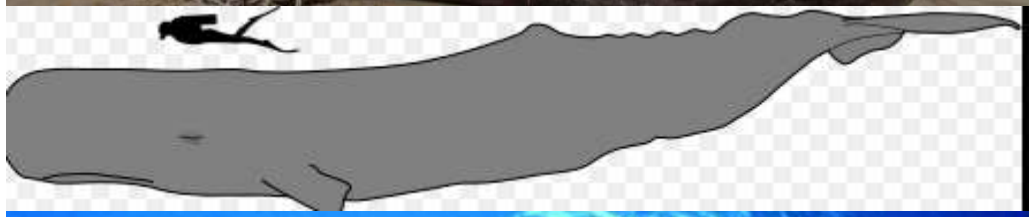




As with the **sensory cortex**, **Wilder Penfield** was responsible for **mapping the motor cortex…**
Chimps also have a motor cortex, but the **area of cortex devoted to vocal control is restricted** relative to what you see in the human animal.
Their brains are just not built for the detailed vocalizations 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

Absolute Brain Weight – Does it reflect intelligence?

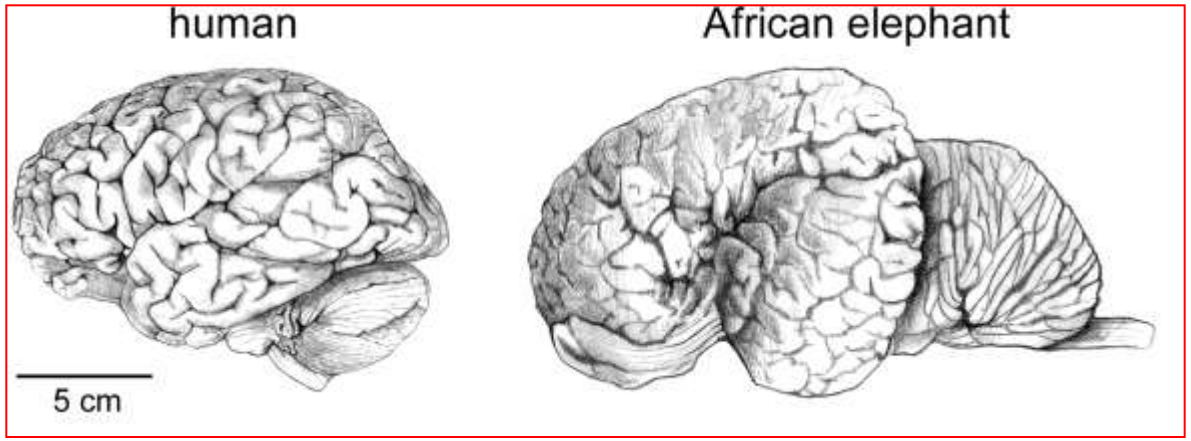


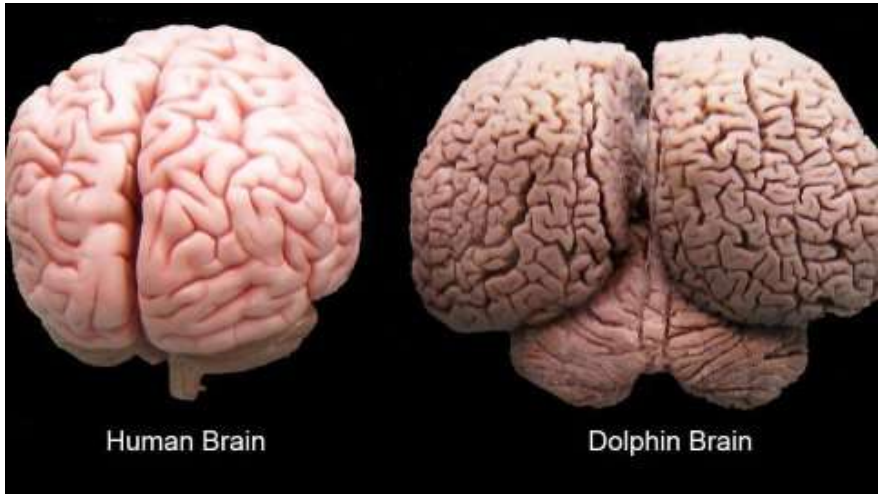
Capodoglio (*Physeter*

Species	Adult Brain Weight (grams)
Chimpanzee	450
Human	1,350
Bottlenosed dolphin	1,600
African elephant	6,075
Fin whale	7,200
Sperm Whale	9,200

What is more important in **determining the complexity and richness of the functions** of a brain / mind?
The **mass / volume**? The **number of neurons**? The **number of connections**? The **organization of neuronal circuits**?

The human brain is not the largest.





Across species, brain size correlates with body size in a way that can be described mathematically with a power function, thus allowing **the predicted brain mass to be calculated for any species**

Size of Adult Human Brain

- Range: 1000 to 2000 grams
- Average male = 1,350 g
- Average female = 1,200 g
  - Anatole France = 1,000 g (20th century poet)
  - **Albert Einstein = 1,230 g**
  - Lord Byron = 2,380 g (Romance poet)

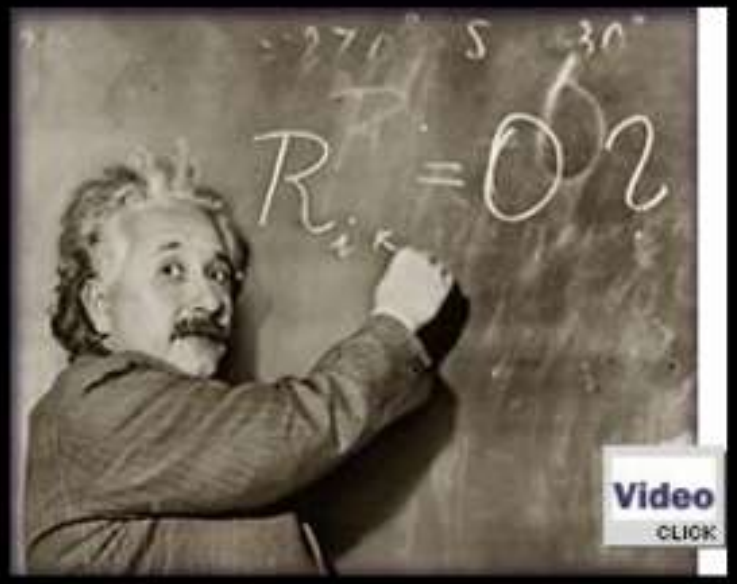
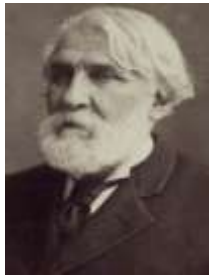


TABLE I.

Name.	Age.	Occupation.	Nationality.	Brain-weight.
Turgenev.	65	Poet and novelist.	Russian.	2012
Bouny.		Jurist.	French.	1935
Cuvier.	63	Naturalist.	German descent.	1830
Knight, E. H.	59	Mechanician.	American.	1814
(Kraus, F. X.).	42	Theologian.	German.	1800
Abercrombie.	64	Physician.	English.	1786
Butler, Benj. F.	74	Statesman.	American.	1758
Olney, Edward.	59	Mathematician.	American.	1701
Levi, Herman.	60	Composer.	German.	1690
Winchell, A.	67	Geologist.	American.	1666
Thackeray.	52	Humorist.	English.	1658
Lenz, Rudolf.		Composer.	German. ?	1636
Goodsir.	53	Anatomist.	English.	1629
Curtice.	68	Mathematician.	American.	1612
Atherton.	49	U. S. Senator.	American.	1602
Siemens.	68	Physicist.	German.	1600
Brown, George.	61	Journalist.	Canadian.	1596
Konstantinoff.	25	Author.	Bulgarian.	1595
Pepper, William.		Physician.	American.	1593
Harrison, R. A.	45	Jurist.	Canadian.	1590
Hermann, F. B. W.	73	Economist.	German.	1590
Riebeck.	61	?	German.	1580
Büchner.	51	Hygienist.	German.	1560
Bittner.	57	Playwright.	German.	1556
Lavollay.		Merchant and publicist.	French.	1550
Cope.	57	Paleontologist.	American.	1545
McKnight.	57	Physician.	American.	1545
Allen, Harrison.	56	Anatomist.	American.	1531
Simpson.	59	Physician.	English.	1531
Train, G. F.	75	Promoter.	American.	1525
Taguchi.	66	Anatomist.	Japanese.	1520
Dirichlet.	54	Mathematician.	French.	1520
De Morny.	54	Statesman.	French.	1520
Webster.	70	Statesman.	American.	1518
Lord Campbell.	82	Statesman.	English.	1517
Wright, C.	45	Philosopher.	American.	1516
Schleich.	55	Author.	German.	1503
Chalmers.	67	Theologian.	English.	1503
Mallery.	63	Ethnologist.	American.	1503
Seguin, E. C.	55	Neurologist.	French descent.	1505
Napoleon III.	65	Sovereign.	French.	1500
Fuchs.	52	Pathologist.	German.	1499
Agassiz.	66	Naturalist.	French descent.	1495
Giacomini.	58	Anatomist.	Italian.	1495
De Morgan.	73	Mathematician.	English.	1494
Gauss.	78	Mathematician.	German.	1492
Letourneau.	71	Anthropologist.	French.	1492
(————.)	53	Statesman.	Swedish.	1489
Powell.	68	Anthropologist.	American.	1488
Pfeufer.	63	Physician.	German.	1488
Wuelfert.	63	Jurist.	German.	1485
Broca.	56	Anthropologist.	French.	1484
Mortillet.	77	Anthropologist.	French.	1480
Aylett.	58	Physician.	American.	1474

TABLE I.—*Continued.*

Name.	Age.	Occupation.	Nationality.	Brain-weight.
Lord Jeffrey.	76	Jurist.	English.	1471
Asseline.	49	Journalist.	French.	1468
Skobeleff.	39	General.	Russian.	1457
Bischoff, C. H. E.	79	Physician.	German.	1452
Gylden.	55	Astronomer.	Swedish.	1452
Kobell.	79	Geologist.	German.	1445
Mihalkovicz.	55	Biologist.	Hungarian.	1440
Dupuytren.	58	Surgeon.	French.	1437
Siljeström.	76	Physicist.	Swedish.	1422
Rice, A. T.	35	Diplomat and editor.	American.	1418
Oliver.	65	Mathematician.	American.	1418
Meyr, M.	61	Philosopher.	German.	1415
Leidy, Philip.	53	Physician.	American.	1415
Nussbaum.	61	Surgeon.	German.	1410
Grote.	75	Historian.	English.	1410
Huber.	49	Author.	German.	1409
Pond, J. B.	65	Soldier and lecture-manager.	American.	1407
Babbage.	79	Mathematician.	English.	1403
Assézat.	45	Journalist.	French.	1403
Kupffer.	73	Anatomist.	German.	1400
Bertillon.	62	Anthropologist.	French.	1398
Goltz.	68	Physiologist.	German.	1395
Coudereau.	50	Physician.	French.	1390
Whewell.	72	Philosopher.	English.	1389
Wistar, Isaac J.	78	General.	American.	1389
Wilson.	61	U. S. Vice-president.	American.	1389
Szilagyi.	61	Statesman.	Hungarian.	1380
Rüdinger.	64	Anatomist.	German.	1380
Schmid.	65	Author.	German.	1374
Hovelacque.	52	Statesman.	French.	1373
Bischoff, T. L. W.	76	Anatomist.	German.	1370
Cheve.		?	French.	1365
Gross, S. D.		Physician.	American.	1361
Hermann, C. F.	51	Philologist.	German.	1358
Liebig.	70	Chemist.	German.	1352
Schlagintweit.	51 ?	Naturalist.	German.	1352
Fallmerayer.	71	Historian.	German.	1349
Bennett.	63	Physician.	English.	1332
Pettenkofer.	82	Pathologist.	German.	1320
Senzel.	50	Sculptor.	French.	1312
Zeyer.	56	Architect.	German.	1320
Kolar.	84	Dramatist.	Bohemian.	1300
Grant, R. E.	80	Astronomer.	English.	1290
Whitman.	72	Poet.	American.	1282?
Cory.	55	Physician.	English.	1276
Guardia.	67	?	Spanish.	1272
Seguin, Edouard.	68	Psychiatrist.	French.	1257
Tiedemann.	79	Anatomist.	German.	1254
Lasaulx.	57	Philologist.	German.	1250
Laborde.	73	Physiologist.	French.	1234
Buhl.	64	Anatomist.	German.	1229
Hausmann.	71	Naturalist.	German.	1226
Ferris.	89	Jurist.	American.	1225
Gall.	70	Phrenologist and anatomist.	German.	1198



Ivan Turgenev 2012 gr

Interestingly, the smallest brain was that of Franz **Joseph Gall** (1758–1828) the father of ***phrenology***

Anatole France 1100 gr.

Table I from [Spitzka (1907)] which includes the name, age, occupation, nationality, and brain weight of different personalities (the average adult brain today is about 1,450 grams)

Encephalization Quotient (EQ)

????????	9.0
Human	7.4
Dolphin	5.6
Killer whale	2.9
Chimpanzee	2.5
Rhesus Monkey	2.1
Elephant	1.9
Whale	1.8
Dog	1.2
Cat	1.0
Horse	0.9
Sheep	0.8
Mouse	0.5
Rabbit	0.4

Anatomical estimate of species' intelligence based on brain/body size and not behavior

EQ = ratio of brain weight of animal to brain weight of "typical" animal of same body weight

EQ represents residual value of brain mass

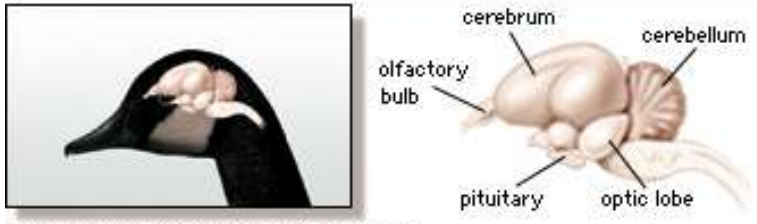
Encephalization Quotient (EQ)

Hummingbird	9.0
Human	7.4
Dolphin	5.6
Killer whale	2.9
Chimpanzee	2.5
Rhesus Monkey	2.1
Elephant	1.9
Whale	1.8
Dog	1.2
Cat	1.0
Horse	0.9
Sheep	0.8
Mouse	0.5
Rabbit	0.4

1 g brain for hummingbird

(Colibrì)

Brain structure of the bird (goose)



The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost

Suzana Herculano-Houzel[1]

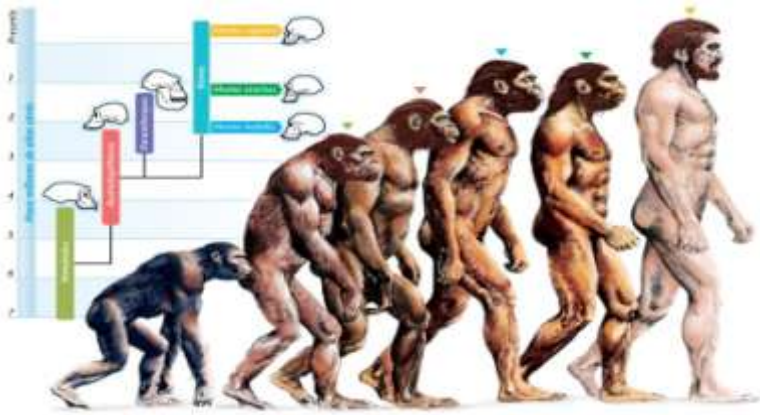
Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, 21941-902, Rio de Janeiro, Brazil; and Instituto Nacional de Neurociência Translacional, Instituto Nacional de Ciência e Tecnologia/Ministério de Ciência e Tecnologia, 04023-900, Sao Paulo, Brazil

Neuroscientists have become used to a number of "facts" about the human brain: It has 100 billion neurons and 10- to 50-fold more glial cells; it is the largest-than-expected for its body among primates and mammals in general, and therefore the most cognitively able; it consumes an outstanding 20% of the total body energy budget despite representing only 2% of body mass because of an increased metabolic need of its neurons; and it is endowed with an overdeveloped cerebral cortex, the largest compared with brain size. These facts led to the widespread notion that the human brain is literally extraordinary: an outlier among mammalian brains, defying evolutionary rules that apply to other species, with a uniqueness seemingly necessary to justify the superior cognitive abilities of humans over mammals with even larger brains. These facts, with deep implications for neurophysiology and evolutionary biology, are not grounded on solid evidence or sound assumptions, however. Our recent development of a method that allows rapid and reliable quantification of the numbers of cells that compose the whole brain has provided a means to verify these facts. Here, I review this recent evidence and argue that, with 86 billion neurons and just as many nonneuronal cells, the human brain is a scaled-up primate brain in its cellular composition and metabolic cost, with a relatively enlarged cerebral cortex that does not have a relatively larger number of brain neurons yet is remarkable in its cognitive abilities and metabolism simply because of its extremely large number of neurons.

Se si paragonano **la corteccia cerebrale dell'uomo è quella dello scimpanzé** si scopre che la prima pur avendo un **volume 2,75 maggiore della seconda ha solo 1,25 volte più neuroni…**

Quello che conta, ormai lo sappiamo da almeno 25 anni, non è il numero dei neuroni ma l'organizzazione, la quantità e soprattutto la qualità delle connessioni interneuronali..

Molti **neuro-anatomisti** sottolineano che, **ripercorrendo la scala dei primati fino all'uomo, non c'è stata una semplice e progressiva somma di abilità**, come si era ipotizzato, ma una **riorganizzazione complessiva del cervello**



The most cited journal in psychology and the most cited open-access neuroscience journal

frontiers in Human Neuroscience

Front. Hum. Neurosci., 09 November 2009 | http://dx.doi.org/10.3389/neuro.09.031.2009

The human brain in numbers: a linearly scaled-up primate brain

Suzana Herculano-Houzel*

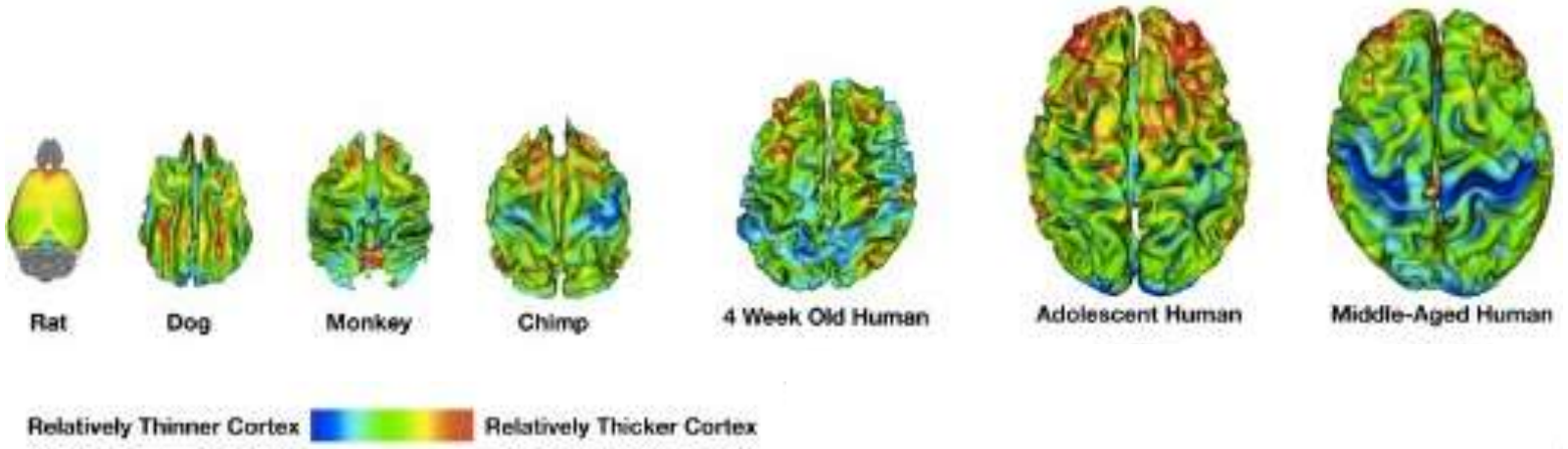
The human brain is **not exceptional in its cellular composition**, as it was found to contain **as many neuronal and non-neuronal cells as would be expected of a primate brain** of its size.

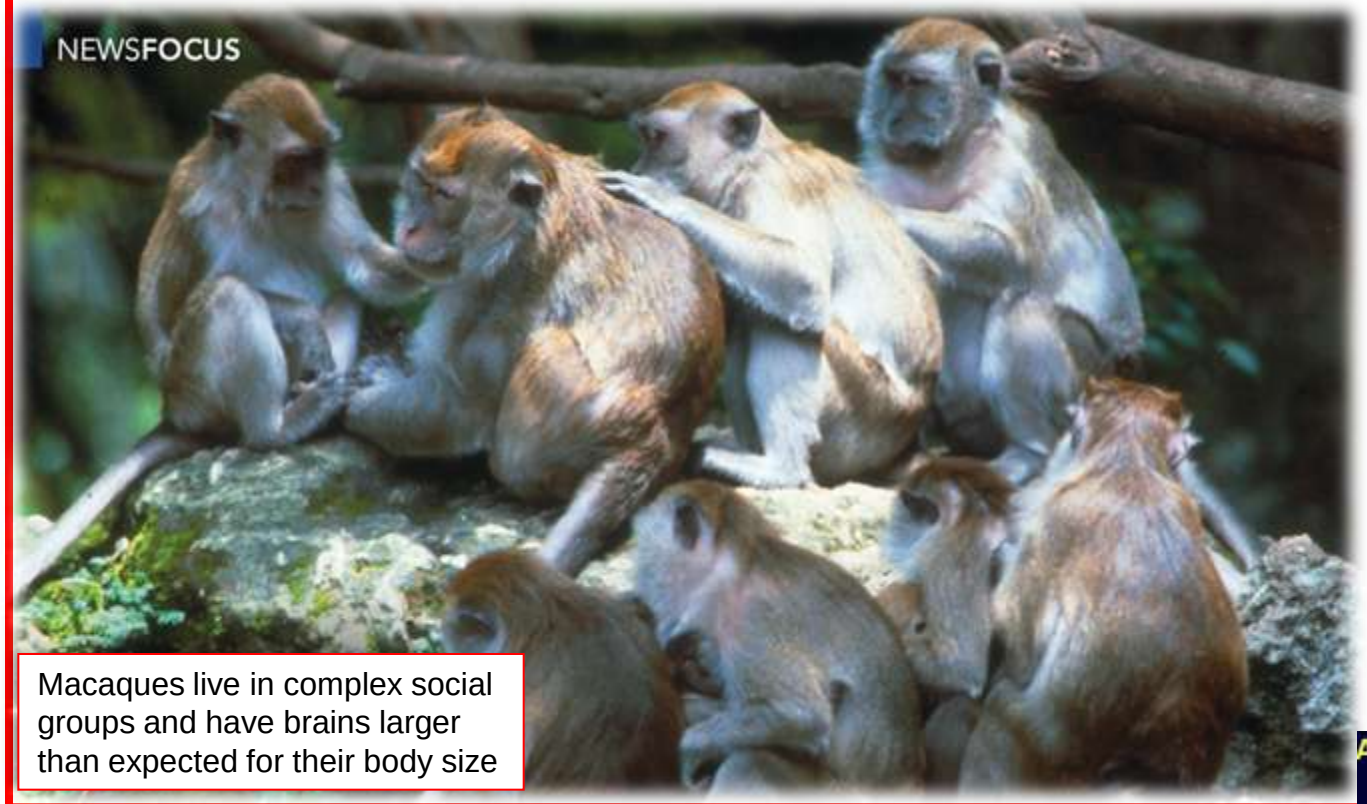
Additionally, **the so-called overdeveloped human cerebral cortex holds only 19% of all brain neurons**, a fraction that is **similar to that found in other mammals**… These findings argue in favor of a view of **cognitive abilities that is centered on absolute numbers of neurons, rather than on body size or encephalization**, and **call for a re-examination of several concepts related to the exceptionality** of the human brain.

Il cervello di un essere umano adulto contiene in media **86 miliardi di neuroni e 85 miliardi di cellule non neuronali.**
Ma soprattutto **la corteccia che costituisce l'82% del volume del cervello, possiede solo il 19% dei neuroni (17 miliardi).**

I lobi frontali e la **corteccia prefrontale** - le aree implicate nei processi di memorie e pianificazione, nella flessibilità cognitiva, nel pensiero astratto…- **hanno un numero di neuroni notevolmente inferiore** rispetto alle **aree visive, alle altre aree sensoriali e a quelle motorie**.

Mentre la maggior parte dei neuroni (**72**%) si trovano nel **cervelletto** che costituisce **appena il 10% della massa cerebrale ed è un organo indubbiamente meno complesso, molto più arcaico e dotato, almeno sulla carta, di funzioni relativamente primordiali**, rispetto a quelle intellettuali superiori gestite dalla corteccia.



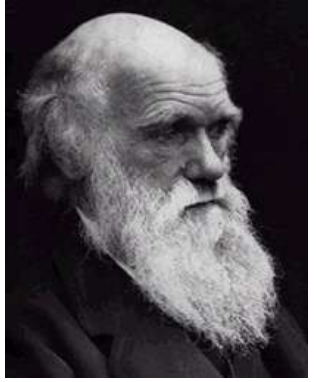


Macaques live in complex social groups and have brains larger than expected for their body size

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

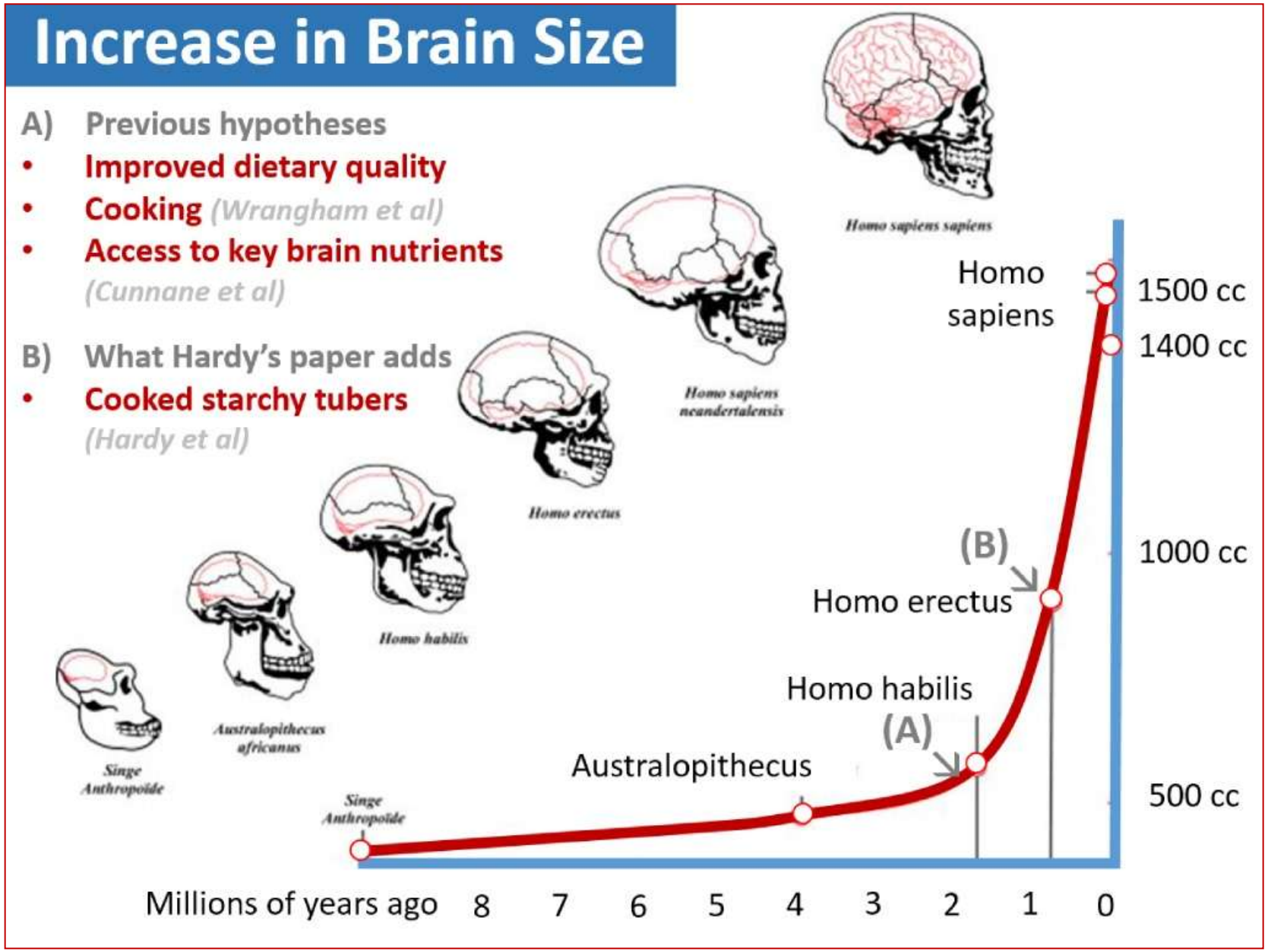
Chimpanzees

Humans

20 million years ago: **opposable thumb** and **frontal position of the eyes** ..

Tarsius tarsier (Tarsio spettro)

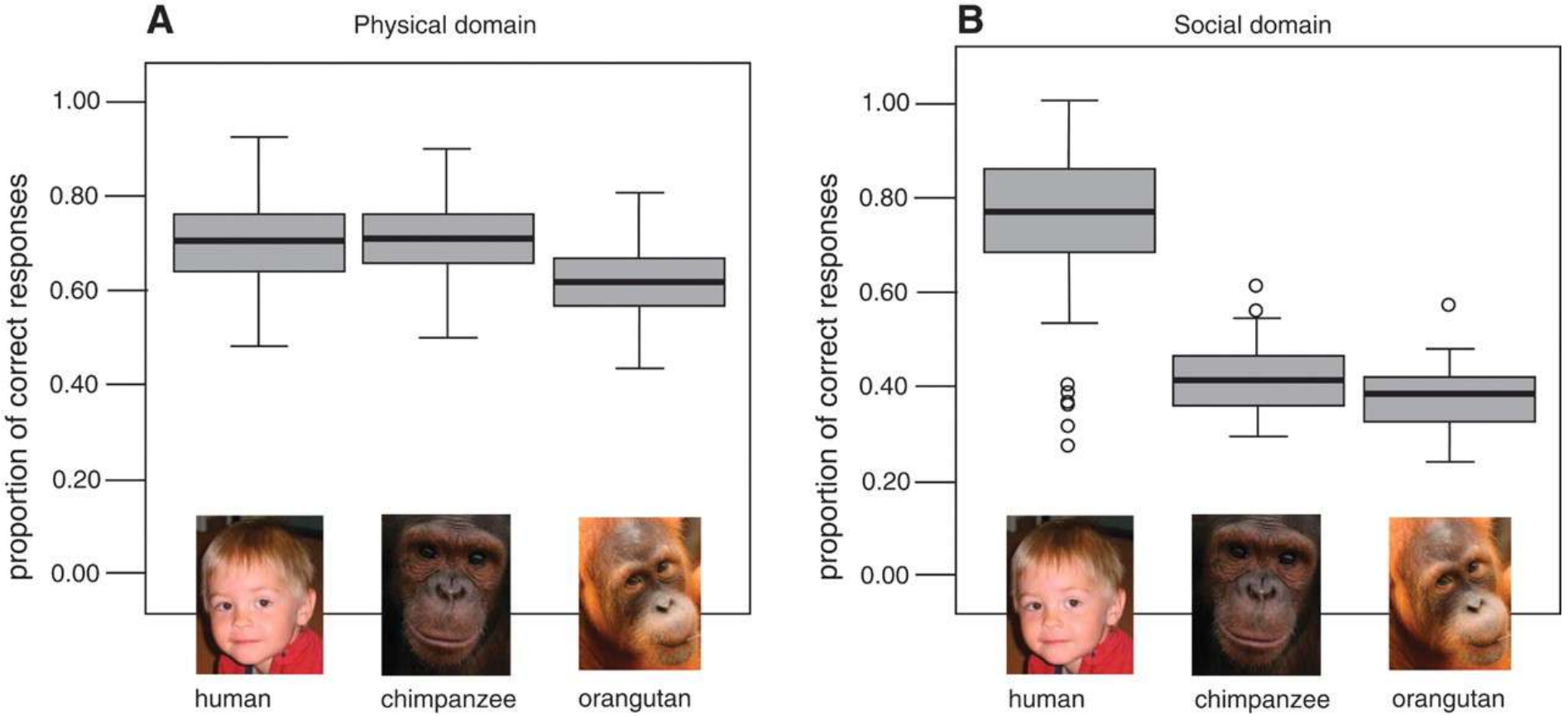
Brain Size and Intellectual Capabilities The absolute **brain size of hominids has tripled since the Pliocene** age (from an average of **450 cm^3 in *Australopithecus*** to 1,345 cm^3 in *H. sapiens*: Holloway, 1996)



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

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

Jan M. Engelmann*, Esther Herrmann, Michael Tomasello

Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

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

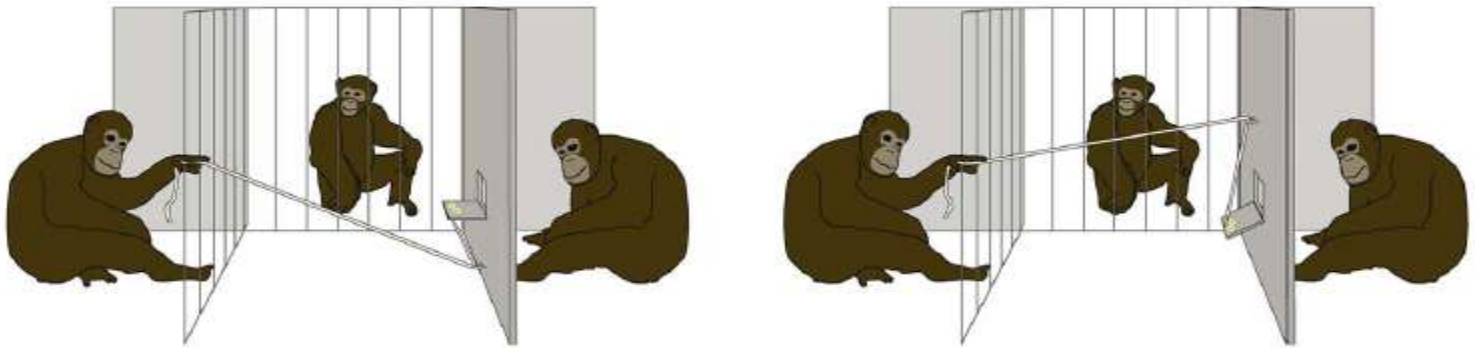


Figure. 3. Setup of the chimpanzee study. Illustration of the experimental setup for chimpanzees, viewed from the experimenter's point of view. The observed condition (pictured here) consisted of three different roles, subject (left), observer (middle) and receiver (right). In the stealing task (left), 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

Published online before print 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

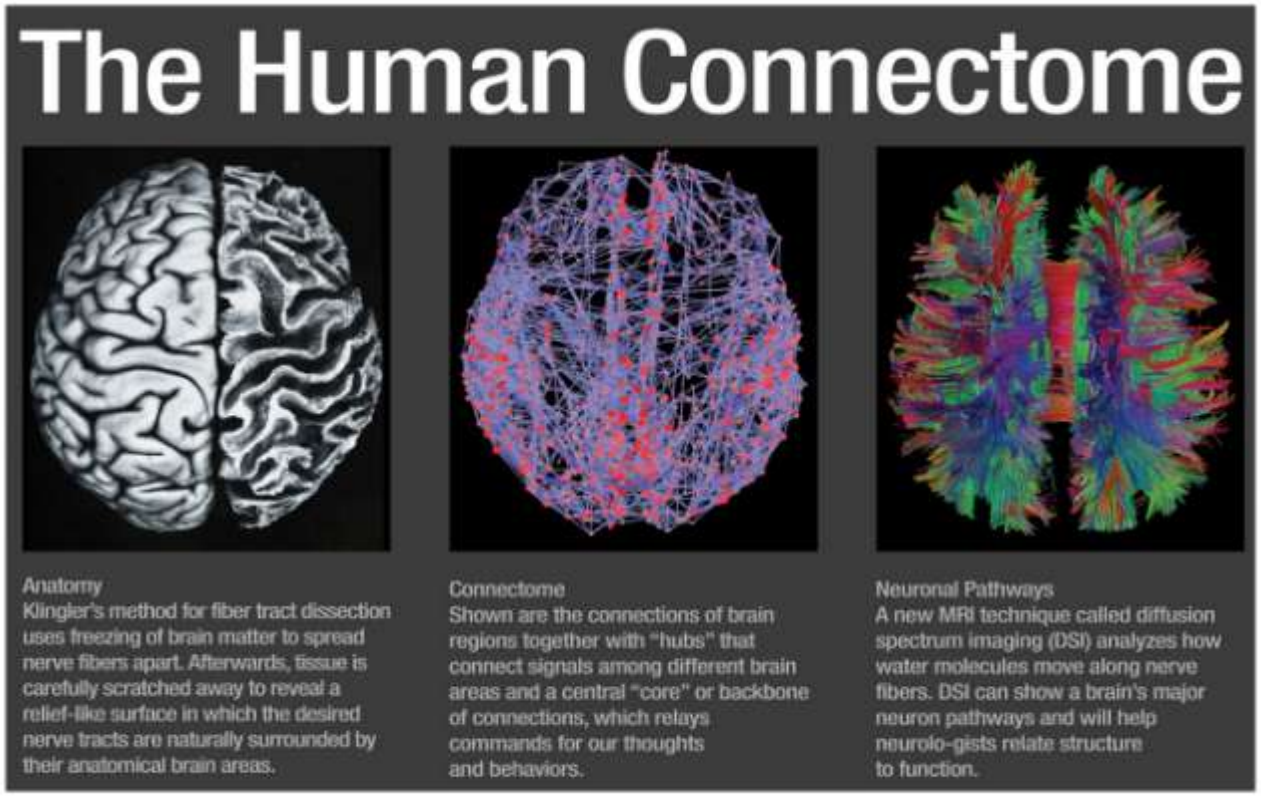
Madhura Ingalhalikar[a,1], Alex Smith[a,1], Drew Parker[a], Theodore D. Satterthwaite[b], Mark A. Elliott[c], Kosha Ruparel[b], Hakon Hakonarson[d], Raquel E. Gur[b], Ruben C. Gur[b], and Ragini Verma[a,2]

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.

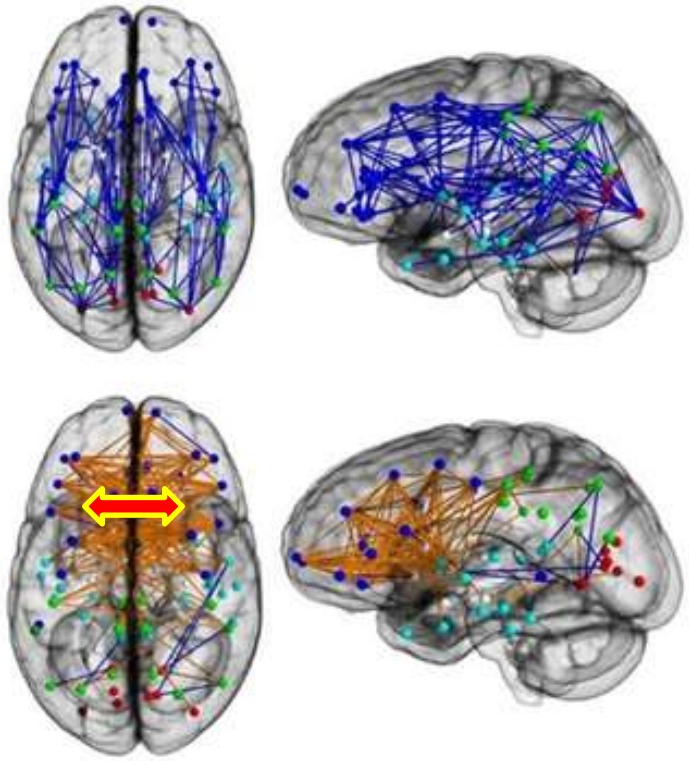
Sex differences are of high scientific and societal interes
because of their **prominence in behavior of humans and nonhuman species**. This work is highly significant because it studies **a very large population of 949 youths** (8–22 y, 428 males and 521 females) **using the diffusion-based structural 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

Innate linguistic knowledge

One of the most important of Chomsky's ideas is that most of this knowledge is innate, with the result **that a baby can have a large body of prior knowledge about the structure of language in general**, and **needs only actually *learn* the idiosyncratic features of the language(s) it is exposed to.**

Chomsky was not the first person to suggest that **all languages had certain fundamental things in common** (he quotes philosophers writing several centuries ago who had the same basic idea), **but he helped to make the innateness theory respectable after a period dominated by more behaviorist** attitudes towards language

Universal Grammar

- Innate linguistic knowledge which consists of a set of principles common to all languages

Neural language networks at birth

Daniela Perani[a,b,c,1], Maria C. Saccuman[a], Paola Scifo[b,c], Alfred Anwander[d], Danilo Spada[a], Cristina Baldoli[b,e], Antonella Poloniato[f], Gabriele Lohmann[g], and Angela D. Friederici[h,1]

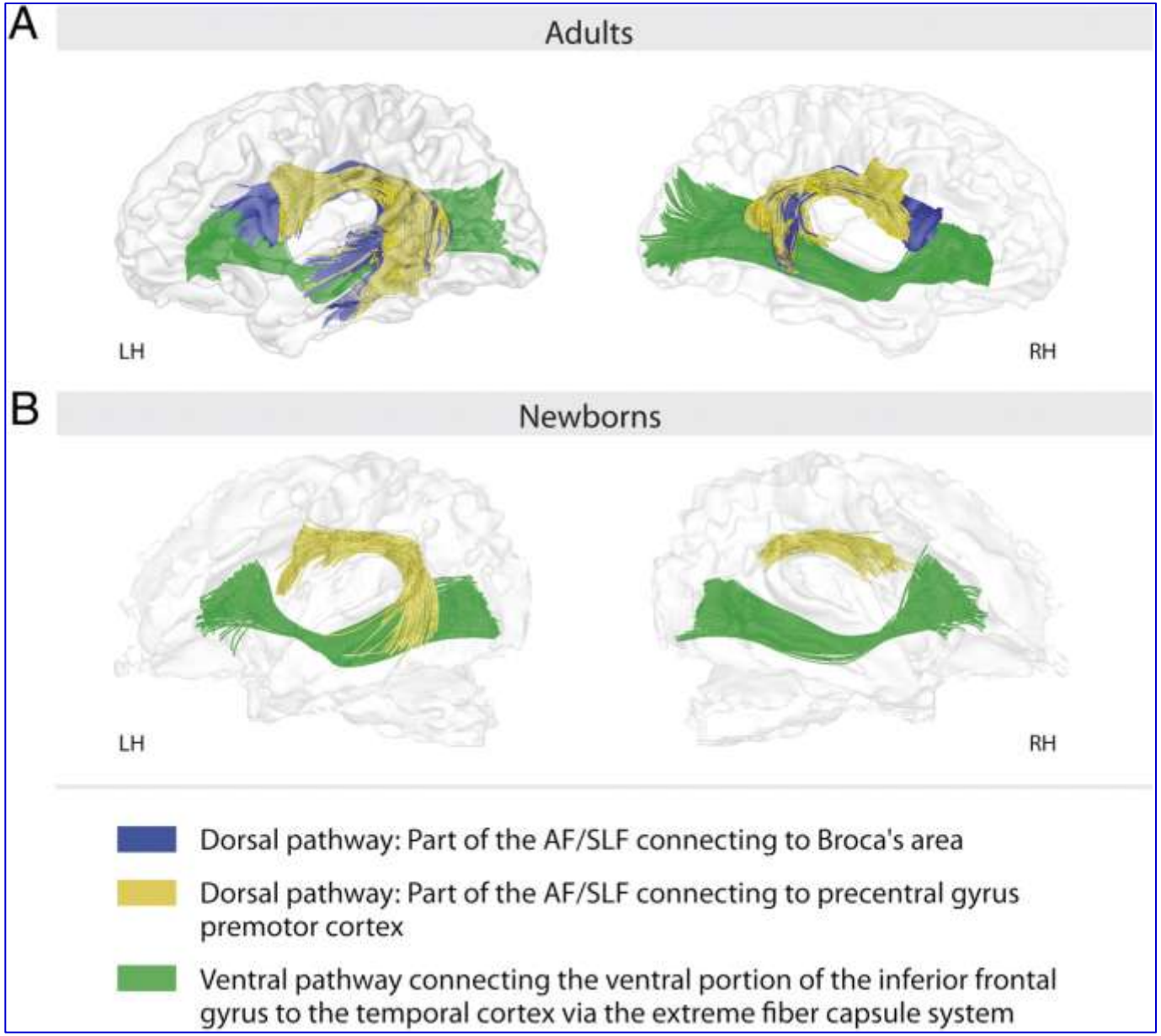
The ability to learn language is a human trait. In adults and children, brain imaging studies have shown that auditory language activates a bilateral frontotemporal network with a left hemispheric domi-
nance. It is an open question whether these activati
the complete neural basis for language present at b
demonstrate that in 2-d-old infants, the language-r
substrate is fully active in both hemispheres with a p
in the right auditory cortex. Functional and structural
within this neural network, however, are immature
connectivities only between the two hemispheres, co
the adult pattern of prevalent intrahemispheric
Thus, although the brain responds to spoken lang
at birth, thereby providing a strong biological bas
language, progressive maturation of intrahemisphe
connectivity is yet to be established with language ex
brain develops.

16056–16061 | PNAS | September 20, 2011 | vol. 108 | no. 38

The ability to learn language is a human trait. In adults and children, **brain imaging studies have shown that auditory language activates a bilateral frontotemporal network with a left hemispheric dominance**

Here we demonstrate that **in 2-d-old infants, the language-related neural substrate is fully active in both hemispheres with a preponderance in the right auditory cortex**. **Functional and structural connectivities within this neural network, however, are immature, with strong connectivities only between the two hemispheres, contrasting with the adult pattern of prevalent intrahemispheric connectivities**. Thus, **although the brain responds to spoken language already at birth, thereby providing a strong biological basis to acquire language, progressive maturation of intrahemispheric functional connectivity is yet to be established with language exposure as the brain develops**

Structural connectivity results.



Daniela Perani et al. PNAS 2011;108:16056-16061

The *ancestral* wiring 2: emotions

THE

EXPRESSION OF THE EMOTIONS

IN

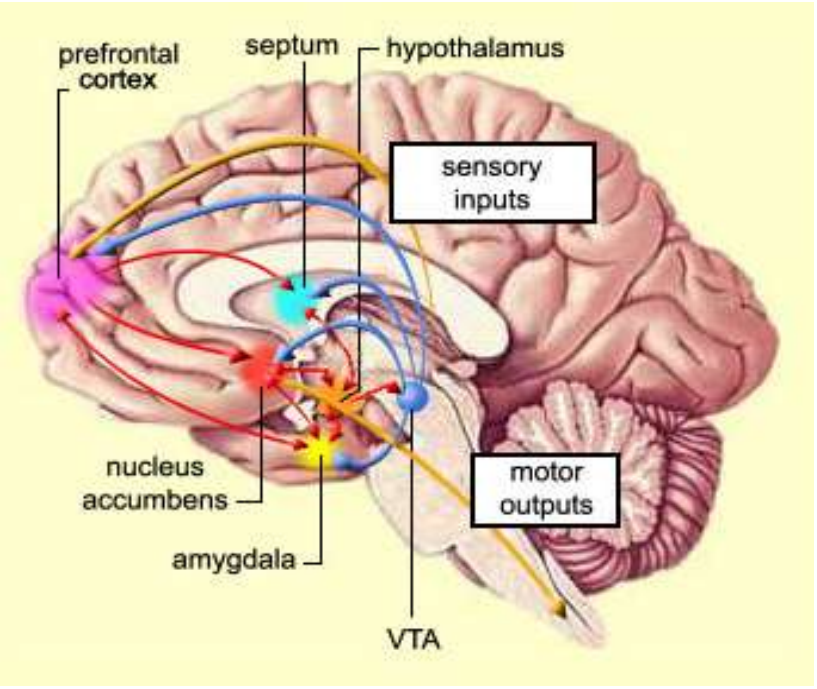
MAN AND ANIMALS.

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

WITH PHOTOGRAPHIC AND OTHER ILLUSTRATIONS.

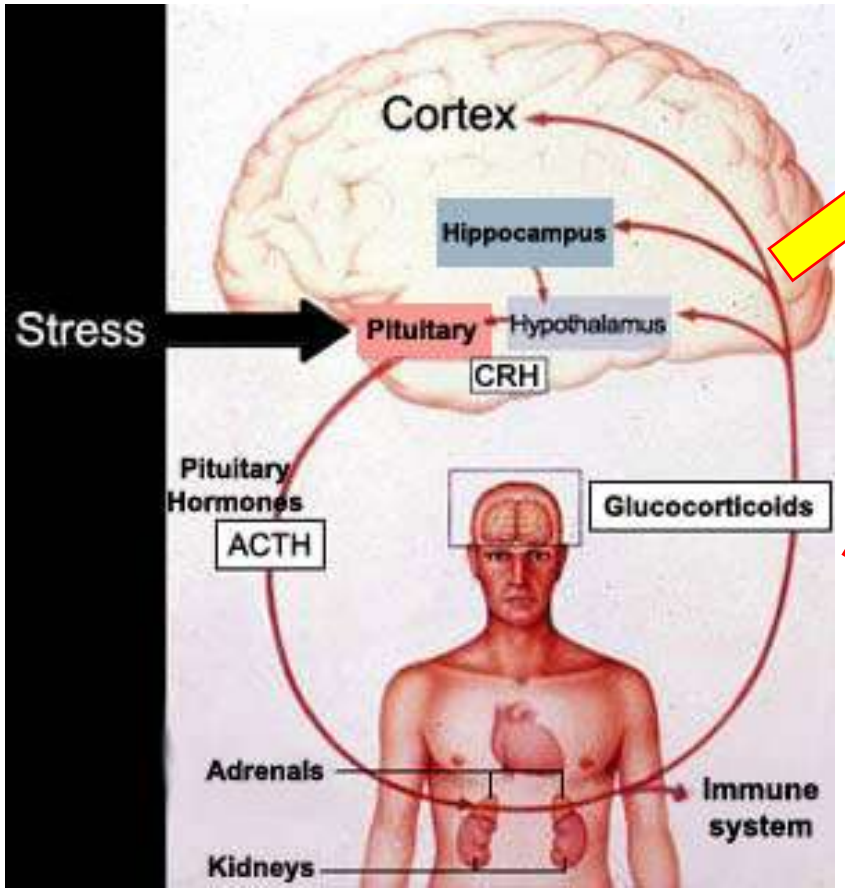
LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1872.

THE PLEASURE CENTRES

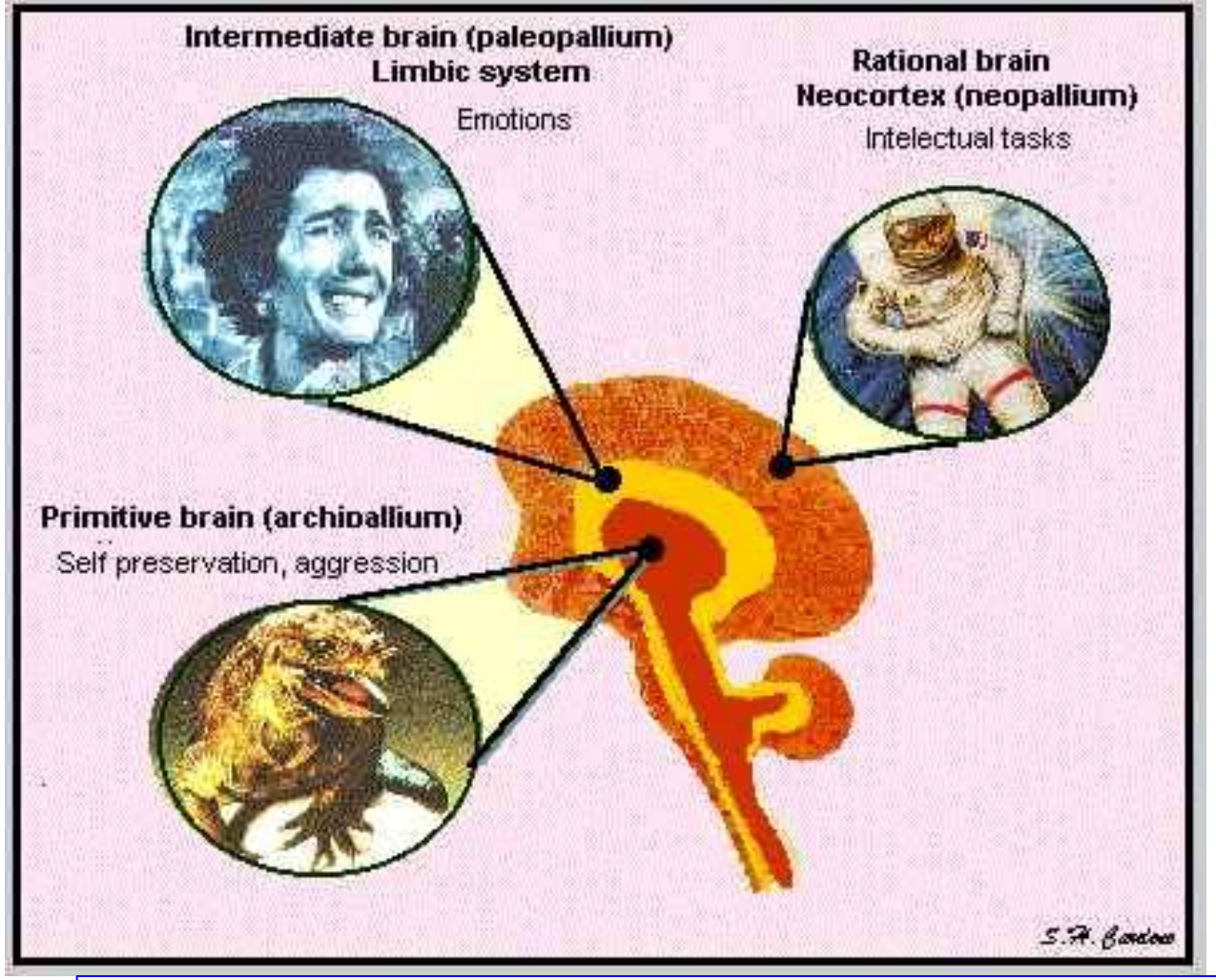


Ventral Tegmental Area

WHEN FEAR TAKES THE CONTROLS



DEPRESSION

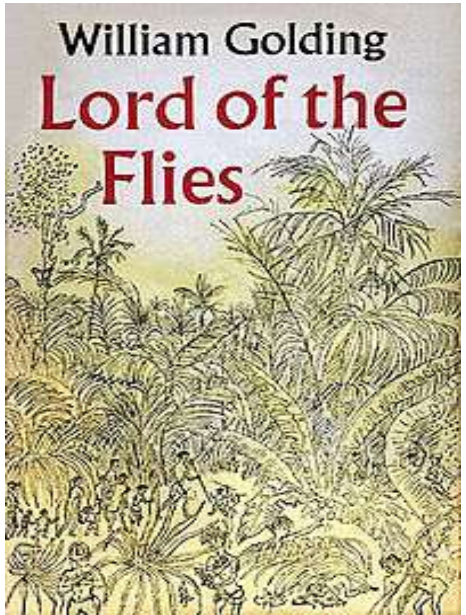


The Ghost in the Machine is a book written by Arthur Koestler and published in 1967. One of the book's central concepts is that
- as the human triune brain has evolved, it has retained and **built upon earlier, more primitive brain structures**.
- The **head portion** of the "ghost in the machine" has,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

Nurture
Culture

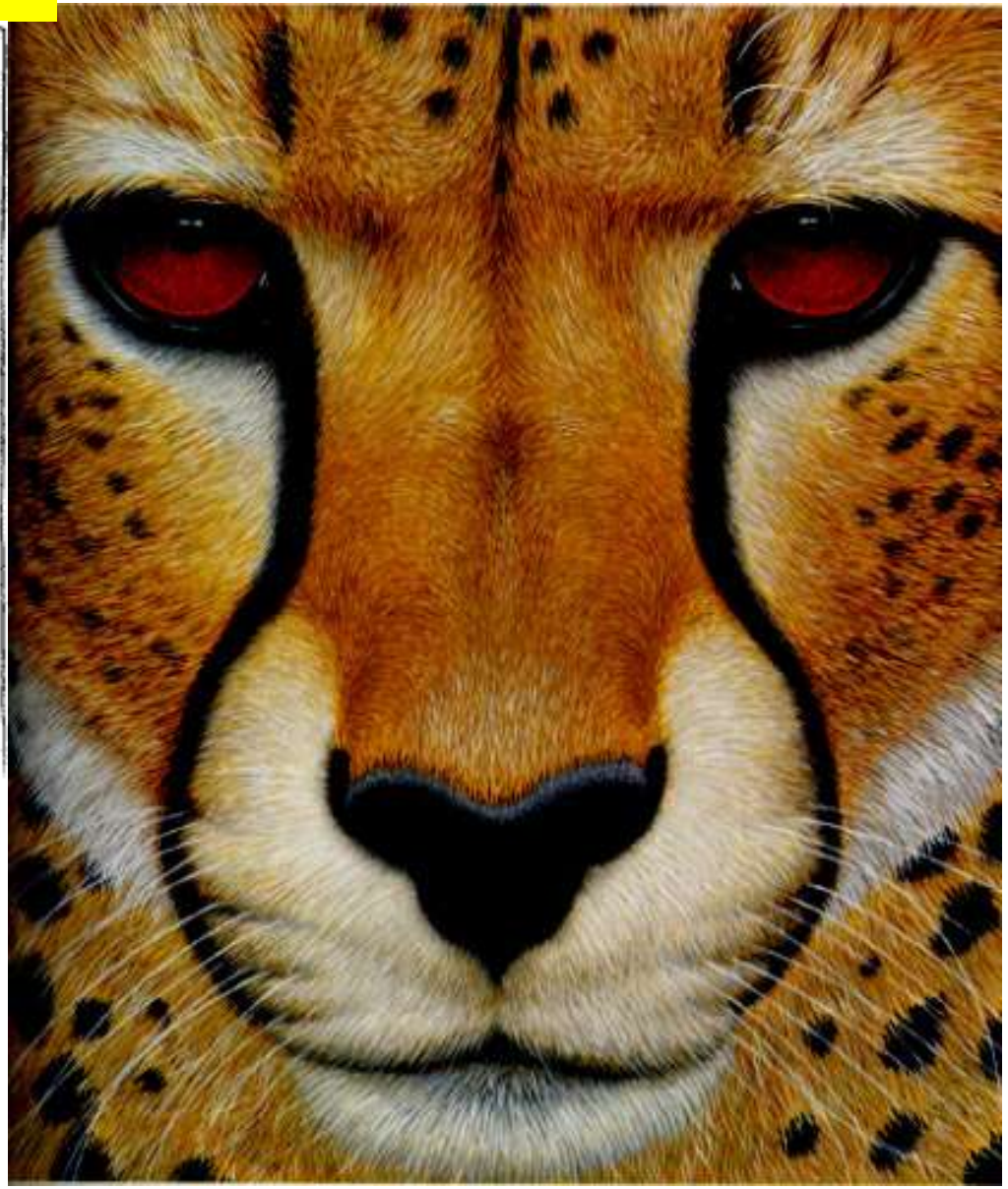
WAR
HOLOCAUST

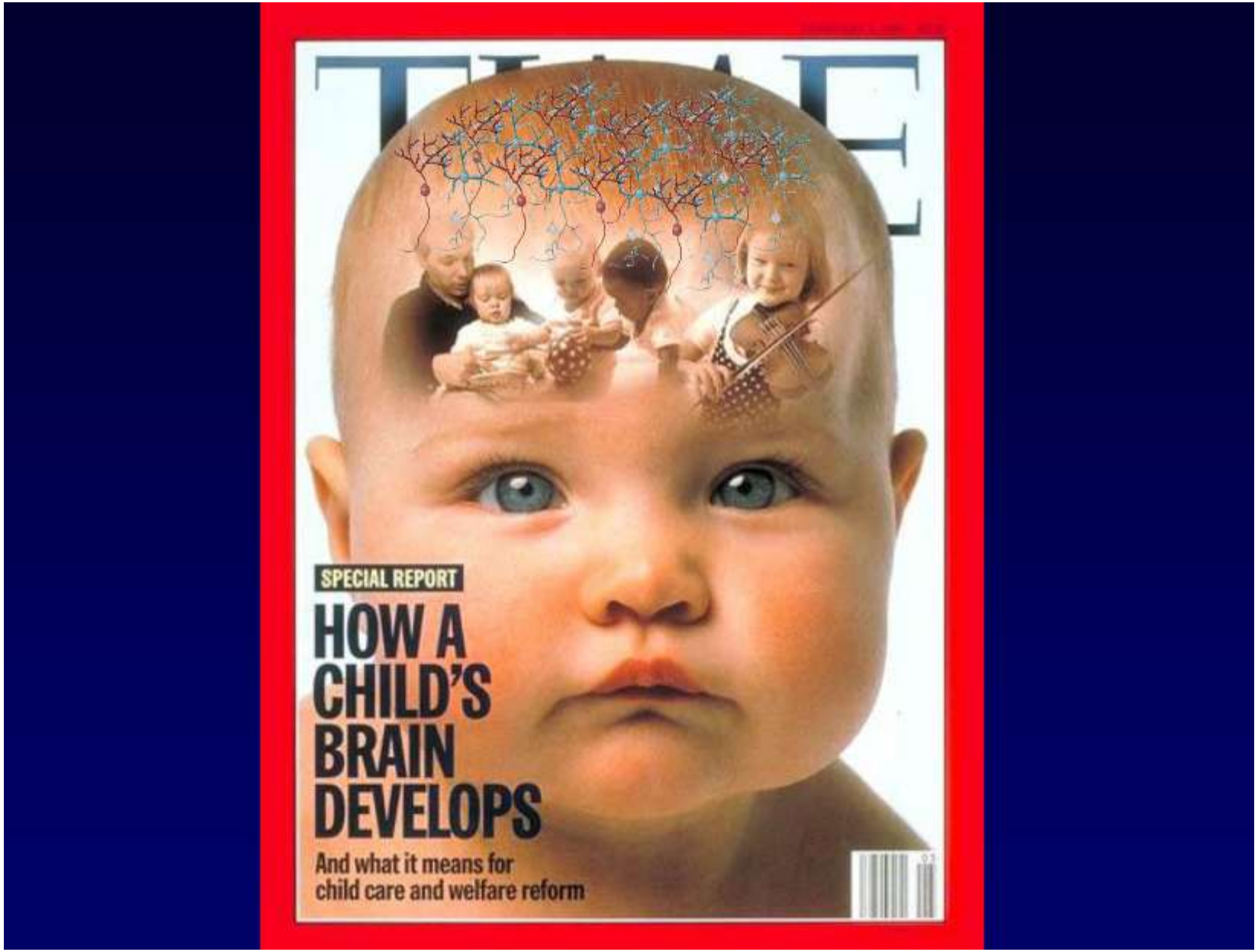
The Lucifer Principle is a book by Howard Bloom.
It sees a **social group, not an individual, as a main subject of human evolution**. It "explores the **intricate relationships among genetics, human behavior, and culture**" and argues that **"evil is a by-product of nature's strategies for creation and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



1961

INTELLIGENT DESIGN ?





Adolescenza, Stili di Vita, Psicopatologia

Giovanni Biggio

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

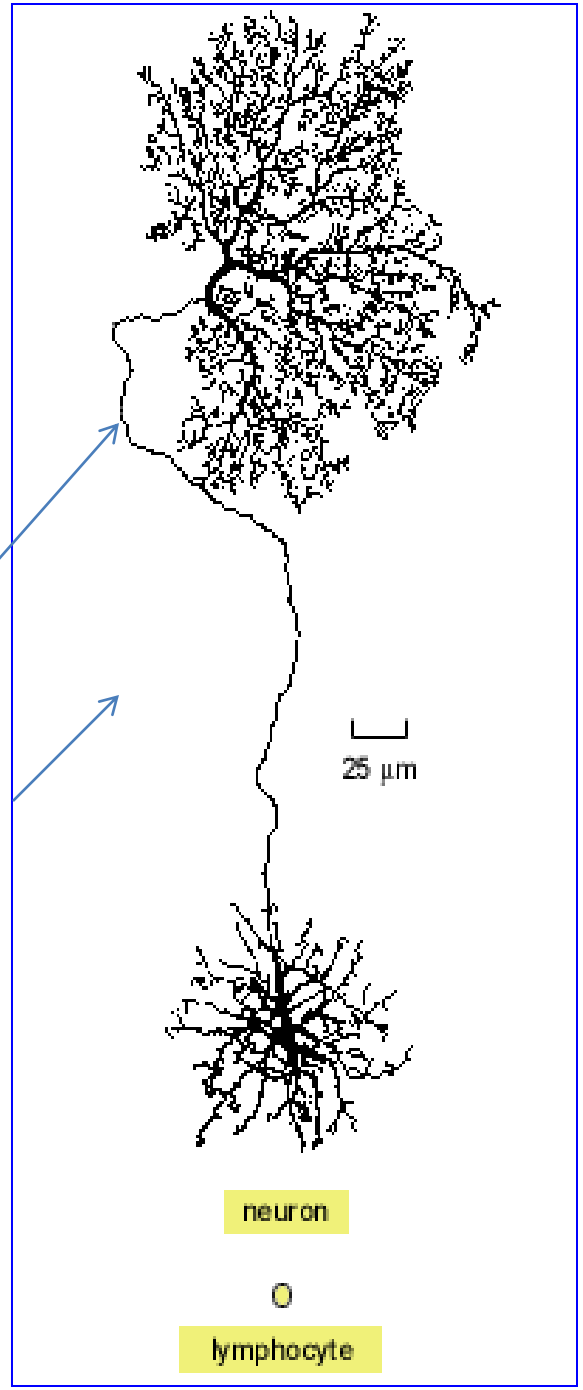
The ***Individual*** wiring

.. 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*** **(…)**

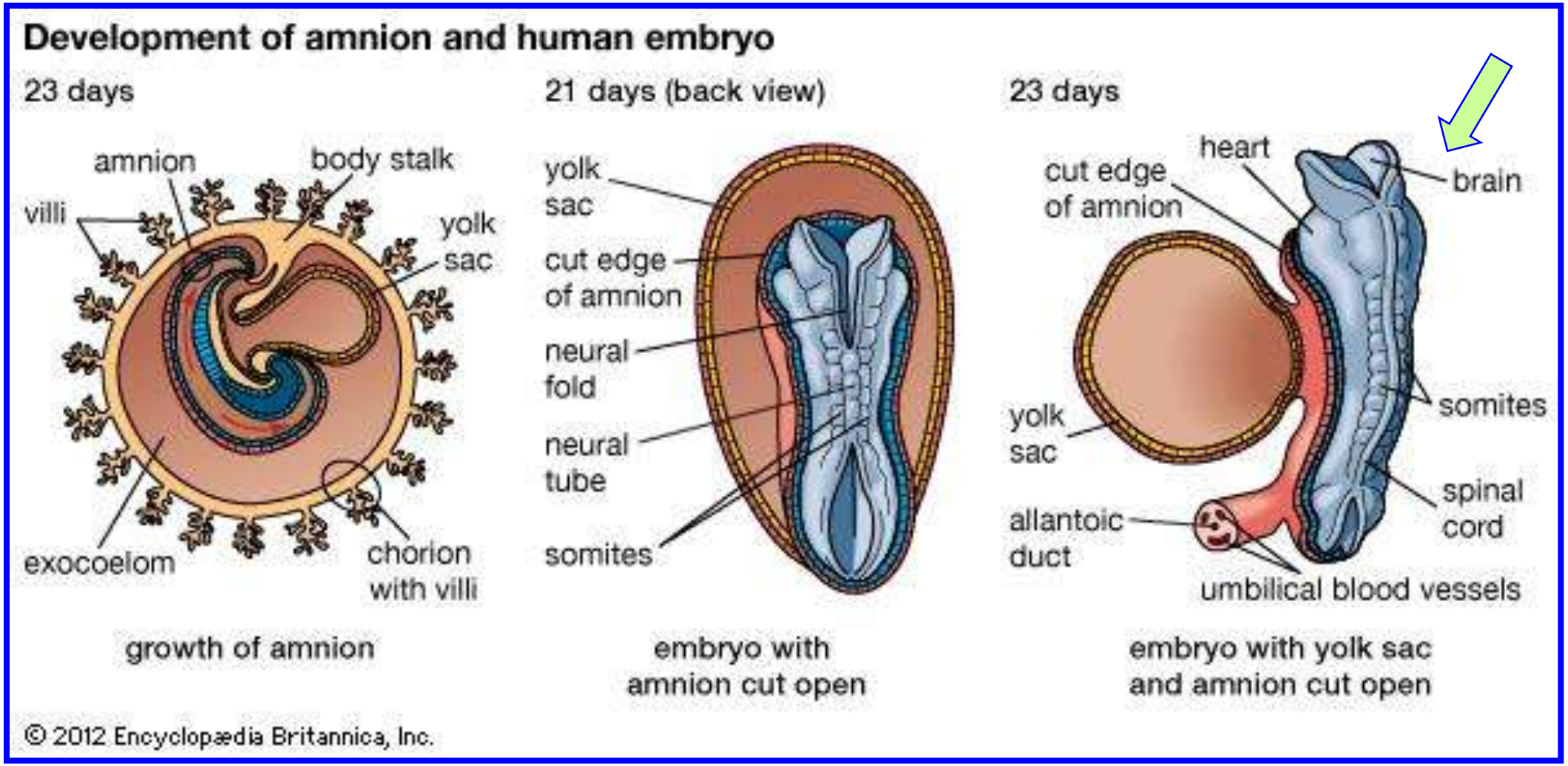
your **connectome* changes throughout your life**.

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

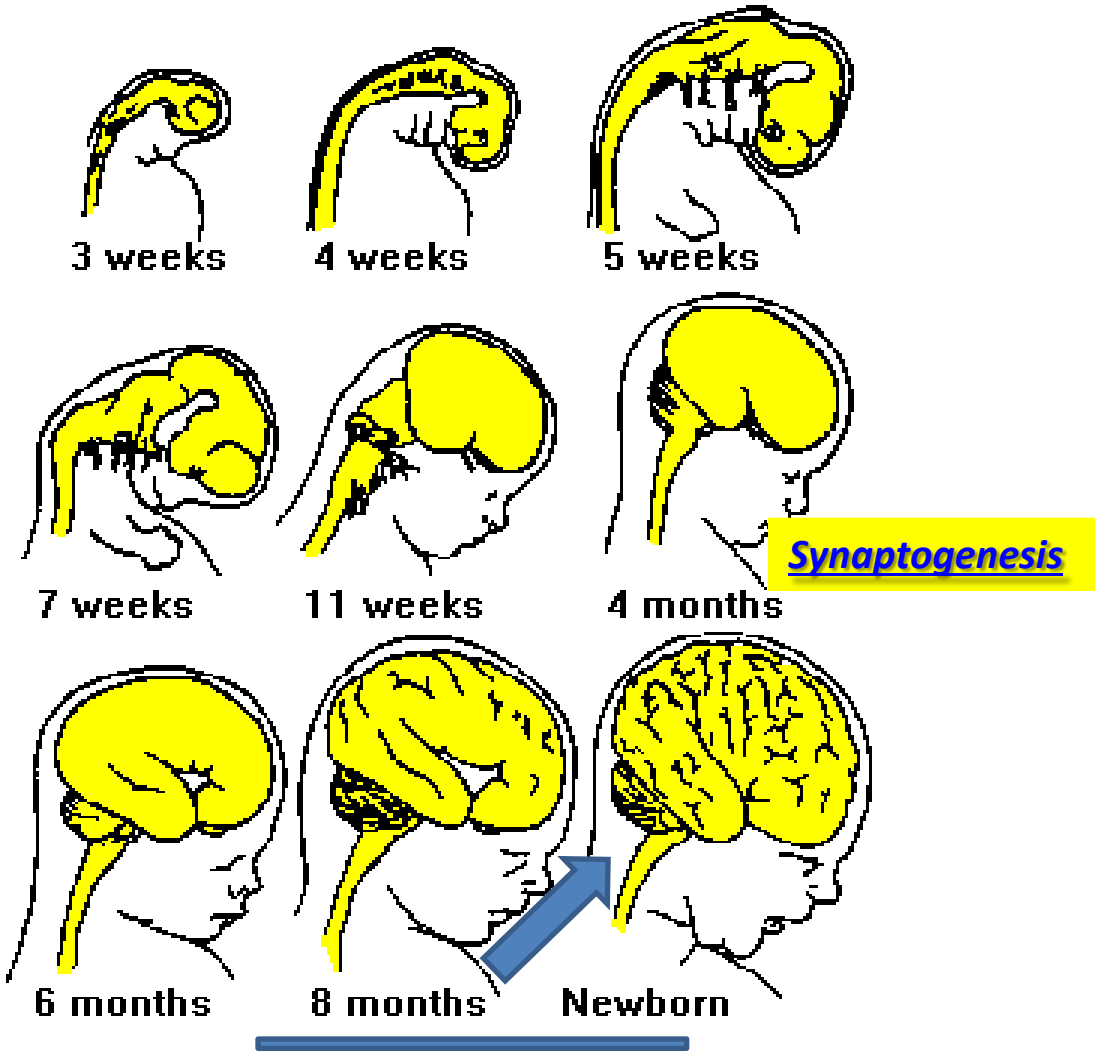
Neurons **reconnect by creating and eliminating synapses**, and **they rewire by growing and retracting branches**.

***You are more than your genes. You are your connectom* (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.

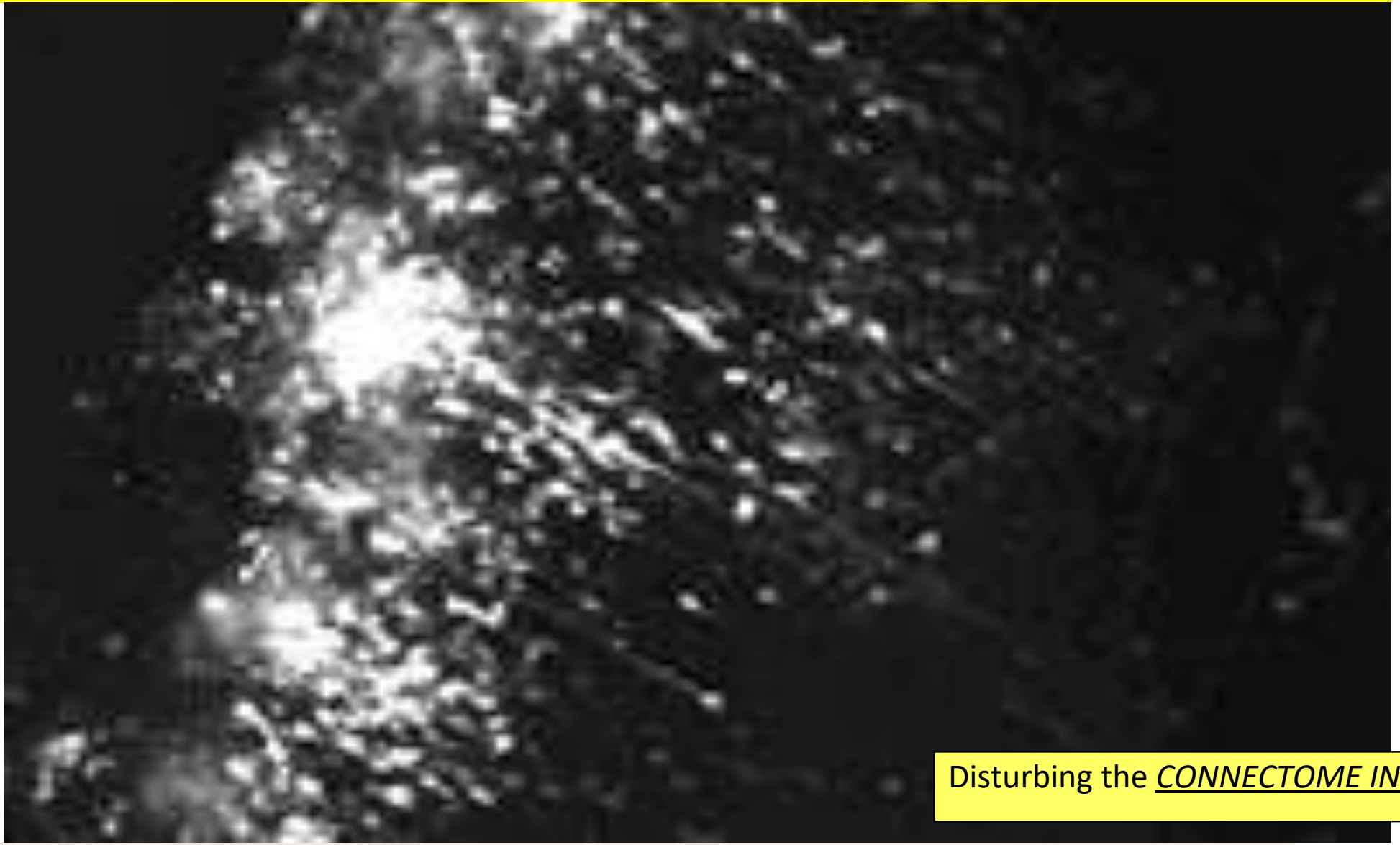
However, the brain continues to grow for many years after birth.

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*

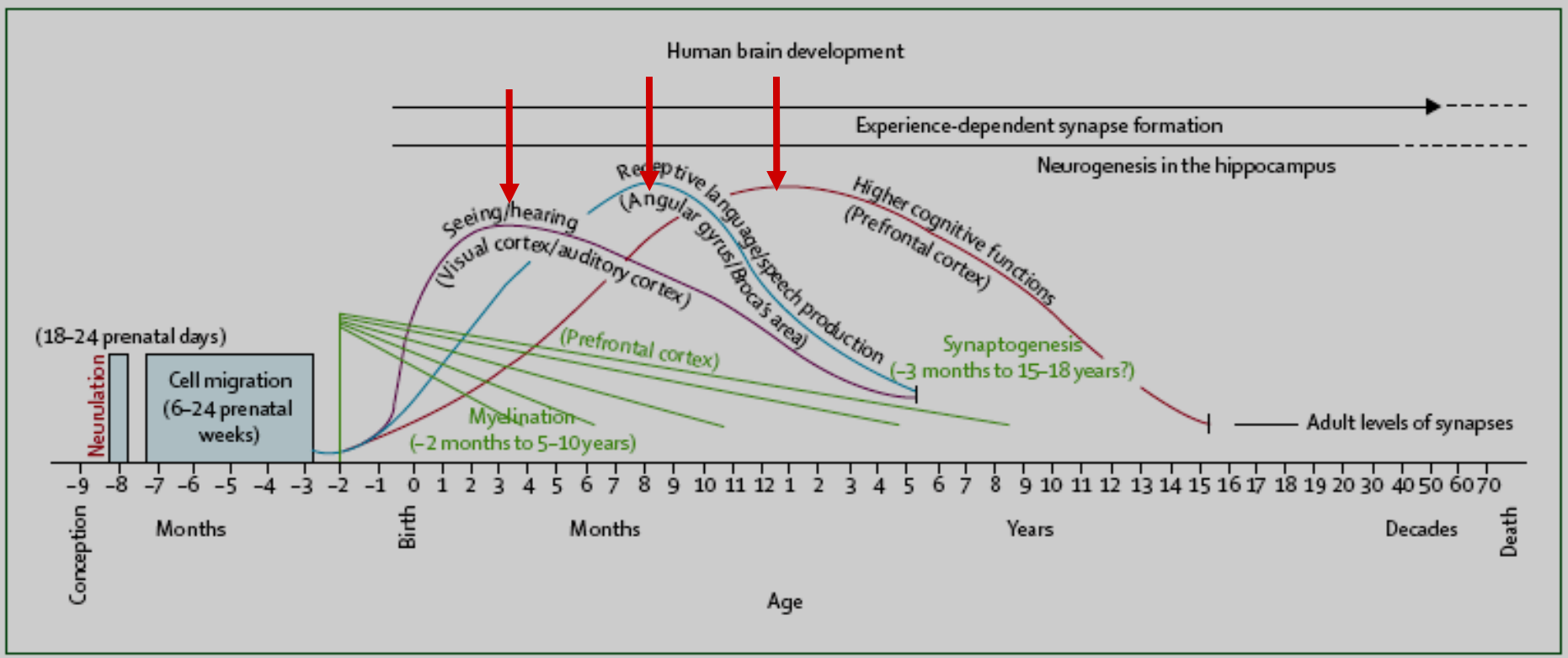


Figure 1: **Human brain development**
Reproduced with permission of authors and American Psychological Association[37] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; **56**: 5–15).

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.

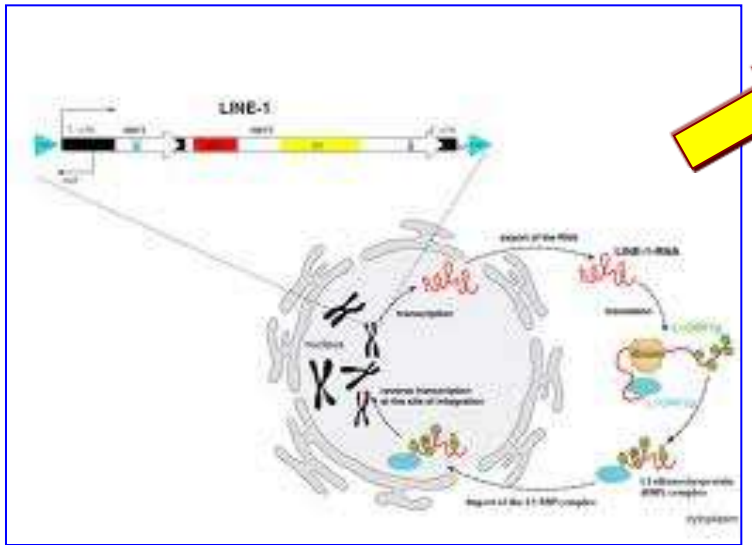
Researchers are now beginning to investigate whether jumping genes help us adapt to rapidly changing environmental conditions.

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

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.

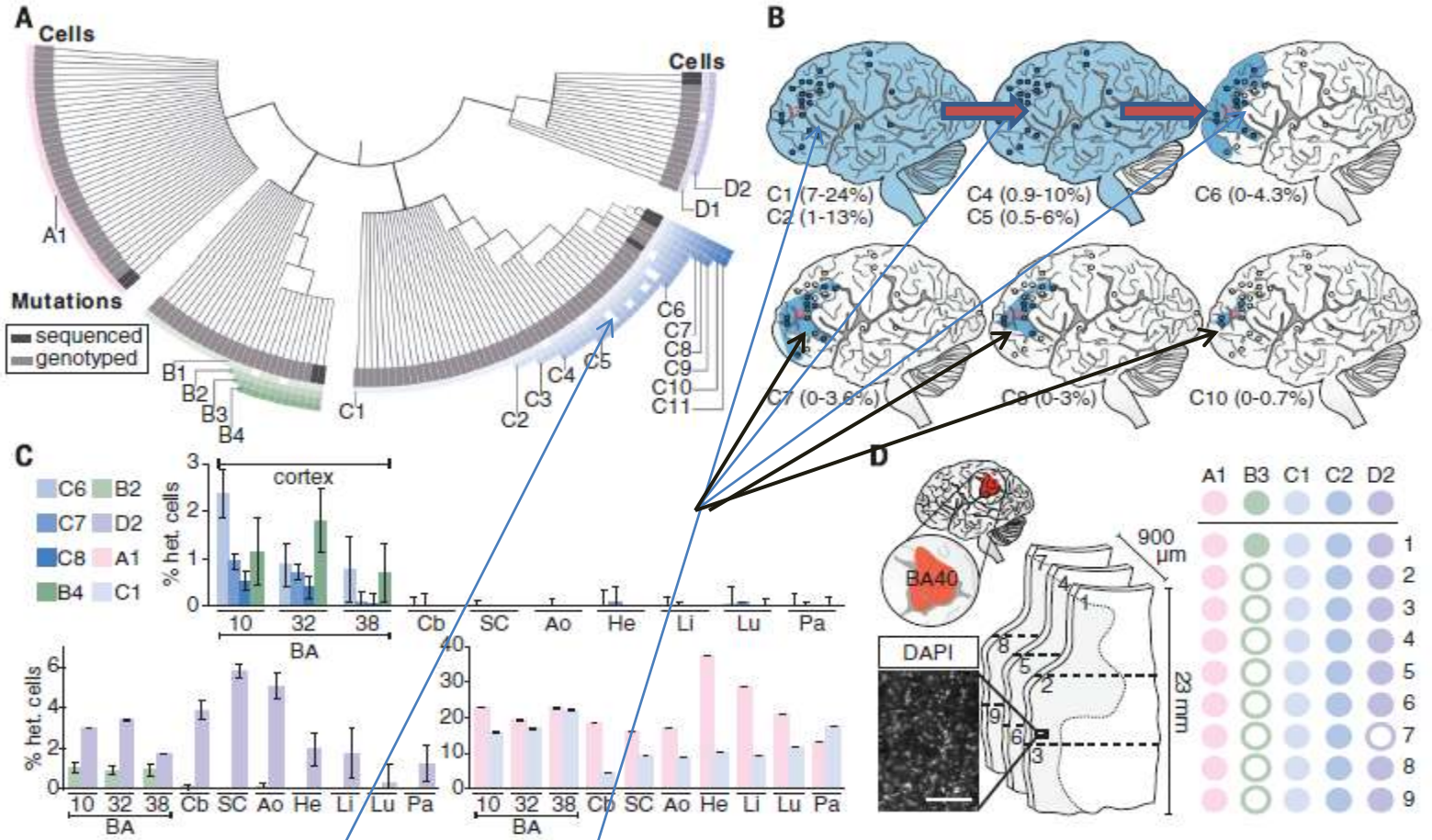


Fig. 3. Somatic mutations are shared between multiple neurons and demonstrate lineage relationships. (**A**) Lineage map of 136 human cortical neurons from brain B derived from 18 clonal somatic mutations, including SNVs, long interspersed nuclear element (LINE) insertions, and a TG-dinucleotide expansion. 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.

Leading Edge
Previews

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

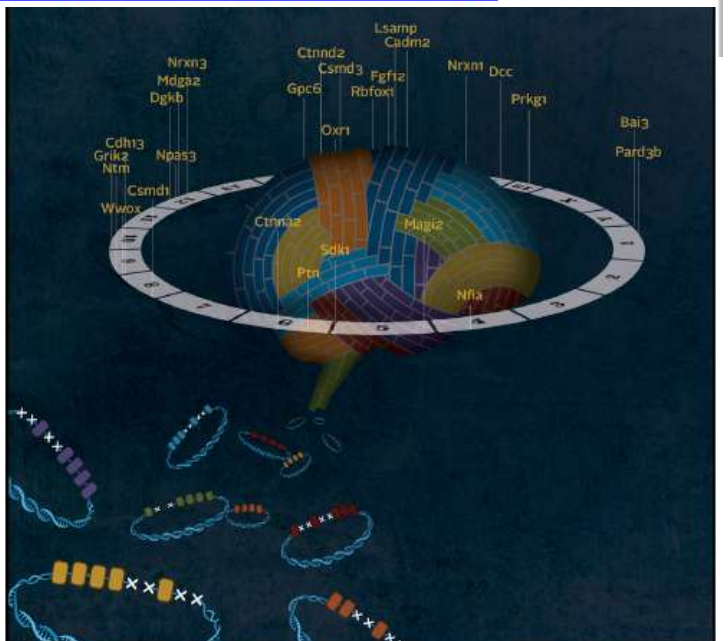
Cell

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



Developmental Plasticity: Synaptic Pruning

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

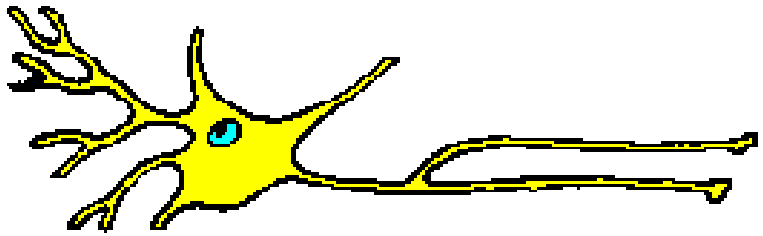
By the time an infant is **two or three years old**, the number of synapses is approximately **15,000 synapses per neuron** (Gopnick, et al., 1999). This amount is **about twice that of the average adult brain**.

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

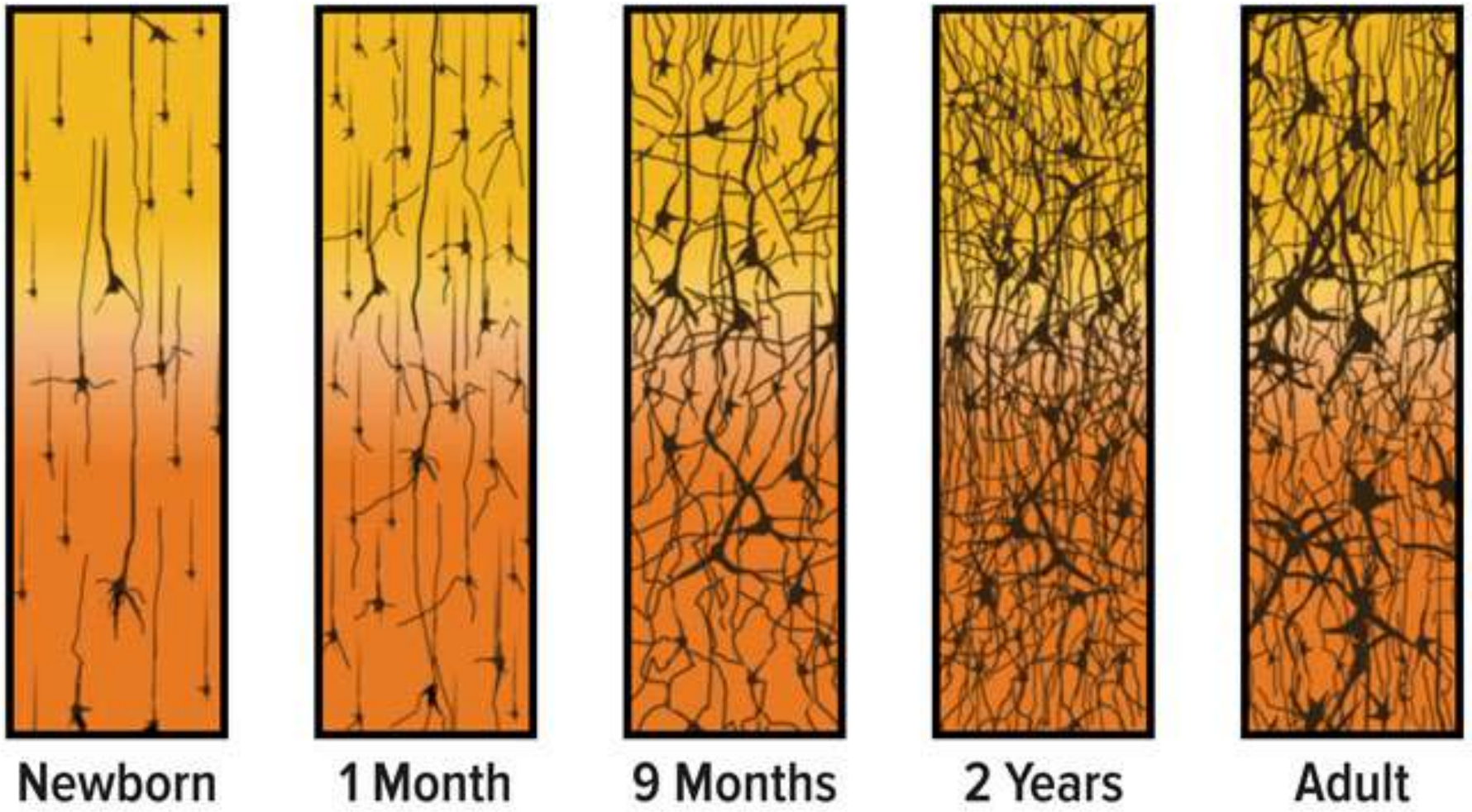
Ineffective or weak connections are "pruned" in much the same way a gardener would prune a tree or bush, giving the plant the desired shape.

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

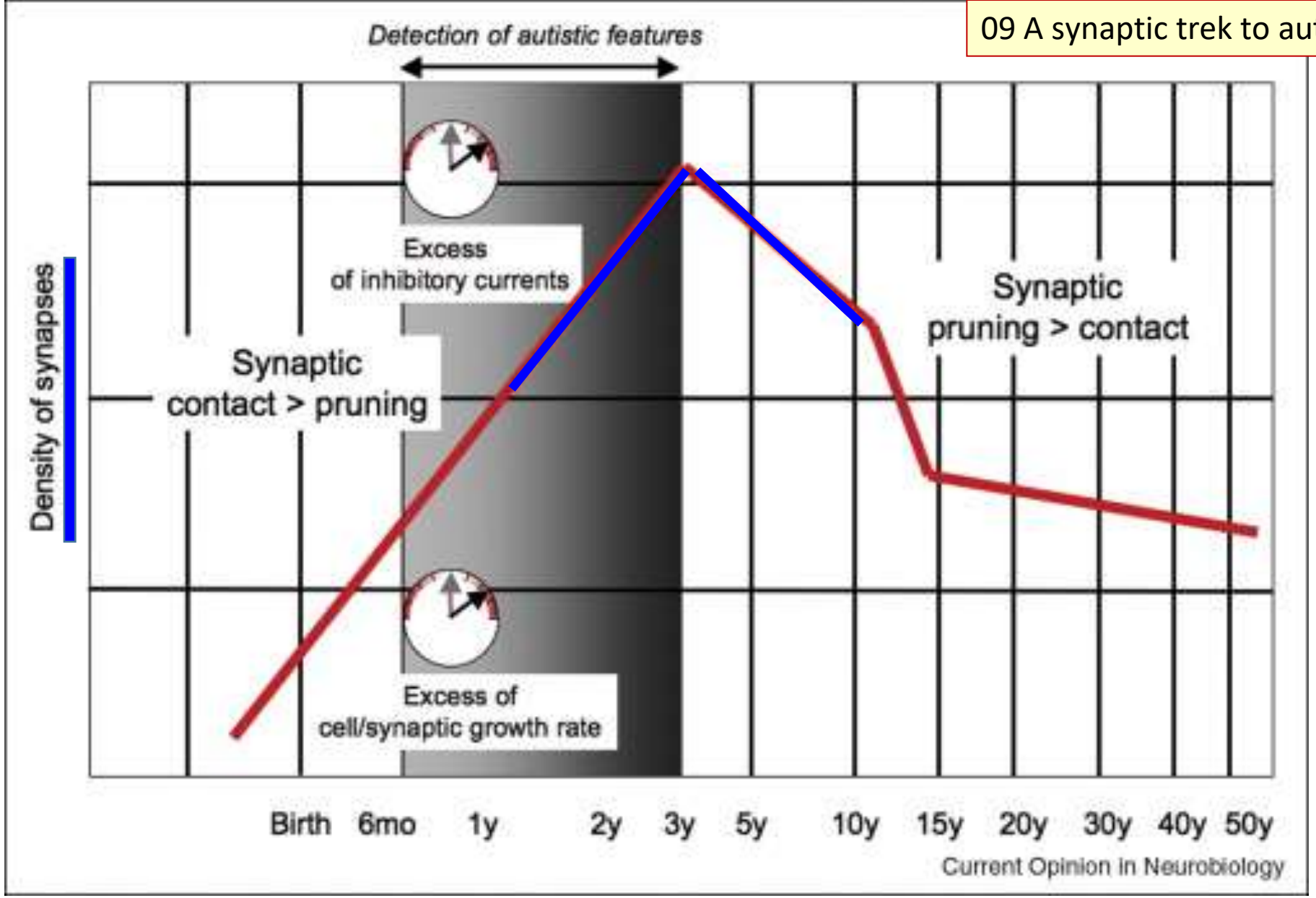
https://faculty.washington.edu/chudler/plast.html



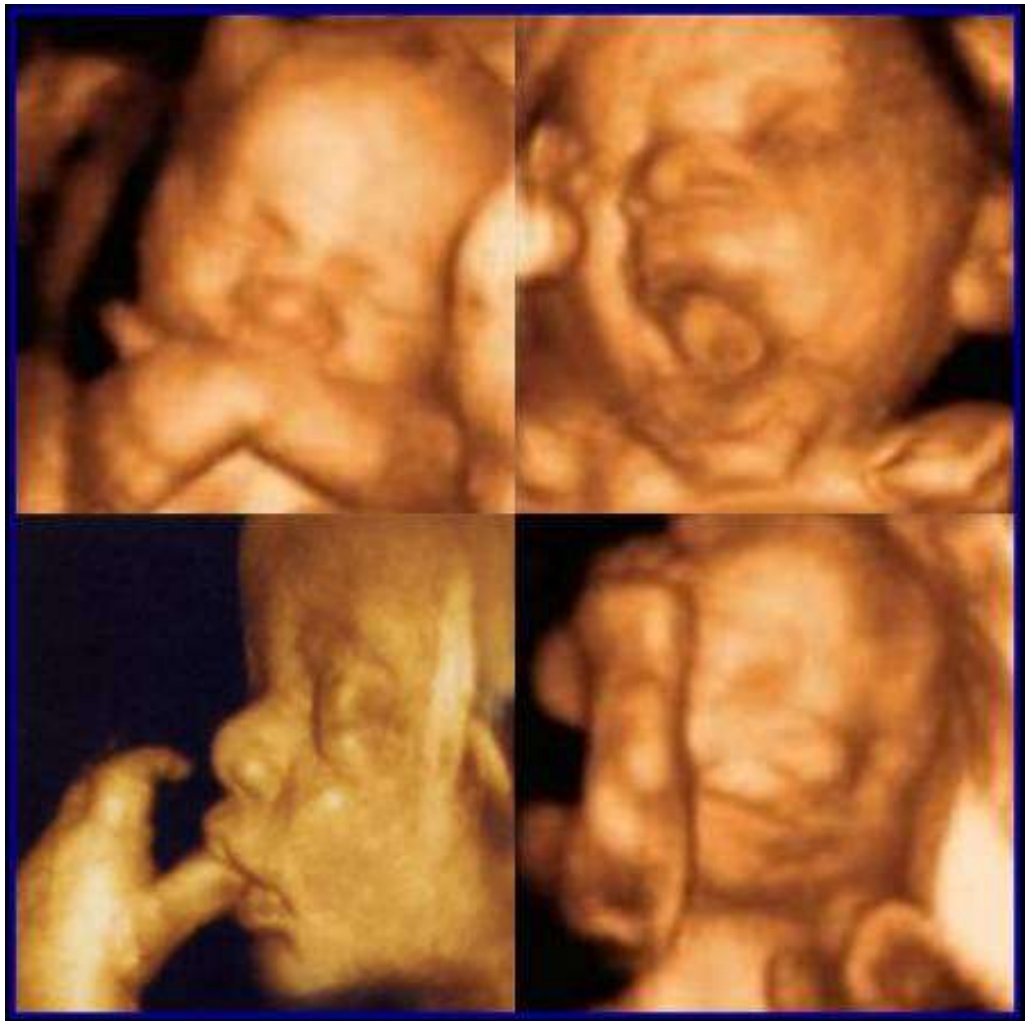
Connessioni interneurali dall'infante all'adulto umano



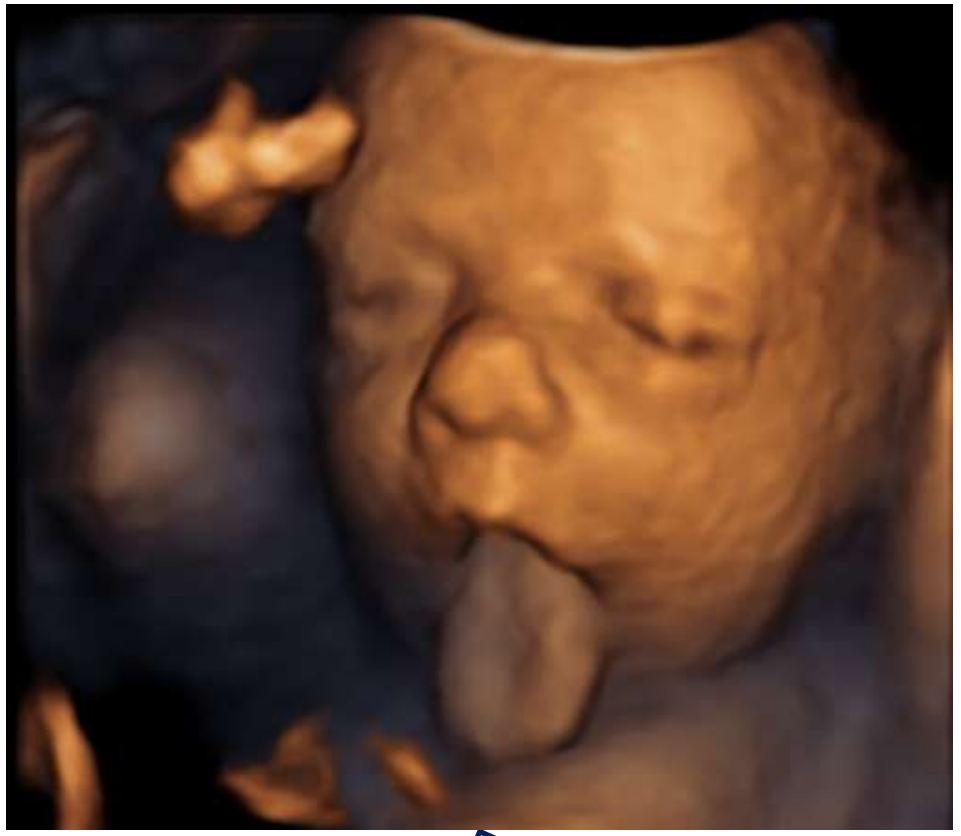
09 A synaptic trek to autism



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.

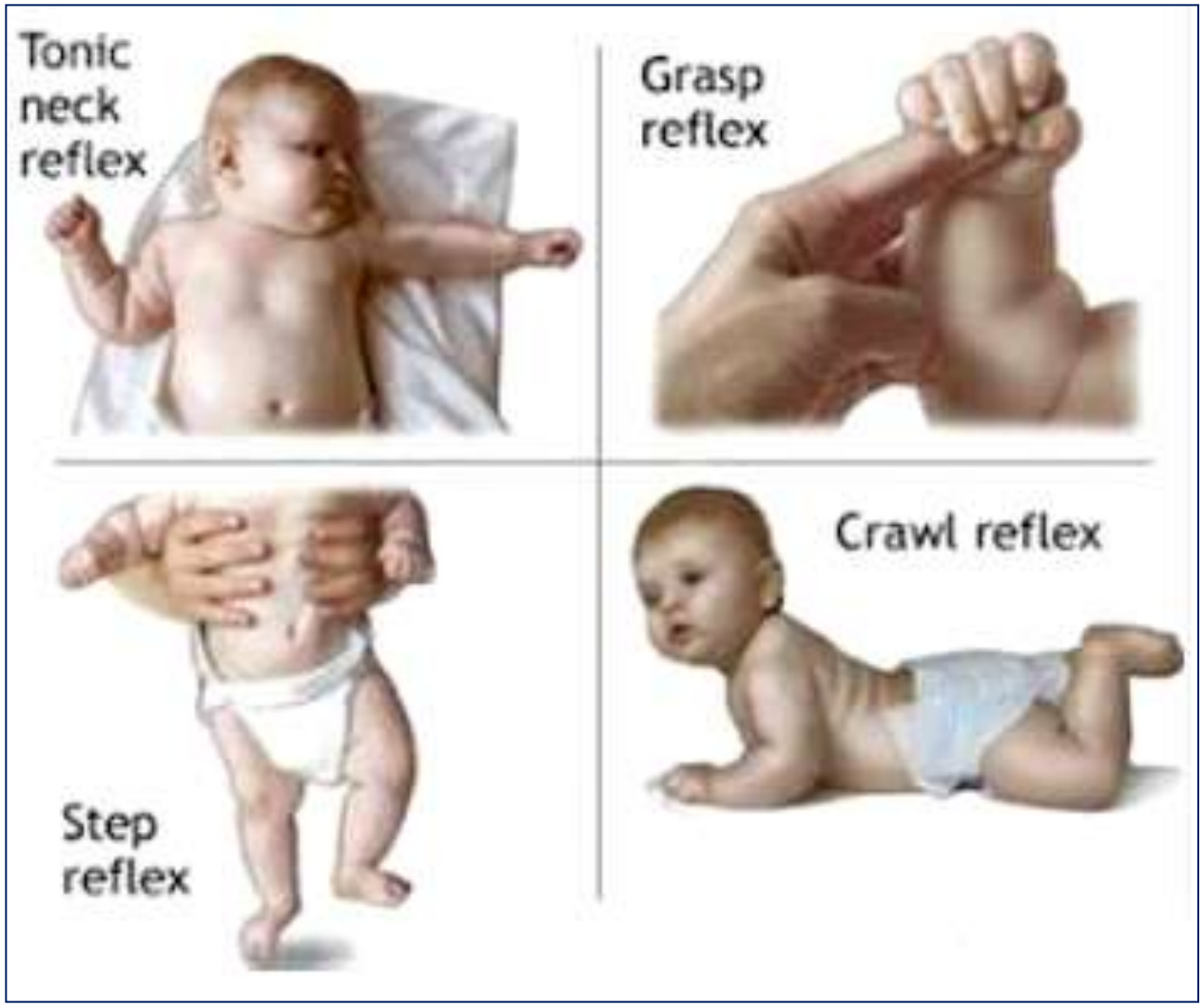


1040-ecografie-prentale-3d-reggio-emilia



Submitted to appropriate **stimuli**, the **fetus yawns, he sneezes, he has the hiccups, he blinks**, he presents **several ancestral brain-reflex-responses (that will disappear** way, way that the brain matures)

Archaic neonatal reflexes

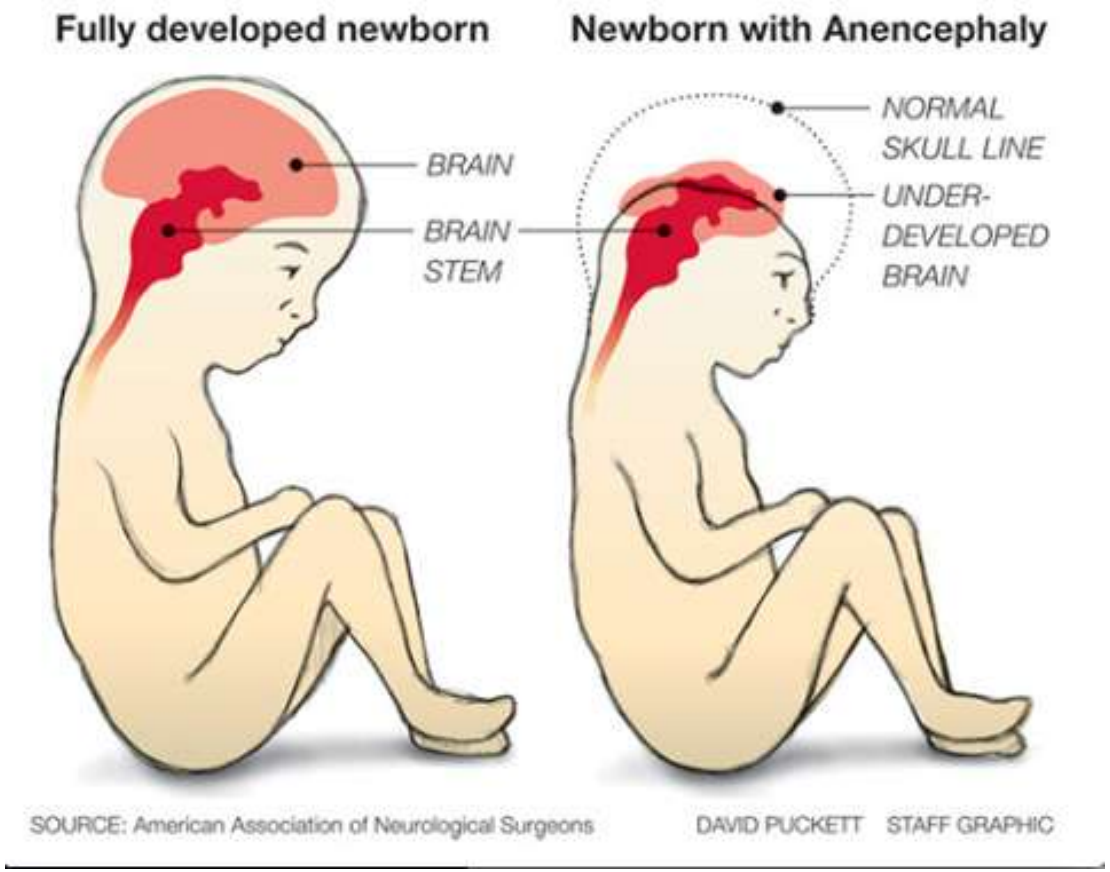


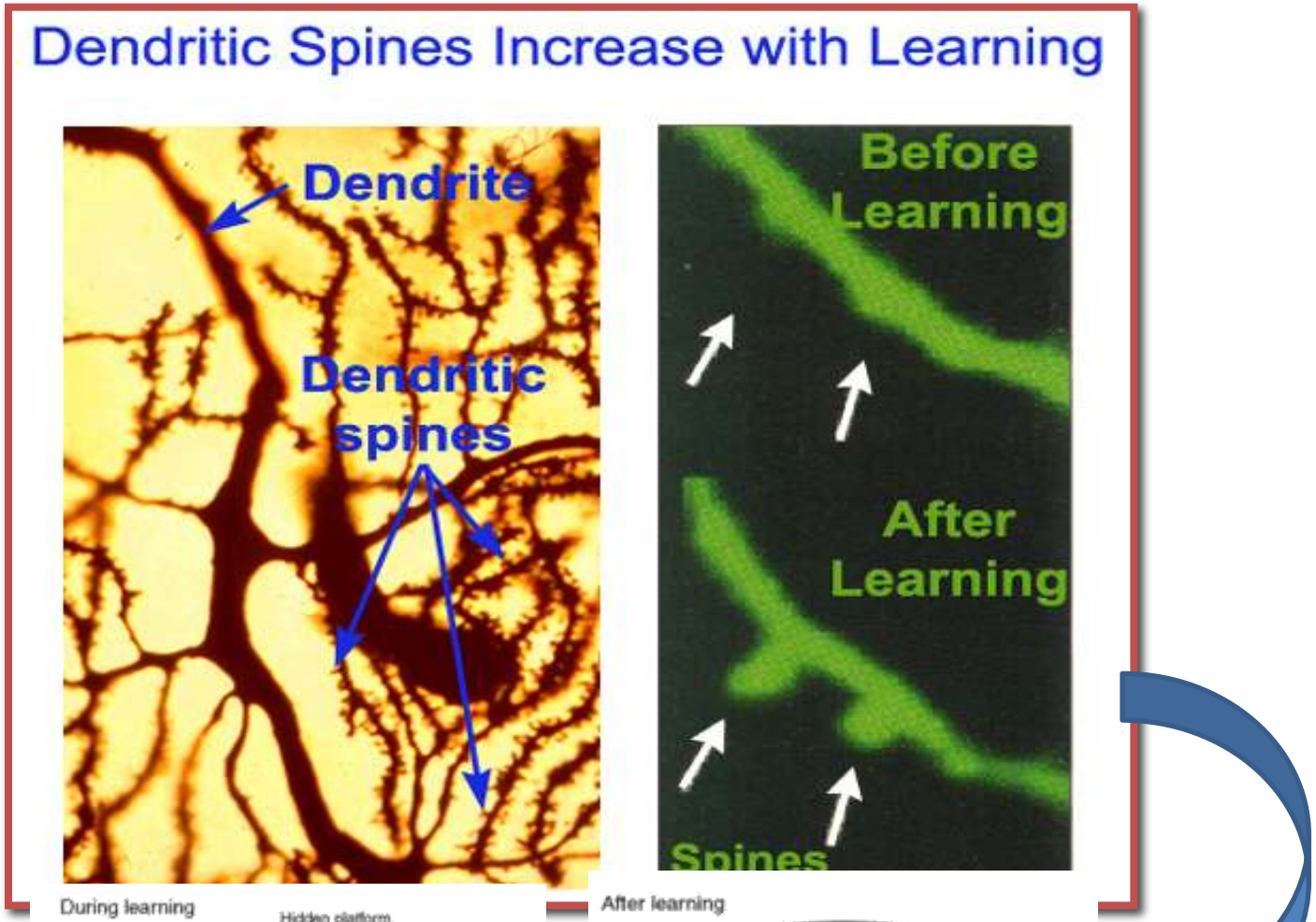
Les réflexes archaïques néonatales

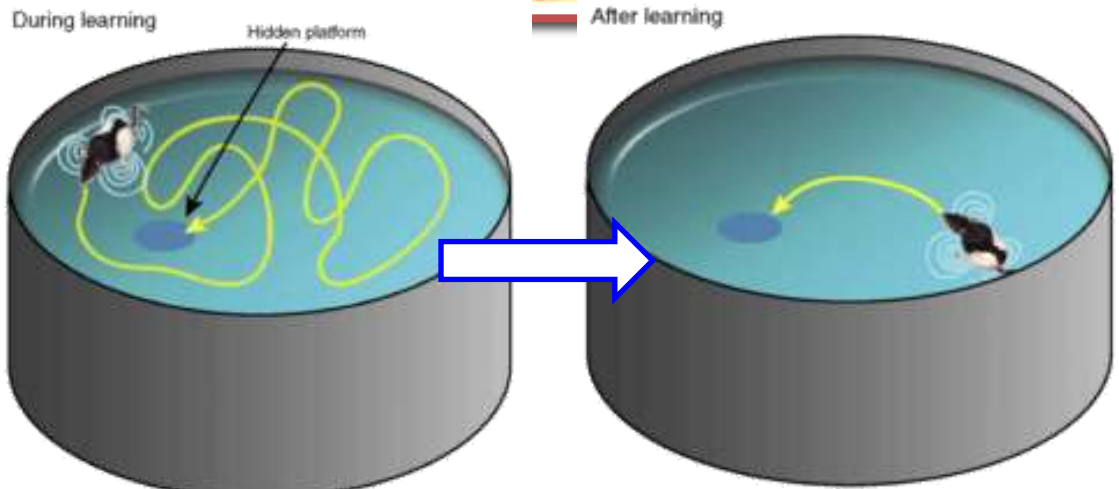
Until the **age of three months** the infant has **virtually no need, in order to survive, of the cerebral hemispheres !**

All that he needs is a **spinal cord** intact below the phrenic nerve ... because **breathing is more important (needed) than thinking** or walking

Until 30 years ago **some newborn without cerebral hemispheres was discharged from the hospital** and taken home for months, without anyone noticing the drama!

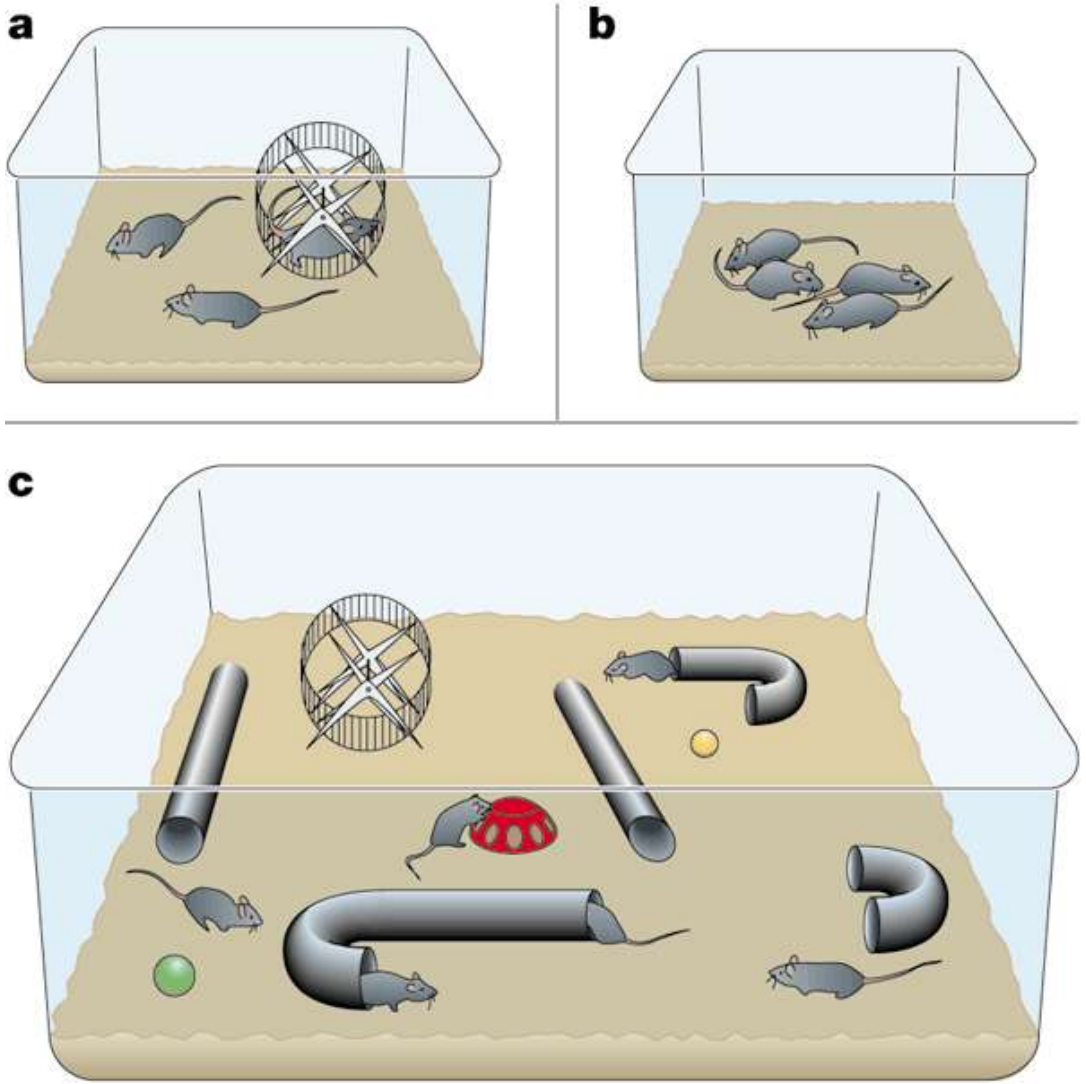






Spine plasticity is implicated in **motivation, learning** and **memory**. In particular **long-term memory** is mediated by the **growth of new dendritic spines** (or the enlargement of pre-existing spines) to **reinforce a particular neural pathway**.

- 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

How Music shapes our Brain

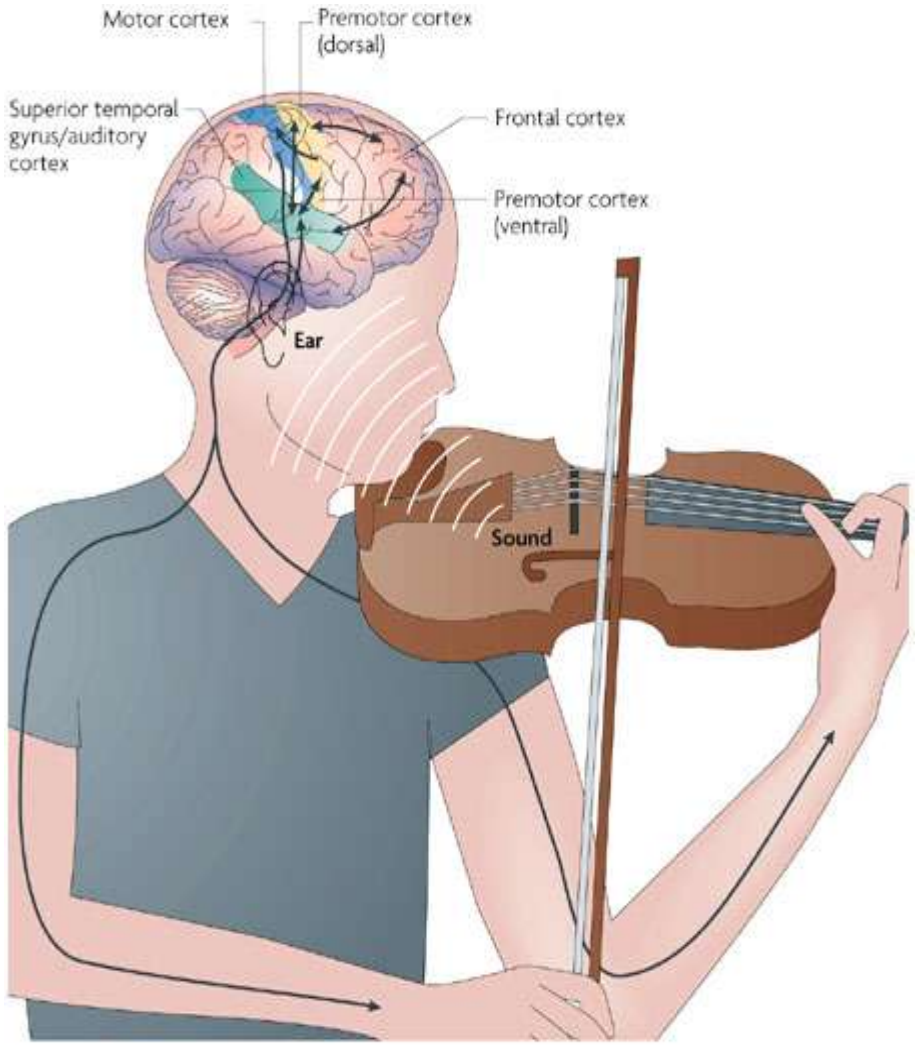
Un caso estremamente interessante è quello del **cervello del musicista** che presenta una **struttura alquanto particolare, almeno nei casi in cui lo studio della musica ha avuto inizio nelle primissime fasi della vita..**

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

Music training can significantly improve our motor and reasoning skills

We generally assume that learning a musical instrument can be beneficial for kids, but it's actually useful in more ways than we might expect.

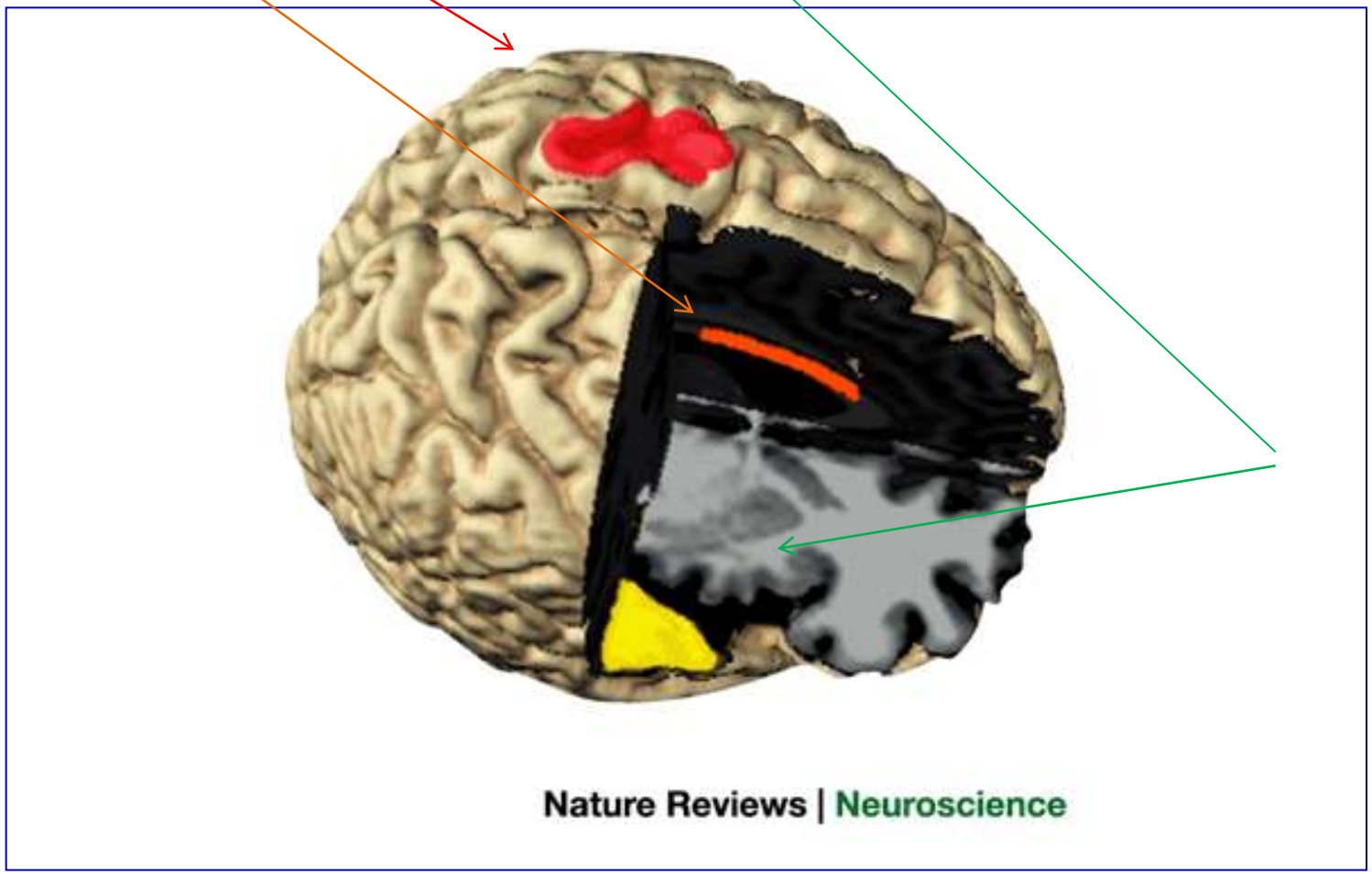
One study showed that **children who had three years or more musical instrument training performed better than those who didn't learn an instrument in auditory discrimination abilities and fine motor skills**.



Nature Reviews | Neuroscience

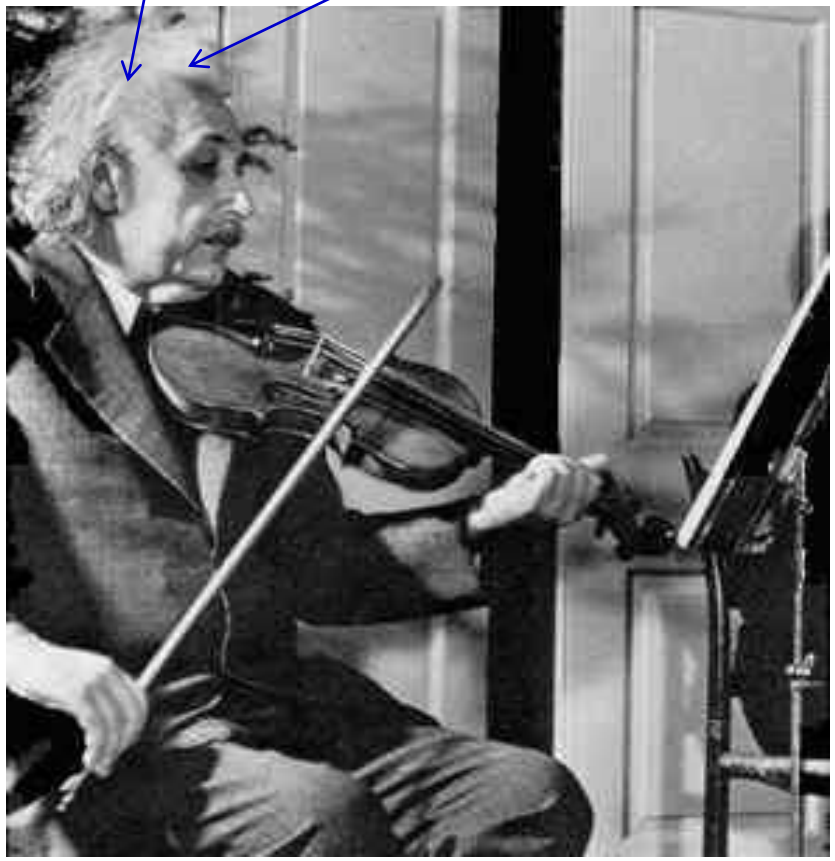
08 PLOS ONE ***Practicing a Musical Instrument in Childhood is Associated with Enhanced Verbal Ability and Nonverbal Reasoning***

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** ..



Navigation-related structural change in the hippocampi of taxi drivers

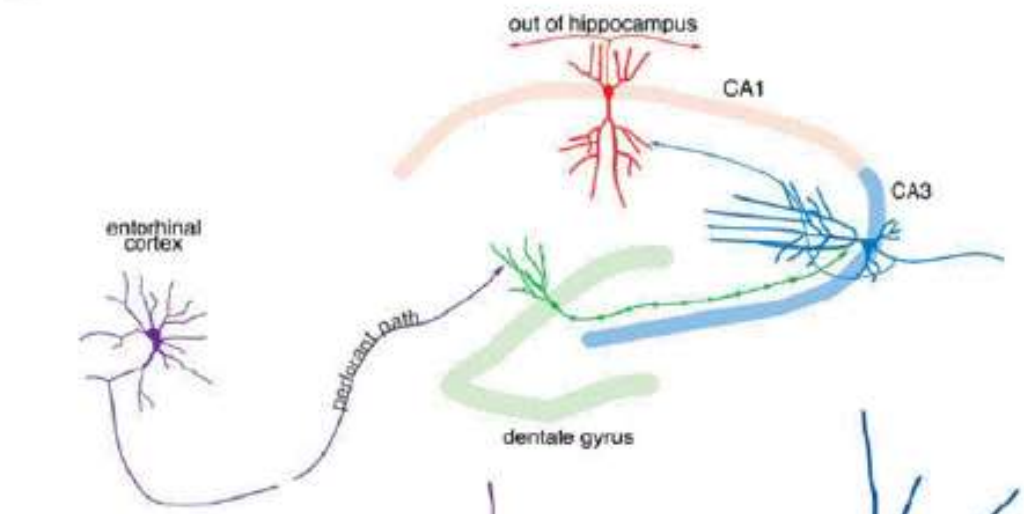
Maguire EA,. Gadian DG., Johnsrude IS., Good CD., Ashburner J-, Frackowiak RSJ., Frith CD.

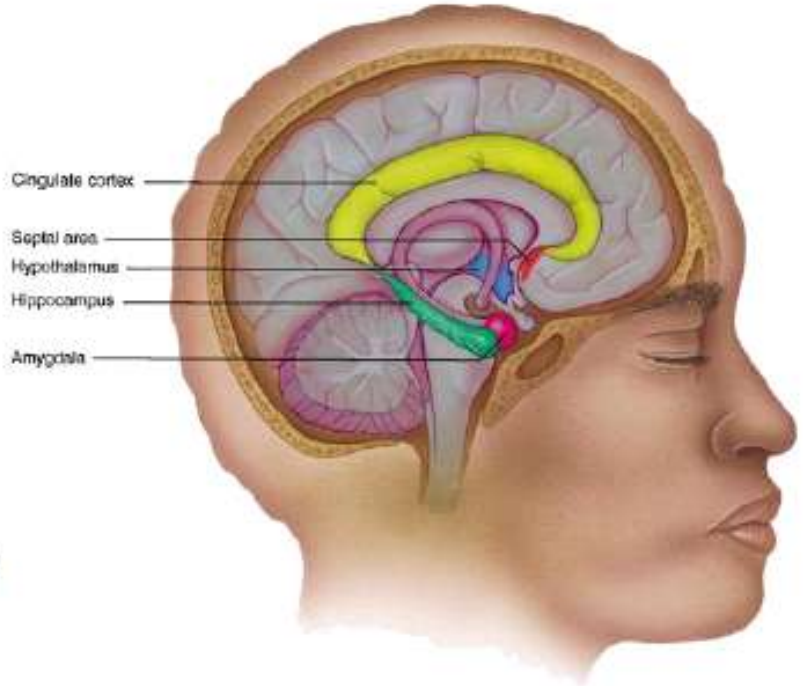
PNAS, 2000

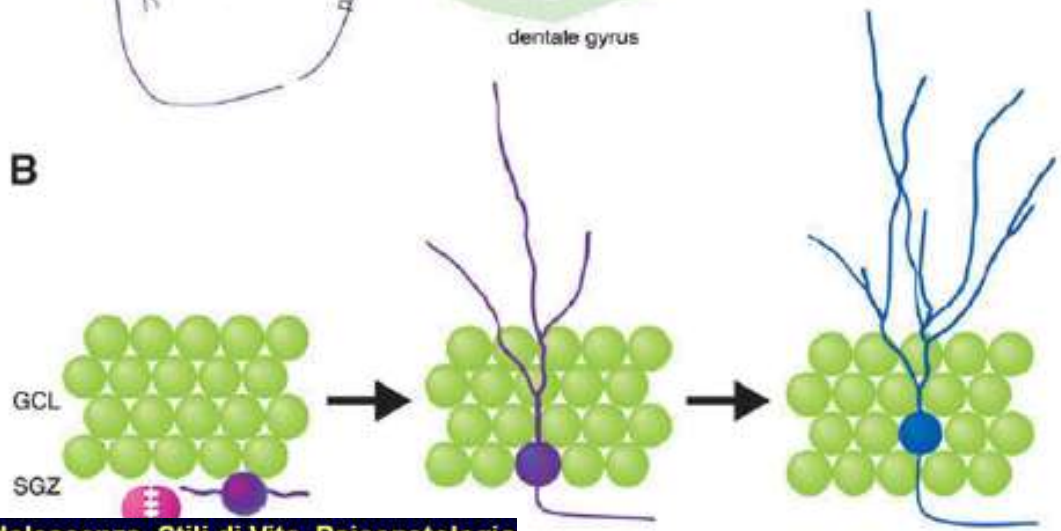
The **posterior hippocampi of taxi drivers were significantly larger relative to those of control subjects**.. volume correlated with the **amount of time spent** as a taxi driver (→ local **plastic change** in the structure of adult human brain in response to the environment)

The Incredible Elastic Brain: How Neural StemCells Expand Our Minds

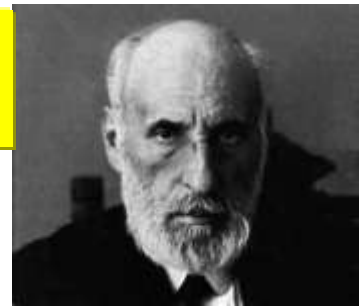
Neuron, 2008







Ramón y Cajal
Death of a DOGMA

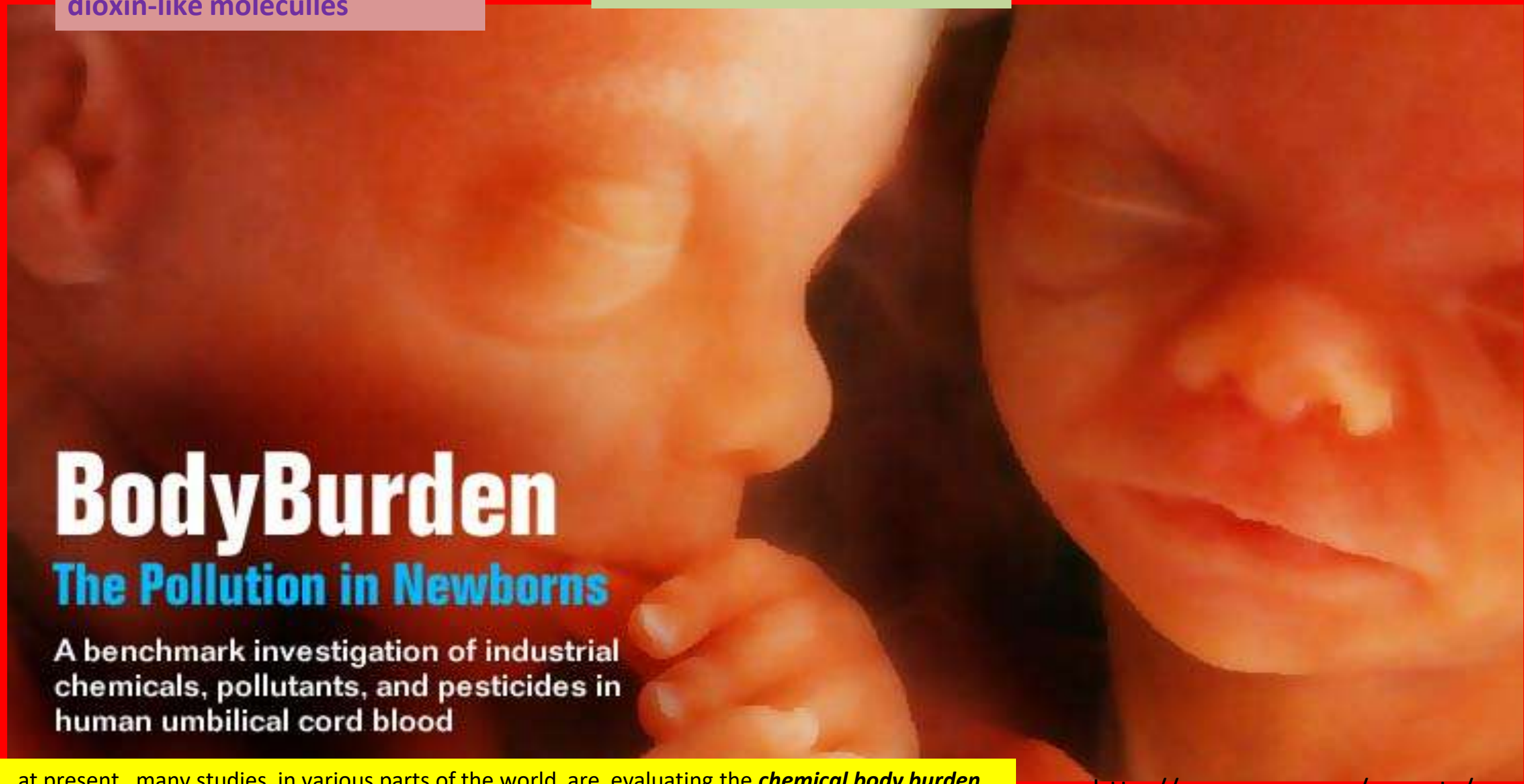


Adolescenza, Stili di Vita, Psicopatologia
Giovanni Biggio
Centro di Eccellenza per la "Neurobiologia delle Dipendenze"

CHEMICAL FALL OUT

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

The gift our mothers never wanted to give us

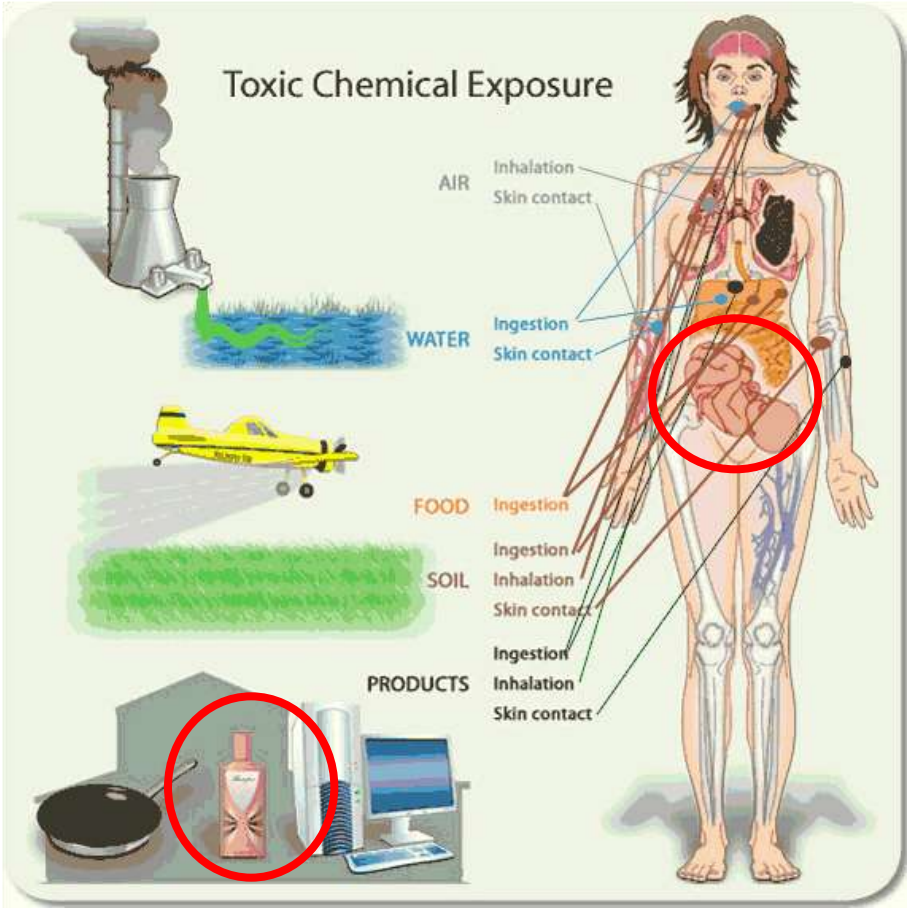


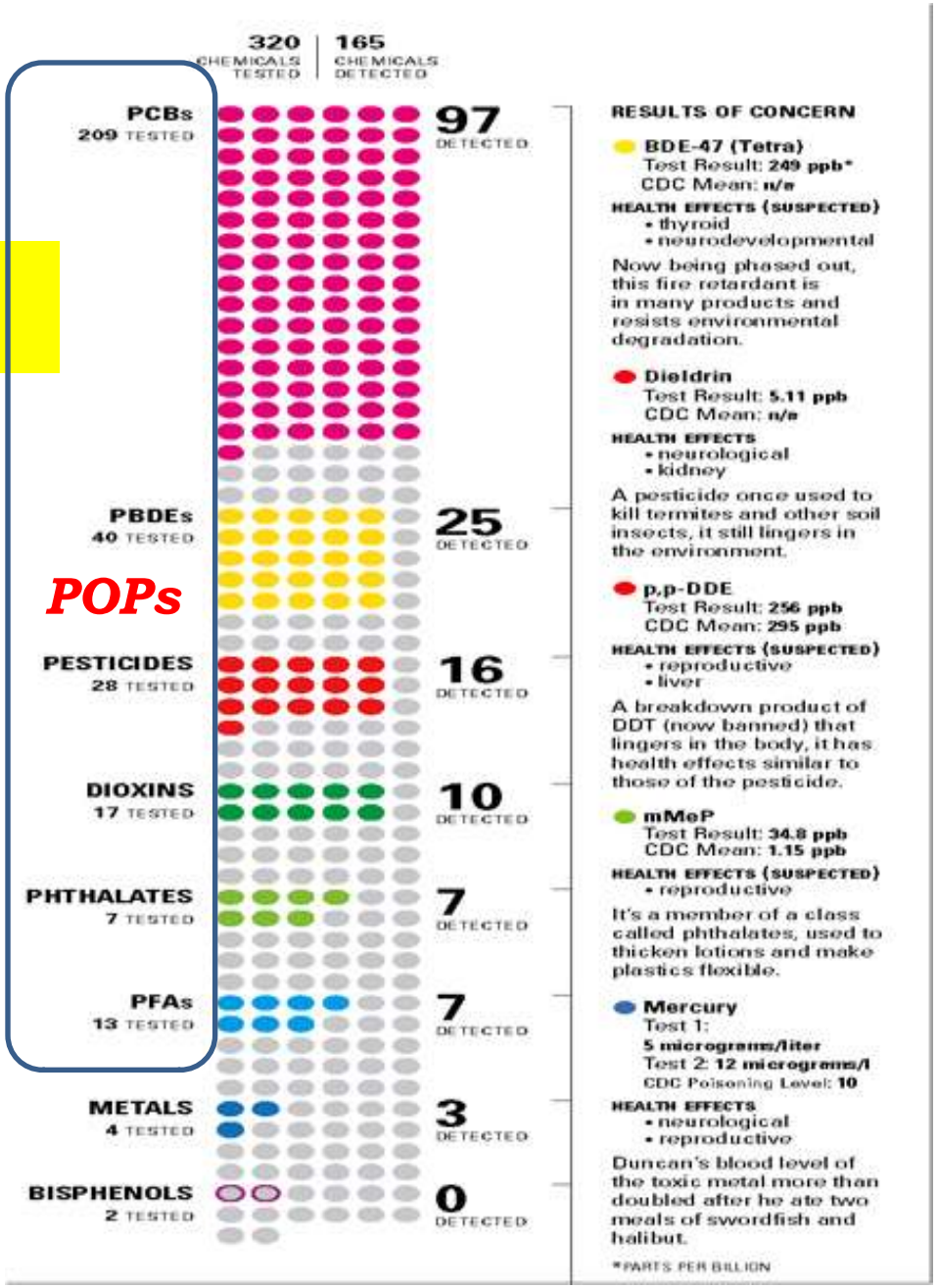
.. at present many studies in various parts of the world are evaluating the ***chemical body burden*** .. especially in women, children, embryos / fetuses, **providing dramatic results**

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**).

Environmental Health

Environmental Health 2008, **7**:50 doi:10.1186/1476-069X-7-50

Review

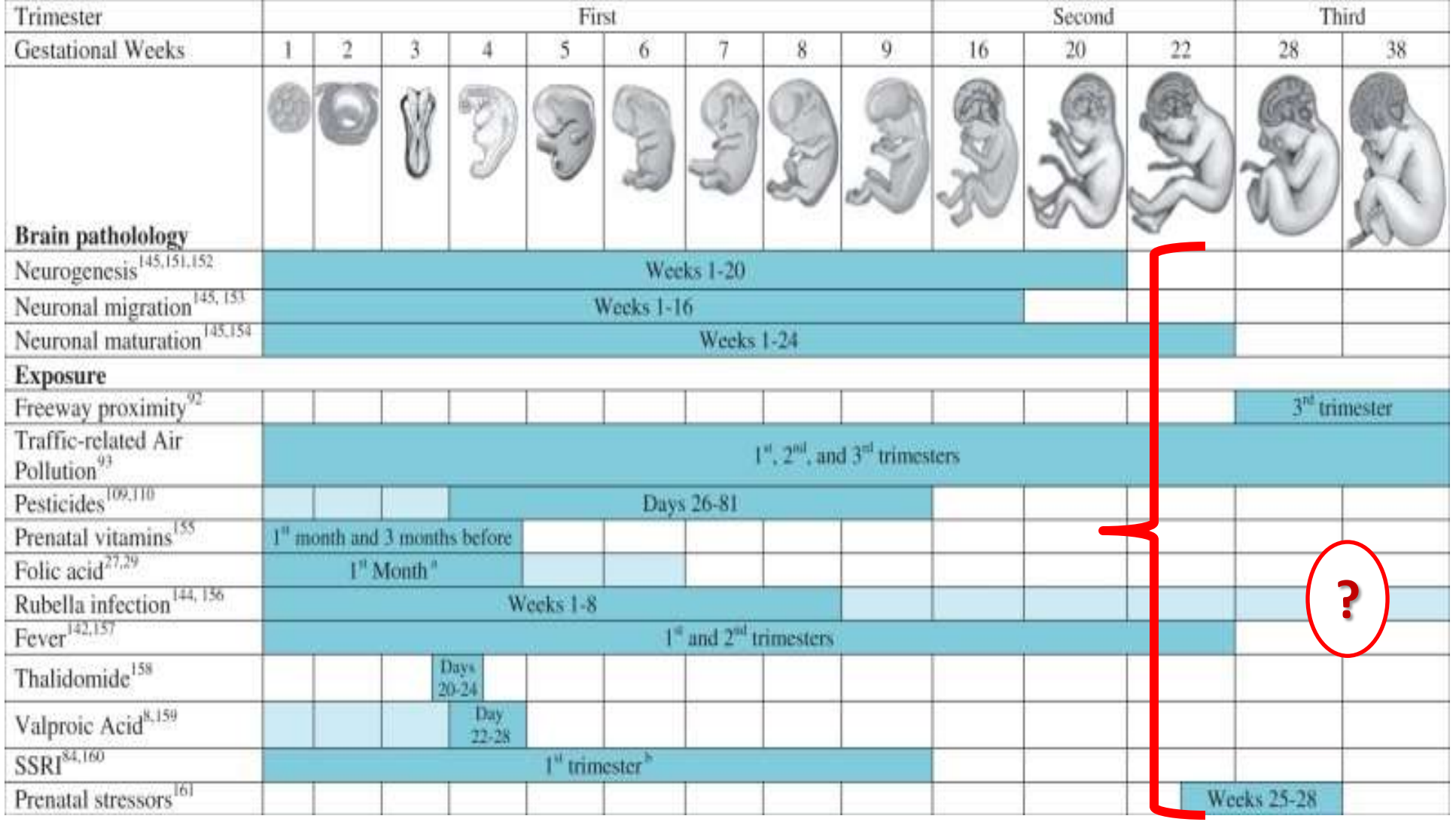
Open Access

Potential developmental neurotoxicity of pesticides used in Europe

Marina Bjørling-Poulsen*[1], Helle Raun Andersen[1] and Philippe Grandjean[1,2]

Pesticides used in agriculture are designed to protect crops against unwanted species, such as weeds, insects, and fungus. Many compounds target the nervous system of insect pests. Because of the similarity in brain biochemistry, such pesticides may also be neurotoxic to humans. Concerns have been raised that the developing brain may be particularly vulnerable to adverse effects of neurotoxic pesticides. Current requirements for safety testing do not include developmental neurotoxicity. We therefore undertook a systematic evaluation of published evidence on neurotoxicity of pesticides in current use, with specific emphasis on risks during early development. Epidemiologic studies show associations with neurodevelopmental deficits, but mainly deal with mixed exposures to pesticides. Laboratory experimental studies using model compounds suggest that many pesticides currently used in Europe – including organophosphates, carbamates, pyrethroids, ethylenebisdithiocarbamates, and chlorophenoxy herbicides – can cause neurodevelopmental toxicity. Adverse effects on brain development can be severe and irreversible. Preven and other t are known que vulnera calls for inv ties should be considered in light of the need for precautionary action to protect brain development.

Estimating Burden and Disease Costs of Exposure to EDCs in the EU:
" The ***neurodevelopment panel*** estimated a strong probability (70–100%) that **each year in Europe, 13.0 million IQ points are lost** (sensitivity analysis, 4.24–17.1 million) **due to prenatal organophosphate exposure**"



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.

Published in final edited form as:
Epidemiology. 2014 November ; 25(6): 851–858. doi:10.1097/EDE.0000000000000150.

In Utero Exposure to Toxic Air Pollutants and Risk of Childhood Autism

Methods—Among the cohort of children born in Los Angeles County, California 1995–2006, those whose mothers resided during pregnancy in a 5km buffer around air-toxics monitoring stations were included (n=148,722). To identify autism cases in this cohort, birth records were linked to records of children diagnosed with primary autistic disorder at the California Department of Developmental Services between 1998 and 2009 (n=768). We calculated monthly average exposures during pregnancy for 24 air toxics selected based on suspected or known neurotoxicity or neurodevelopmental toxicity. Factor analysis helped us identify the correlational structure among air toxics, and we estimated odds ratios (ORs) for autism from logistic regression analyses.

Results—Autism risks were increased per interquartile-range increase in average concentrations during pregnancy of several correlated toxics mostly loading on one factor, including 1,3-butadiene (OR=1.59 [95% confidence interval=1.18–2.15]), meta/para-xylene (1.51 [1.26–182]), other aromatic solvents, lead (1.49 [1.23–1.81]), perchloroethylene (1.40 [1.09–1.80]), and formaldehyde (1.34 [1.17–1.52]), adjusting for maternal age, race/ethnicity, nativity, education, insurance type, maternal birth place, parity, child sex, and birth year.

Autism risks were increased per interquartile-range increase in average concentrations during pregnancy of several correlated toxics mostly loading on one factor, **including 1,3-butadiene (OR=1.59** [95% confidence interval 1.18–2.15]), **meta/para-xylene** (**1.51** [1.26–182]), **other aromatic solvents, lead** (**1.49** [1.23–1.81]), **perchloroethylene** (**1.40** [1.09–1.80]), and **formaldehyde** (1.34 [1.17–1.52]),

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.

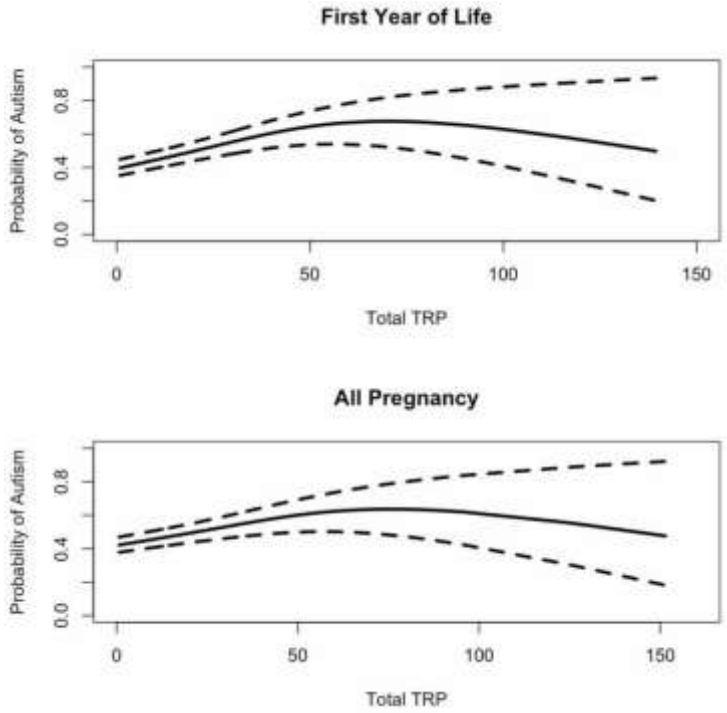
ASDs risk (OR> 50%) increased significantly among mothers exposed to fine particles (PM 2.5) and not to PM 2.5-10 especially during the **third trimester of pregnancy (Synaptogenesis!)**

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**

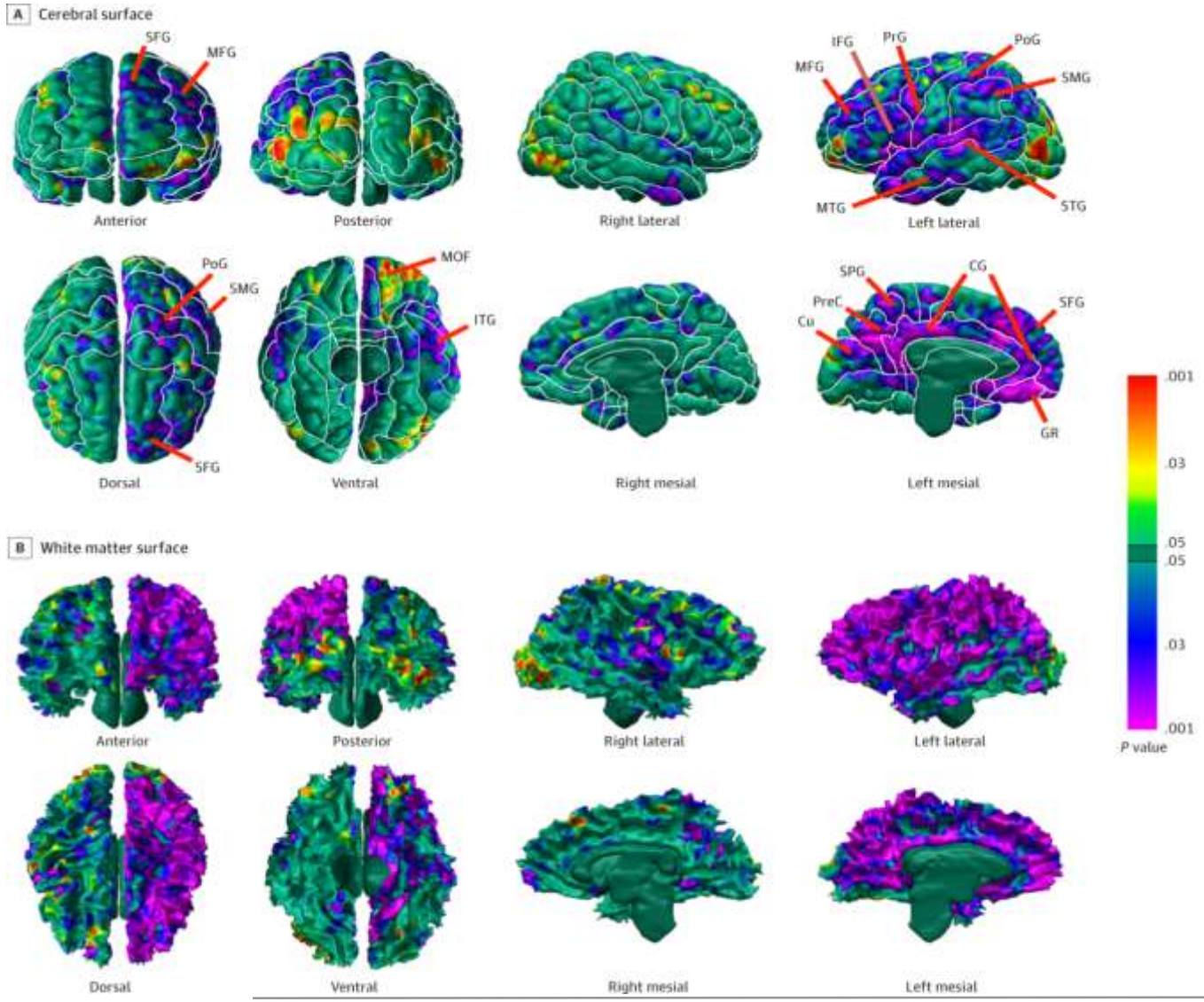
PM2.5, PM10, and NO2 at residences were higher in children with autism.

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

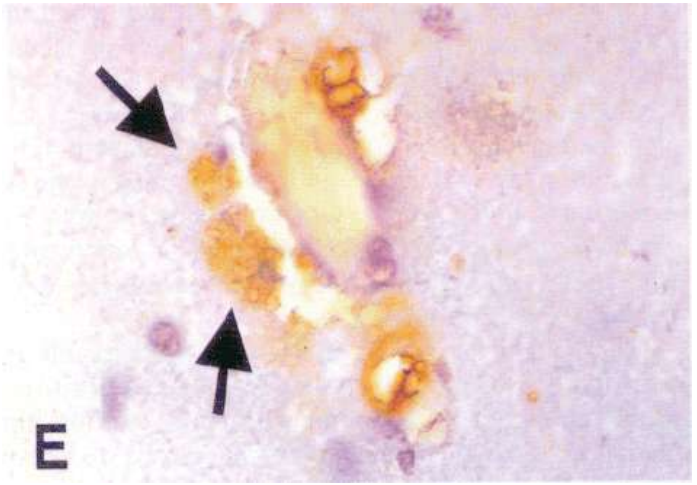
Toxicologic Pathology
http://tpx.sagepub.com

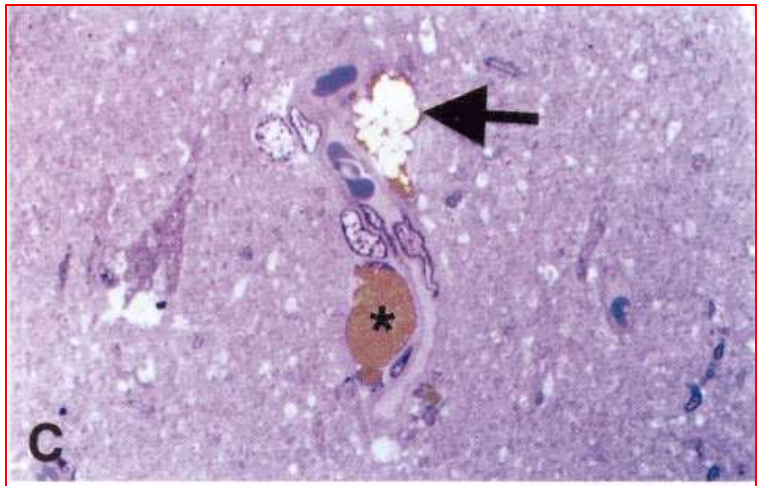
Air Pollution and Brain Damage

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-κB) 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-κB 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.





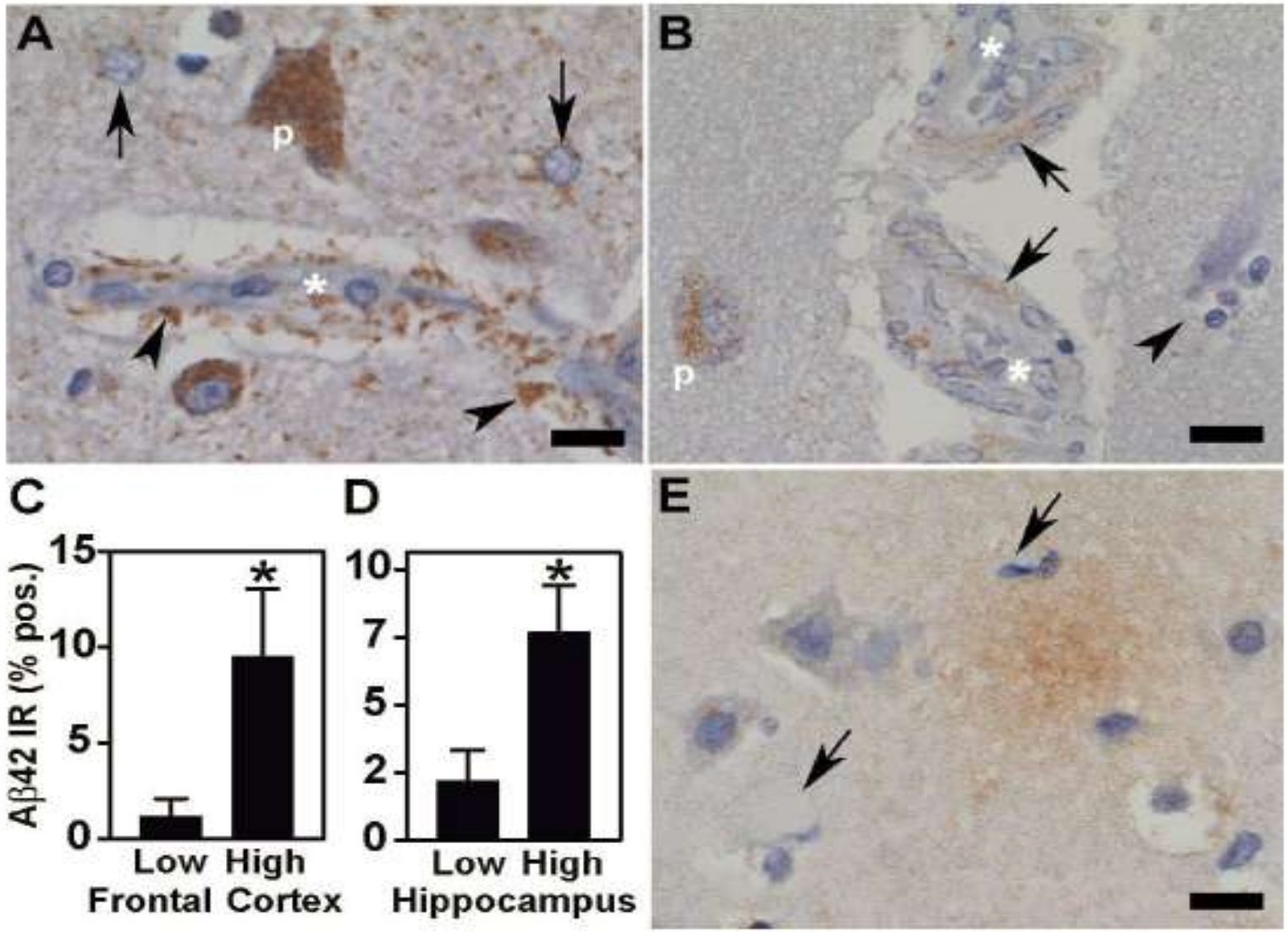


Figure 3

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

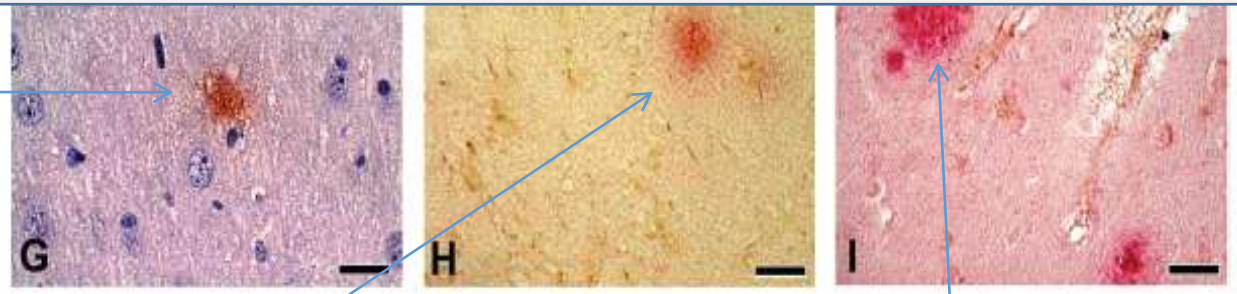
Exposures to **particulate matter and gaseous air pollutants** have been associated with **respiratory tract inflammation**, disruption of the nasal respiratory and olfactory barriers, **systemic inflammation**, production of mediators of inflammation capable of **reaching the brain and systemic circulation 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 o**f 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 **e**xhibits **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

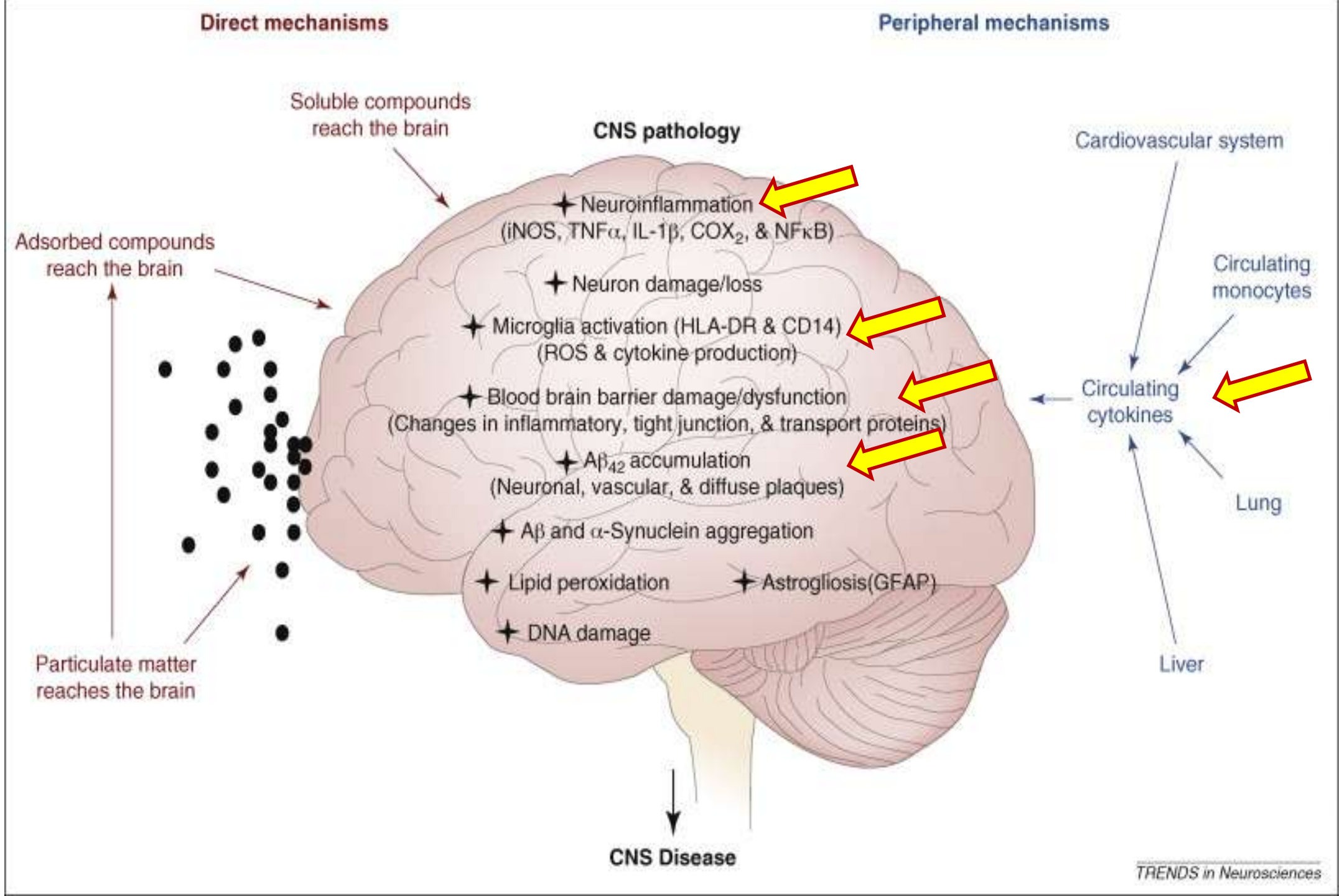
Michelle L. Block[1] and Lilian Calderón-Garcidueñas[2,3]

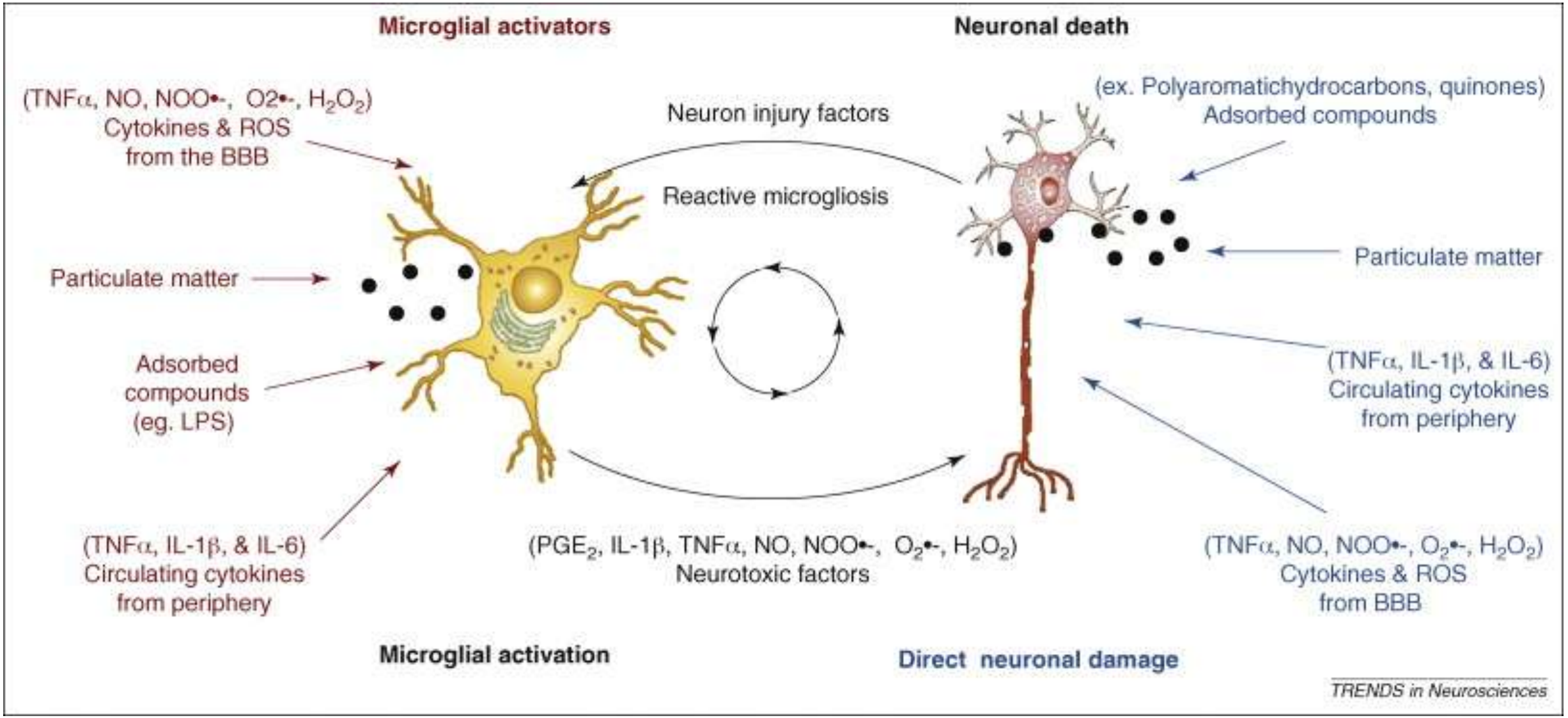
Volume 32, Issue 9, September 2009, Pages 506–516

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
Particulate matter reaches the brain
Liver
CNS Disease
TRENDS in Neurosciences

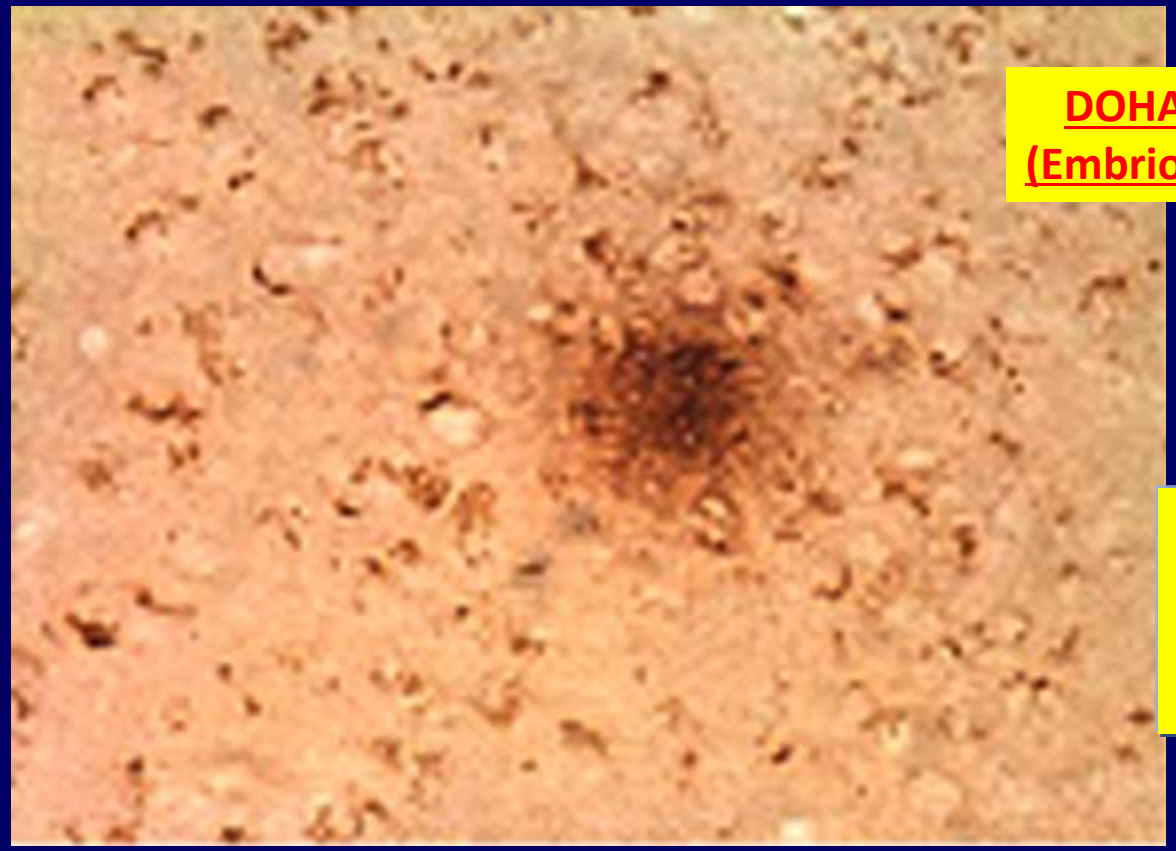


Air pollution can contribute to toxic microglial activation by triggering the cycle of ***reactive microgliosis*** through three mechanisms: (i) components of **air pollution may directly activate microglia**; (ii) ***cytokines*** from the peripheral systemic inflammatory response **may activate microglia**; (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.

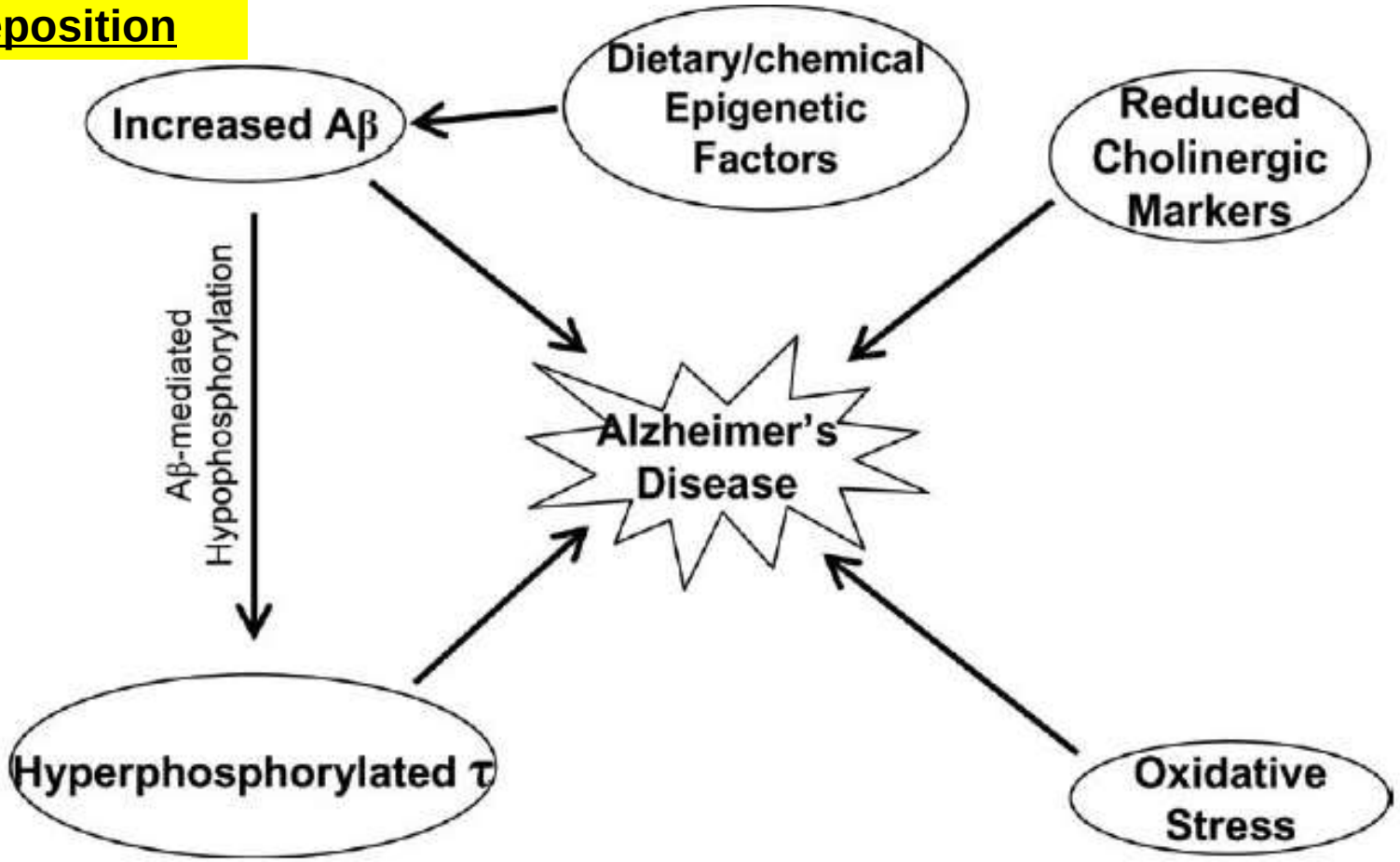
Early life exposures

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

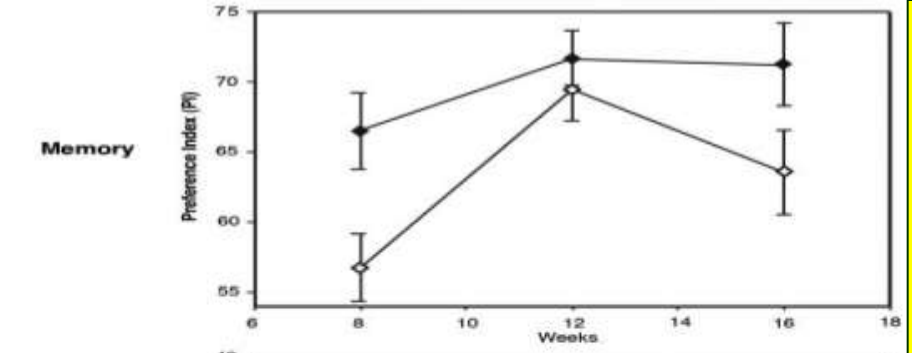
www.nature.com

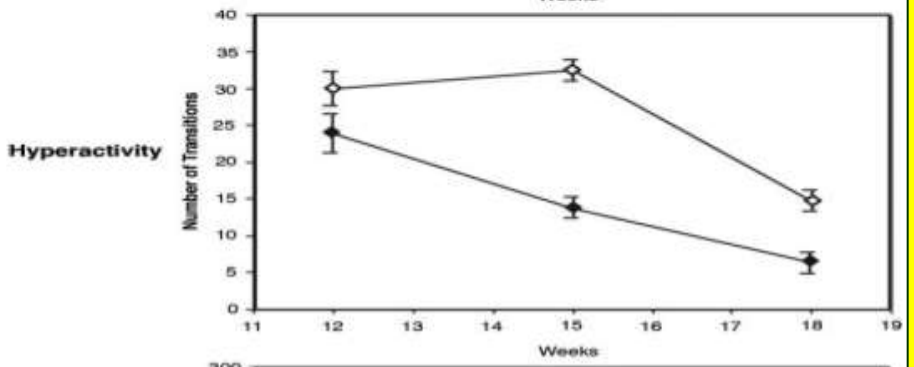
SCIENTIFIC REPORTS | 2 : 312 | DOI: 10.1038/srep00312

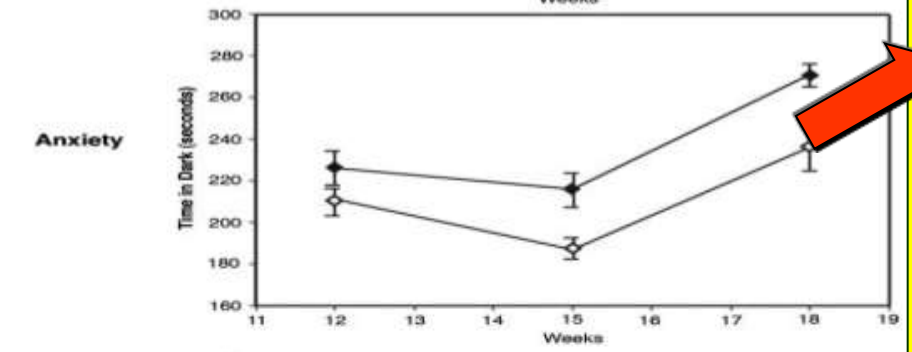
Fetal Radiofrequency Radiation Exposure From 800-1900 Mhz-Rated Cellular Telephones Affects Neurodevelopment and Behavior in Mice

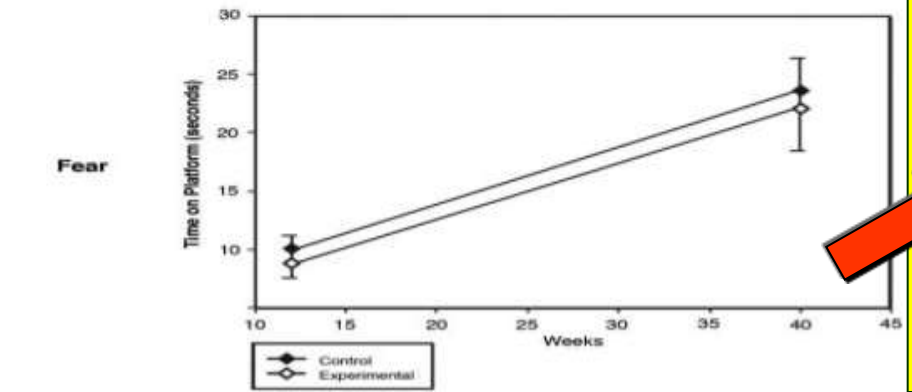
Tamir S. Aldad[1,2], Geliang Gan[2], Xiao-Bing Gao[2,3] & Hugh S. Taylor[1,2,4]

..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**.

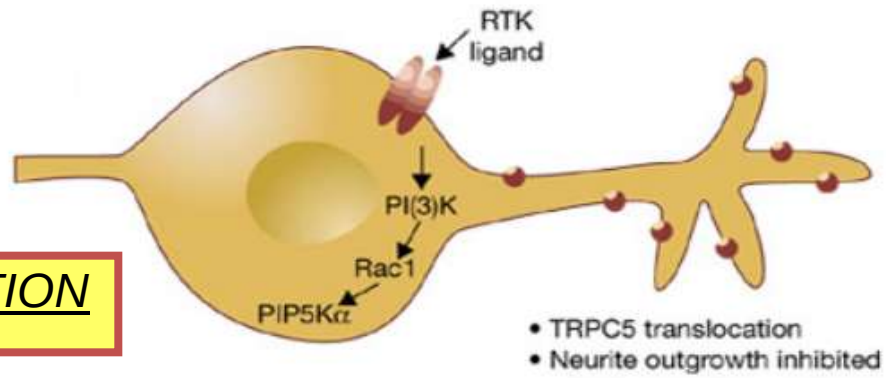
Our findings that **stem cells are the most sensitive to microwave exposure,** and **react to more frequencies than do differentiated cells may be important for cancer risk assessment and indicate that**

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

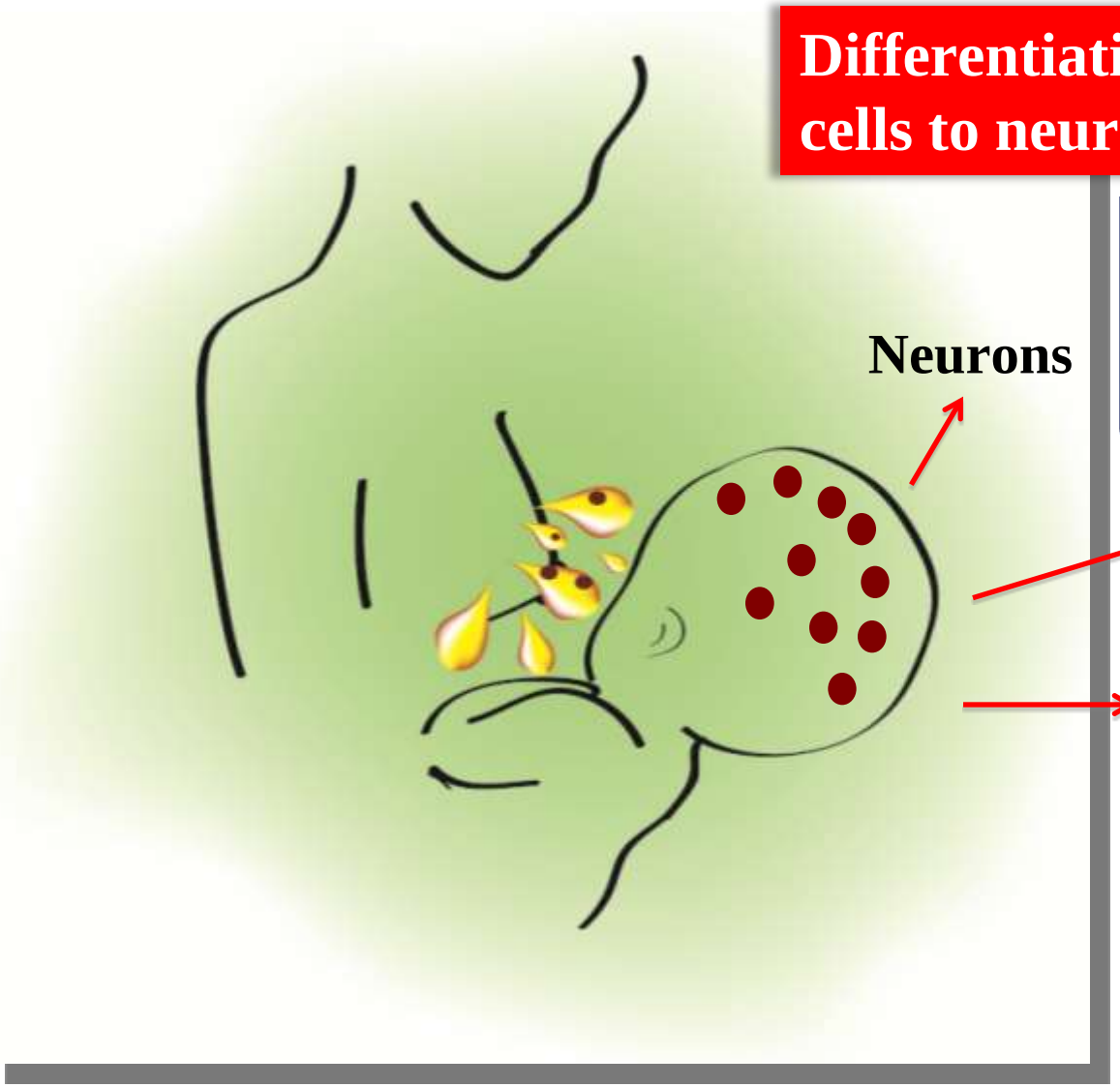
A radiofrequency electromagnetic field (RF-EMF) of 1800 MHz is widely used in mobile communications. However, the effects of RF-EMFs on cell biology are unclear. Embryonic neural stem cells (eNSCs) play a critical role in brain development. **Thus, detecting the effects of RF-EMF on eNSCs is important 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*

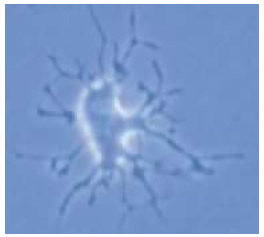
FROM BREAST MILK TO BRAIN

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

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

Published in final edited form as:
Neurosci Biobehav Rev. 2008 October ; 32(8): 1519–1532. doi:10.1016/j.neubiorev.2008.06.004.

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
neuroinflammato
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..**

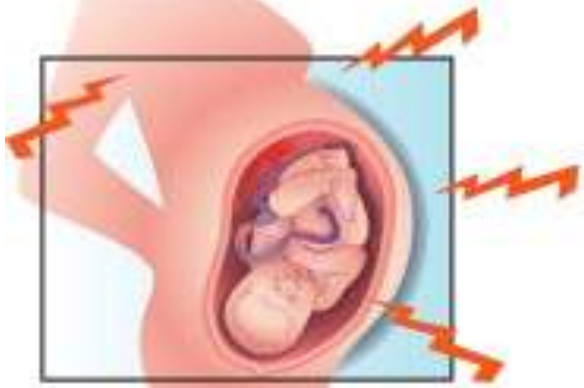
Prenatal stress can produce both

(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



Human evidence

Elevated risk of schizophrenia in children

Repeated experimental stressors

Animal studies

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

Molecular changes in the brain

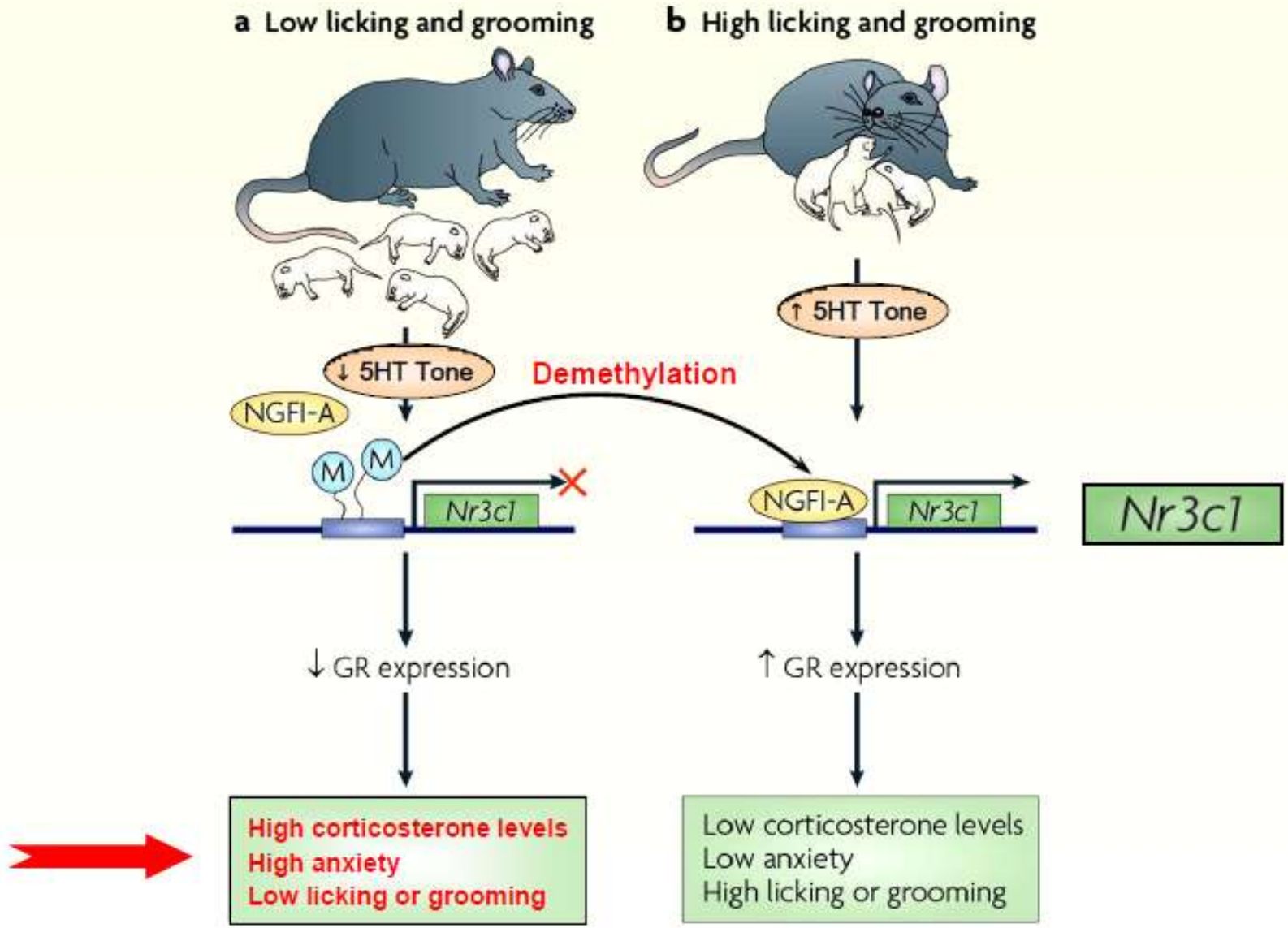
- Altered DNA methylation in prefrontal cortex
- Disrupted maturation of prefrontal cortex
- Impaired HPA axis regulation
- Impaired synaptic plasticity

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 postn
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

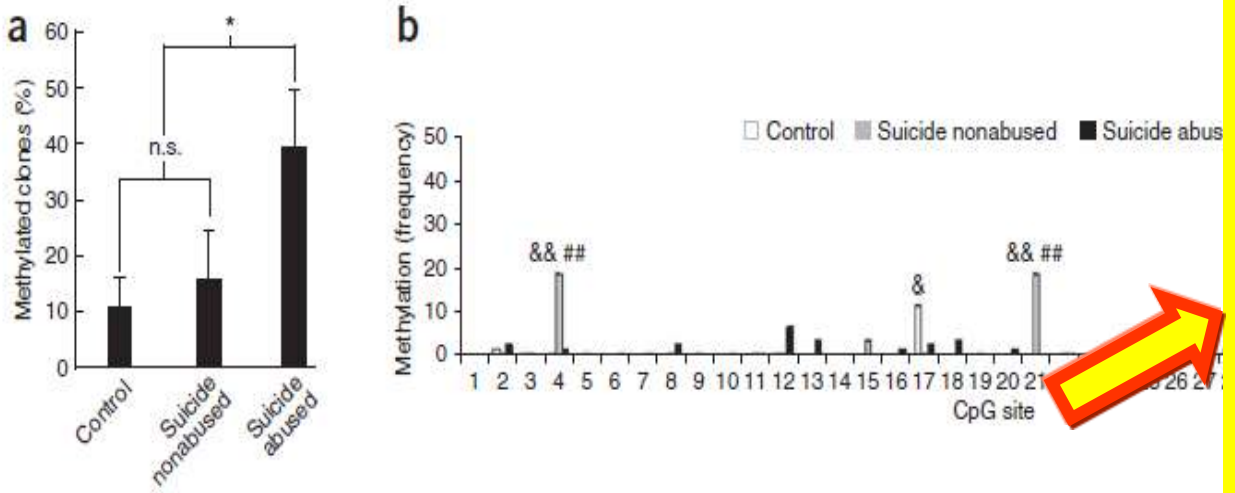


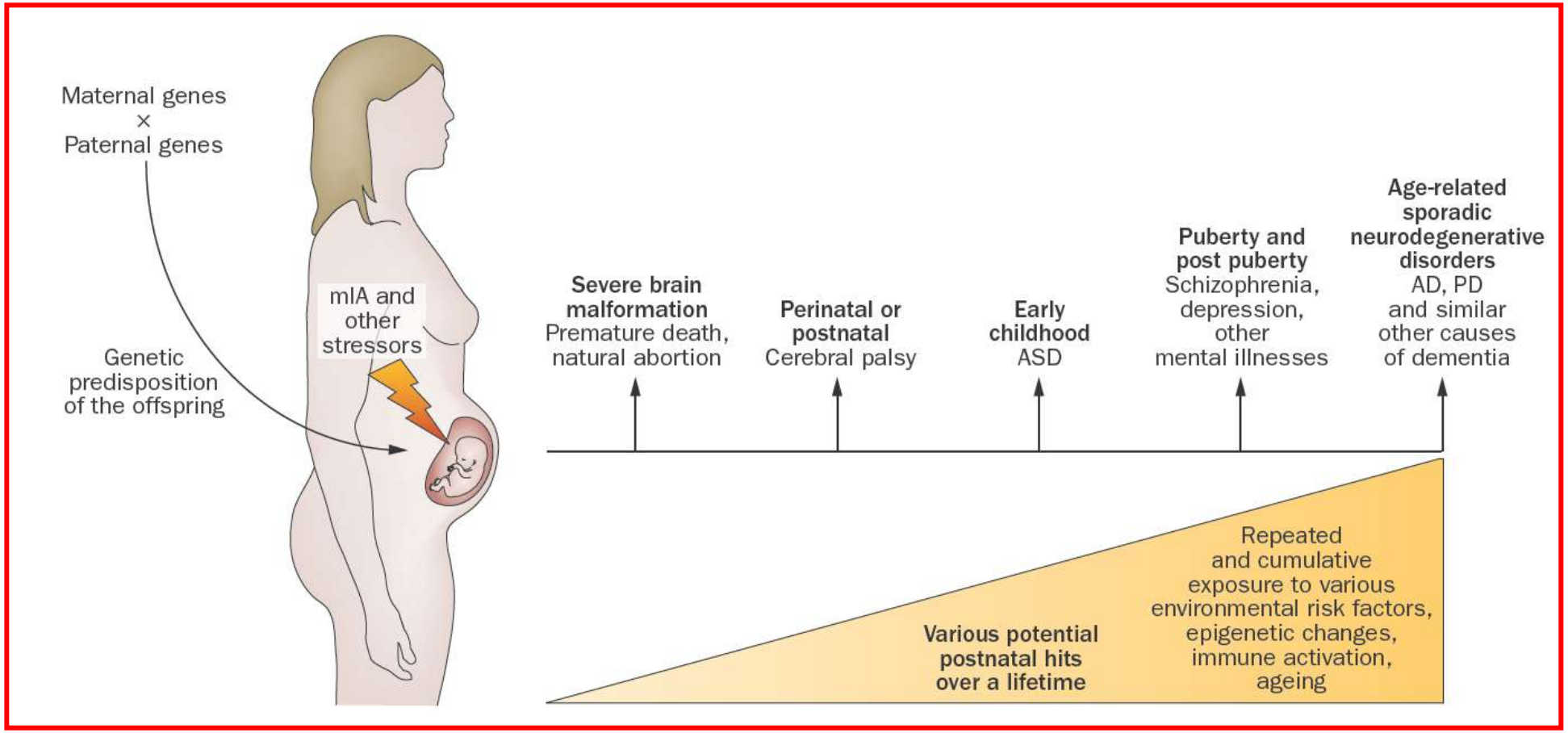
Figure 2 Methylation of the *NR3C1* promoter in the hippocampus. Twenty clones were sequenced for each subject for m
percentage of methylated clones for suicide victims with a history of childhood abuse ($n = 12$), suicide victims without a
and controls ($n = 12$). The methylation percentage was calculated 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 hi
control subjects ($^{*}P < 0.05$, $^{**}P < 0.001$, abused suicides versus controls; $^{\&}P < 0.05$, $^{\&\&}P < 0.001$, non-abused sui
$^{\#\#}P < 0.001$, 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**.

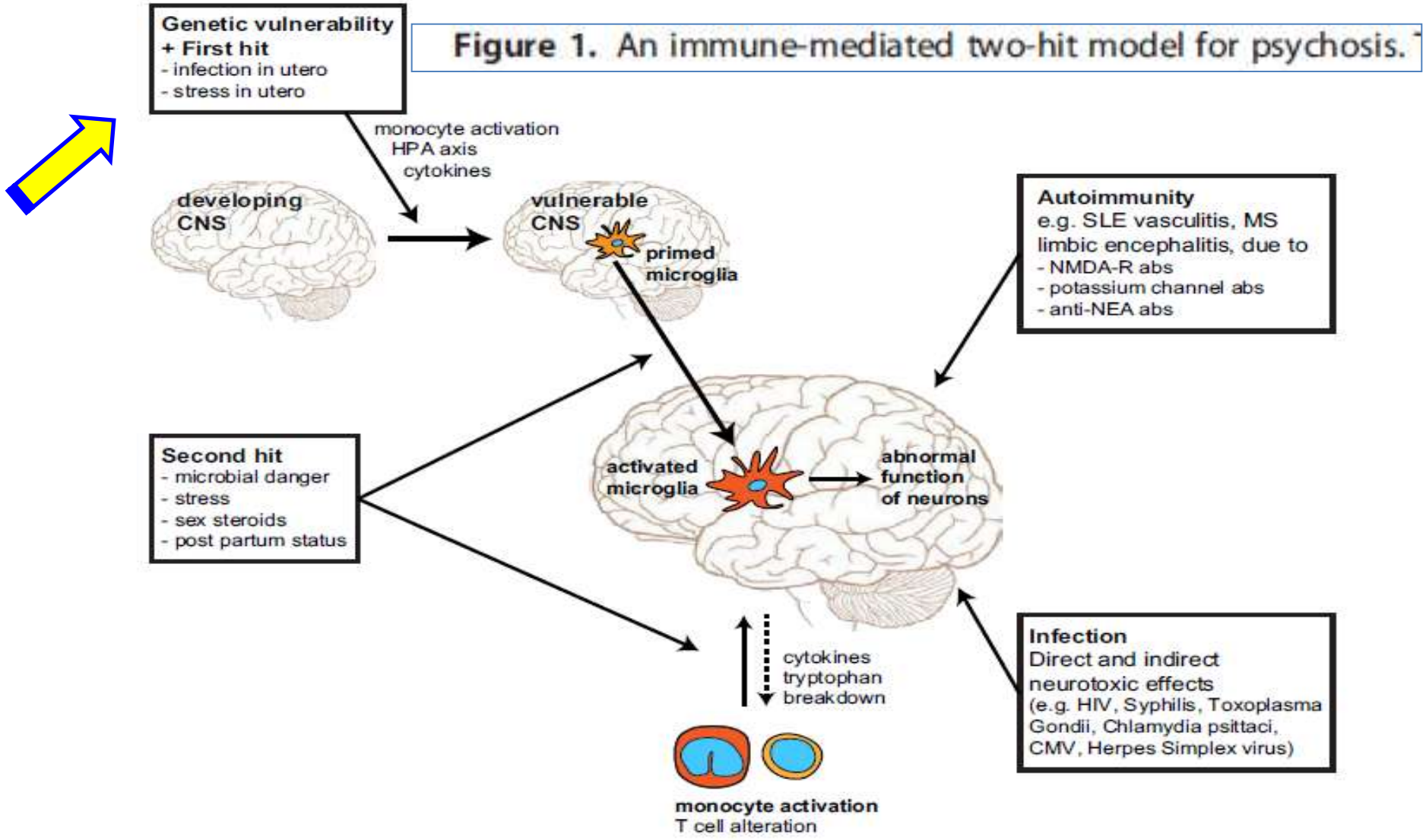


Figure 1. An immune-mediated two-hit model for psychosis.

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

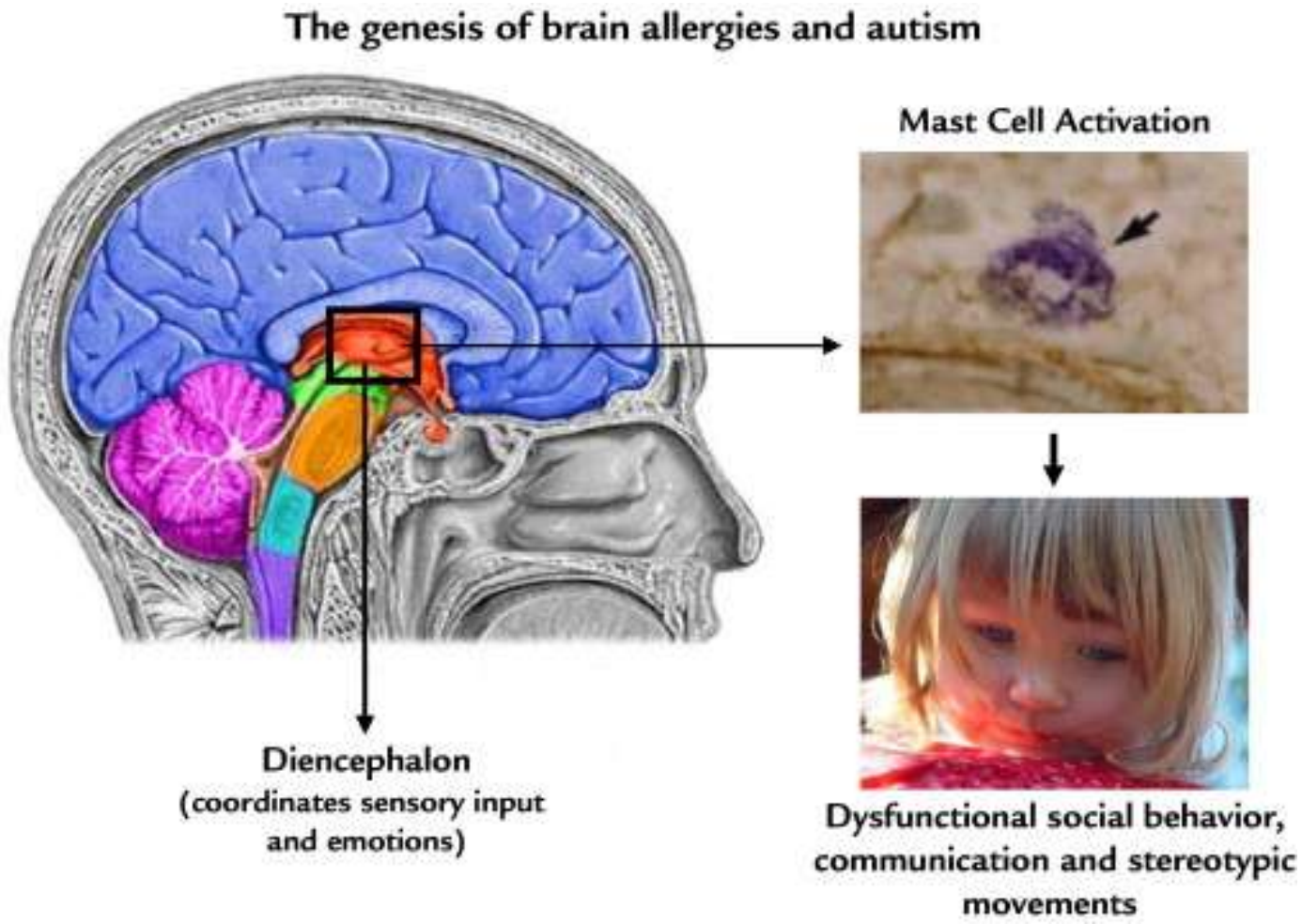
New "atopic" clinical entities in search of pathogenesis and treatment

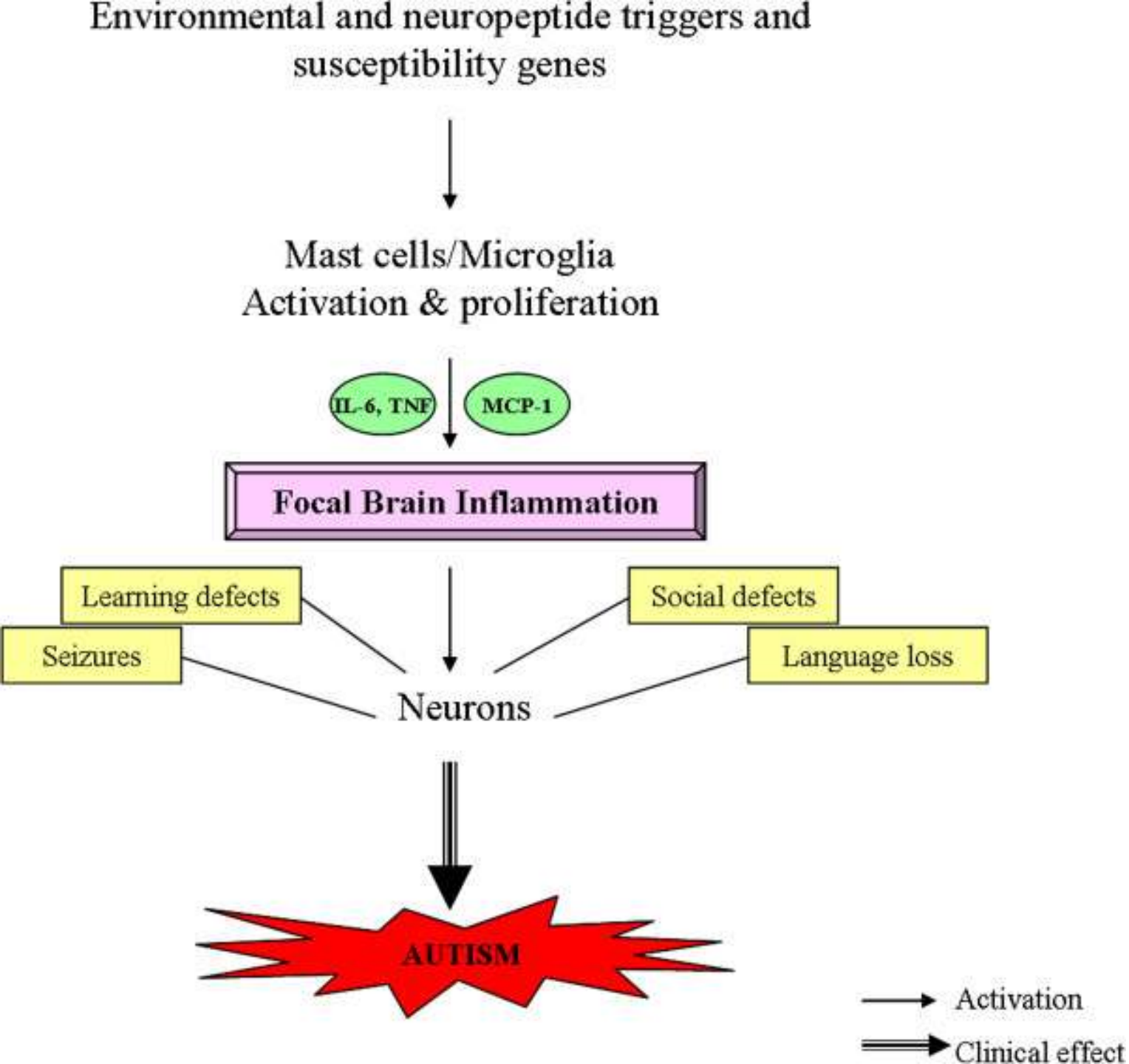
Is a Subtype of Autism an Allergy of the Brain?

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

Sistema immunitario e disturbi dello spettro autistico

IL-1β, IL-6, IL-12
TNF-α
Monociti, NK, T

IL-10 e TNF-β
T reg

XXVIII Congresso Nazionale
Società Italiana di Pediatria Preventiva e Sociale

RADICI PROFONDE
PER L'ADULTO DI DOMANI

15-18 Settembre 2016
Reggia di Caserta - Grand Hotel Vanvitelli

PFAPA syndrome e disturbi del neurosviluppo: possibili *pathways* molecolari comuni?

Cristina Panisi, *Maura Rota, Ernesto Burgio*

cristina.panisi@tin.it

Laboratorio Autismo
Dipartimento di Scienze del Sistema Nervoso e del Comportamento
Università degli Studi di Pavia

Vanoni et al. Pediatric Rheumatology (2016) 14:38
DOI 10.1186/s12969-016-0101-9

Pediatric Rheumatology

REVIEW Open Access

PFAPA syndrome: a review on treatment and outcome

Federica Vanoni[1*], Katerina Theodoropoulou[2] and Michaël Hofer[3]

Abstract

The syndrome of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA syndrome) is the most common cause of periodic fever in childhood. The current pharmacological treatment includes corticosteroids, which usually are efficacious in the management of fever episodes, colchicine, for the prophylaxis of febrile episodes, and other medication for which efficacy has not been proven so far. Tonsillectomy is an option for selected patients. Usually PFAPA syndrome resolves during adolescence, but there is increasing evidence that this condition may persist into adulthood.

Keywords: PFAPA treatment, PFAPA outcome, Tonsillectomy, Glucocorticoids, Colchicine

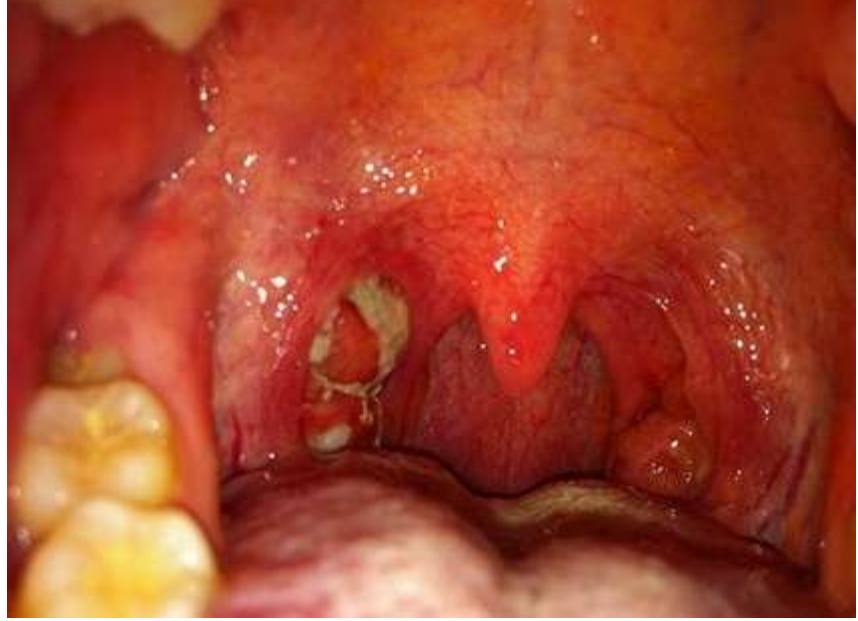
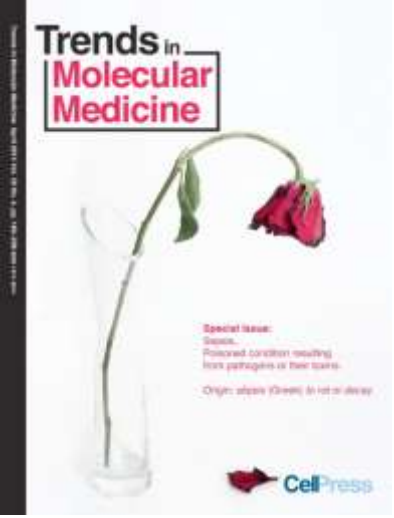


Table I

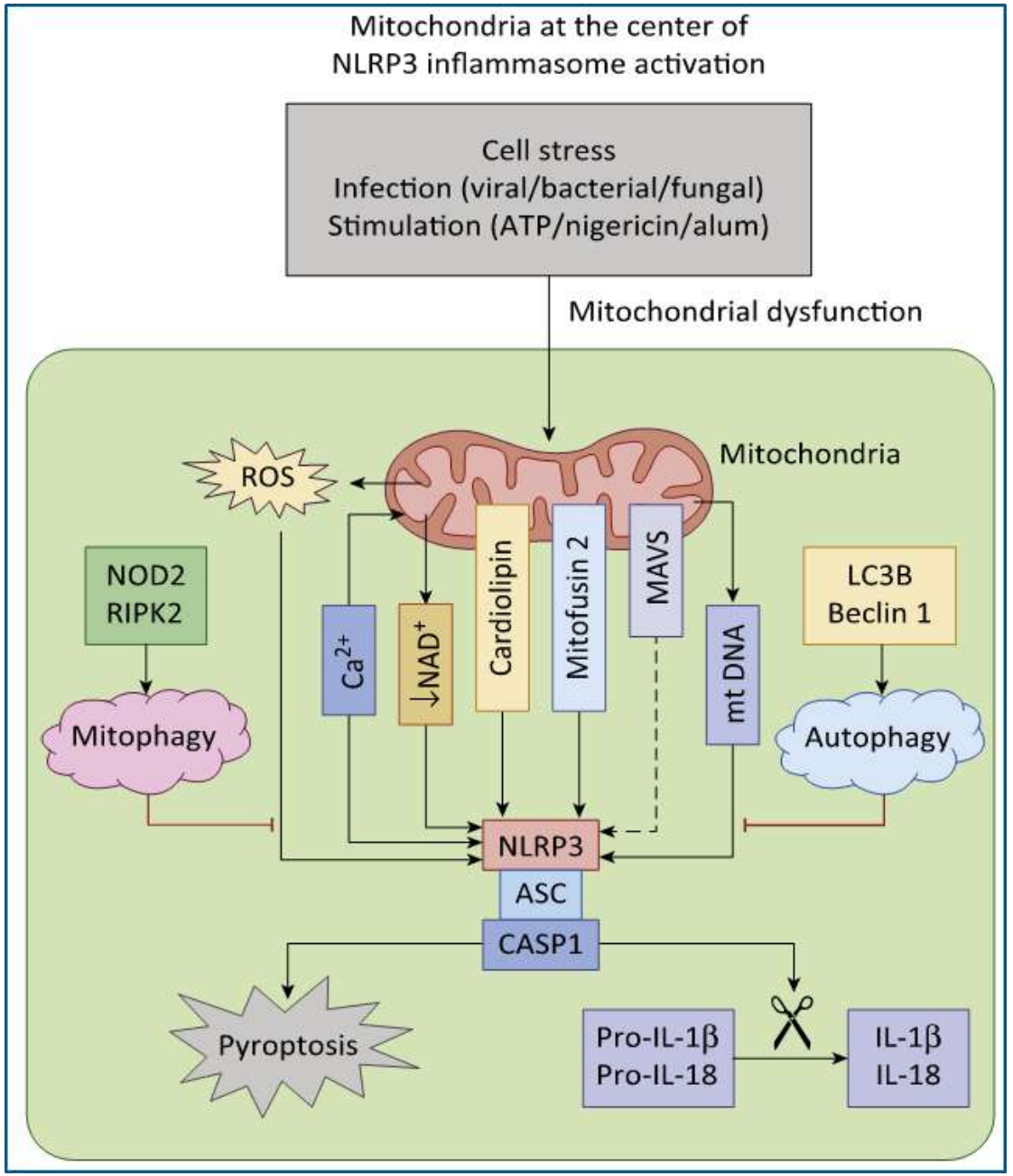
Diagnostic criteria used for PFAPA

1. Regularly recurring fevers with an early age of onset (< 5 years of age)
2. Constitutional symptoms in the absence of upper respiratory infection with at least one of the following clinical signs:
   a) Aphthous stomatitis
   b) Cervical lymphadenitis
   c) Pharyngitis
3. Exclusion of cyclic neutropenia
4. Completely asymptomatic interval between episodes
5. Normal growth and development

The syndrome of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA syndrome) is **the most common cause of periodic fever in childhood.**



Mitochondria: Diversity in the regulation of NLRP3 inflammasome
Gurung et al, 2015



L'incremento di alcune citochine infiammatorie, sia nella PFAPA sia in alcuni disturbi del neurosviluppo e **il riscontro di entrambi i quadri nel medesimo bambino,** potrebbero spiegarsi **con meccanismi patogenetici comuni, con ricadute sul sistema immune e sul sistema nervoso centrale.**

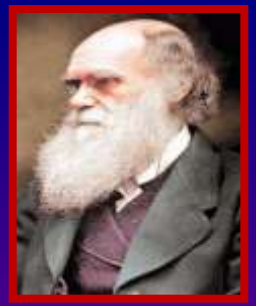
Per approfondire tale ipotesi, è auspicabile che ricerche future includano una valutazione comportamentale nell'assessment diagnostico dei bambini con PFAPA.

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

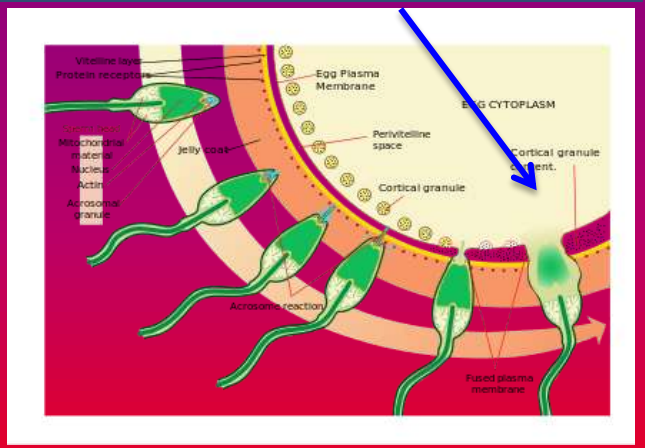
30 avril 2015

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)

ECERI
European Cancer and Environment Research Institute

INTERNATIONAL SOCIETY OF DOCTORS FOR ENVIRONMENT ISDE

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

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.**

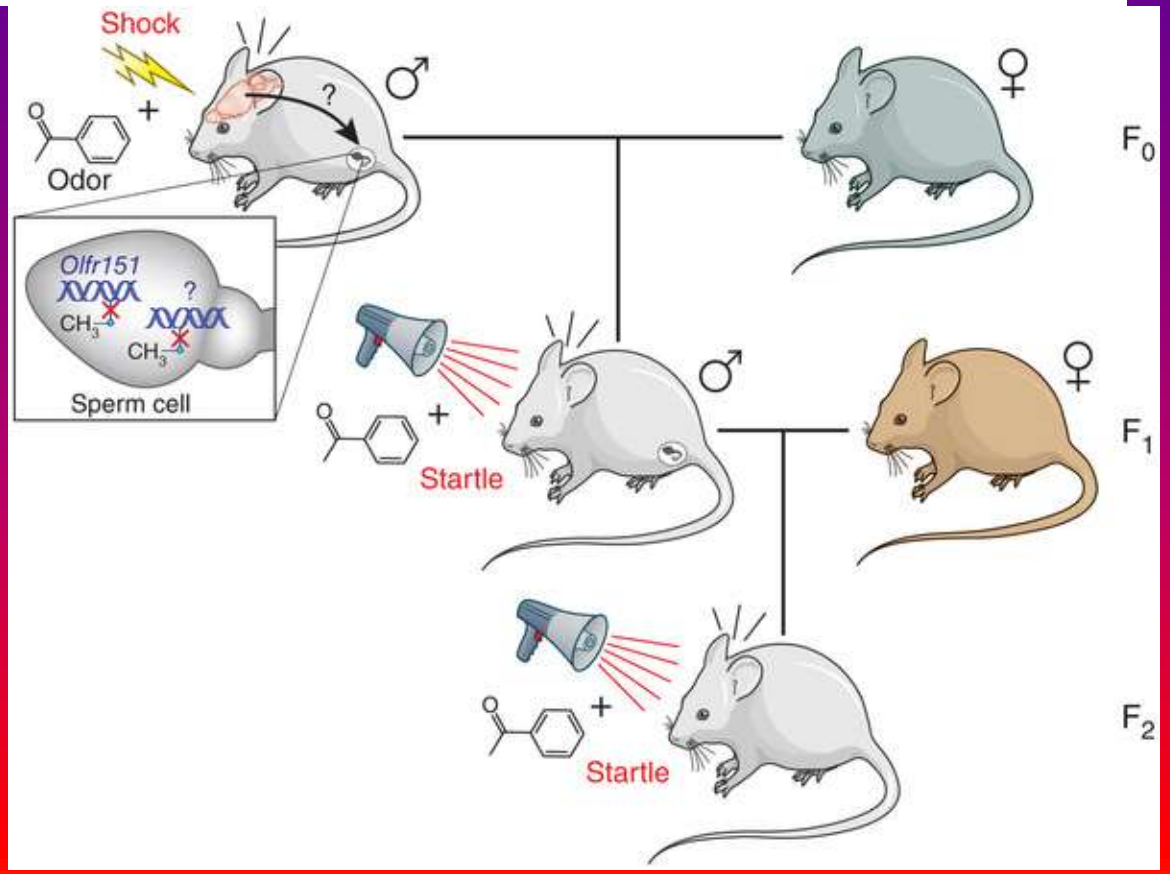
Lamarck revisited: epigenetic inheritance of ancestral odor fear conditioning

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 International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video | For Authors

Archive > Volume 508 > Issue 7496 > News > Article

http://www.nature.com/news/sperm-rna-carries-marks-of-trauma-1.15049

Sperm RNA carries marks of trauma

Stress alters the expression of small RNAs in male mice and leads to depressive behaviours in later generations.

Virginia Hughes

14 April 2014

Nature **508,** 296–297 (17 April 2014)
doi:10.1038/508296°

Mice exposed to stress have **male offspring that show depressive behaviour across three generations**

Trauma is insidious. It not only increases a person's risk for psychiatric disorders, but can also spill over into the next generation. **People who were traumatized during the Khmer Rouge genocide in Cambodia** tended to have **children with depression and anxiety,** for example, and **children of Australian veterans of the Vietnam War have higher rates of suicide than the general population**.

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.

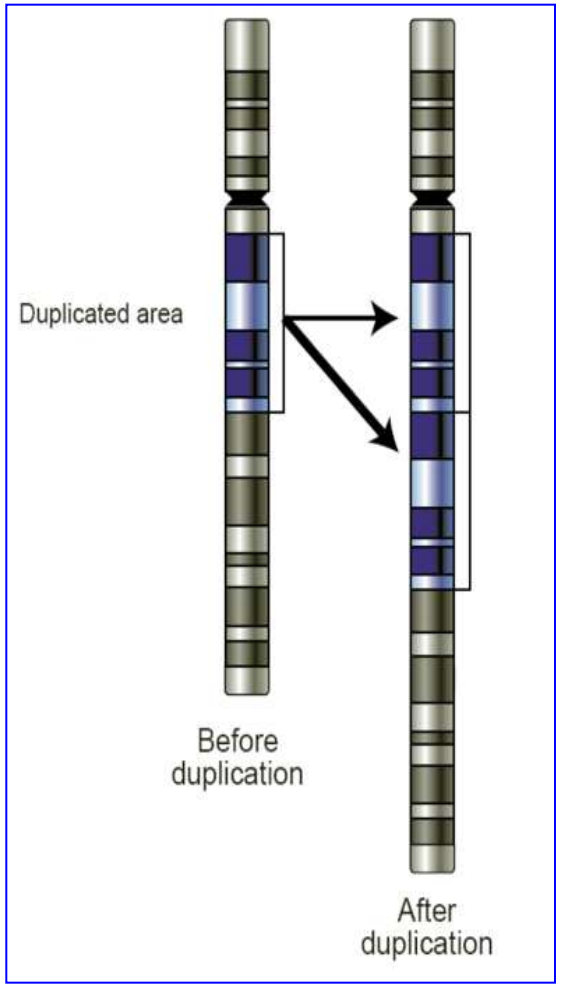
Isabelle Mansuy..**periodically separated mother mice from their young pups and exposed the mothers to stressful situations** — either by placing them in cold water or physically restraining them. These separations occurred every day but at erratic times, **so that the mothers could not comfort their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

Strong Association of De Novo Copy Number Mutations with Autism

Jonathan Sebat *et al.*

Science **316**, 445 (2007);

We tested the hypothesis that de novo copy number variation (CNV) is associated with autism spectrum disorders (ASDs). We performed comparative genomic hybridization (CGH) on the genomic DNA of patients and unaffected subjects to detect copy number variants not present in their respective parents. Candidate genomic regions were validated by higher-resolution CGH, paternity testing, cytogenetics, fluorescence in situ hybridization, and microsatellite genotyping. Confirmed de novo CNVs were significantly associated with autism ($P = 0.0005$). Such CNVs were identified in 12 out of 118 (10%) of patients with sporadic autism, in 2 out of 77 (3%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls. Most de novo CNVs were smaller than microscopic resolution. Affected genomic regions were highly heterogeneous and included mutations of single genes. These findings establish de novo germline mutation as a more significant risk factor for ASD than previously recognized.

Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia

Tom Walsh *et al.*

Science **320**, 539 (2008);

Schizophrenia is a devastating neurodevelopmental disorder whose genetic influences remain elusive. We hypothesize that individually rare structural variants contribute to the illness. Microdeletions and microduplications >100 kilobases were identified by microarray comparative genomic hybridization of genomic DNA from 150 individuals with schizophrenia and 268 ancestry-matched controls. All variants were validated by high-resolution platforms. Novel deletions and duplications of genes were present in 5% of controls versus 15% of cases and 20% of young-onset cases, both highly significant differences. The association was independently replicated in patients with childhood-onset schizophrenia as compared with their parents. Mutations in cases disrupted genes disproportionately from signaling networks controlling neurodevelopment, including neuregulin and glutamate pathways. These results suggest that multiple, individually rare mutations altering genes in neurodevelopmental pathways contribute to schizophrenia.

Trends in Molecular Medicine

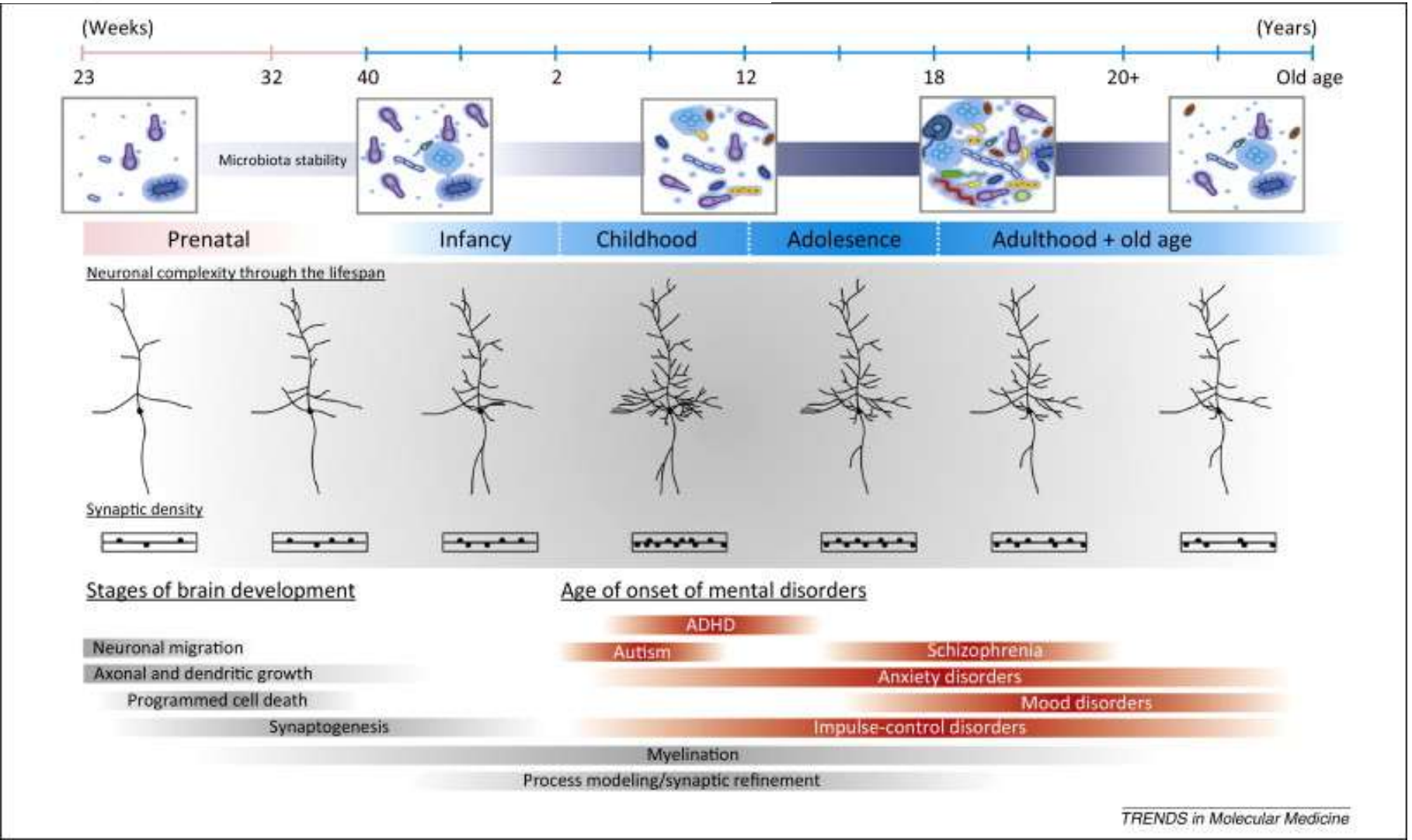
Volume 20, Issue 9, September 2014, Pages 509–518

Review

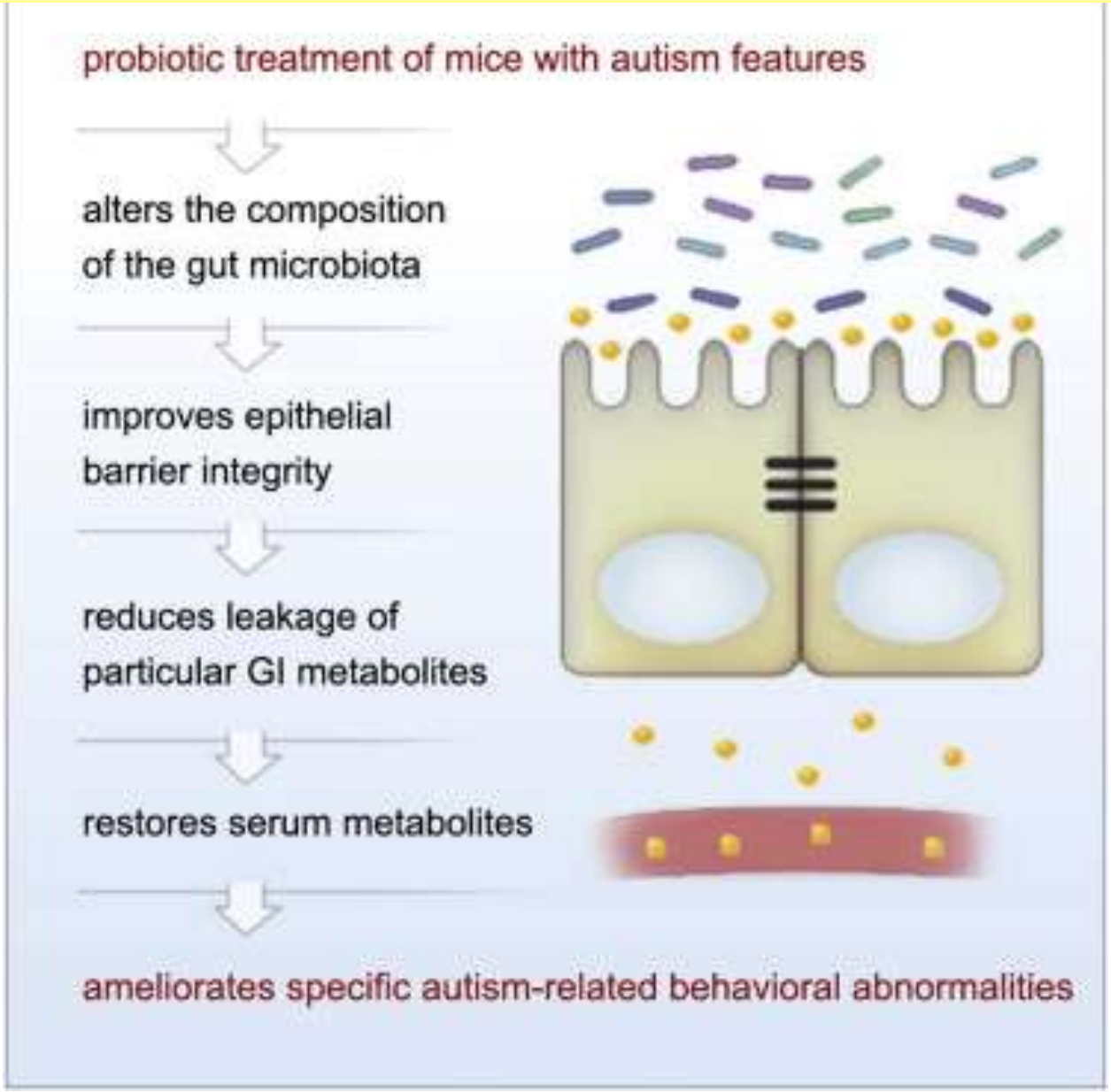
Microbiota and neurodevelopmental windows: implications for brain disorders

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

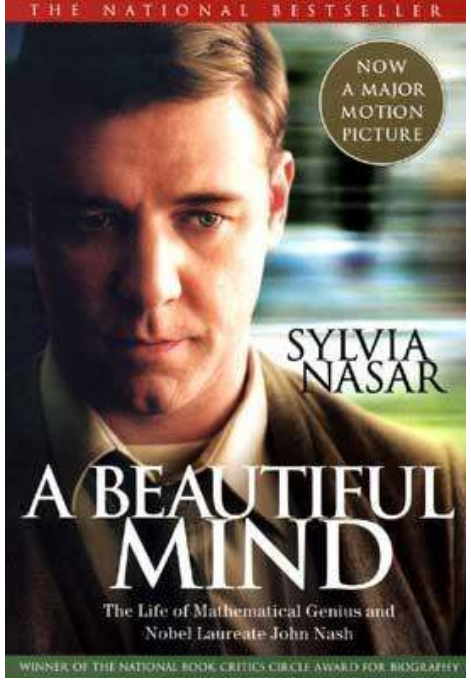
Bacteriotherapy

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)

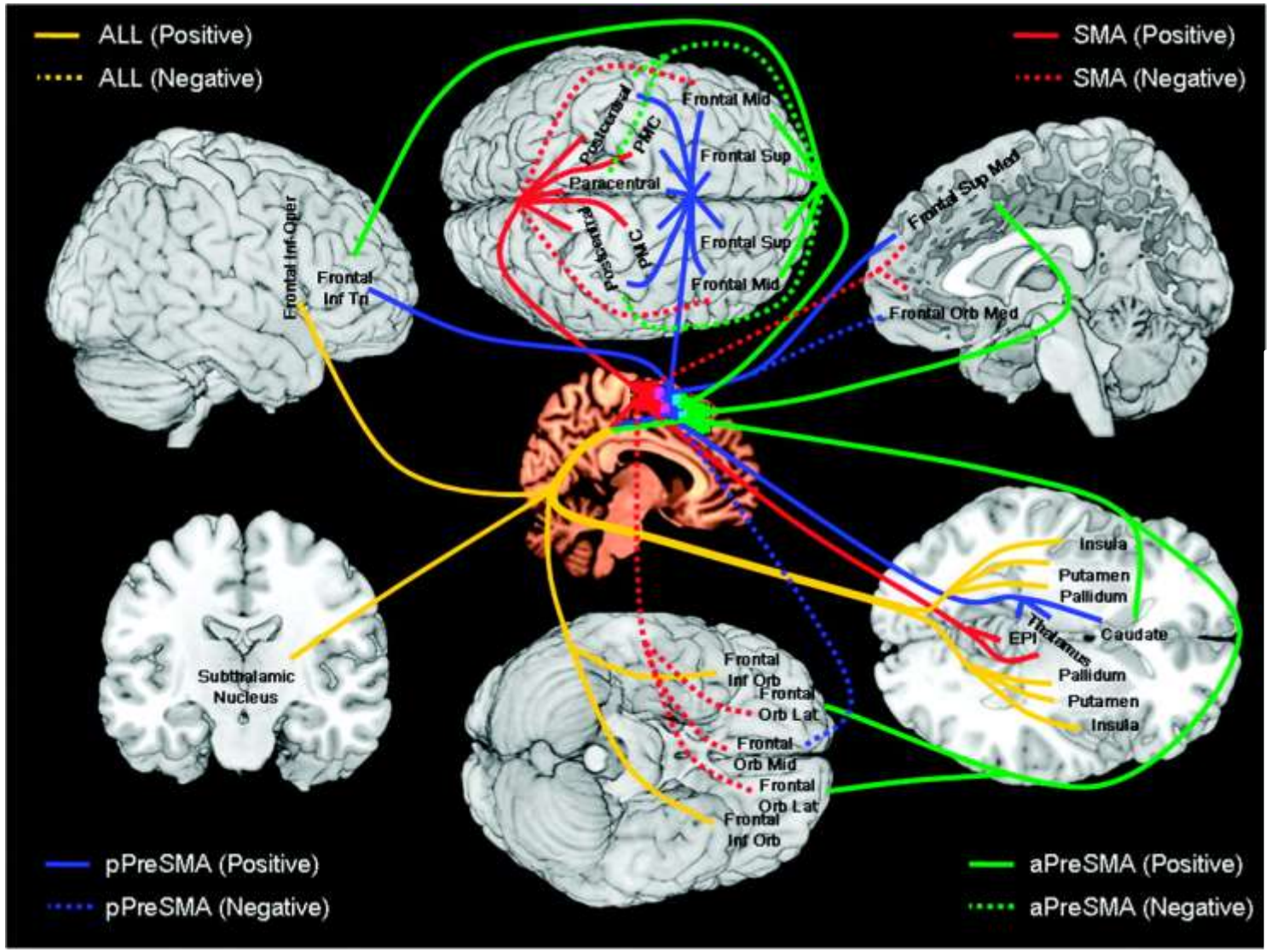
1

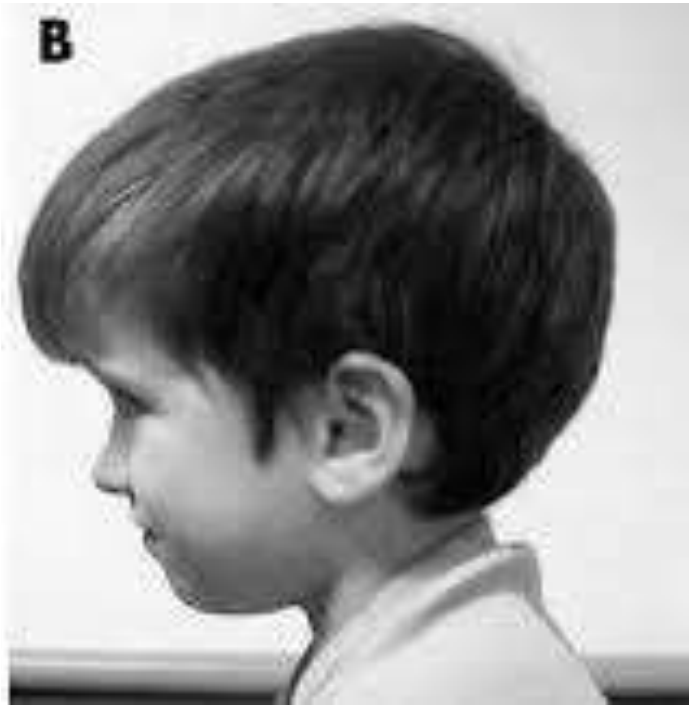
2

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**

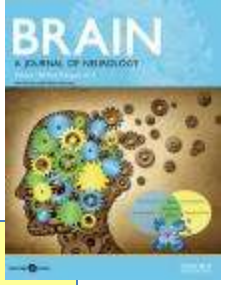
* Uddin etal., ***Reconceptualizing functional brain connectivity in autism from a developmental perspective*** (2013)

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

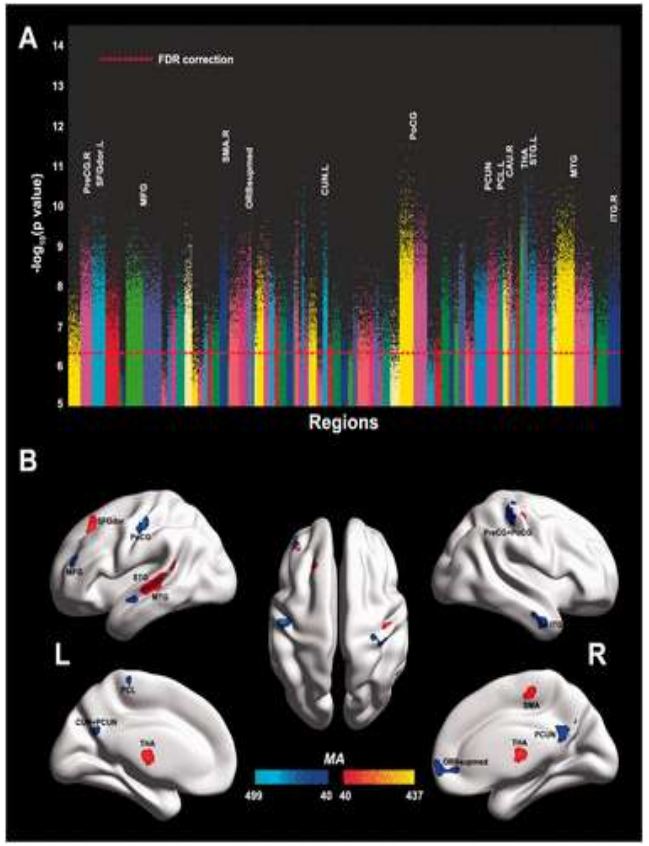
Cheng W, Rolls ET, Gu H, Zhang J, Feng J

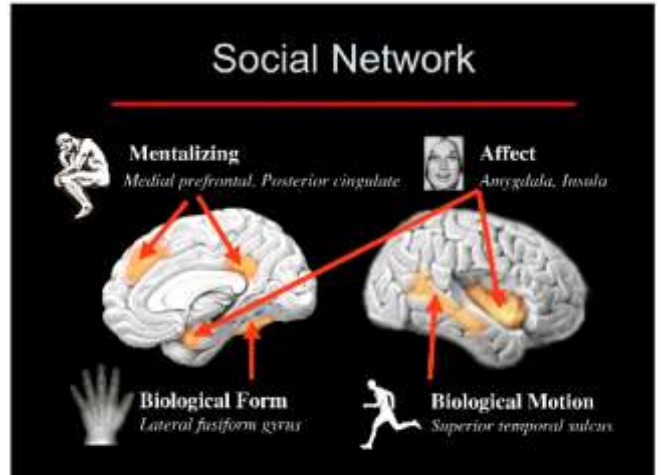
Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. Brain. 2015 May;138(Pt 5):1382-93.

..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

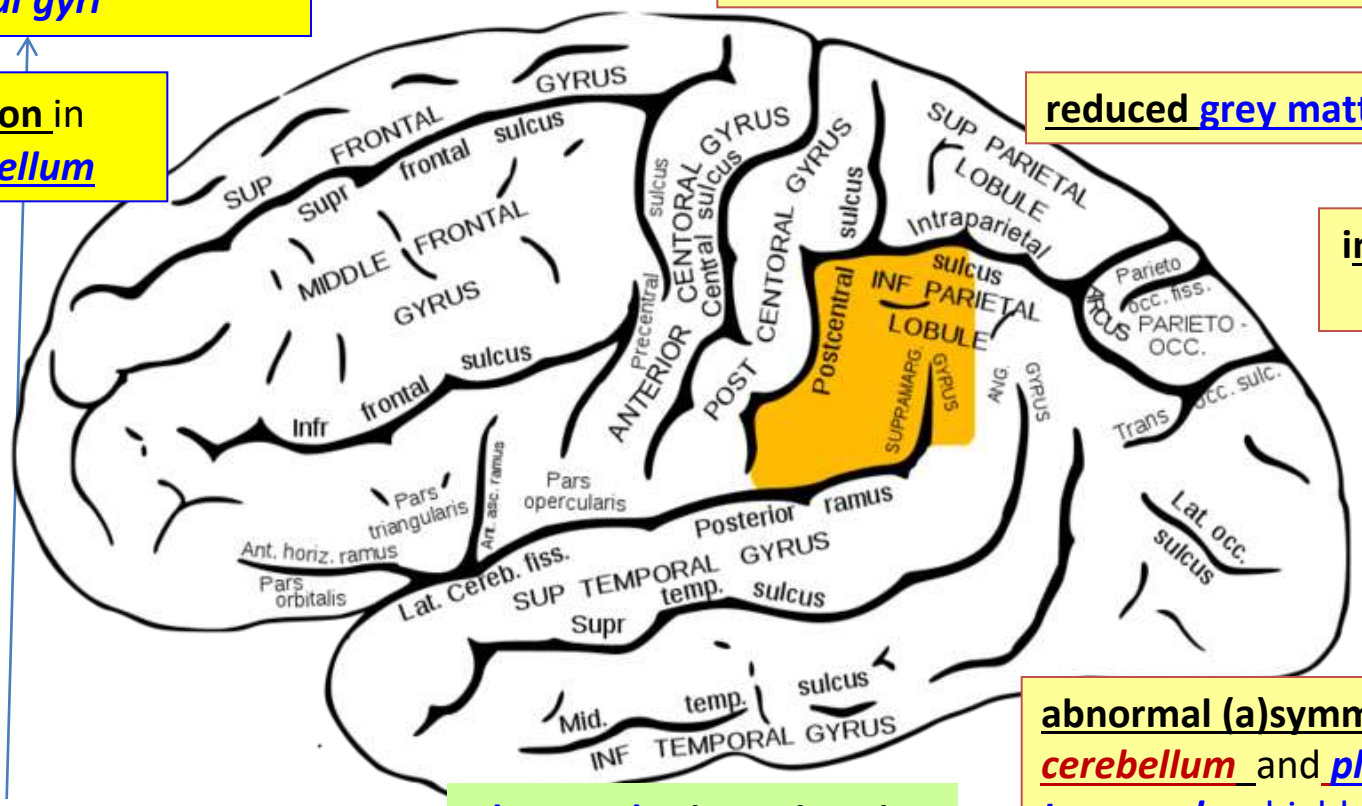
under-activations in the **left hemisphere fusiform** and ***supramarginal gyri***

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***

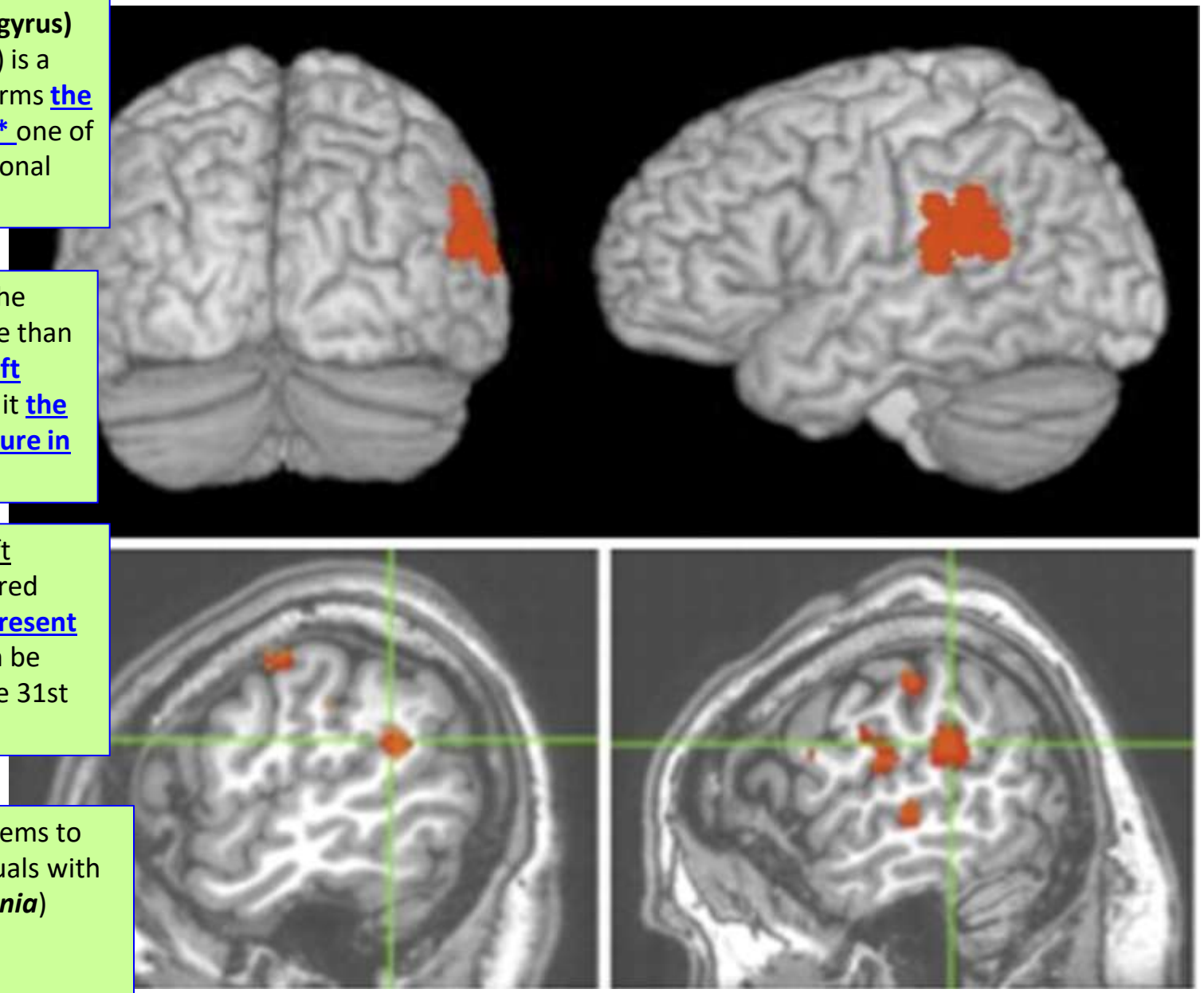
Elnakib A, Soliman A, Nitzken M, Casanova MF, Gimel'farb G, El-Baz A. ***Magnetic resonance imaging findings for dyslexia: a review.*** J Biomed Nanotechnol. **2014** Oct;10(10):2778-805.

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

Leading Edge
Previews

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

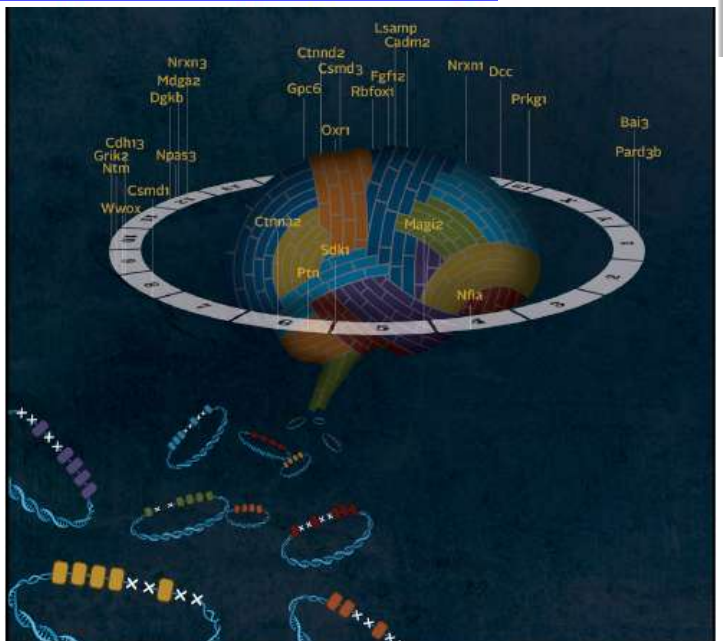
Cell

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



STRESS PROTEINS AND DNA AS A FRACTAL ANTENNA FOR RFR

DNA acts as a 'fractal antenna' for EMF and RFR.

The coiled-coil structure of DNA in the nucleus makes the molecule react like a fractal antenna to a wide range of frequencies.

The structure makes DNA particularly vulnerable to EMF damage.

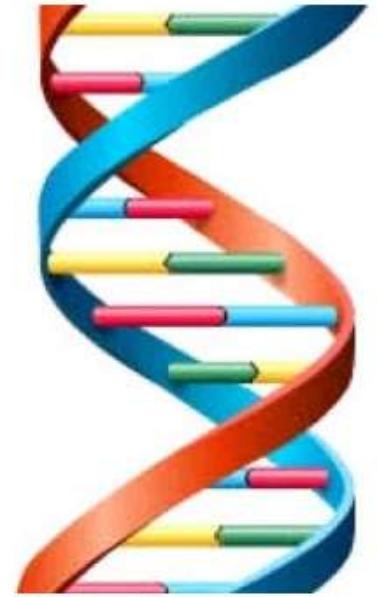
The mechanism involves direct interaction of EMF with the DNA molecule (claims that there are no known mechanisms of interaction are patently false)

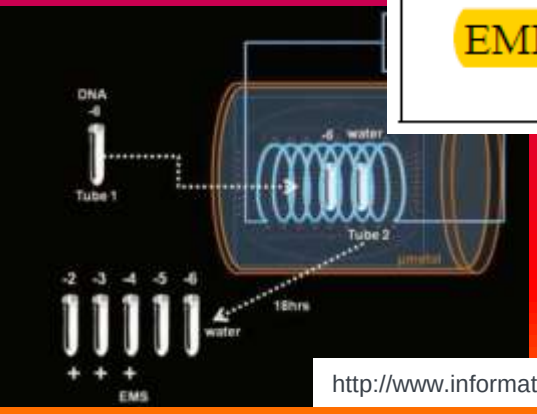
Many EMF frequencies in the environment can and do cause DNA changes.

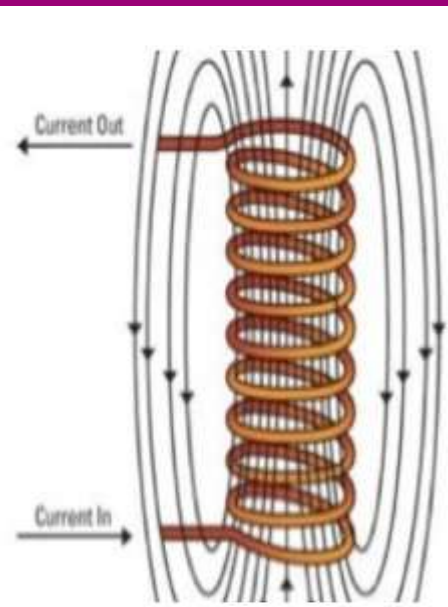
The EMF-activated cellular stress response is an effective protective mechanism for cells exposed to a wide range of EMF frequencies.

EMF stimulates stress proteins (indicating an assault on the cell).

EMF efficiently harms cells at a billion times lower levels than conventional heating.
Blank, 2012 – Section 7)

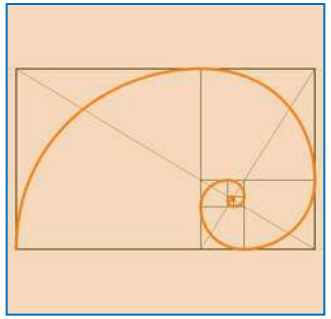


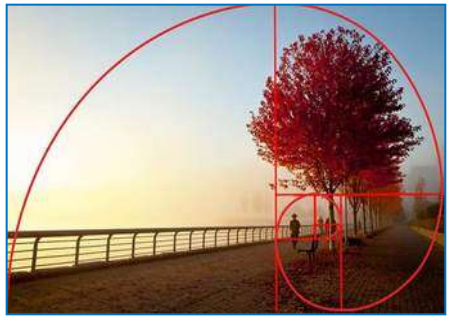


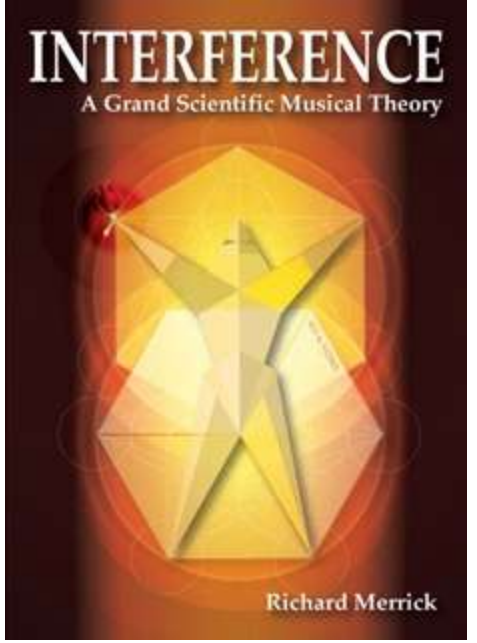


http://www.informationenergymedicine-academy.com/wp-content/uploads/coil-to-generate-7-Hz-carrier-wave-300x228.jpg 300w" sizes="(max-width: 500px) 100vw, 500px" /

Holonomic Brain Model

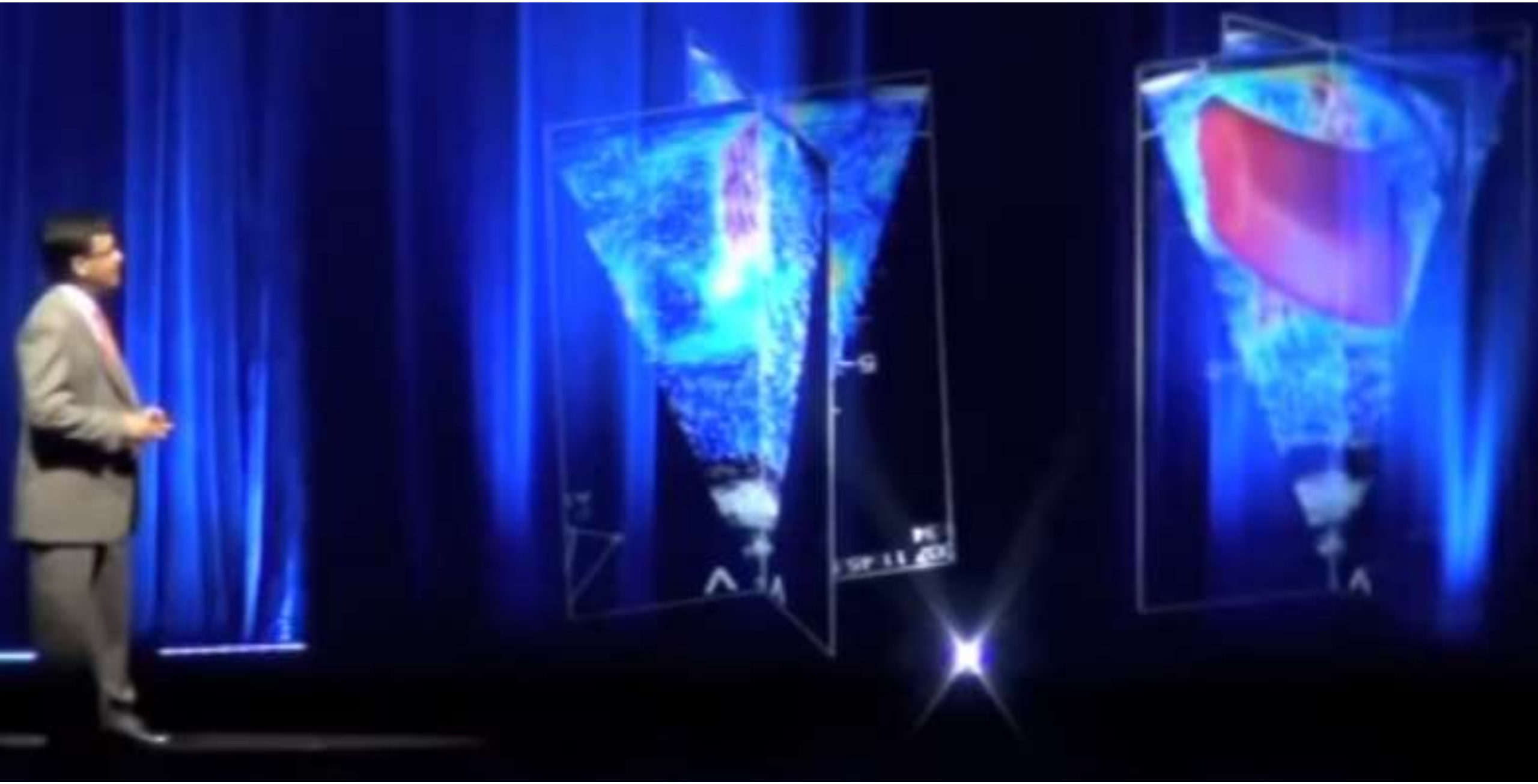






We recognize harmony and harmonics in music by pattern matching standing wave patterns against identical standing wave patterns in our brain. This is compatible with the **Pribram-Bohm holonomic brain model** whereby the **brain is described as a hologram interference pattern resulting from orthogonal standing waves**

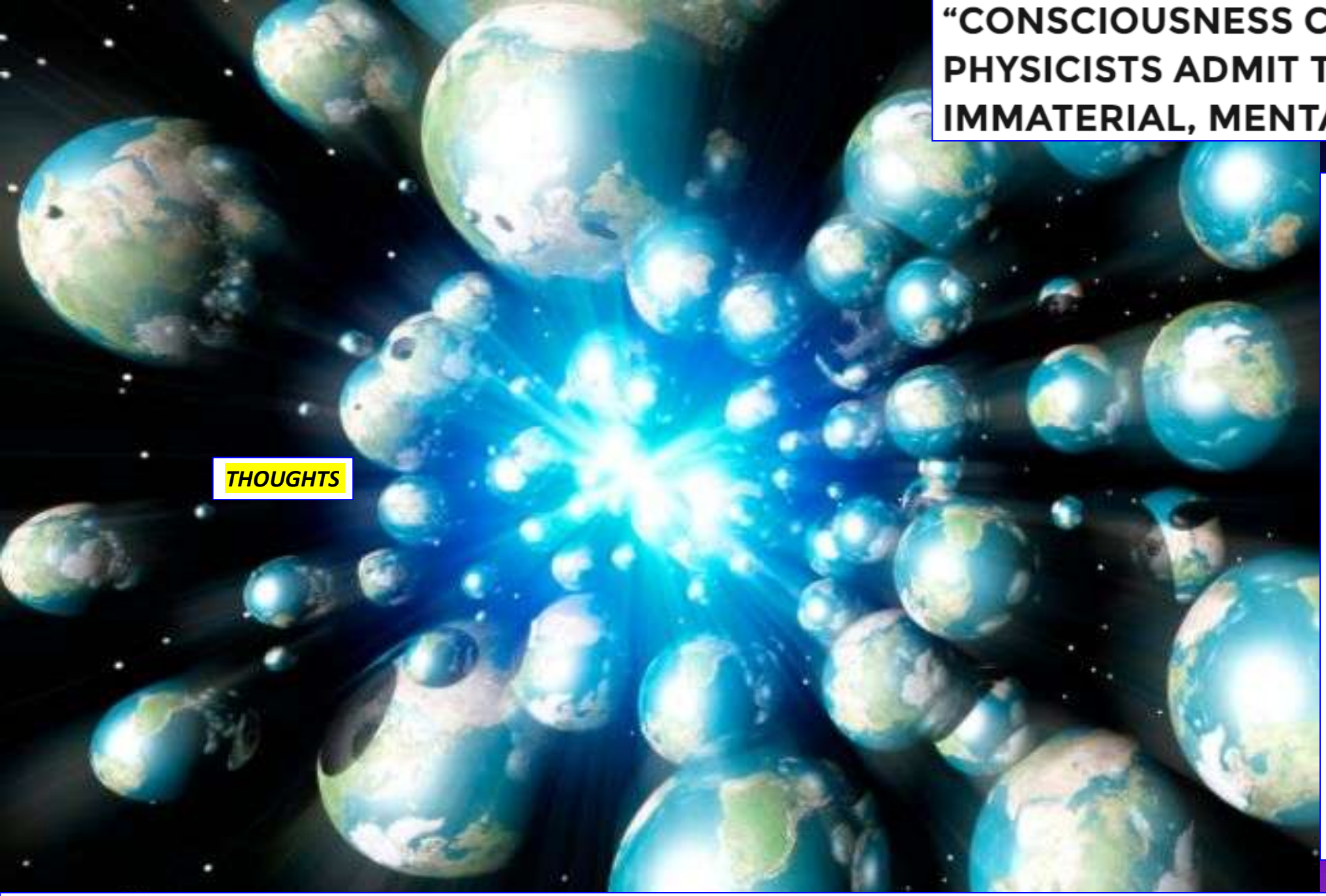
http://www.interferencetheory.com/Blog/files/a08dd0c1778355549834641e6f733b49-40.html



I regard consciousness as fundamental. I regard matter as derivative from consciousness. We cannot get behind consciousness. Everything that we talk about, everything that we regard as existing, postulates consciousness.

(Max Planck)

"CONSCIOUSNESS CREATES REALITY" PHYSICISTS ADMIT THE UNIVERSE IS IMMATERIAL, MENTAL & SPIRITUAL



As observers, we are personally involved with the creation of our own reality…
Physicists are being forced to admit that **the universe is a "mental" construction…** the **universe begins to look more like a great thought than like a great machine.**

Mind no longer appears to be an accidental intruder.. we ought rather hail it as **the creator and governor of the realm of matter**

R.C. Henry ***The Mental Universe*** Nature 436:29,2005

http://www.collective-evolution.com/2014/11/11/consciousness-creates-reality-physicists-admit-the-universe-is-immaterial-mental-spiritual/

Nature **436**, 29 (7 July 2005) | doi:10.1038/436029a; Published online 6 July 2005

nature International weekly journal of science

Concept

The mental Universe

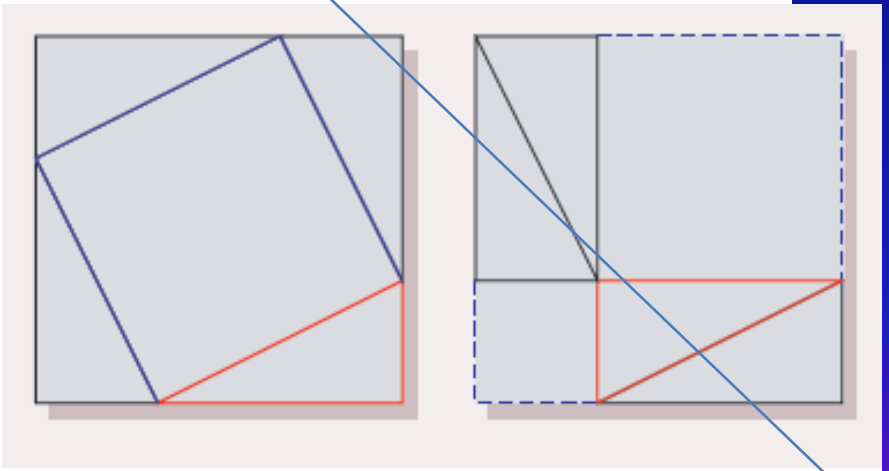
Richard Conn Henry[1]

1. Richard Conn Henry is a Professor in the Henry A. Rowland Department of Physics and Astronomy, The Johns Hopkins University, Baltimore, Maryland 21218, USA.

The only reality is mind and observations, but observations are not of things. To see the Universe as it really is, we must abandon our tendency to conceptualize observations as things.

▲ Top

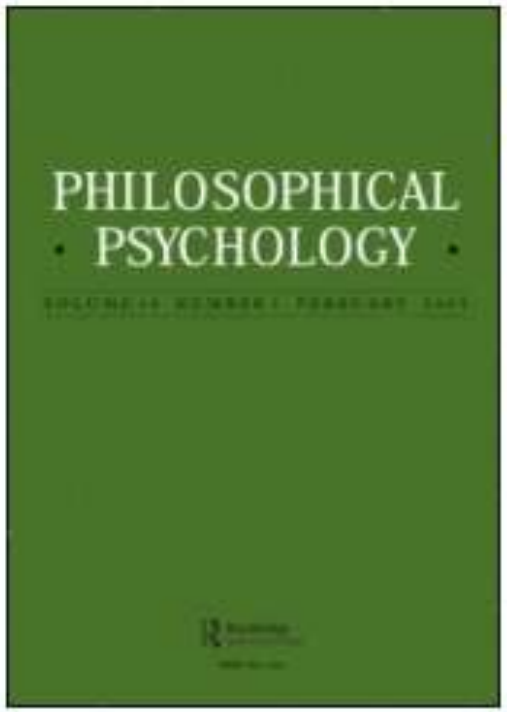
correct understanding of physics was accessible even to Pythagoras. According to Pythagoras, "number is all things", and numbers are mental, not mechanical. Likewise, Newton called light "particles", knowing the concept to be an 'effective theory' — useful, not true. As noted by Newton's biographer Richard Westfall: "The ultimate cause of atheism, Newton asserted, is 'this notion of bodies having, as it were, a complete, absolute and independent reality in themselves.'" Newton knew of Newton's rings and was untroubled by what is shallowly called 'wave/particle duality'.



Proof without words: Pythagoras explained things using numbers.

The 1925 discovery of quantum mechanics solved the problem of the Universe's nature. Bright physicists were again led to believe the unbelievable — this time, that the Universe is mental. According to Sir James Jeans: "the stream of knowledge is heading towards a non-mechanical reality; the Universe begins to look more like a great thought than like a great machine. Mind no longer appears to be an accidental intruder into the realm of matter... we ought rather hail it as the creator and governor of the realm of matter." But physicists have not yet followed Galileo's example, and convinced everyone of the wonders of quantum mechanics. As Sir Arthur Eddington explained: "It is difficult for the matter-of-fact physicist to accept the view that the substratum of everything is of mental character."

Physicists shy from the truth because the truth is so alien to everyday physics. A common way to evade the mental Universe is to invoke 'decoherence' — the notion that 'the physical environment' is sufficient to create reality, independent of the human mind. Yet the idea that any irreversible act of amplification is necessary to collapse the wave function is known to be wrong: in 'Renninger-type' experiments, the wave function is collapsed simply by your human mind seeing nothing. The Universe is entirely mental.



Philosophical Psychology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713441835

A new theory of the relationship of mind and matter

David Bohm[a]
[a] Department of Theoretical Physics, Birkbeck College, University of London, London, United Kingdom

To cite this Article Bohm, David(1990) 'A new theory of the relationship of mind and matter', Philosophical Psychology, 3: 2, 271 — 286
To link to this Article: DOI: 10.1080/09515089008573004
URL: http://dx.doi.org/10.1080/09515089008573004

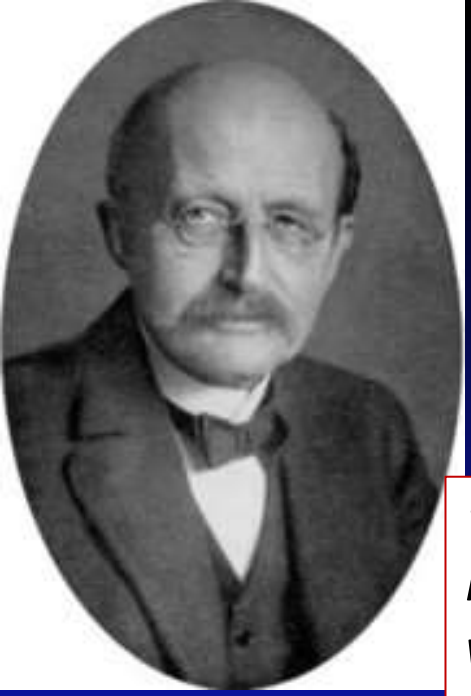
"Ultimately, the entire universe (with all its 'particles', including those constituting human beings, their laboratories, observing instruments, etc.) has to be understood as a single undivided whole, in which analysis into separately and independently existent parts has no fundamental status."

- David Bohm

POST-SCRIPTUM

*"Regard the physical world as made of **information**, with **energy** and **matter** as incidentals." - John Wheeler*

http://wsimag.com/science-and-technology/20365-the-intuitive-evidence-of-being-awareness



"***All matter originates and exists only by virtue of a force*** ***which brings the particle of an atom to vibration*** *and holds this most minute solar system of the atom together.*

We must assume behind this force the existence of a conscious and intelligent mind. This mind is the matrix of all matter."

"***The external world of physics has thus become a world of shadows***. *In removing our illusions we have removed the substance, for indeed we have seen* ***that substance is one of the greatest of our illusions..*** *In the world of physics we watch a shadowgraph performance of the drama of familiar life.* ***The shadow of my elbow rests on the shadow table as the shadow ink flows over the shadow paper.***
It is all symbolic*, and as a symbol the physicist leaves it.*
Then comes the alchemist Mind who transmutes the symbols.
The sparsely spread nuclei of electric force become a tangible solid; their restless agitation becomes the warmth of summer; the octave of aethereal vibrations becomes a gorgeous rainbow…
The frank ***realization that physical science is concerned with a world of shadows is one of the most significant of recent advances****".*

Eddington A. ***The Nature of the Physical World*** (1928)

In science, 'fact' can only mean 'confirmed to such a degree that it would be perverse to withhold provisional assent.' I suppose that apples might start to rise tomorrow, but the possibility does not merit equal time in physics classrooms.

Stephen Jay Gould (1941 - 2002)

MAY GOD US KEEP FROM SINGLE VISION & NEWTON'S SLEEP !

The most important scientific revolutions all include, as their only common feature, the dethronement of human arrogance from one pedestal after another of previous convictions about our centrality in the cosmos.

Stephen Jay Gould (1941 - 2002)