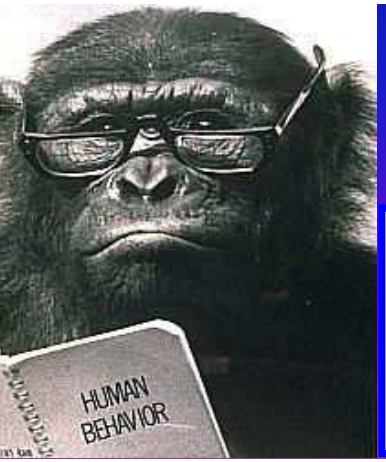
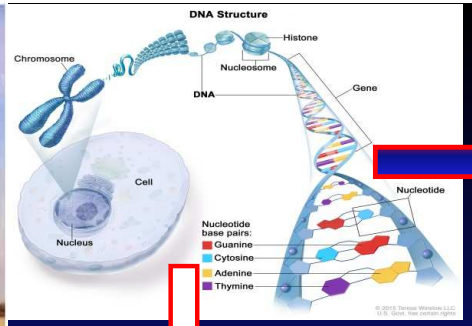
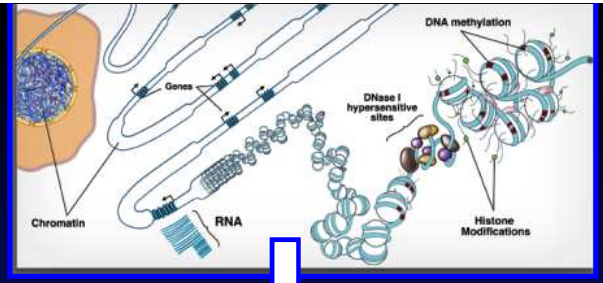
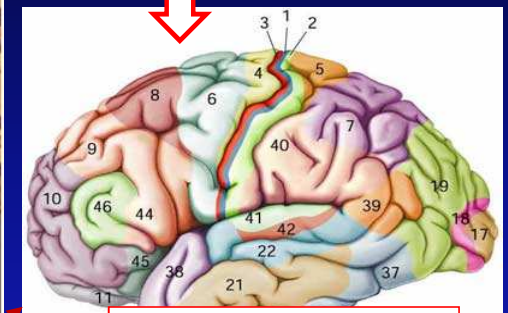
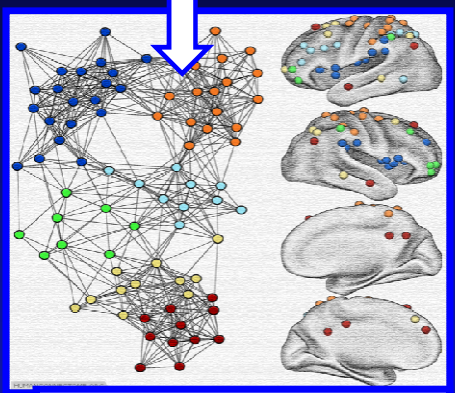
Early/late-life adversities and behavioural phenotypes: insight into metabolomics, genomics and connectomics









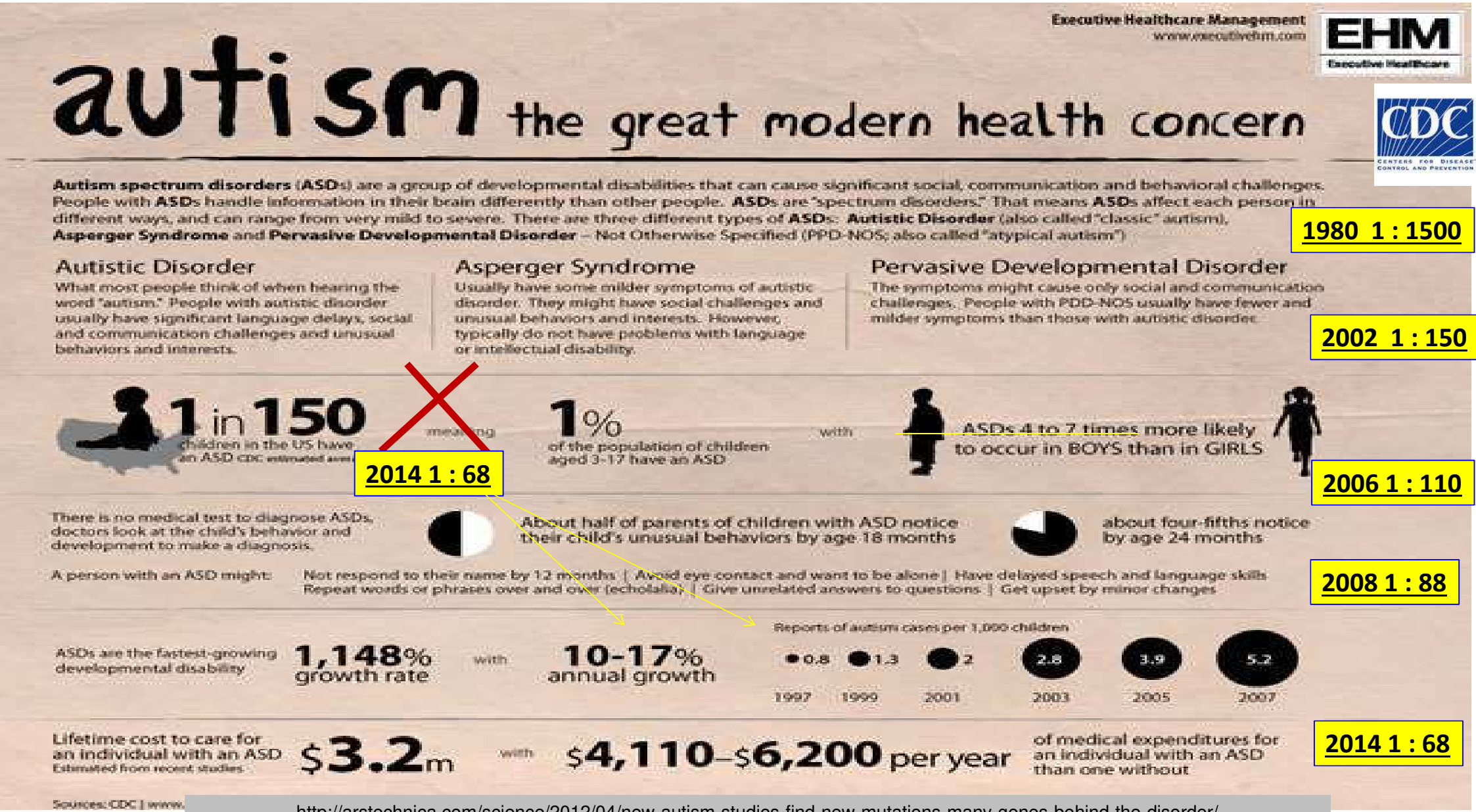


(I) The building of the *hardware* is under ***genetic control***

(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



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

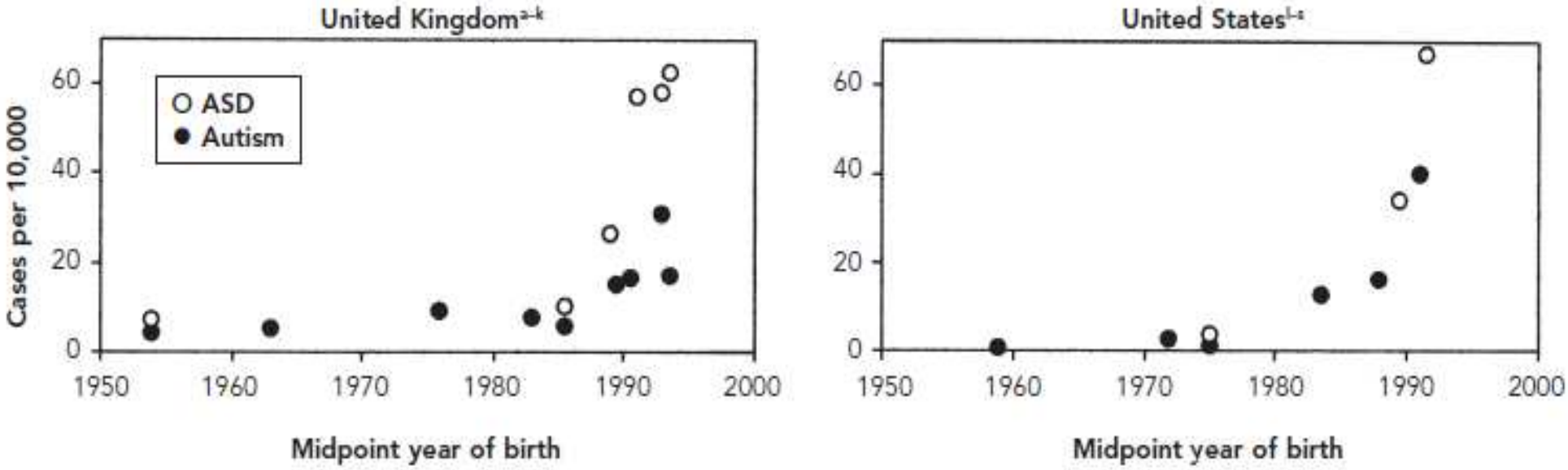
AUTISM
(ASD :Autism Spectrum Disorders)

<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]

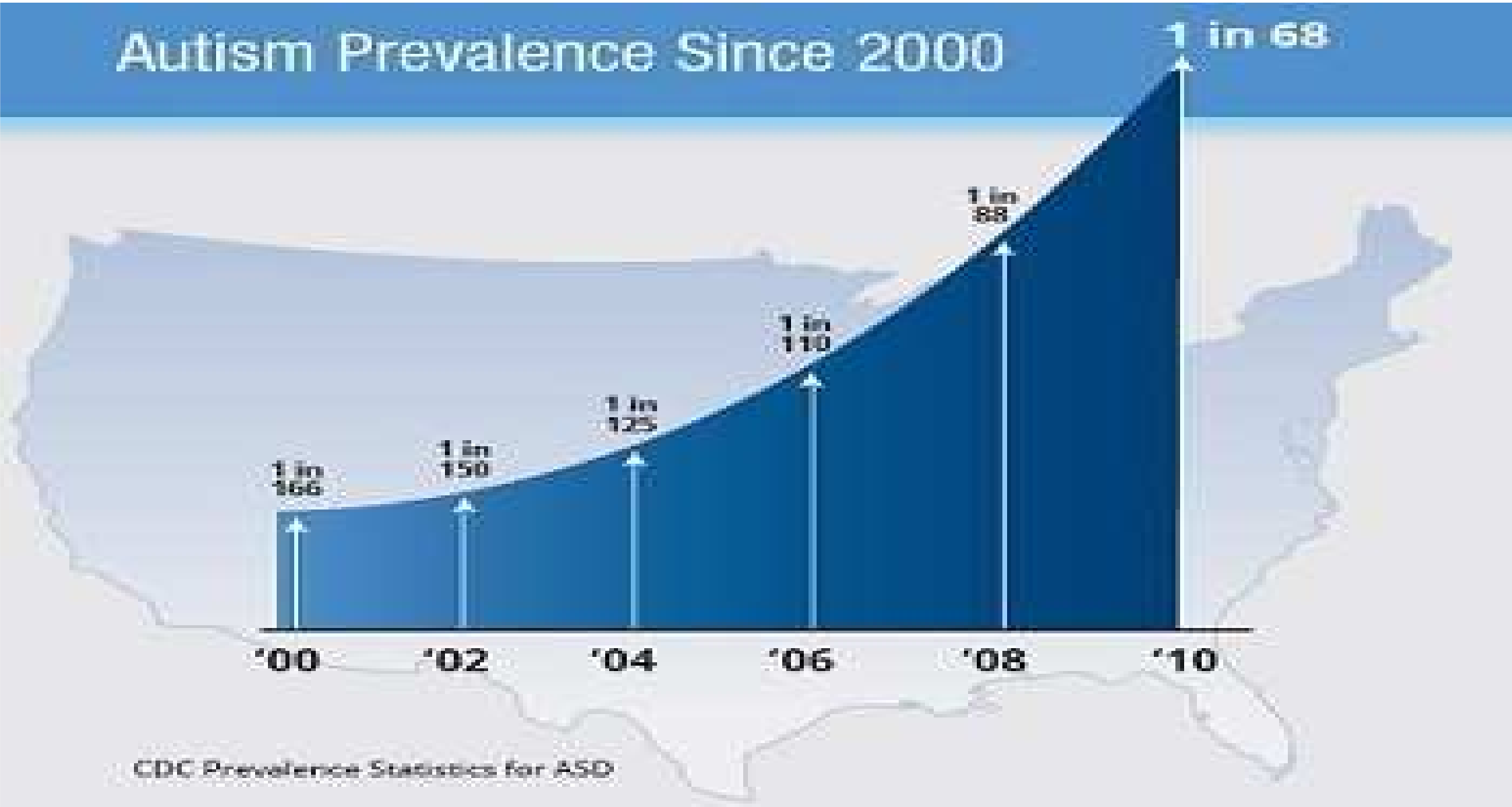
[k]Baird et al. 2000[78]

[l]Treffert 1970[36]

[m]Ritvo et al. 1989[53]

[n]Burd et al. 1987[45]

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



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.**

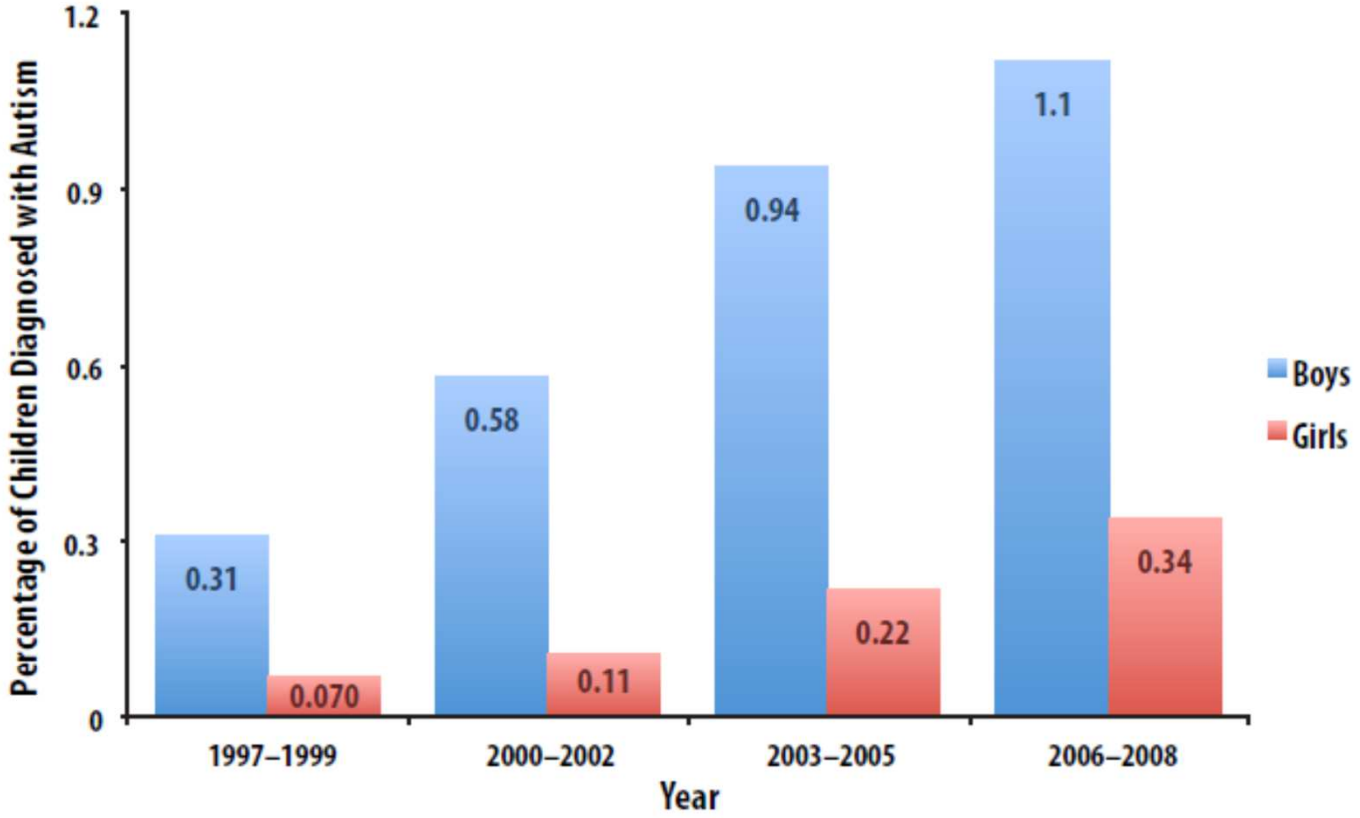
.

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

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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

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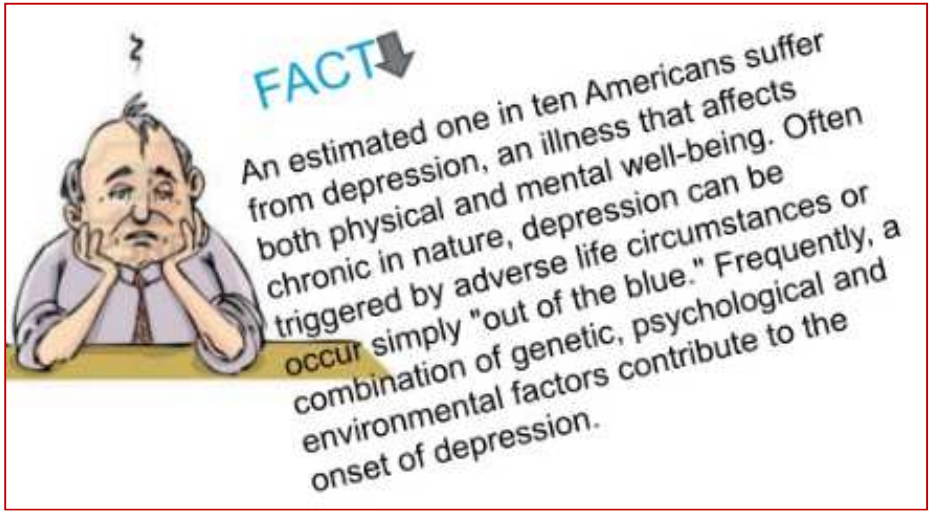
pgrand@hsph.harvard.edu

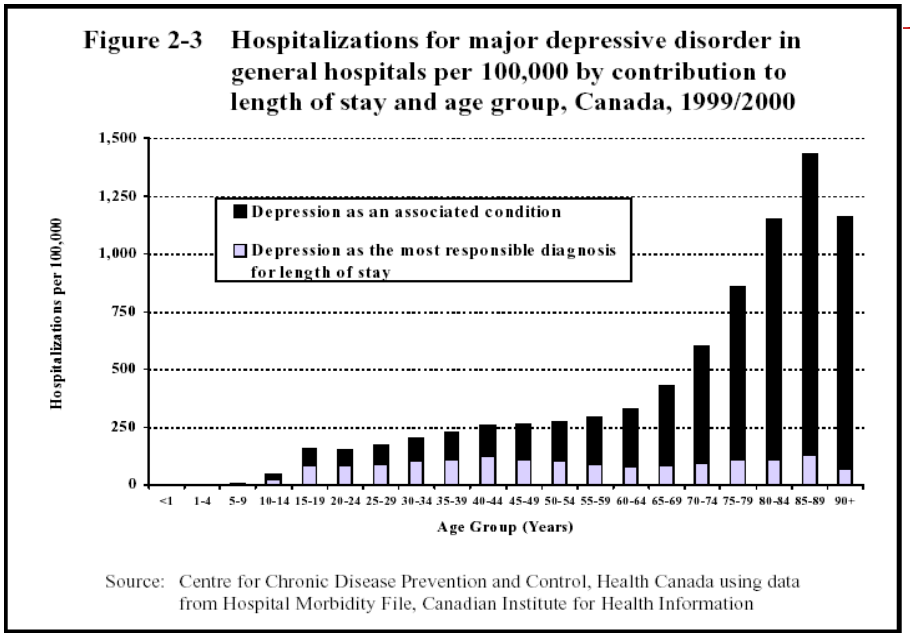
Philippe Grandjean, Philip J Landrigan

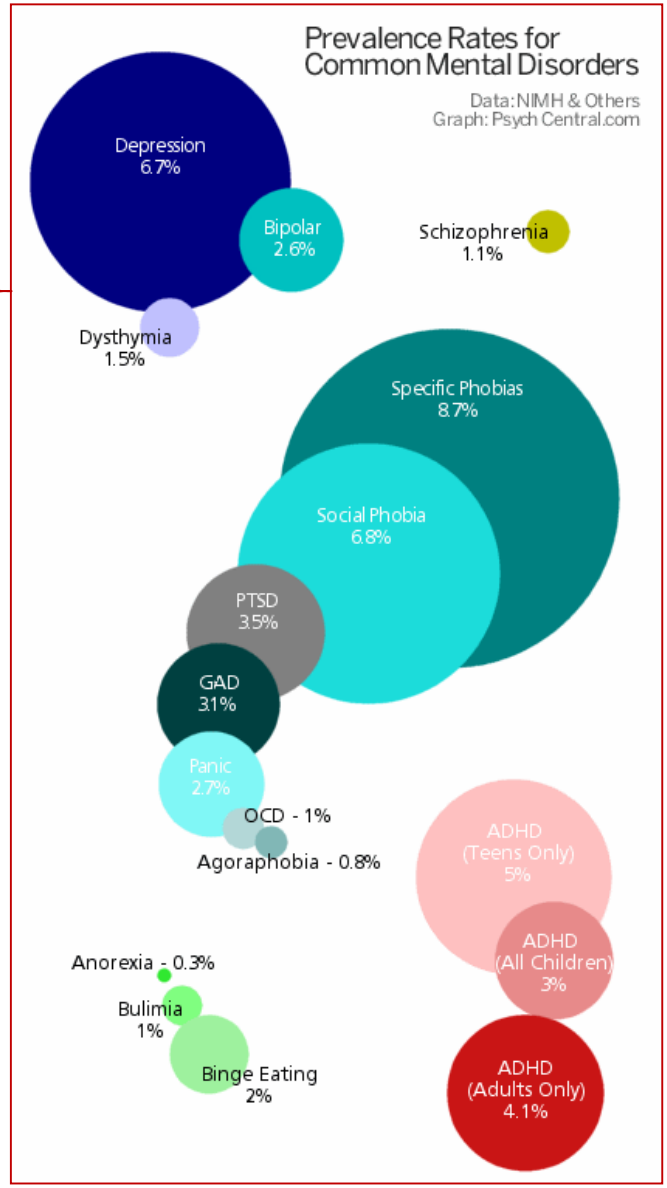
Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known 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

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





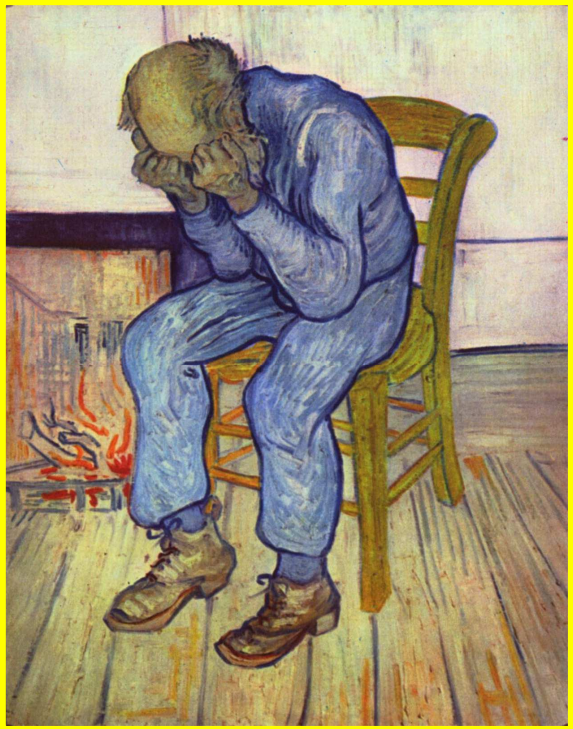


http://psychcentral.com/blog/archives/2009/10/05/prevalence-of-common-mental-disorders/

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***

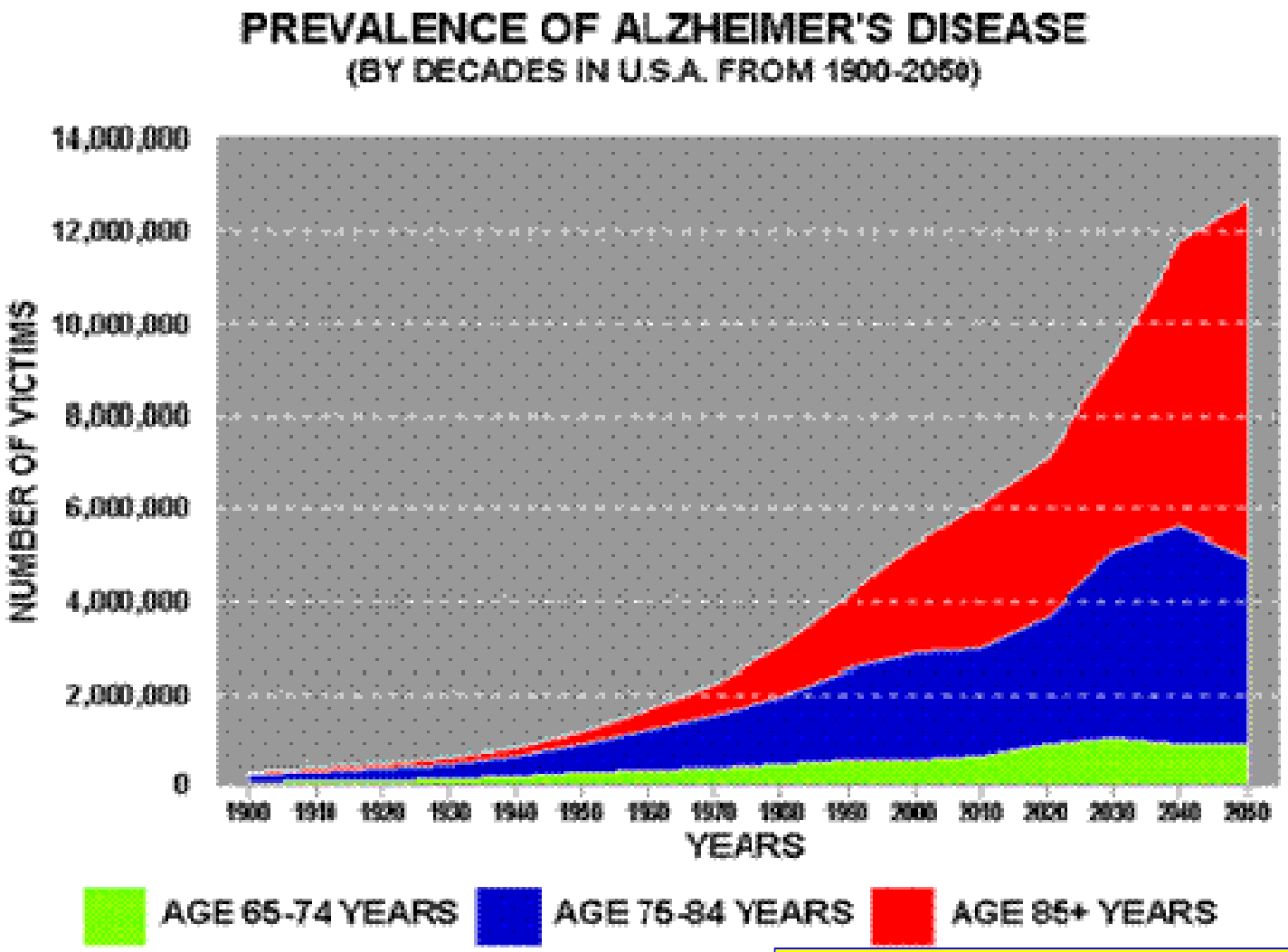
Disturbi del sonno, di **risveglio**, **ipersonnia**

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**.



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

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

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

ATTIVISMO QUANTICO EUROPEO

CENTER FOR QUANTUM ACTIVISM

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Bologna

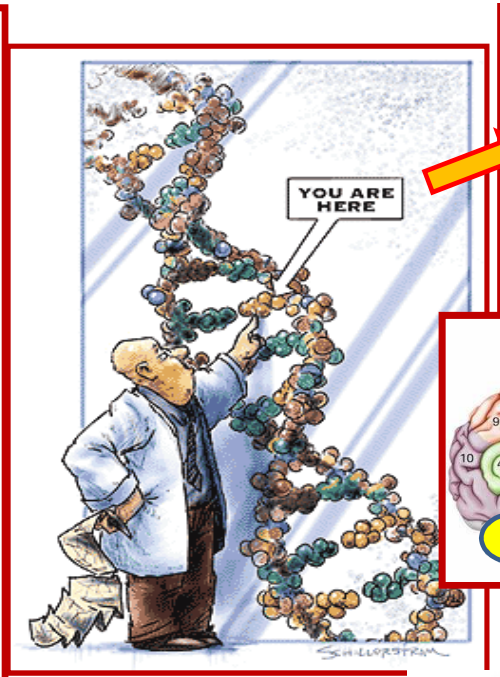
Istituto delle Scienze Neurologiche

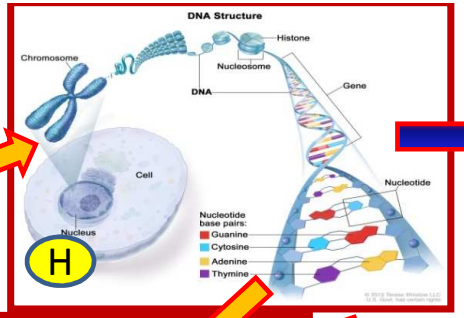
BOLOGNA, 3 MAGGIO 2017

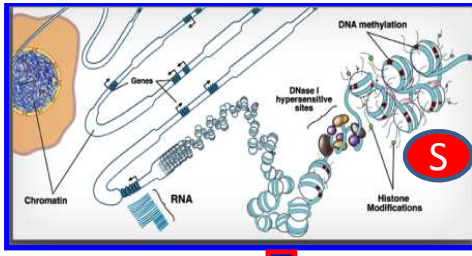
L'ARMONIA MENTE-CORPO, LE FREQUENZE DELLA VITA E I BIOFOTONI

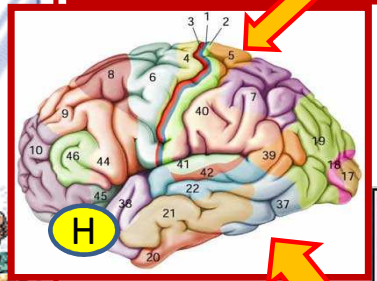
RELATORI

Prof. P. Biava, *IRCCS Multimedica Milano*
Prof. E. Burgio, *ECERI Bruxelles*
Prof. G. Pagliaro, *AUSL Bologna*
Prof. C. Ventura, *Università di Bologna*









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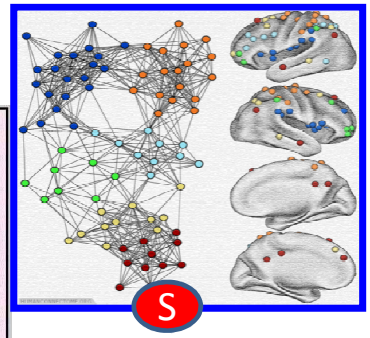

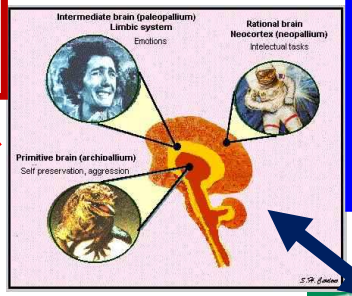

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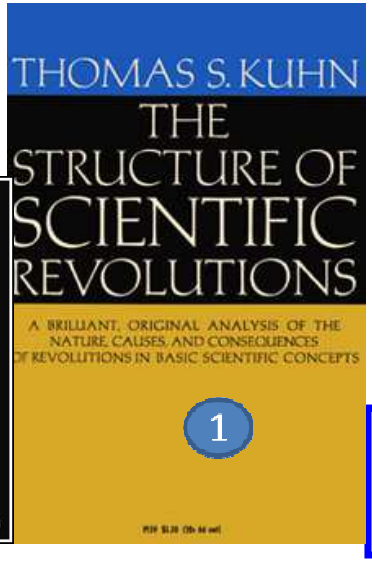
I regard consciousness as fundamental. I regard matter as derivative from consciousness. We cannot get behind consciousness. Everything that we talk about, everything that we regard as existing, postulates consciousness.

(Max Planck)

izquotes.com



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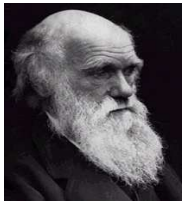

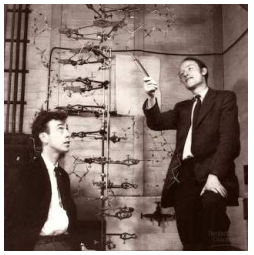

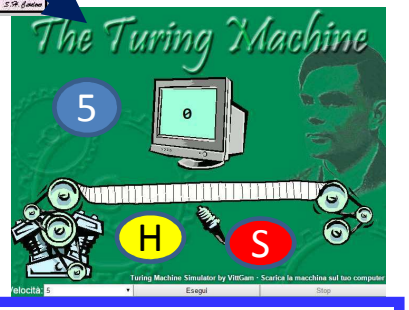

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BioEssays Vol. 18 no. 9
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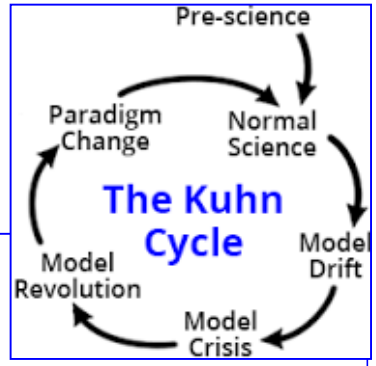


Are there 'Kuhnian' revolutions in biology?

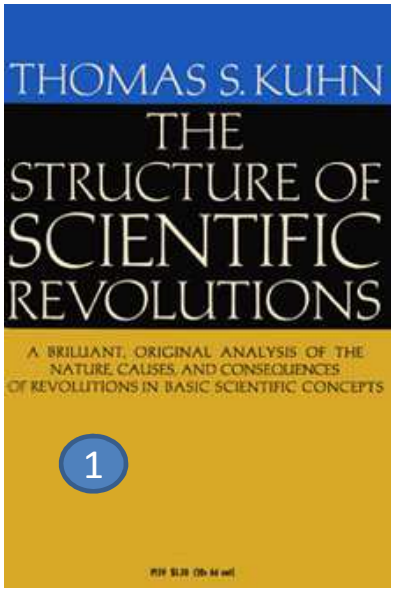
Adam S. Wilkins

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

Kuhn, a professor emeritus at MIT in recent years, had written or coauthored five books and numerous scholarly articles, but he is undoubtedly best known, and will be best remembered, for *The Structure of Scientific Revolutions*[1], first published in 1962. In this seminal work, Kuhn argued persuasively against the traditional idea of 'scientific progress', the notion that scientific knowledge involves the steady growth of understanding through the application of something called 'The Scientific Method'. He argued that, in reality, science involves two distinctly different processes. For the most part, scientists work within certain conceptual frameworks or models, 'paradigms'. This work serves to embellish and strengthen the central paradigm at the heart of each field and is essentially conservative in nature. Kuhn termed such activities 'normal science'. Yet, the continued practice of normal science within a field often shows up weaknesses in the central paradigm. When these weakdigms' and the like. The notion that what scientists believe at any one time is determined in part by group consensus – in some corridors, there were mutterings that the idea involved little more than 'mob rule' in deciding scientific truth, a notion vehemently denied by Kuhn himself[3] – was unsettling. Furthermore, the neurological implications – that young brains are much more likely to generate and be receptive to major conceptual breakthroughs – though not new, could not have been comforting to those past their first youth. Nevertheless, the impact of Kuhn's idea was immediate and pervasive. It would not be inappropriate to refer to the 'Kuhnian revolution' in the philosophy of science.

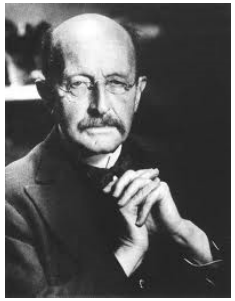
The question of generality, however, still nags. In contrast to many earlier, *a priori*, philosophical theories of knowledge, Kuhn built his case from examples, in effect inductively. (Kuhn's ideas co-exist uneasily today with those of Karl Popper, an arch-foe of argument from induction; it is, in fact,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

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

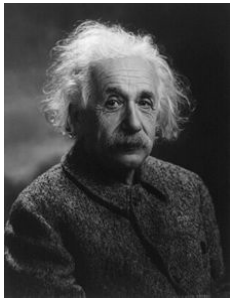


Ludwig Boltzmann

James Clerk Maxwell



Max Planck



Albert Einstein**

Louis de Broglie

E Schrödinger **

Classical physics draws a **distinction between particles and *energy***, holding that only **the latter exhibit waveform characteristics**, ***whereas quantum mechanics* is based on the observation that matter has both wave and particle aspects** and postulates that the state of **every subatomic particle can be described by a wave-function—a mathematical representation** used to calculate the **probability** that the particle, if measured, will be in a given location or state of motion… These **models could not easily be reconciled with the way objects are observed to behave on the macro-scale of everyday life**. The **predictions** they offered often appeared **counter-intuitive and caused much consternation among the physicists —often including their discoverers** **.

W. Heisenberg

Niels Bohr

Boltzmann had a tremendous admiration for **Darwin** and he wished **to extend Darwinism from biological to cultural evolution**. In fact **he considered biological and cultural evolution as one and the same things**. ... In short, **cultural evolution was a physical process taking place in the brain**. Boltzmann included ethics in the ideas which developed in this fashion (S.R. de Groot)

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)

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

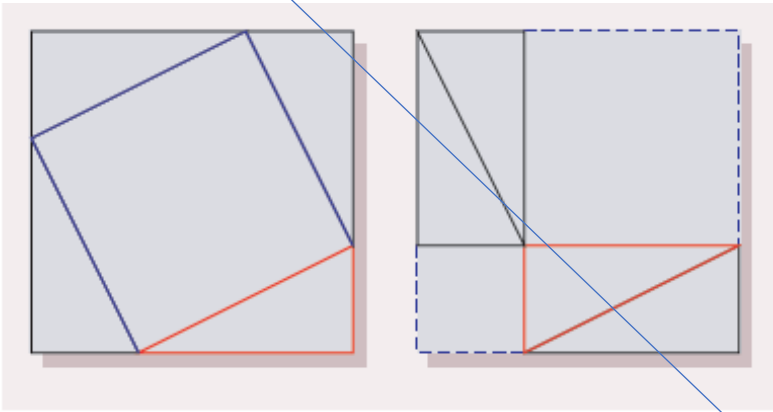
Richard Conn Henry[1]

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.

Towards a Kuhnian Revolution in Biology

nature biotechnology

COMMENTARY

EPIGENESIS AND COMPLEXITY

The coming Kuhnian revolution in biology

Richard C. Strohman

2

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

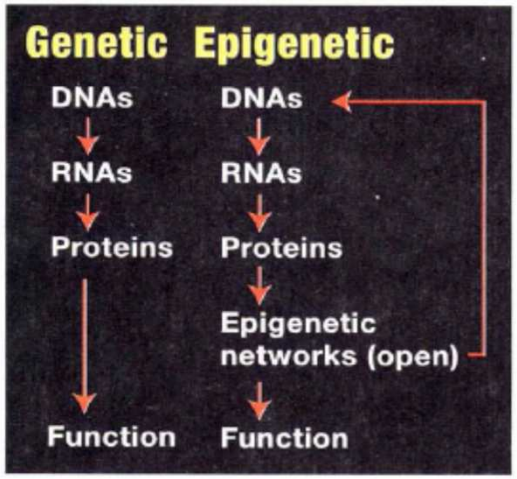


Figure 1. Genetic and epigenetic theories of information processing.

3

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

1

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

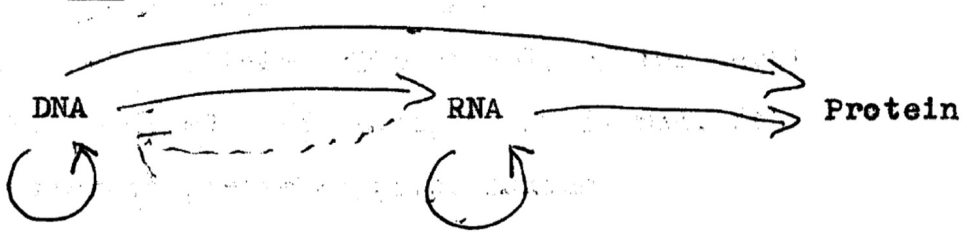
Francis Crick's statement of the central dogma, from an early draft of Crick (1958)
available at http://profiles.nlm.nih.gov/SC/B/B/F/T/_/scbbft.pdf

Ideas on Protein Synthesis (Oct. 1956)

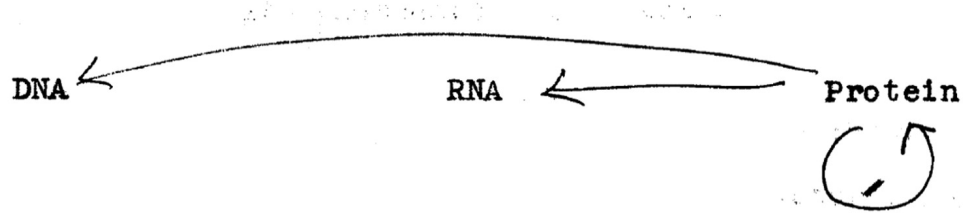
The Doctrine of the Triad.

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it.

That is, we may be able to have



but never



where the arrows show the transfer of information.

biology letters

J.D. Watson and F.H.C. Crick, Nature, *April 25, 1953, p, 737.*

A)The Central Dogma

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

This figure is purely diagrammatic. The two ribbons symbolise the two phosphate–sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their colleagues at King's College, London. One of us (J. D. W.) is aided by a fellowship from the National Foundation for Infantile Paralysis.

Medical Research Council Unit for the Study of Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

[1] Pauling, L., and Corey, R. B., *Nat. Acad. Sci.*, **39**, 84 (1953).

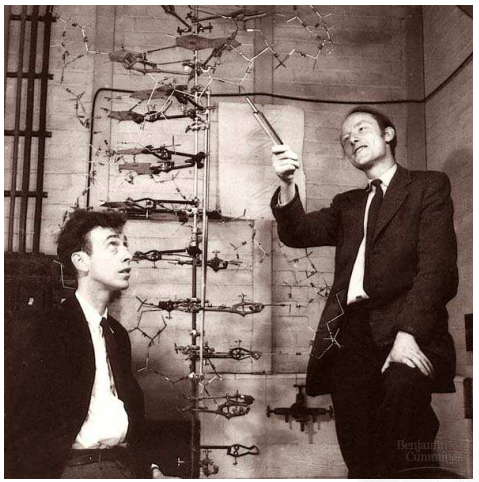
[2] Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).

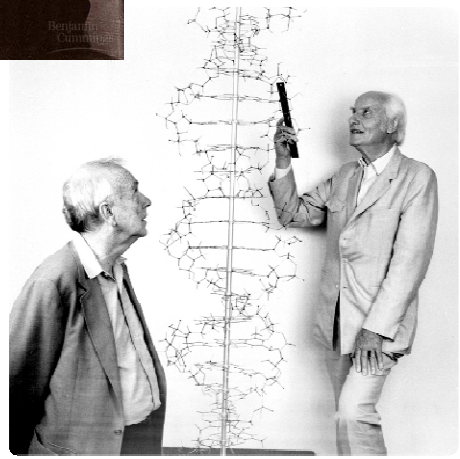
[3] Chargaff, E., for references see Zamenhof, S., Robichon-Szulmajster, H., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).

[4] Wyatt, G. R., *J. Gen. Physiol.*, **36**, 201 (1952).

[5] Astbury, W. T., *Symp. Soc. Exp. Biol. 1, Nucleic Acid*, 66 (Camb. Univ. Press, 1947).

[6] Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, **10**, 192 (1953).





IT IS WITH GREAT REGRET THAT WE HAVE TO ANNOUNCE THE DEATH, ON FRIDAY 18TH JULY 1952 OF D.N.A. HELIX (CRYSTALLINE)

DEATH FOLLOWED A PROTRACTED ILLNESS WHICH AN INTENSIVE COURSE OF BIBLICAL INJECTIONS HAS FAILED TO RELIEVE.

A MEMORIAL SERVICE WILL BE HELD NEXT MONDAY OR TUESDAY.

IT IS HOPED THAT DR. M.H.F. WILKINS WILL SPEAK IN MEMORY OF THE LATE HELIX

R.E. Franklin

R.C. Corey

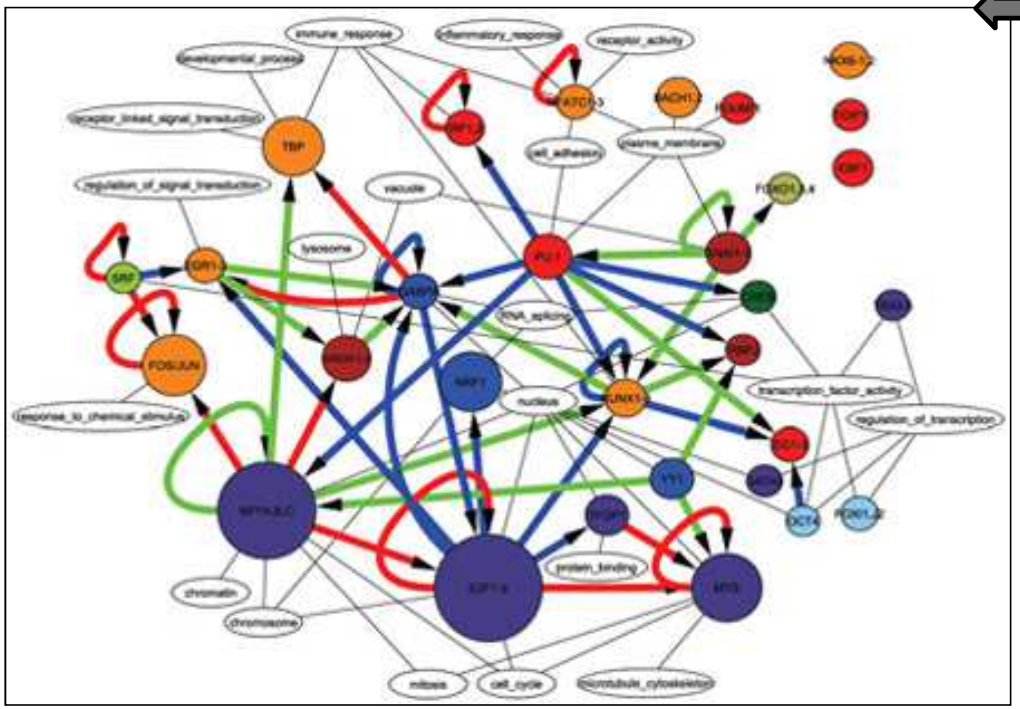
So, winning a Nobel Prize only requires one page (of very good work):

Science
AAAS

ScienceInsider
Breaking news and analysis from the world of science policy

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

….Genes Know How to Network…BUT…



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

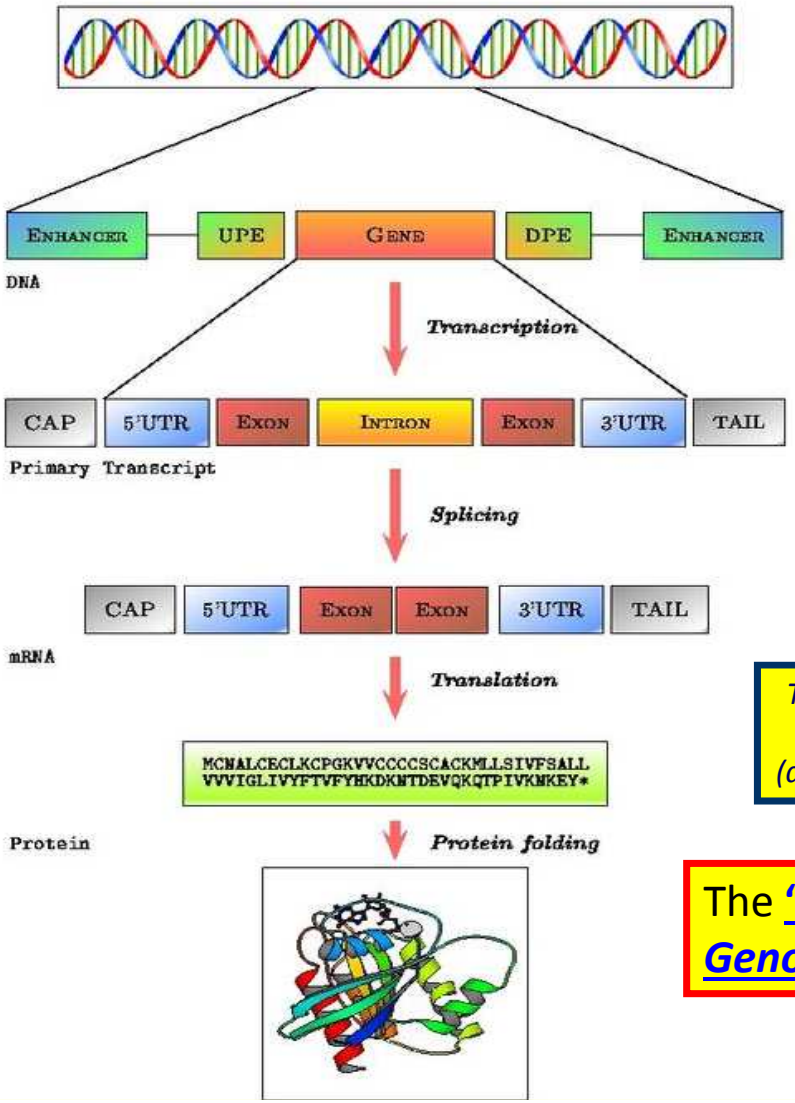
<u>IN FACT Genes</u> <u>need to be told to switch "off" and "on":</u>

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

Strohman R. , April 2001 Beyond genetic determinism

If the **Central Dogma** of Molecular Biology depicted **one direction-flow of genetic information**.....

we now know that things are quite different: **information flow is circular between genome and environment**



SYSTEMS **GENOMICS** ***(BIOLOGY)***

REVERSE TRANSCRIPTION

GRNetworks

TRANSPOSABLE ELEMENTS

NATURAL GENETIC ENGINEERING

TRANSCRIPTION FACTORS (and COFACTORS)

EPIGENETIC CHANGES

ENVIRONMENT

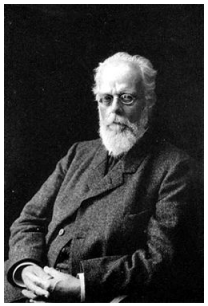
The ***"Fluid Genome"***

The main *dogmas* of the twentieth century biology

Genetic determinism

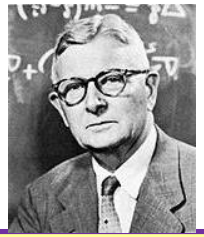
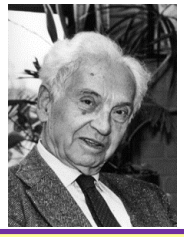
Genetic determinism is the belief that **genes** determine **morphological and behavioral traits** and do so with **little or no influence from environmental factors.**

August Weismann



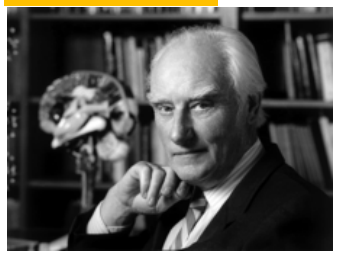
The **Weismann barrier** is the principle that **hereditary information moves only from genes to body cells**, and never in reverse. In more precise terminology **hereditary information moves only from germline cells to somatic cells** (that is, **soma to germline feedback is impossible**).



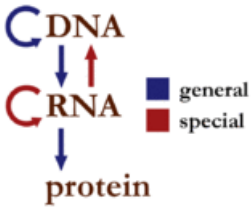



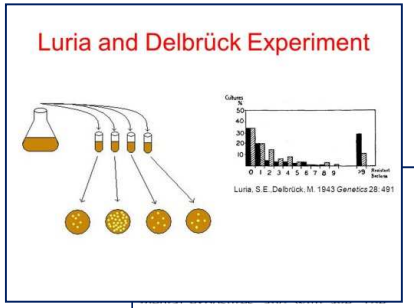

The Modern Synthesis: Following the rediscovery of Mendel's principles of genetics, several theorists such as **RA Fisher, JBS Haldane, Sewall Wright, Ernst Mayr** and **Theodosius Dobzhansky** contributed to the **synthesis of Mendel and Darwin's concept of natural selection…** The **organism** responds to a **dual causation**, one based on **laws of physics**, the other based on a **genetic program…** reflecting the **mechanics** of its constituent parts & the **phylogenetic history encoded in its genes**

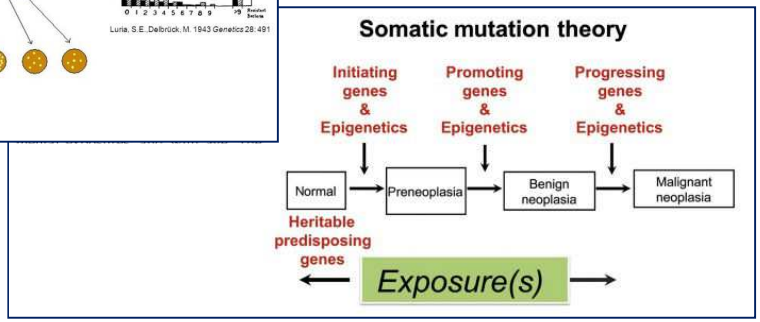
Francis Crick



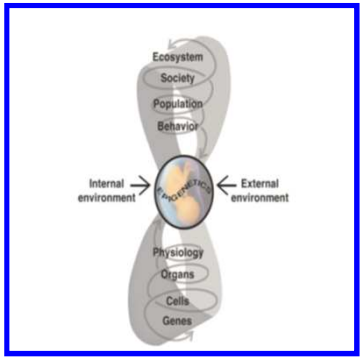
The **Central Dogma of molecular biology** deals with the **detailed residue-by-residue transfer of sequential information.** It states that such **information cannot be transferred back from protein to either protein or nucleic acid.**







The 7 keywords: from genetics to *epigenetics*



3

Fetal programming

2

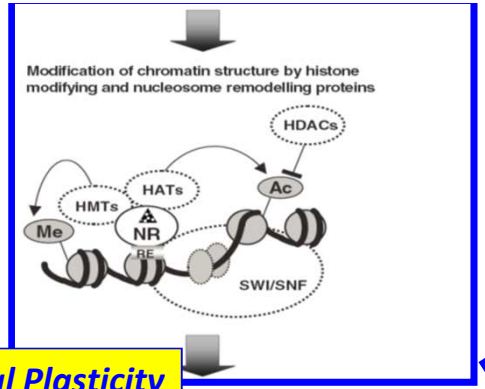
Environment

1

From Genetics to Epigenetics

*Ontogeny**

4



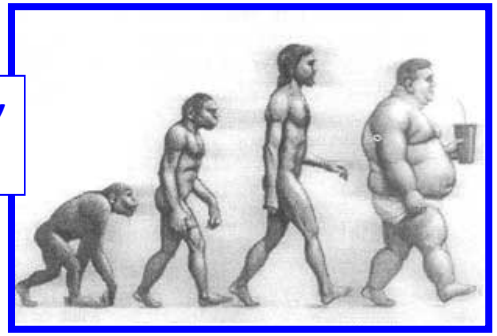
Developmental Plasticity

Devo → Evo

*Phylogeny**

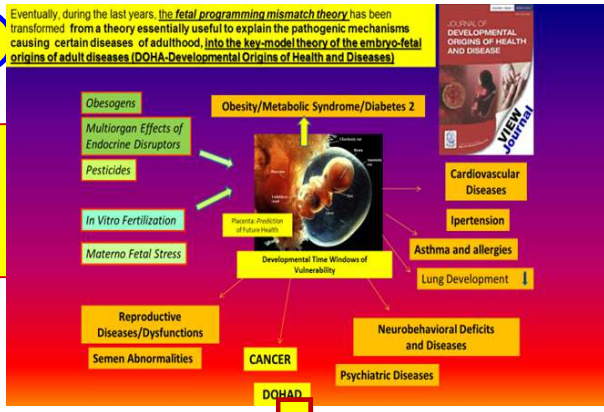
5

Evolutionary Medicine



Epi-genetic Mismatch DOHA

6



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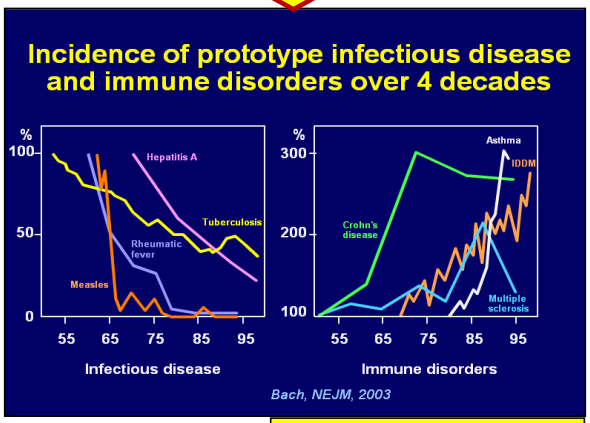
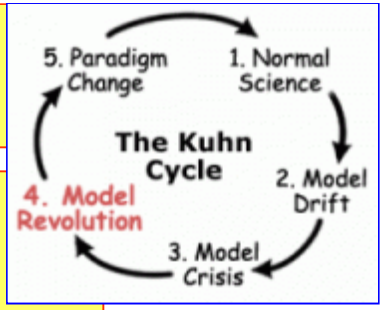


XXI Century Epidemiological Transition

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

The **Obesity-Diabesity Pandemic** is the **most evident manifestation** of the **XXIth Century Epidemiological Transition**

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

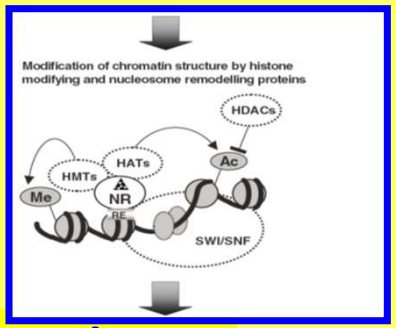


For the last 50 years it was agreed to consider **DNA as the code and the key project for the assembly of our phenotype**.

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**

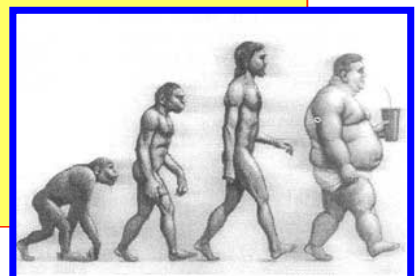
and the **information** deeply inscribed **inside the DNA**



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

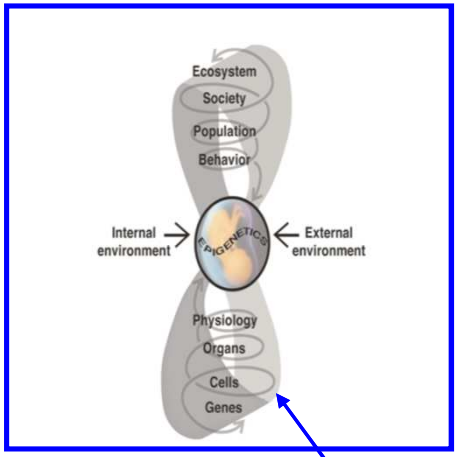


The other **key concepts** (obviously interdependent) are:

- ***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

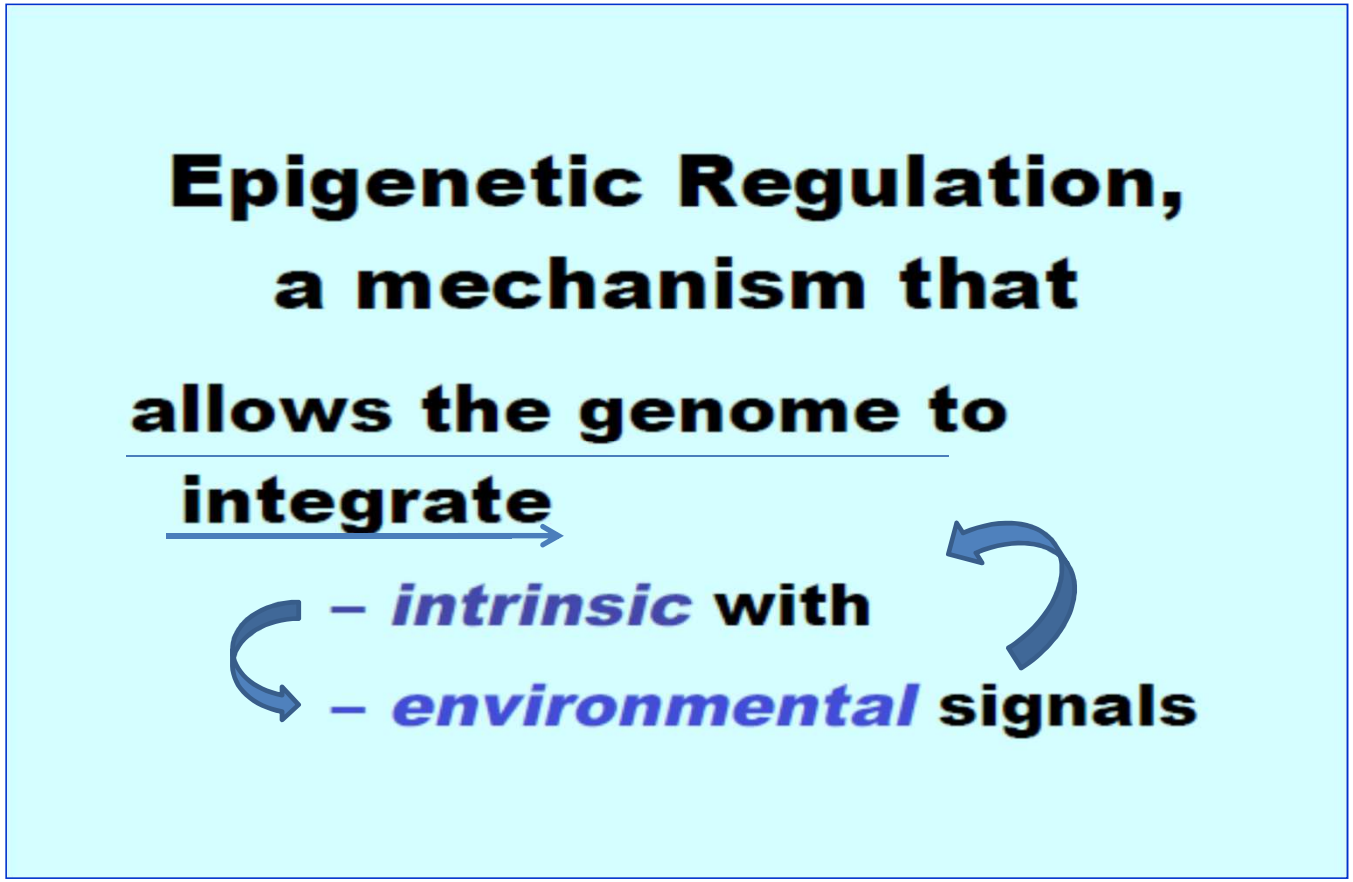
***incorrect information* (*pollutants, endocrine disruptors* ..)** and /or

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** ..

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

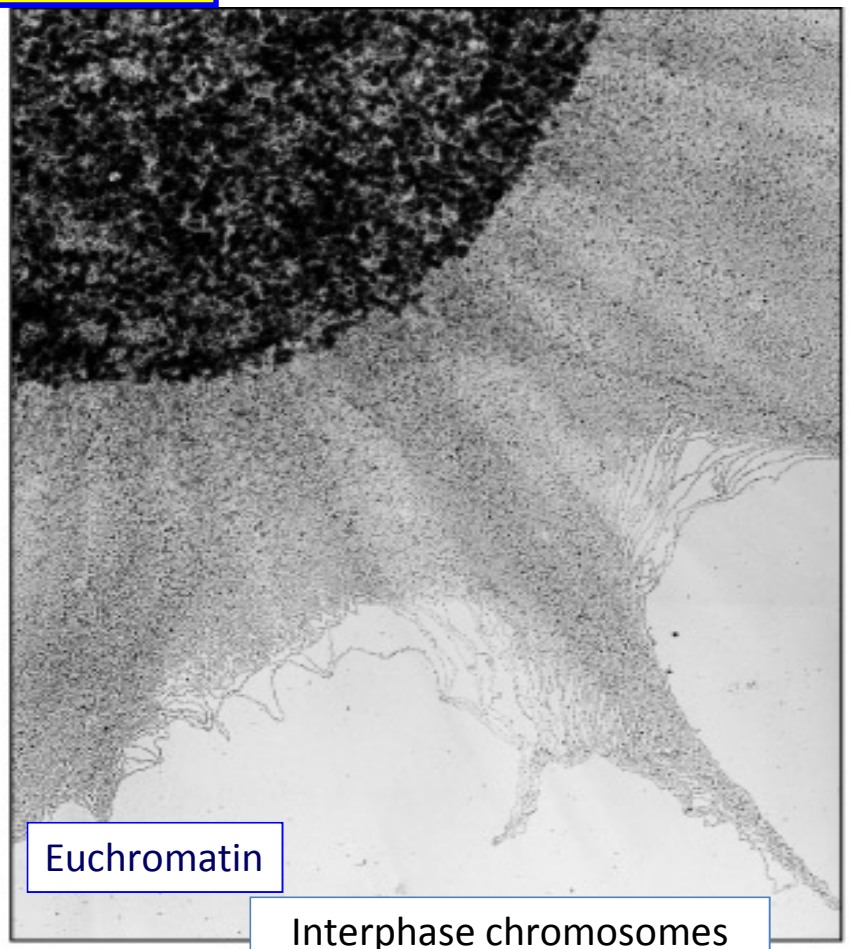


Rudolf Jaenisch- Whitehead Institute and Dept. of Biology, MIT, Cambridge, MA

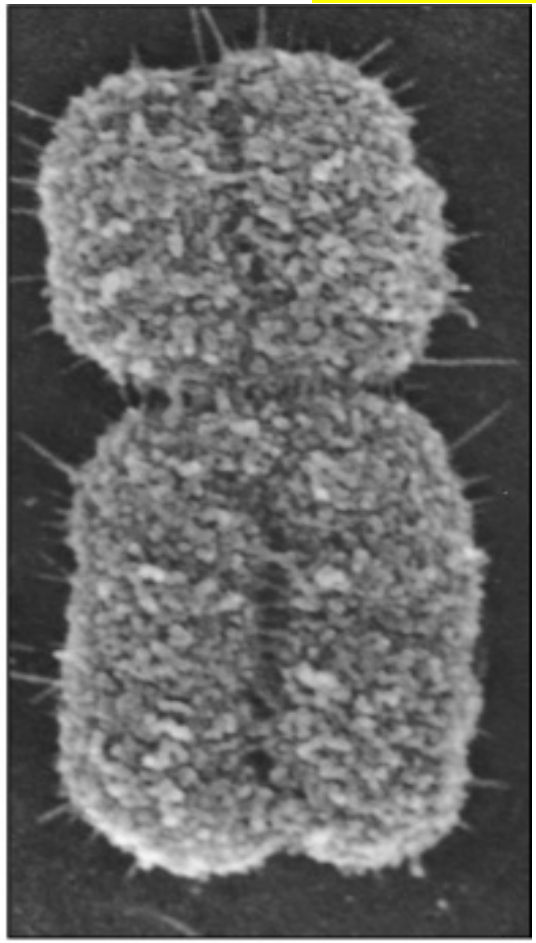
The first keyword: **Epigenetics**

Heterochromatin

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



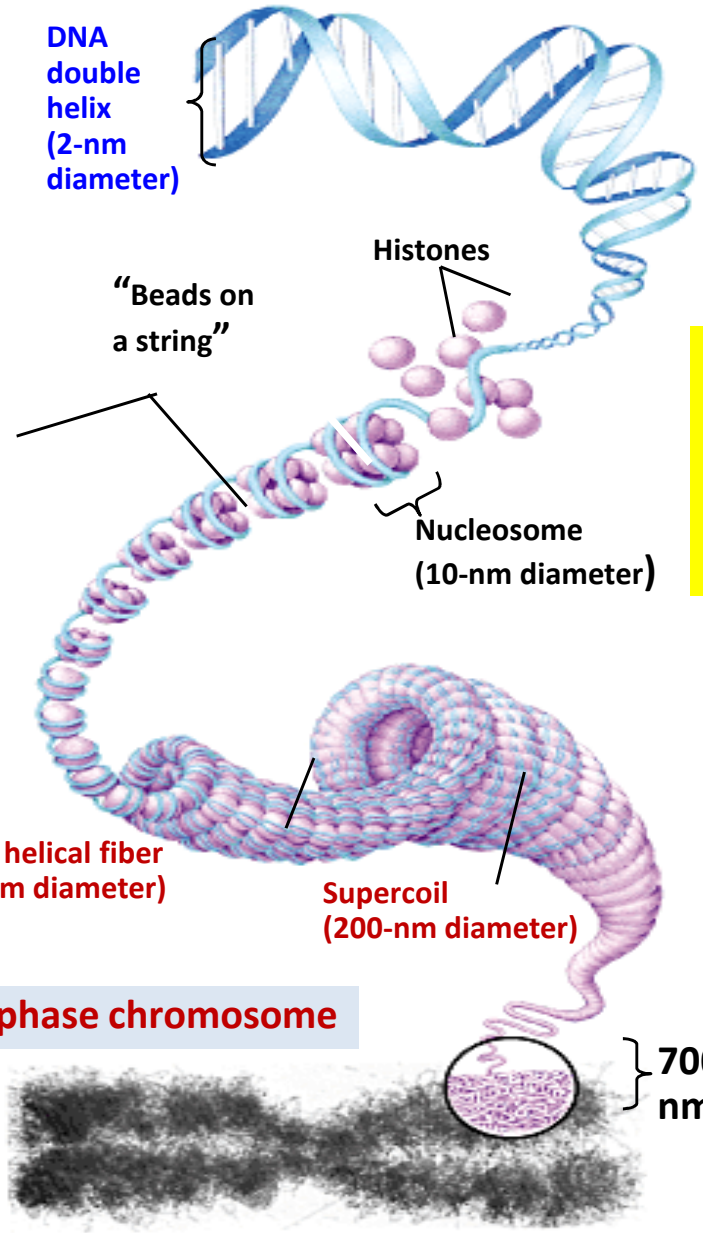
Mitotic chromosome



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

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

.. it has become evident that the **genome** is a complex **molecular system (*network*)** made up not only by DNA sequence, but also **by a dynamic and responsive structure of histones** and an **"epigenetic" cloud of molecules** (methyl and acetyl groups, **enzymes**, transcription factors, microRNAs)..



Euchromatin

Multiple levels of packing are required **to fit the DNA** into the cell **nucleus**

Heterochromatin

Metaphase chromosome

Campbell NE et al (Eds):
Biology: Concepts & Connections
4th Edition, 2003

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

The **tails of histones** could be regarded as the **sensory / receptive component** of the genome

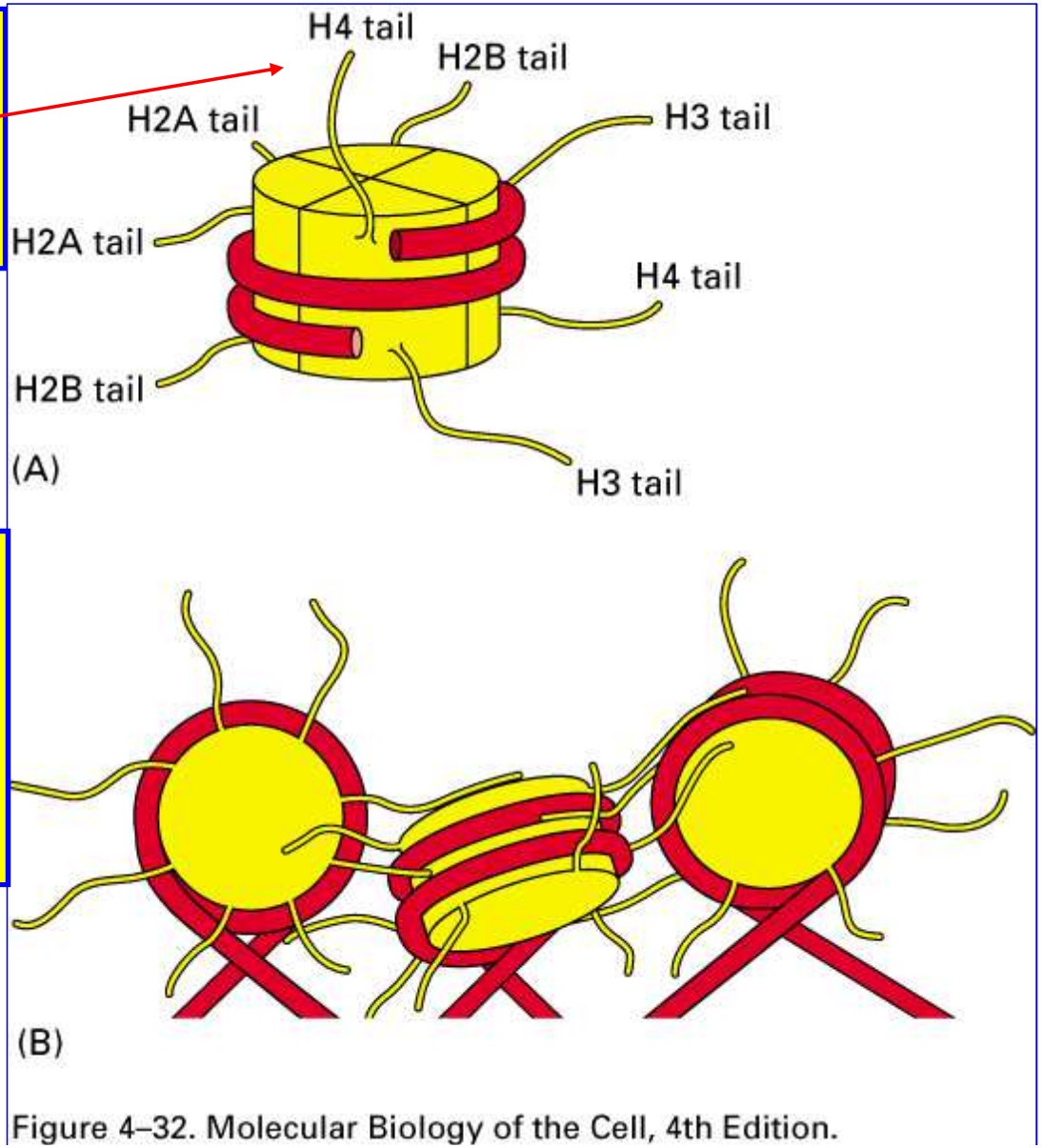


Figure 4–32. Molecular Biology of the Cell, 4th Edition.

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

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

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

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

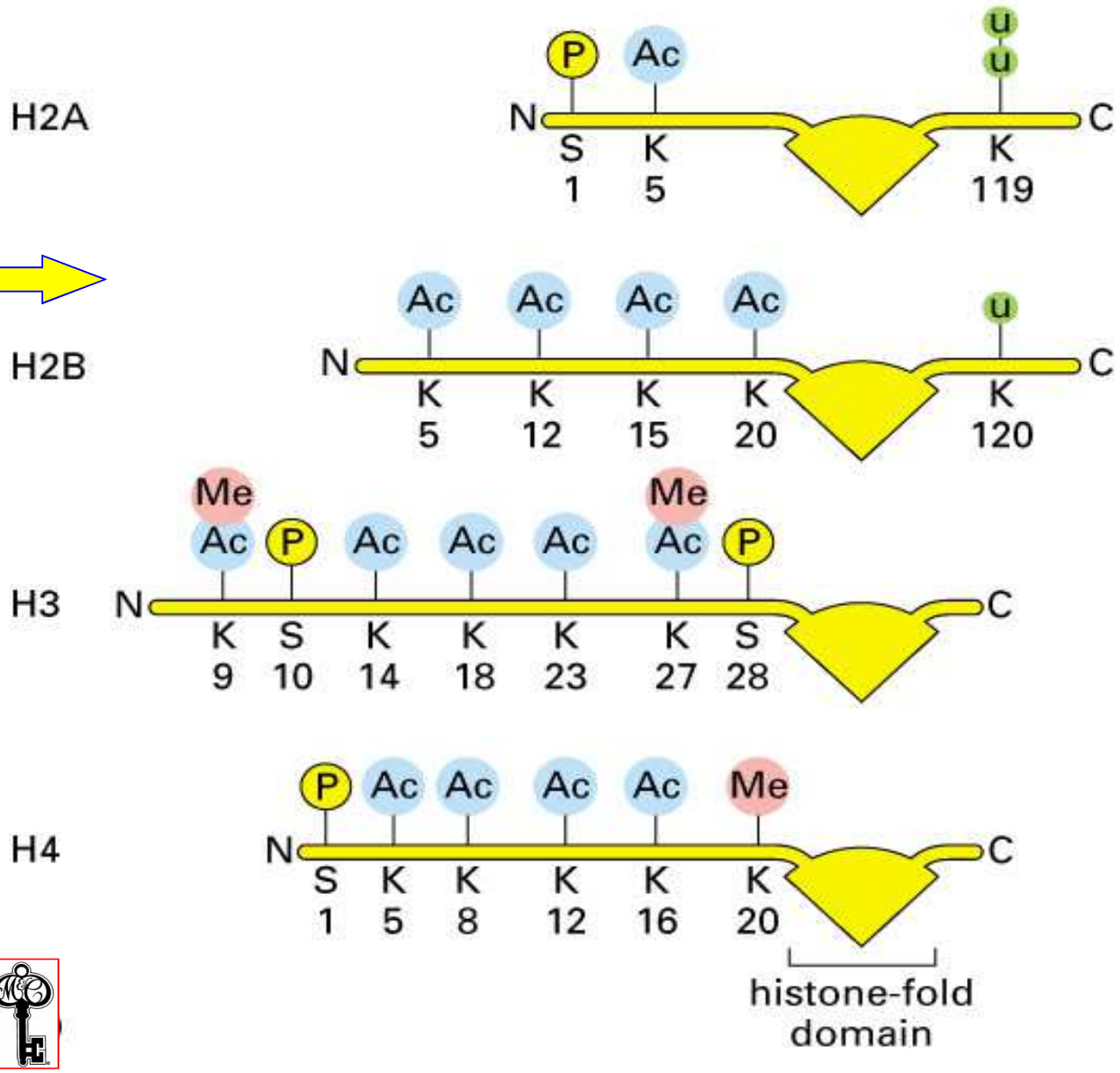
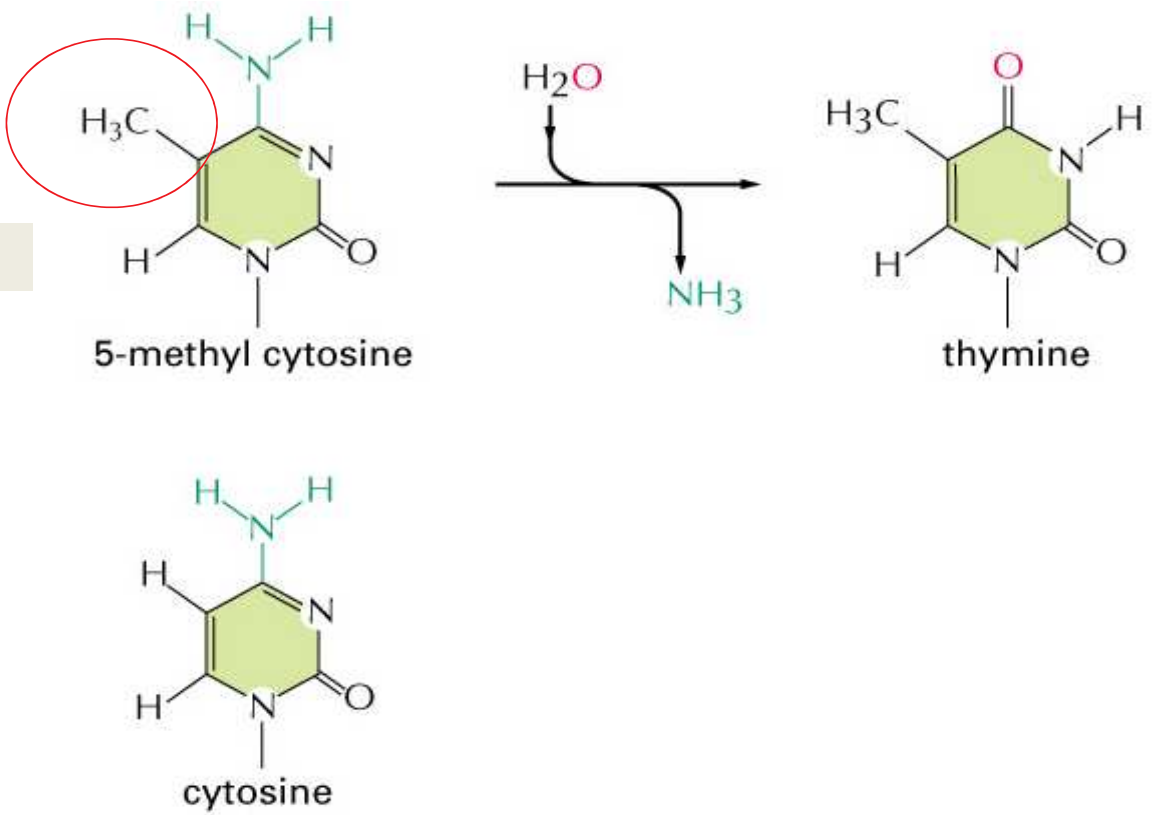


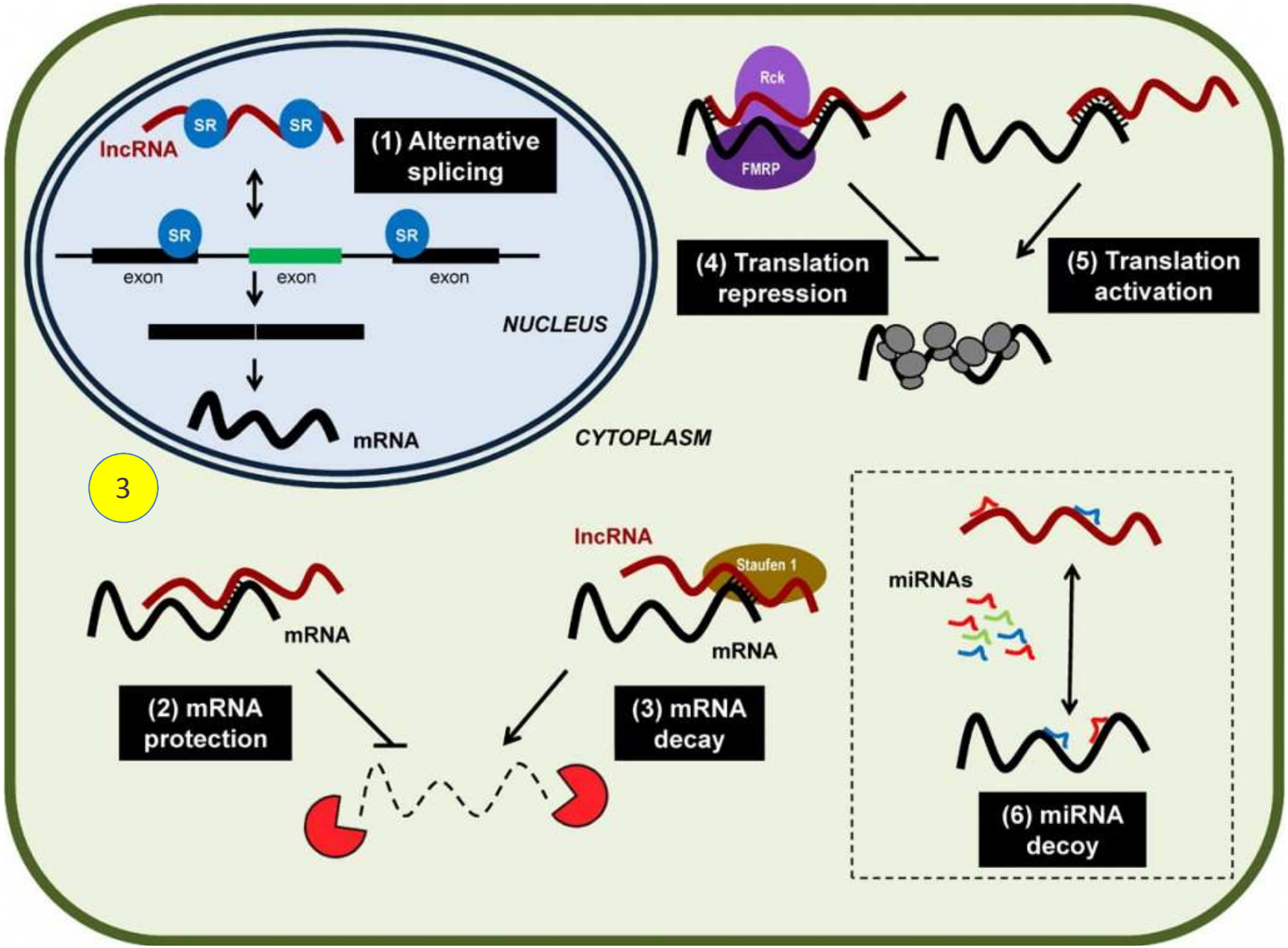
Figure 4–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

DNA methylation

Covalent modification of the DNA is important for gene silencing human cells.
Most genes have GC rich areas of DNA in their promoter regions.
These are referred to as CpG islands.
Methylation of the C residues within the CpG islands leads to gene silencing

(highly *unstable* base)




lncRNA
SR
SR
(1) Alternative splicing
SR
SR
exon
exon
exon
NUCLEUS
mRNA
CYTOPLASM
Rck
FMRP
(4) Translation repression
(5) Translation activation
3
lncRNA
Staufen 1
mRNA
mRNA
(2) mRNA protection
(3) mRNA decay
miRNAs
(6) miRNA decoy

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

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

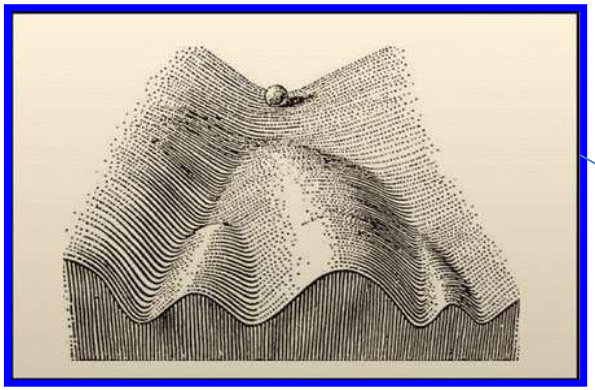
International Journal of Epidemiology

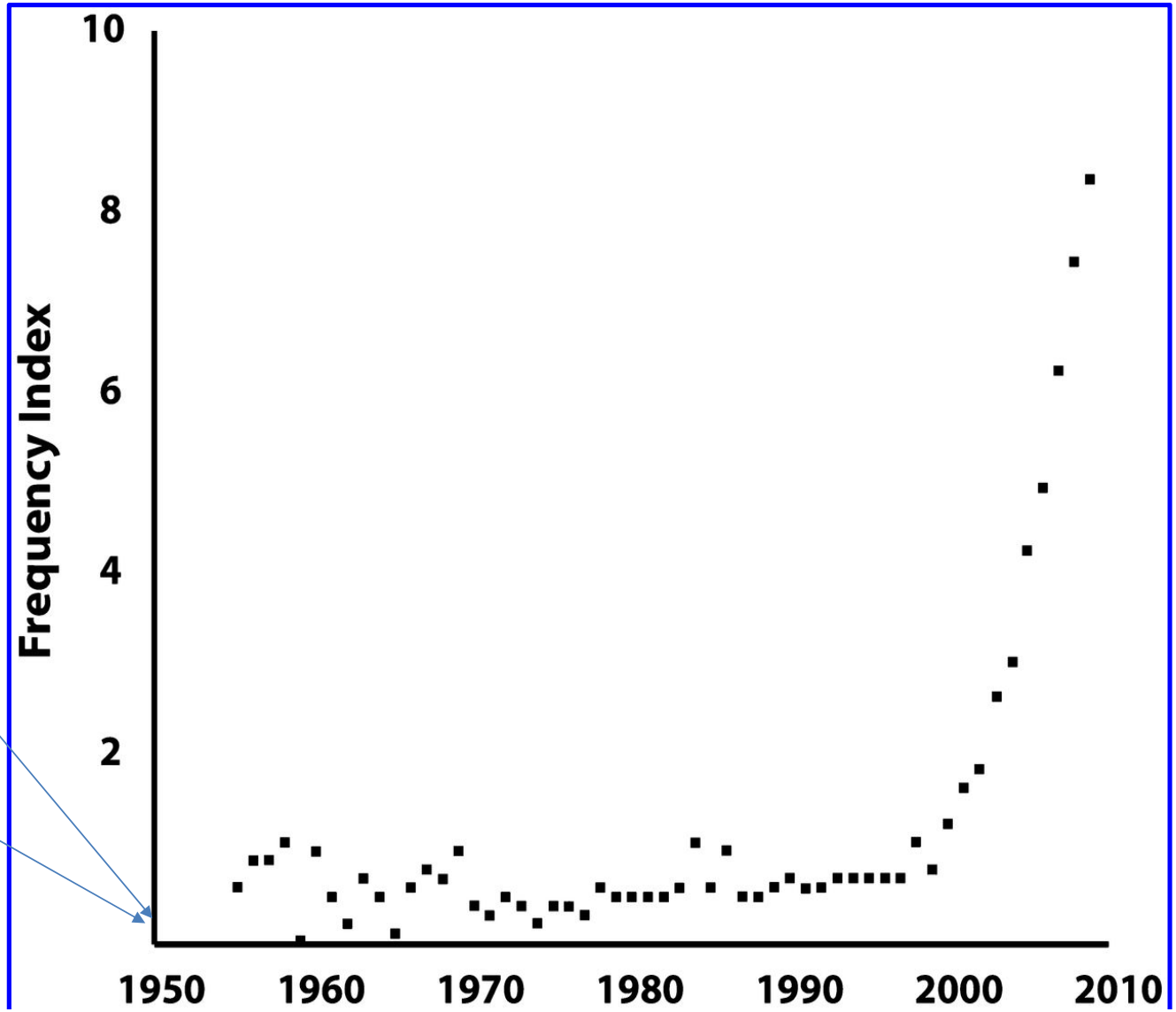
Foreword 1

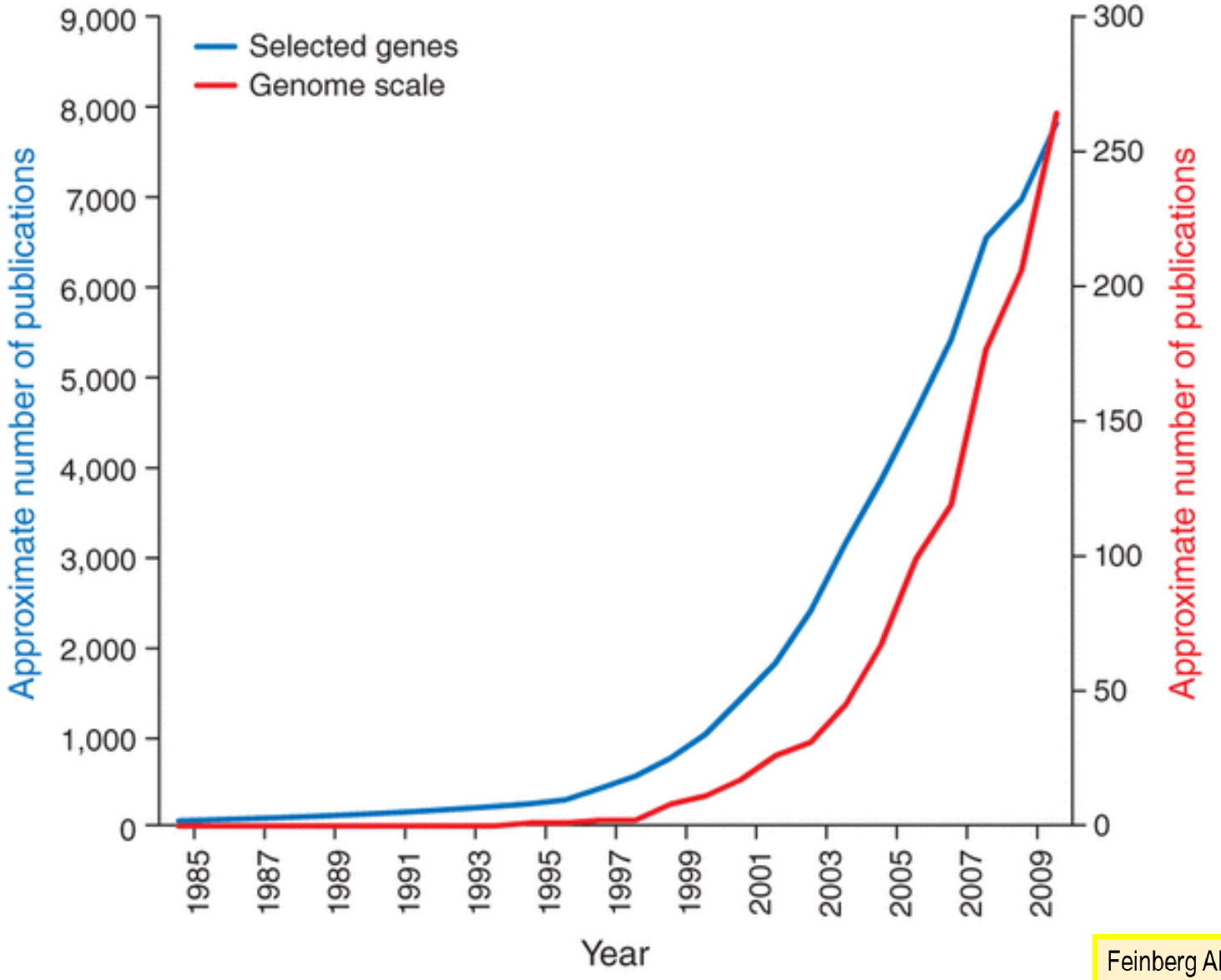
Photo: Ramsey & Muspratt

THE AUTHOR

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

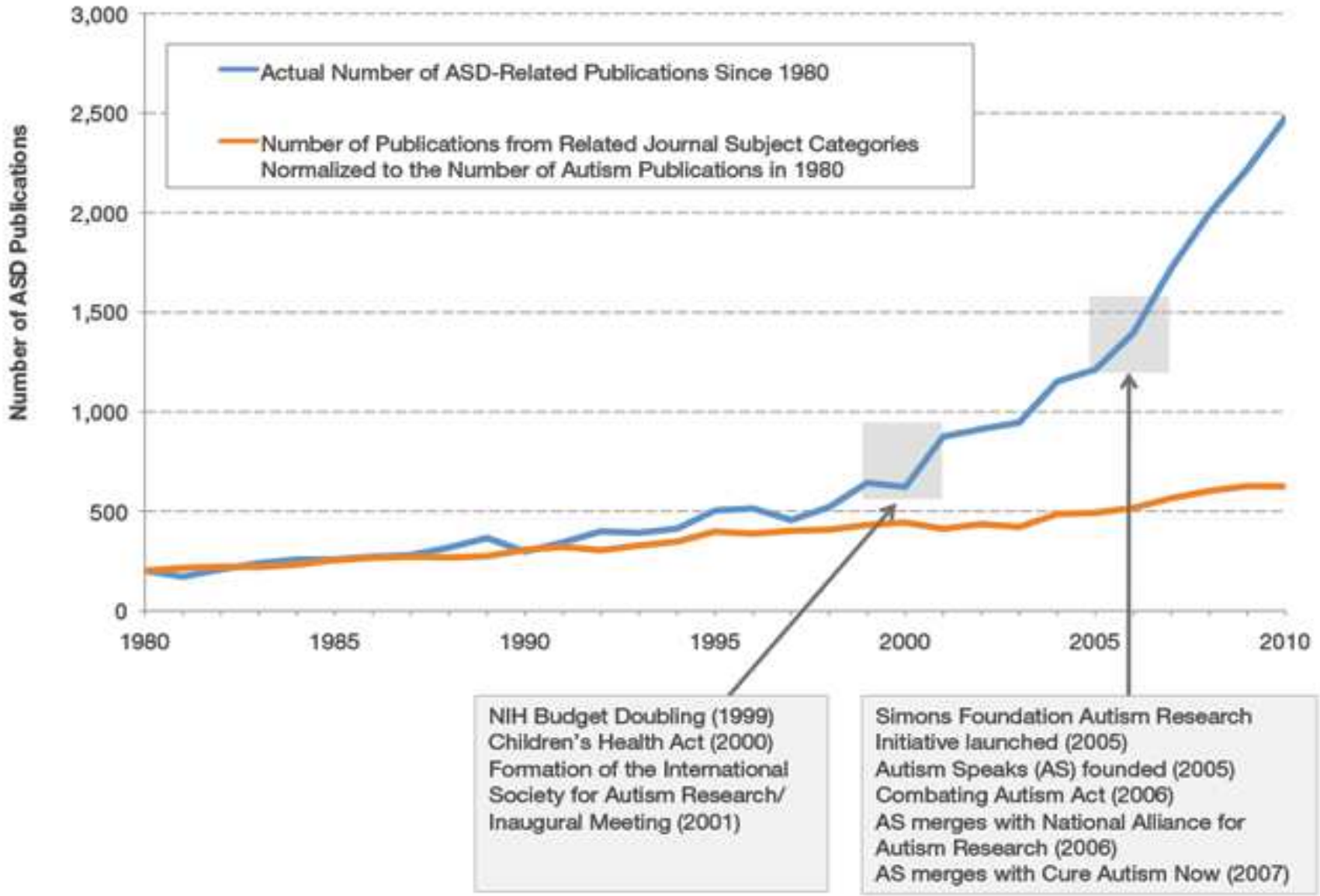






The **rate of increase** of **genome-scale publications addressing *cancer (epi)genomics*** has become **greater than that of publications in the same area focused on selected genes**

Feinberg AP **Epigenomics reveals a functional genome anatomy and a new approach to common disease** Nature Biotechnology 28, 1049–1052 (2010)


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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

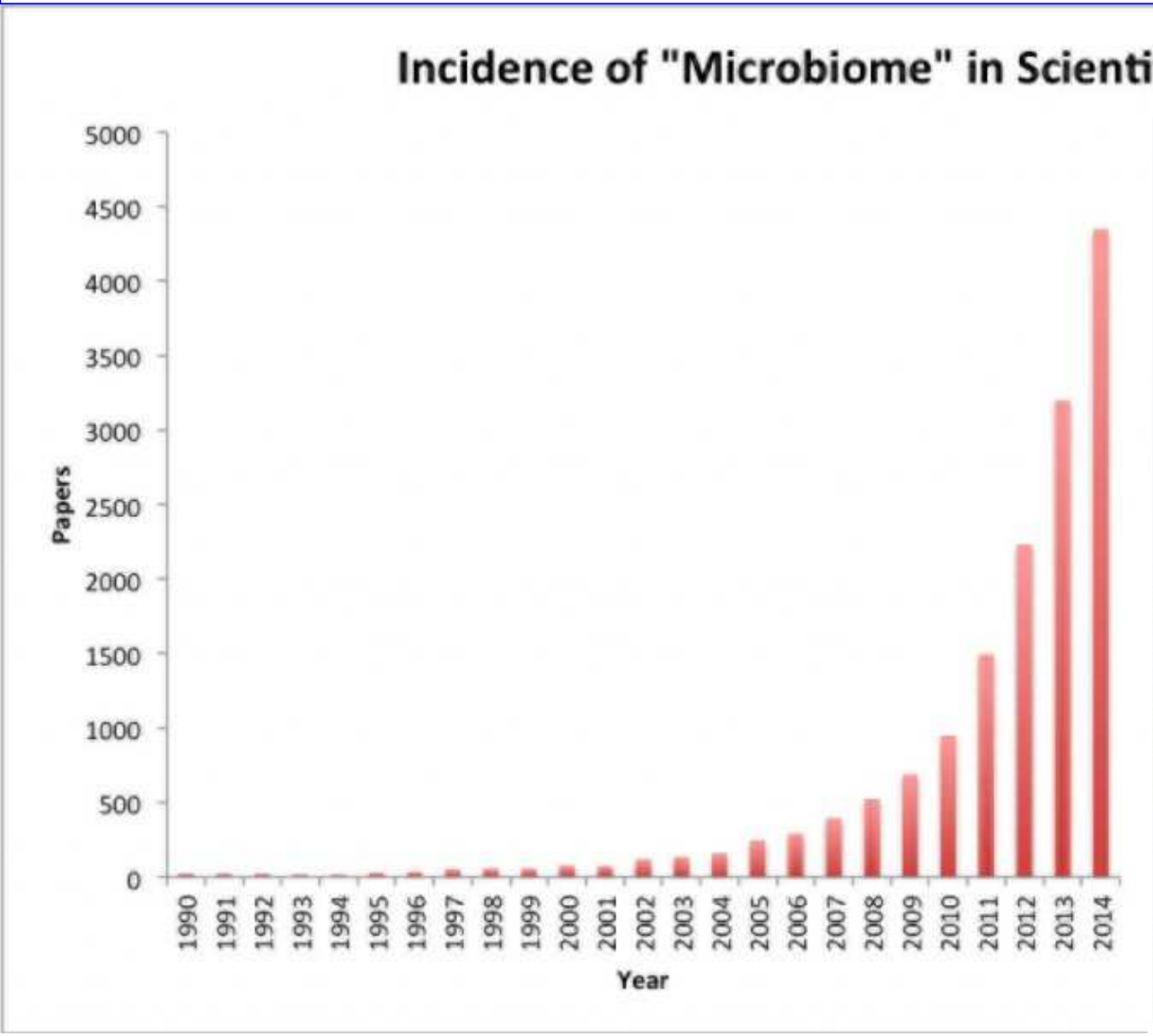
For 1999, a PubMed search using the term "brain" shows that 34,828 papers were published.

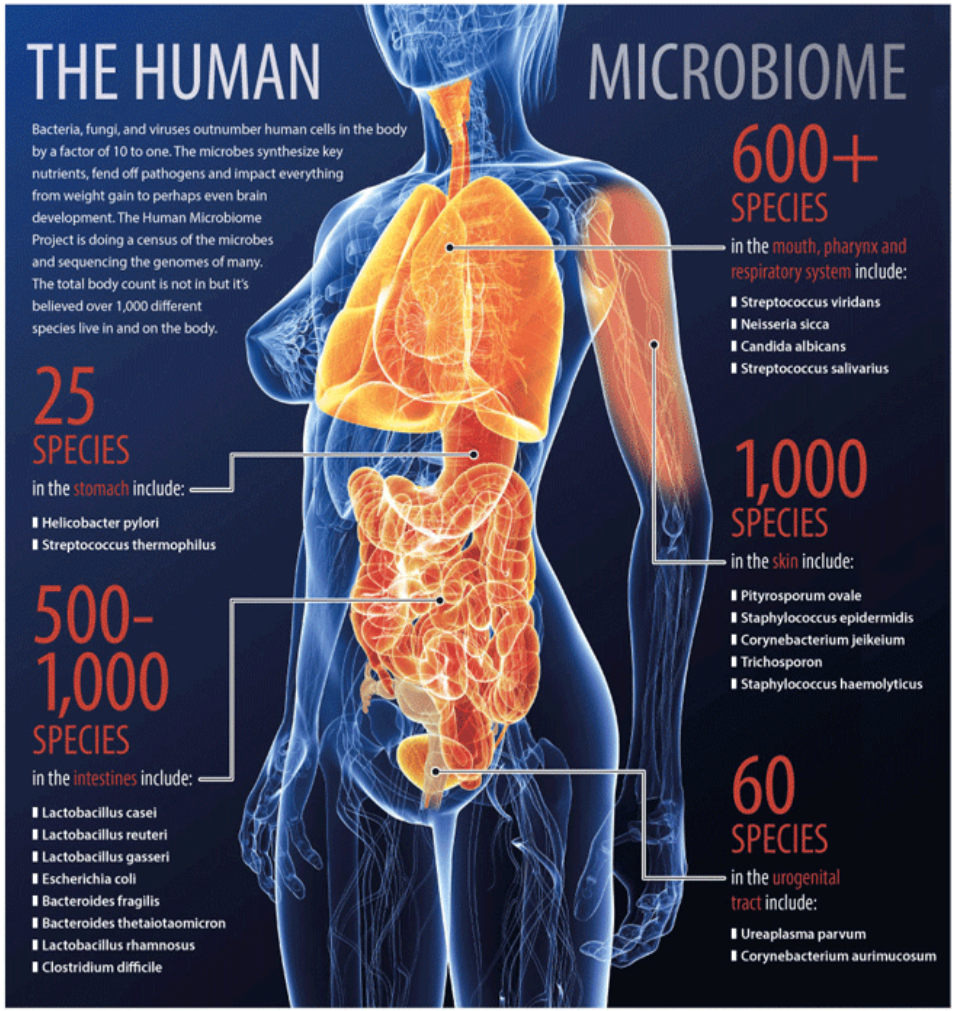
For 1998, a PubMed search using the term "brain" shows that 33,027 papers were published.

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

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

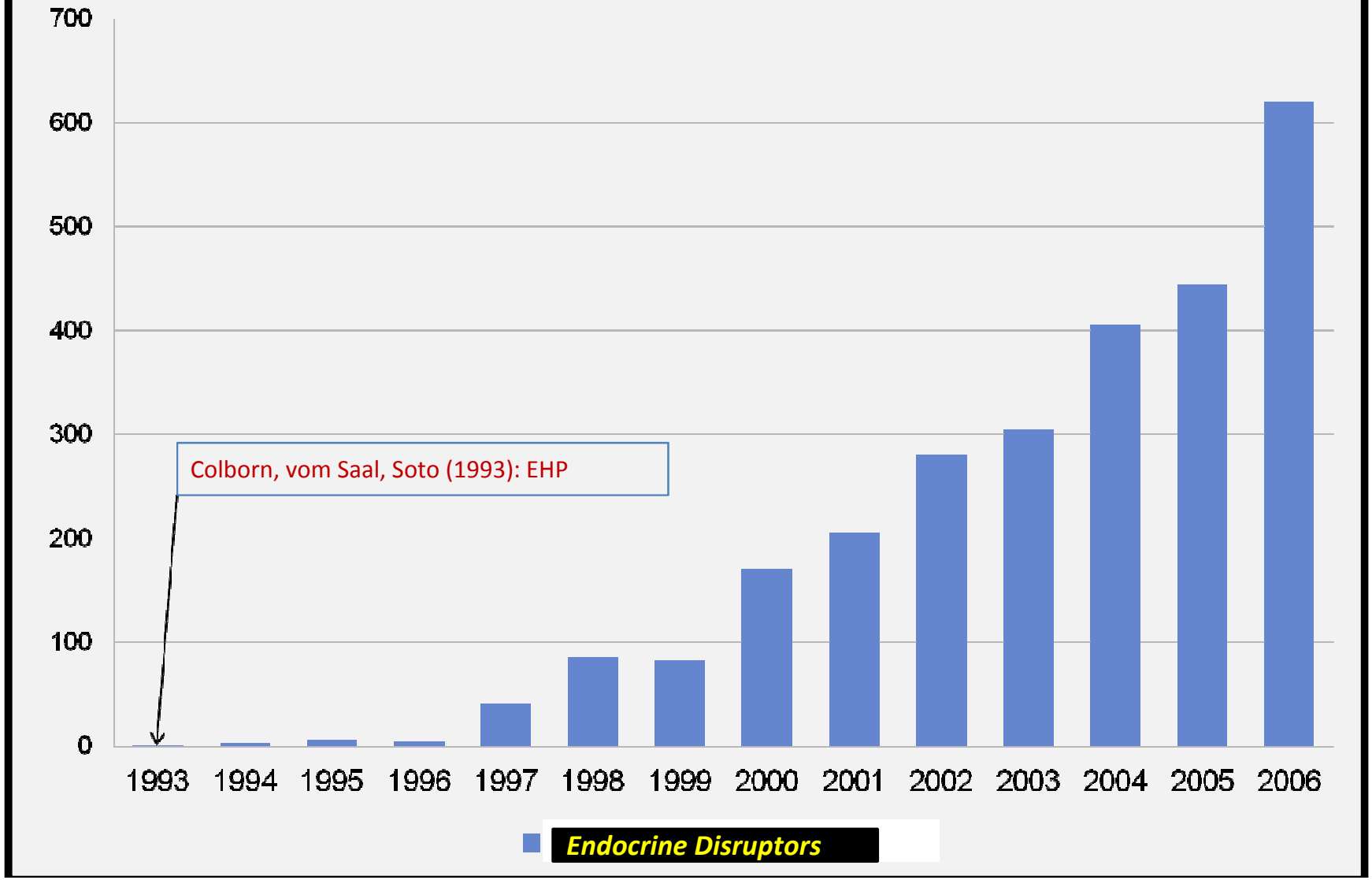
*A quick search for "**Microbiome**" in **scienctific journals online** demonstrates how significantly this field of research has been **growing over the past ten years***





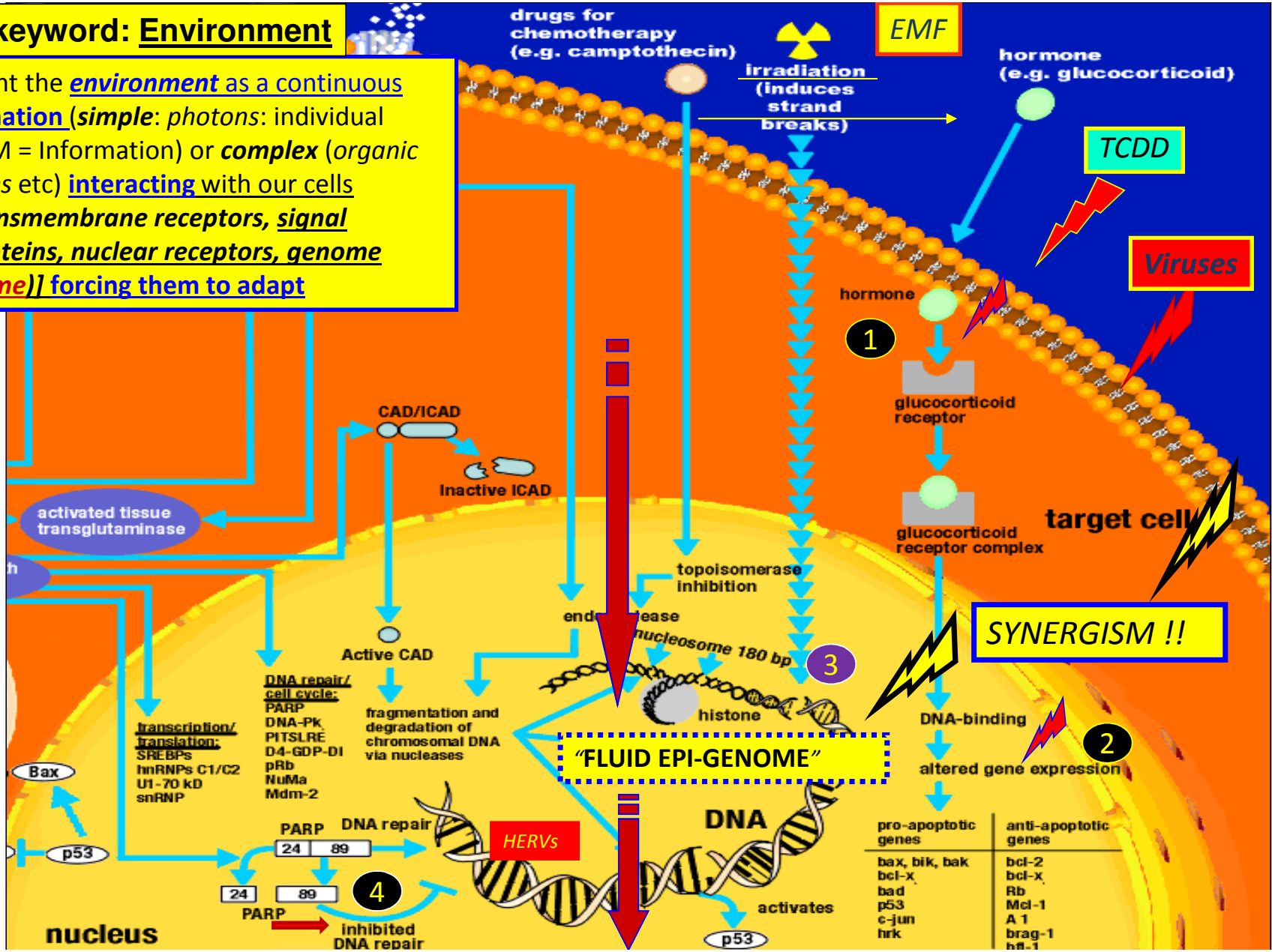
ACADEMY FOR ENVIRONMENTAL MEDICINE

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



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**

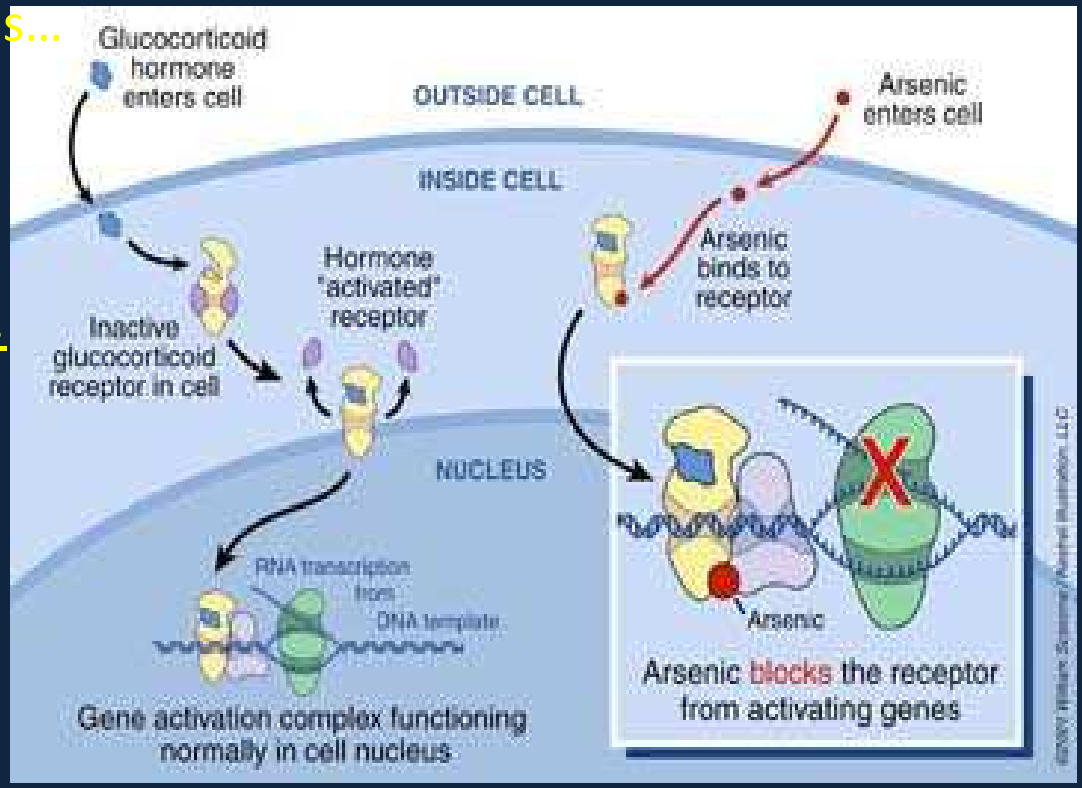


Everyday levels matter

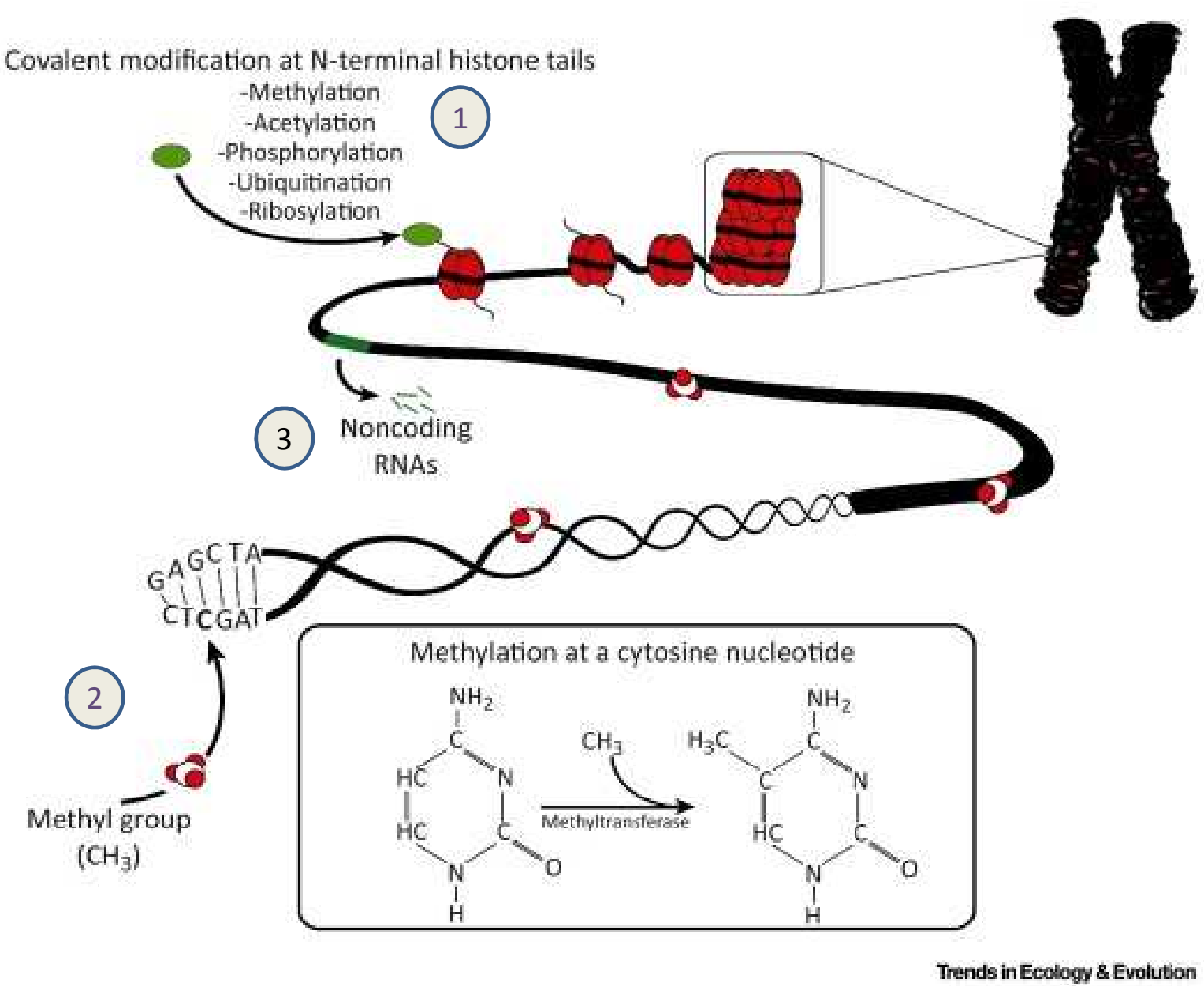
At high levels… arsenic kills people

At moderately low levels… it causes a range of diseases

At truly low levels … it interferes with gene activation

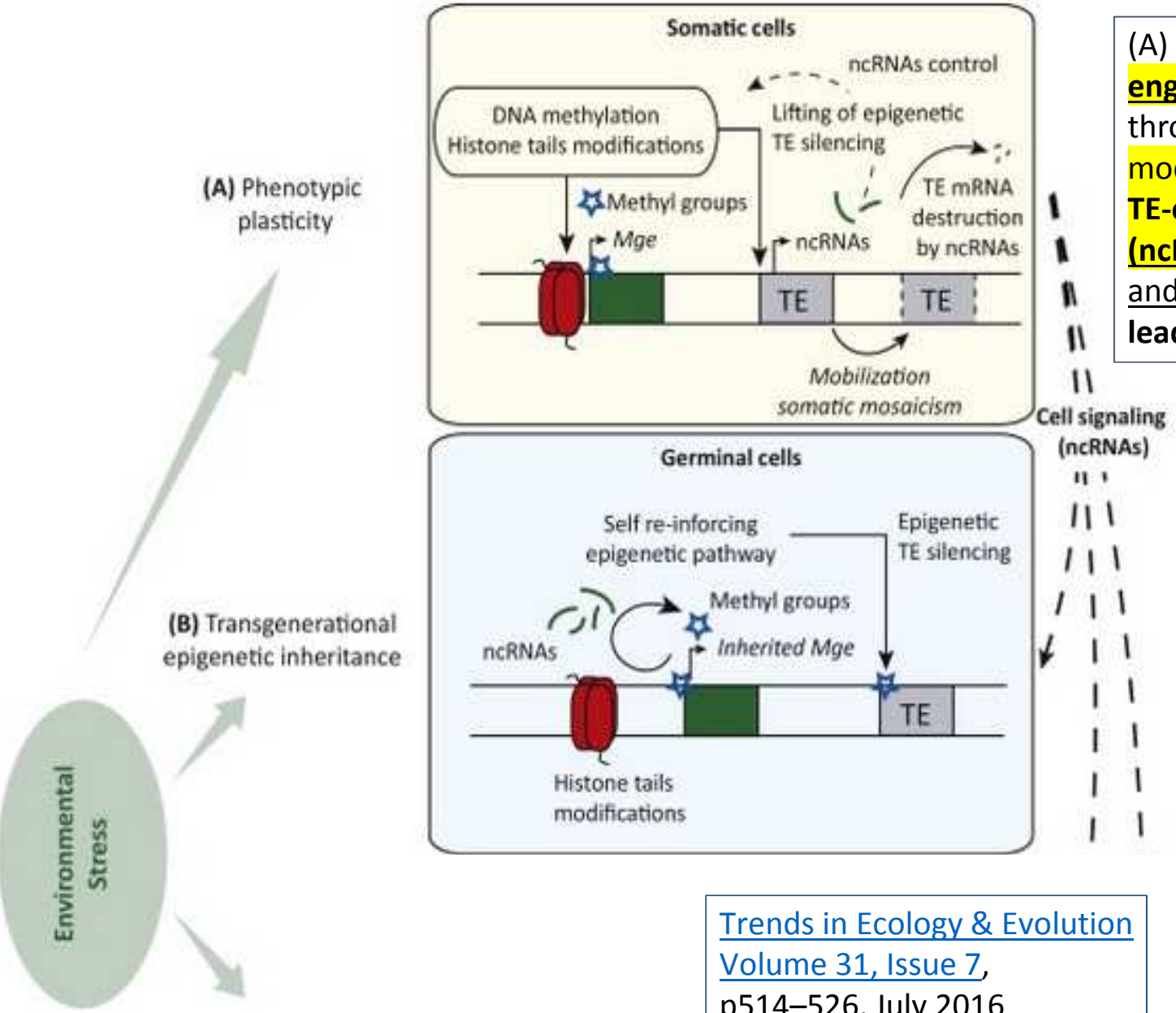


Kaltreider *et al*. 2002



Adaptation to Global Change: A Transposable Element–Epigenetics Perspective

Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016

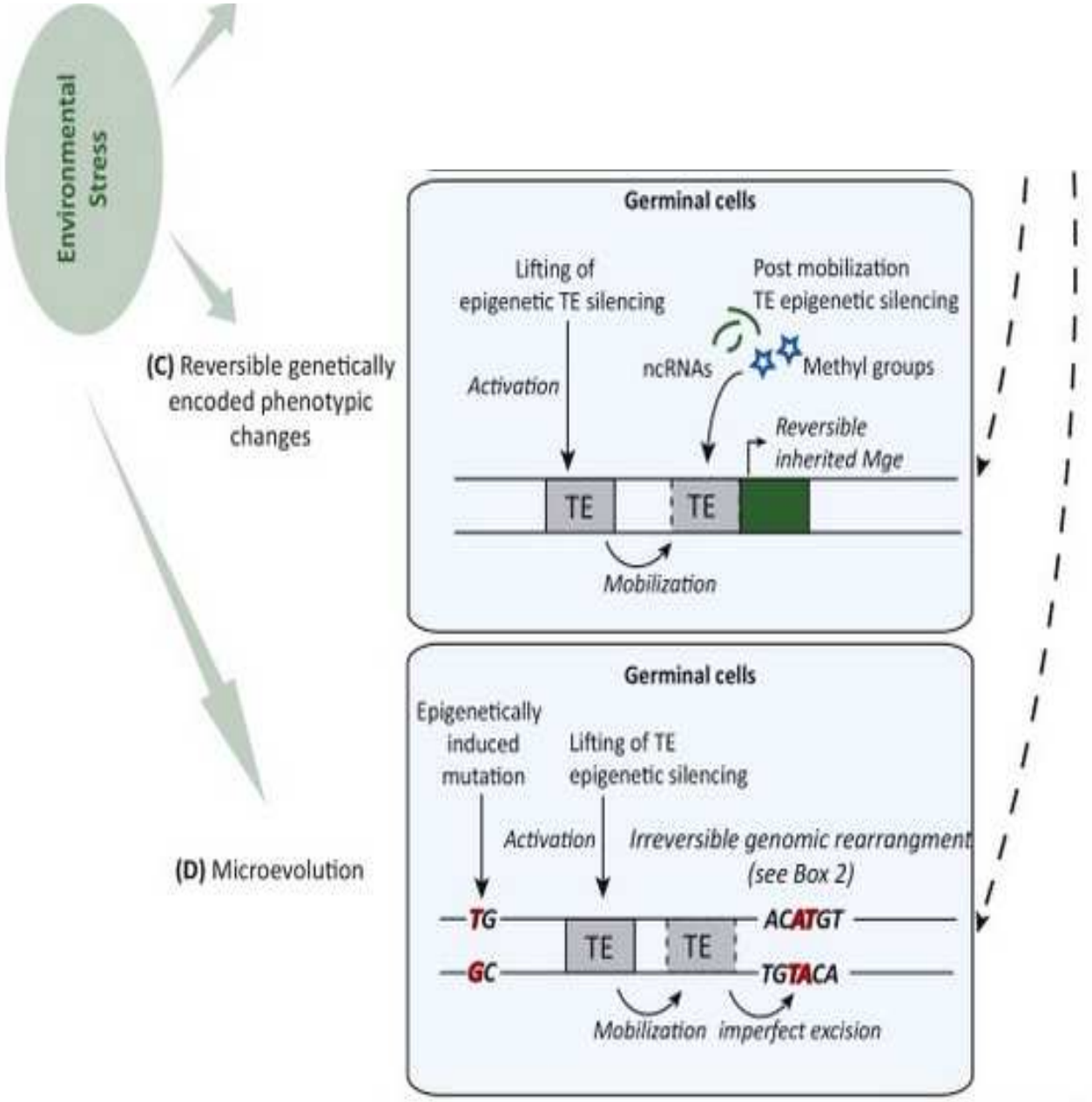


(A) **Under stress, the activation of the TE–EC engine** in somatic cells induces **plastic responses** through: (i) DNA methylation and/or modifications of histone tails; (ii) **transcription of TE-encoded regulatory noncoding RNAs (ncRNAs)**; and (iii) lifting of epigenetic silencing and **mobilization of TEs in somatic cells**, **leading to somatic mosaicism.**

(B) **Stress induces epigenetic modifications in germline cells**. The resulting **phenotypes can be stabilized over generations (transgenerational epigenetic inheritance) through self-reinforcing epigenetic pathways**.

Stress perceived in somatic cells can also induce the **production of circulating ncRNAs that may modify the epigenome of remote germline cells** [dashed arrow from (A) to (B)].

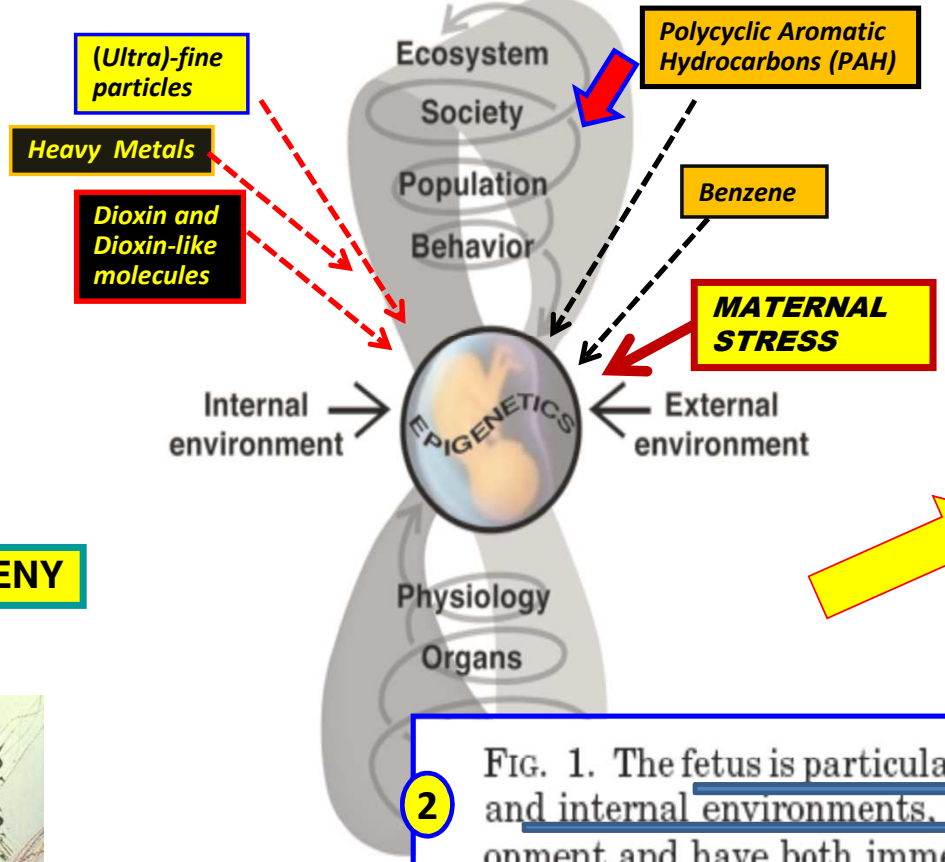
Trends in Ecology & Evolution
Volume 31, Issue 7,
p514–526, July 2016



(C) **Stress** can induce the **lifting of epigenetic silencing of TEs in germinal cells, resulting in the mobilization of TEs across the genome**. The resulting phenotypes are **thus transmitted to the next generations.** However, because newly inserted TEs are targets for epigenetic silencing, the resulting heritable phenotypes are expected to be, in some cases, reversible. Similarly to (B), stress perceived in somatic cells can induce the production of circulating ncRNAs that may modify the epigenome of remote germline cells. [dashed arrow from (A) to (D)].

(D) **Stress can induce modifications of epigenetic patterns that can result in irreversible genomic changes either directly** (mutagenic effect of epigenetic patterns) **or indirectly through the release of epigenetic silencing of TEs** and the resulting mobilization of TEs throughout the genome. As in (B) and (C), stress perceived in somatic cells can induce **the production of circulating ncRNAs that may modify the epigenome of remote germline cells** [dashed arrow from (A) to (D)].

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



ONTOGENY

… 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..

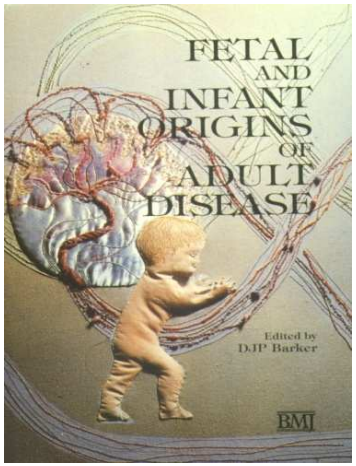


FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular 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.

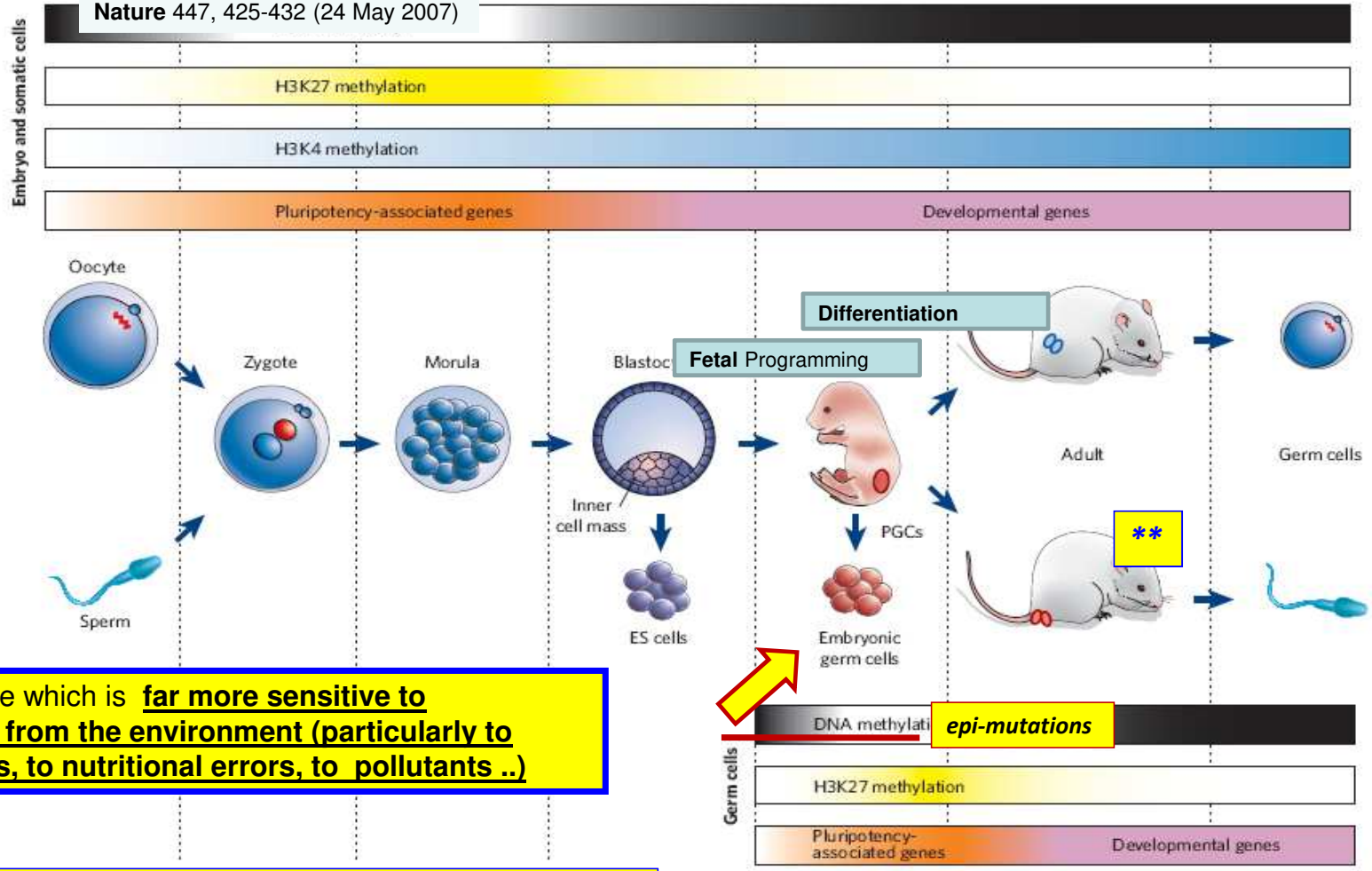
The **fourth** keyword is ***developmental plasticity***

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

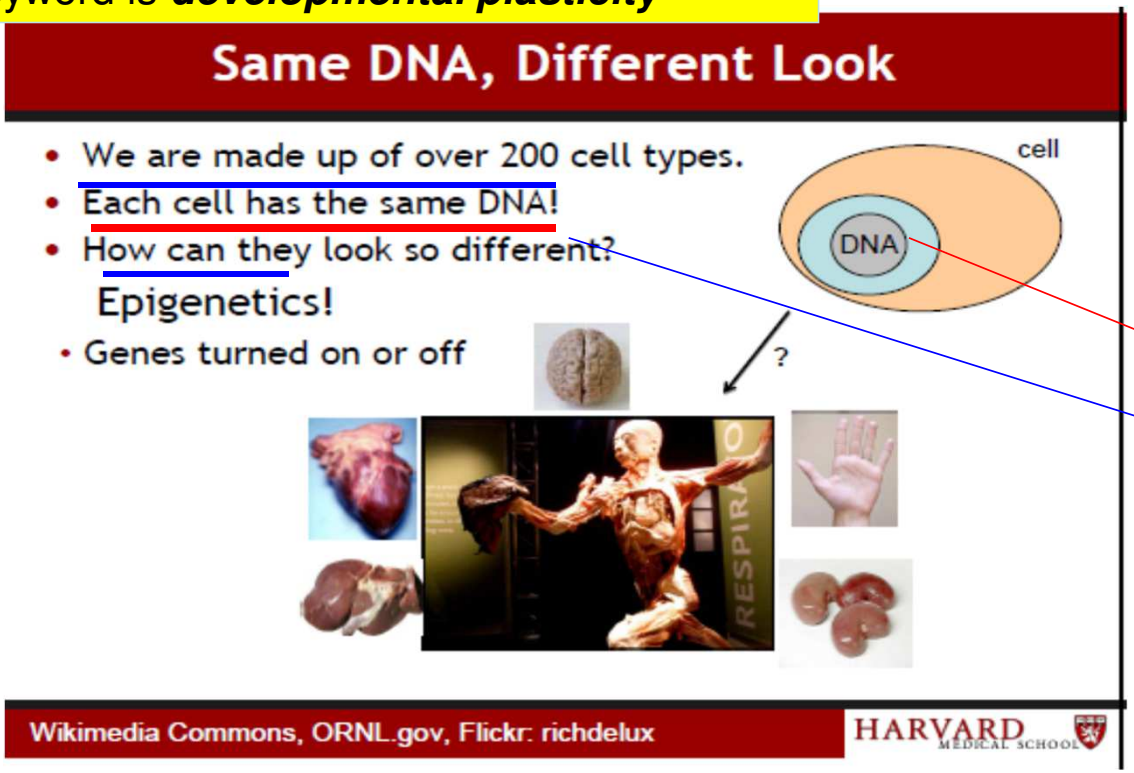
Differentiation is the process through wich the organism changes from a zygote to a complex system of tissues and 200 cell types (genetically identical.. each with its own epigenetic and morpho-functional characteristics)..

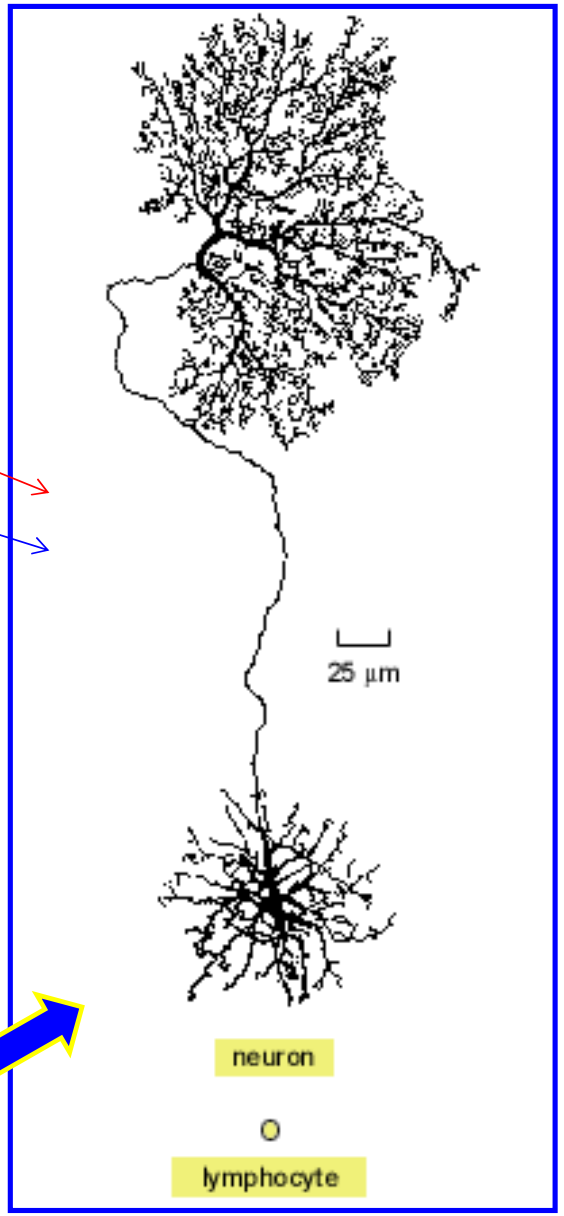
3

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***





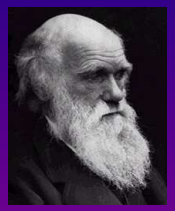
This image clearly shows the **"power" of the epigenome** and the **predominant role of environmental information in the phenotypic shaping of cells, tissues , organisms** .. the **huge phenotypic (morpho- functional) difference** between a *lymphocyte* and a *neuron* **is not due to DNA, which is virtually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

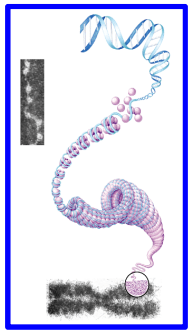
Gorilla

Chimpanzee

Human

Sanger Institute

Phylogeny



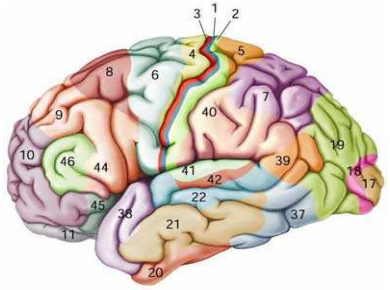
of 4 billion years of molecular coevolution * (in particular, our **DNA** is the **product** of this long journey) ..

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

Mismatch

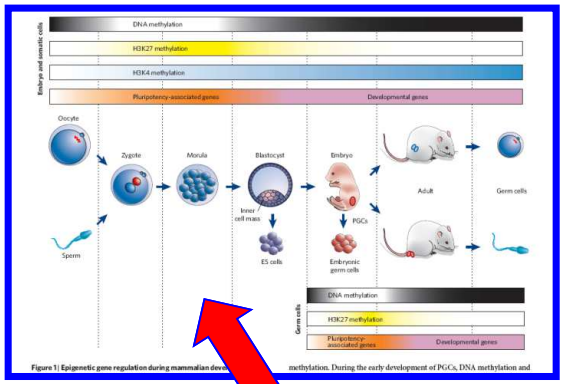
and of **9 months of an individual development**

Devo-Evo

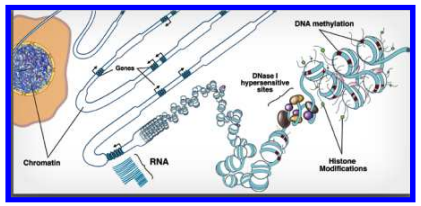


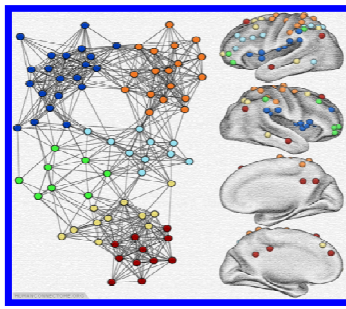
The **epigenome** being the product of nine months of ***cellular and tissue programming*** (**adaptive** to an environment that is rapidly changing)..

Ontogeny



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





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

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

Editorial

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

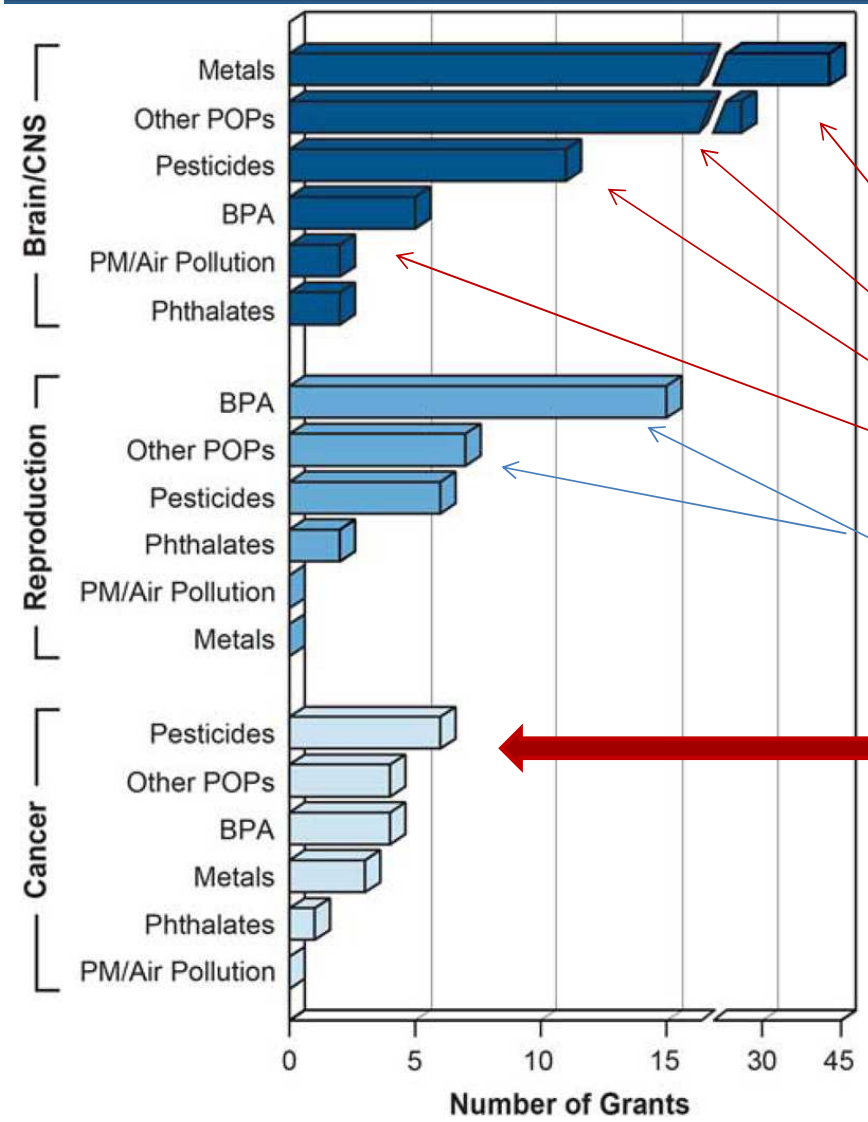
Ernesto Burgio

ECERI – European Cancer and Environment Institute, Bruxelles, Belgium
ISDE – International Society of Doctors for Environment (Scientific Office), Arezzo, Italy

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

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

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



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

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

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

Obesogens

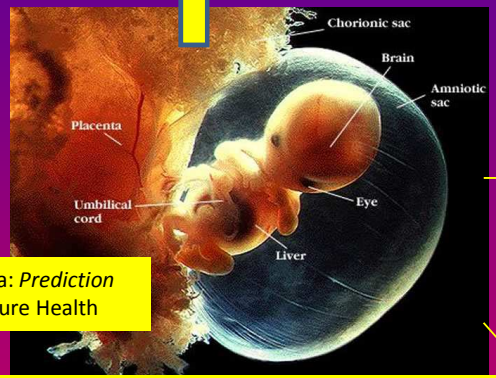
Multiorgan Effects of Endocrine Disruptors

Pesticides

In Vitro Fertilization

Materno Fetal Stress

Obesity/Metabolic Syndrome/Diabetes 2



Placenta: *Prediction* of Future Health

Developmental Time Windows of Vulnerability

Cardiovascular Diseases

Ipertension

Asthma and allergies

Lung Development ⇓

Reproductive Diseases/Dysfunctions

Semen Abnormalities

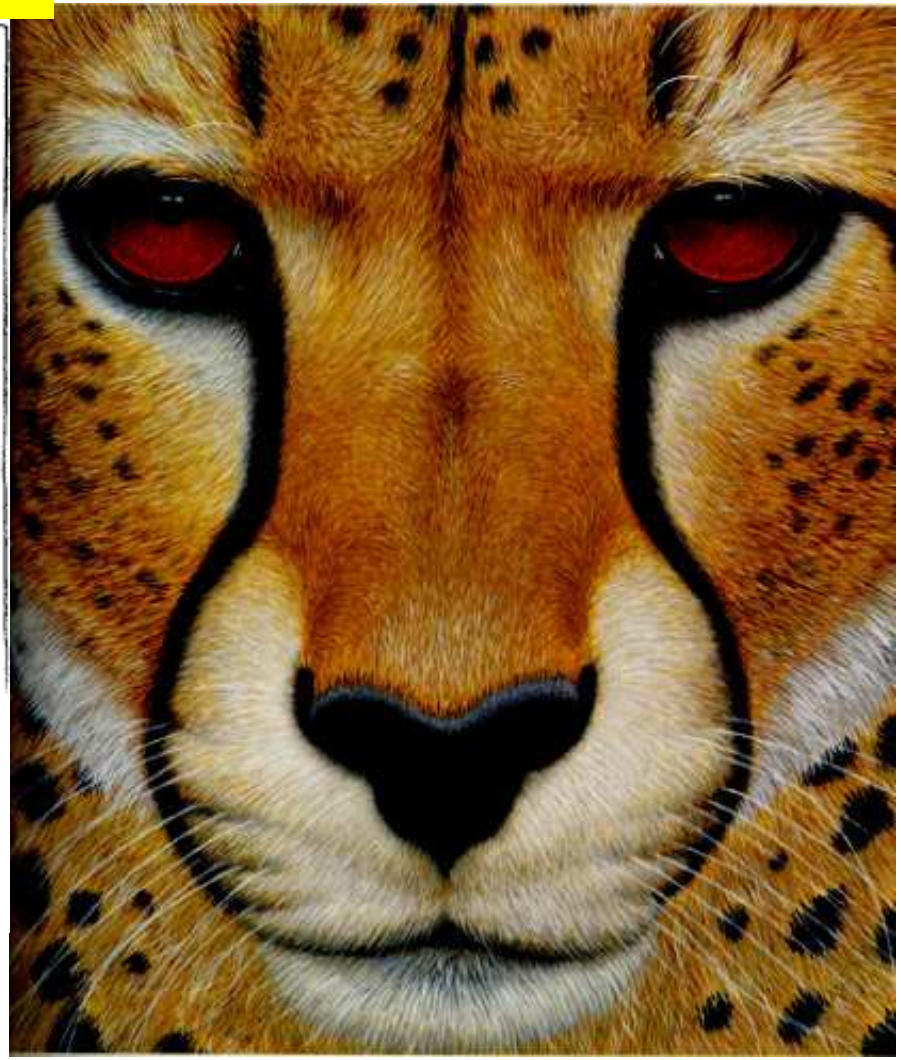
CANCER

DOHAD

Neurobehavioral Deficits and Diseases

Psychiatric Diseases

INTELLIGENT DESIGN ?



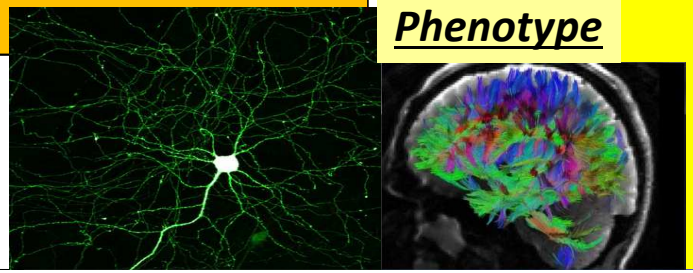
Key *words*

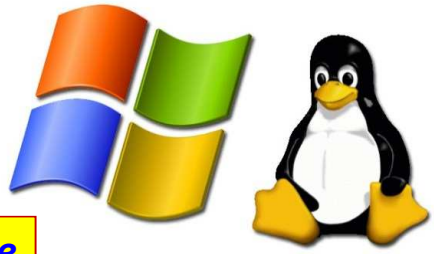
Hardware

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*).**

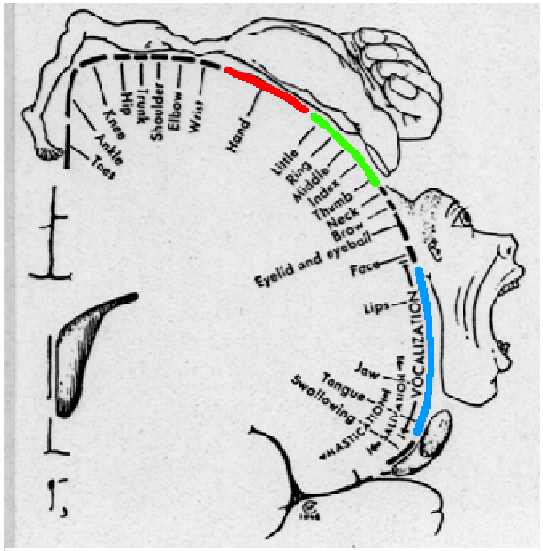
Mind/Soul

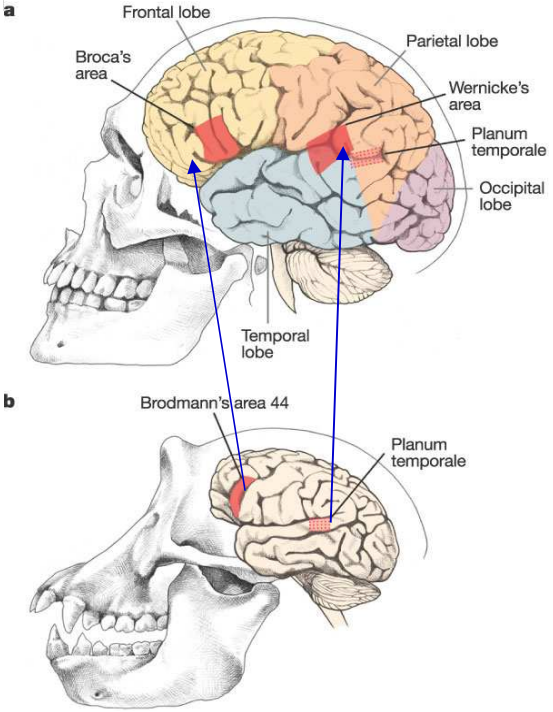
DNA ***Genome*** ***Epigenome***
Genotype

Individual Cablage - *Connectome*

Phenotype

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





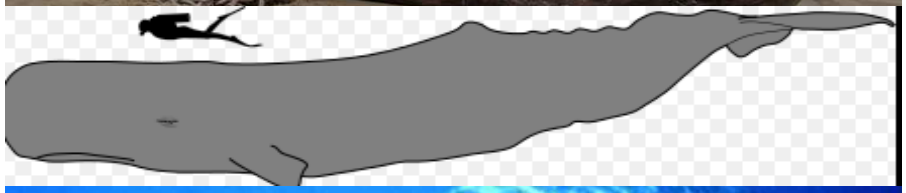
The ***ancestral*** wiring

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?

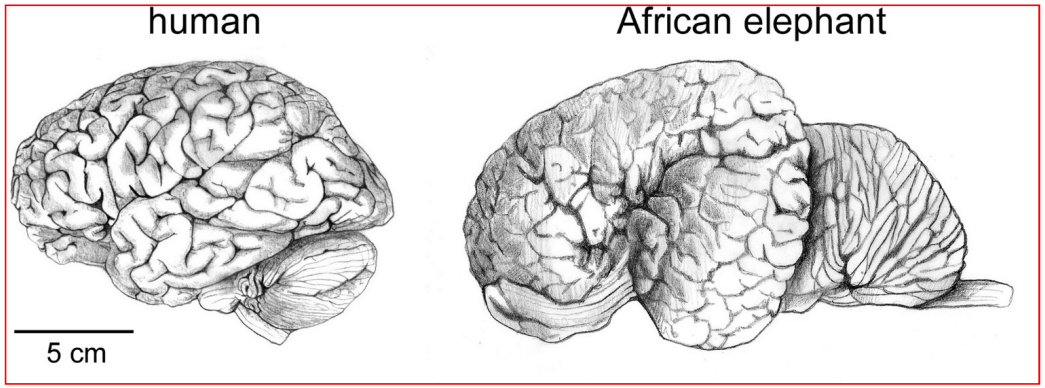


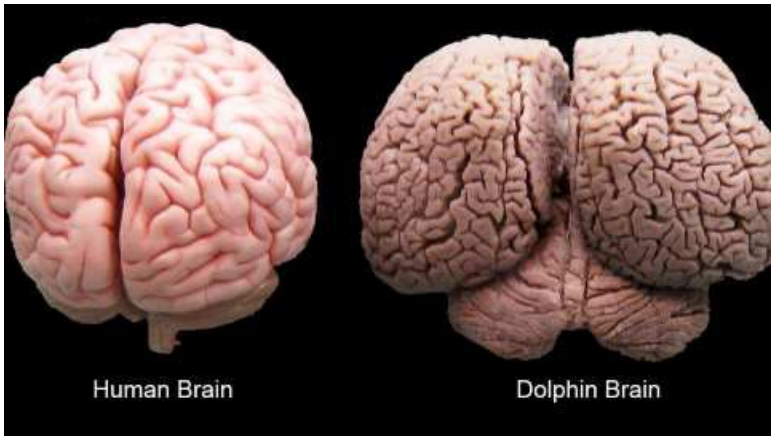
Capodoglio (***Physeter***

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)

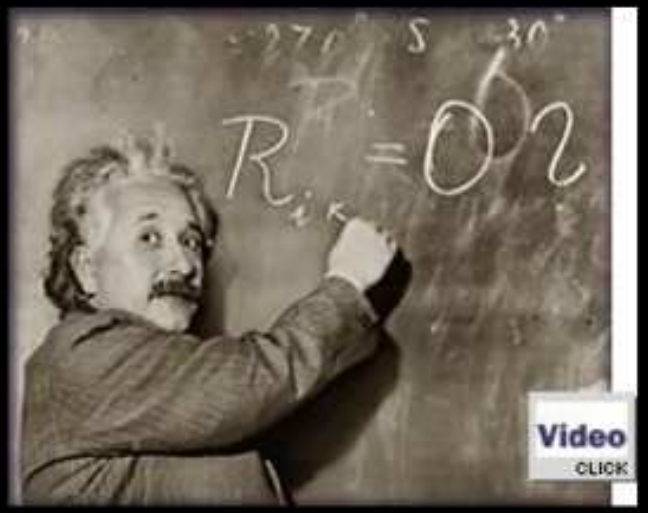
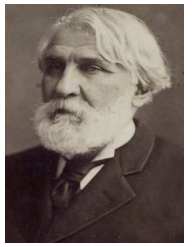


TABLE I.

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

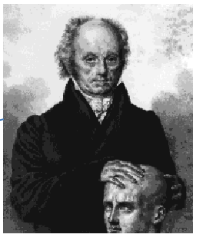
TABLE I.—*Continued.*

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
Asszat.	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

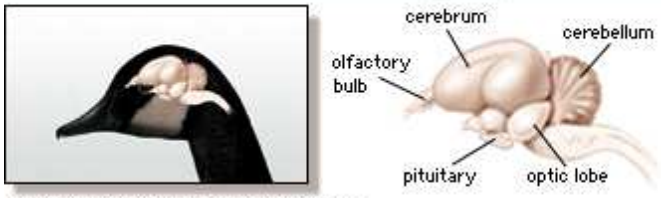
Encephalization Quotient (EQ)

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]

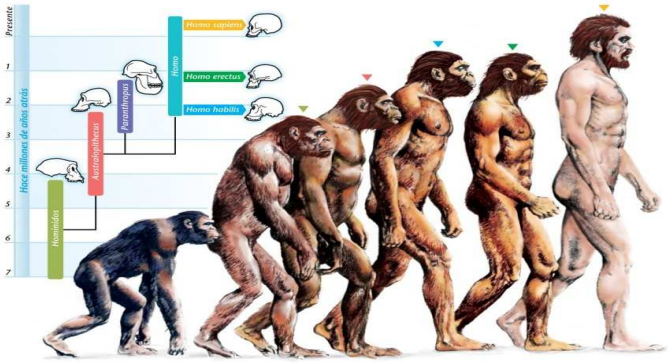
Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, 21941-902, Rio de Janeiro, Brazil; and Instituto Nacional de Neurociência Translacional, Instituto Nacional de Ciência e Tecnologia/Ministério de Ciência e Tecnologia, 04023-900, Sao Paulo, Brazil

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*

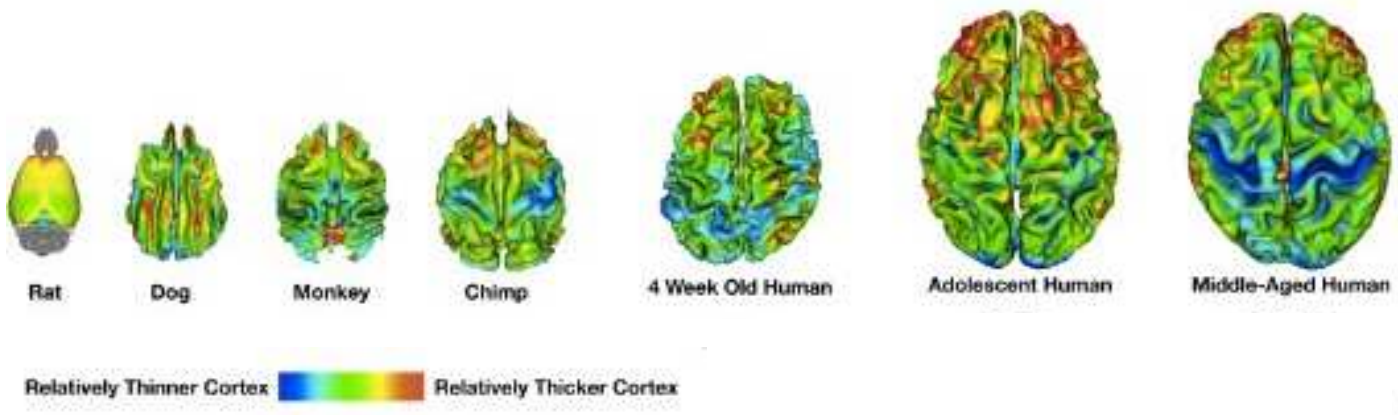
The human brain is **not exceptional in its cellular composition**, as it was found to contain **as many neuronal and non-neuronal cells as would be expected of a primate brain** of its size.

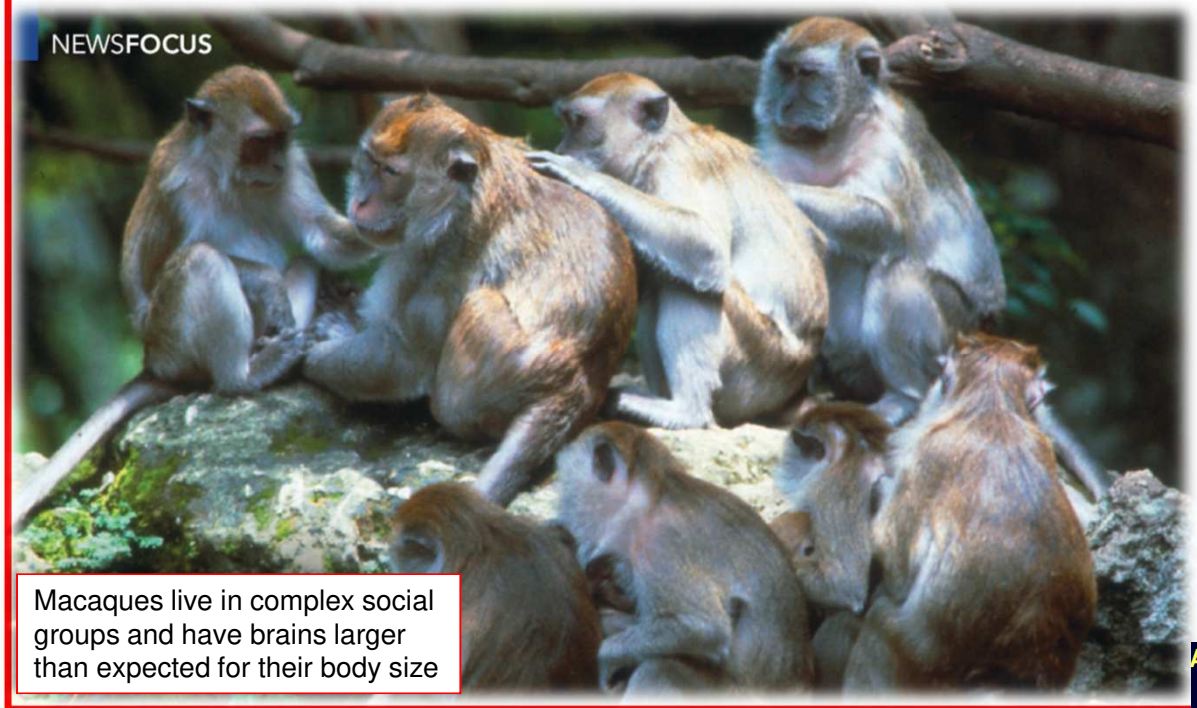
Additionally, **the so-called overdeveloped human cerebral cortex holds only 19% of all brain neurons**, a fraction that is **similar to that found in other mammals**… These findings argue in favor of a view of **cognitive abilities that is centered on absolute numbers of neurons, rather than on body 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

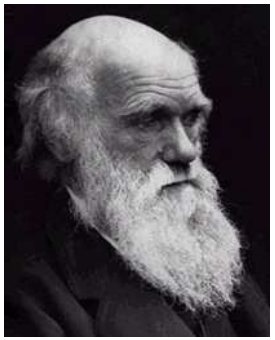
Why Are Our Brains So Big?

Science, 2012

Giovanni Biggio

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

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

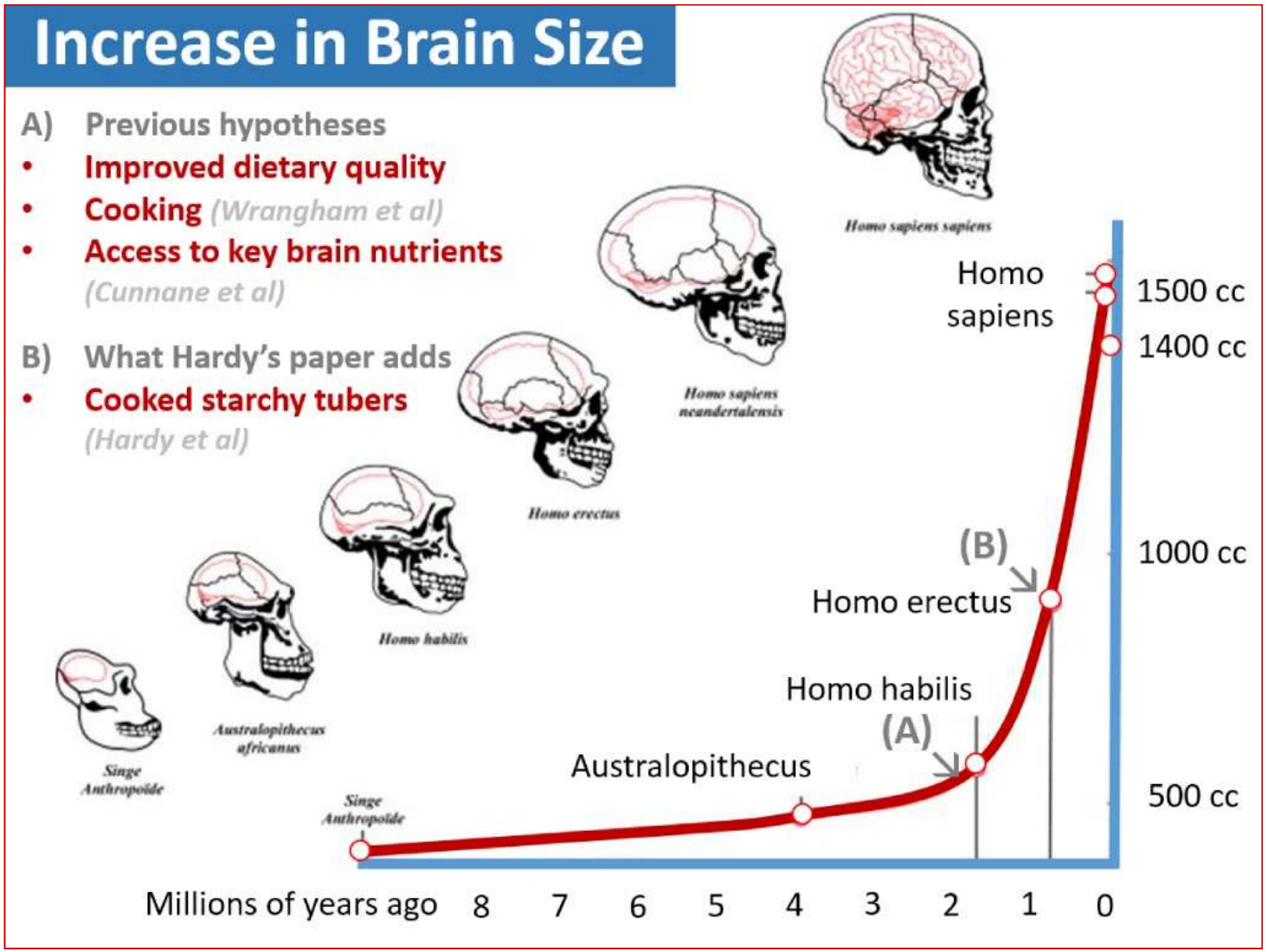
Chimpanzees

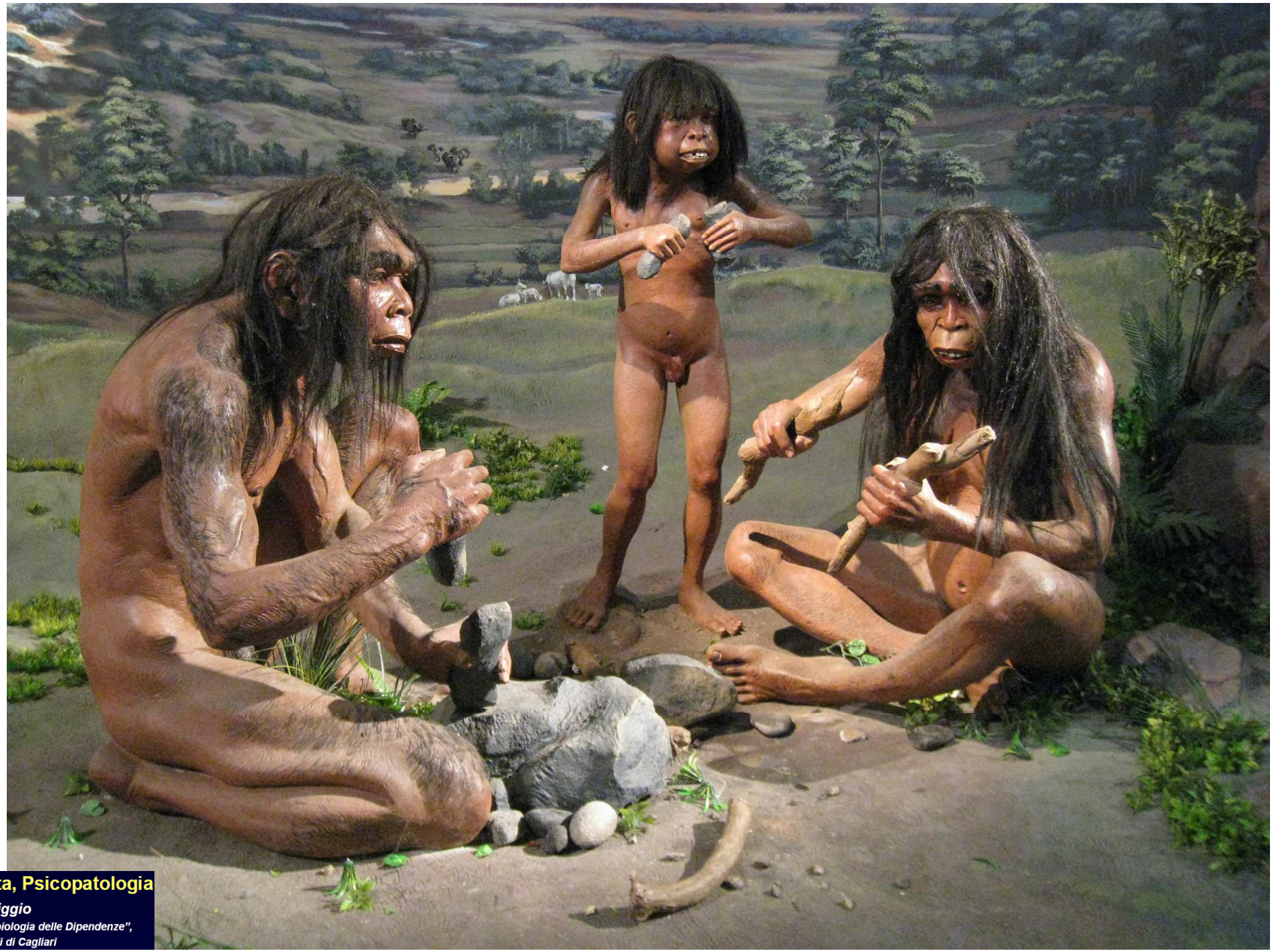
Humans

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

Tarsius tarsier (Tarsio spettro)

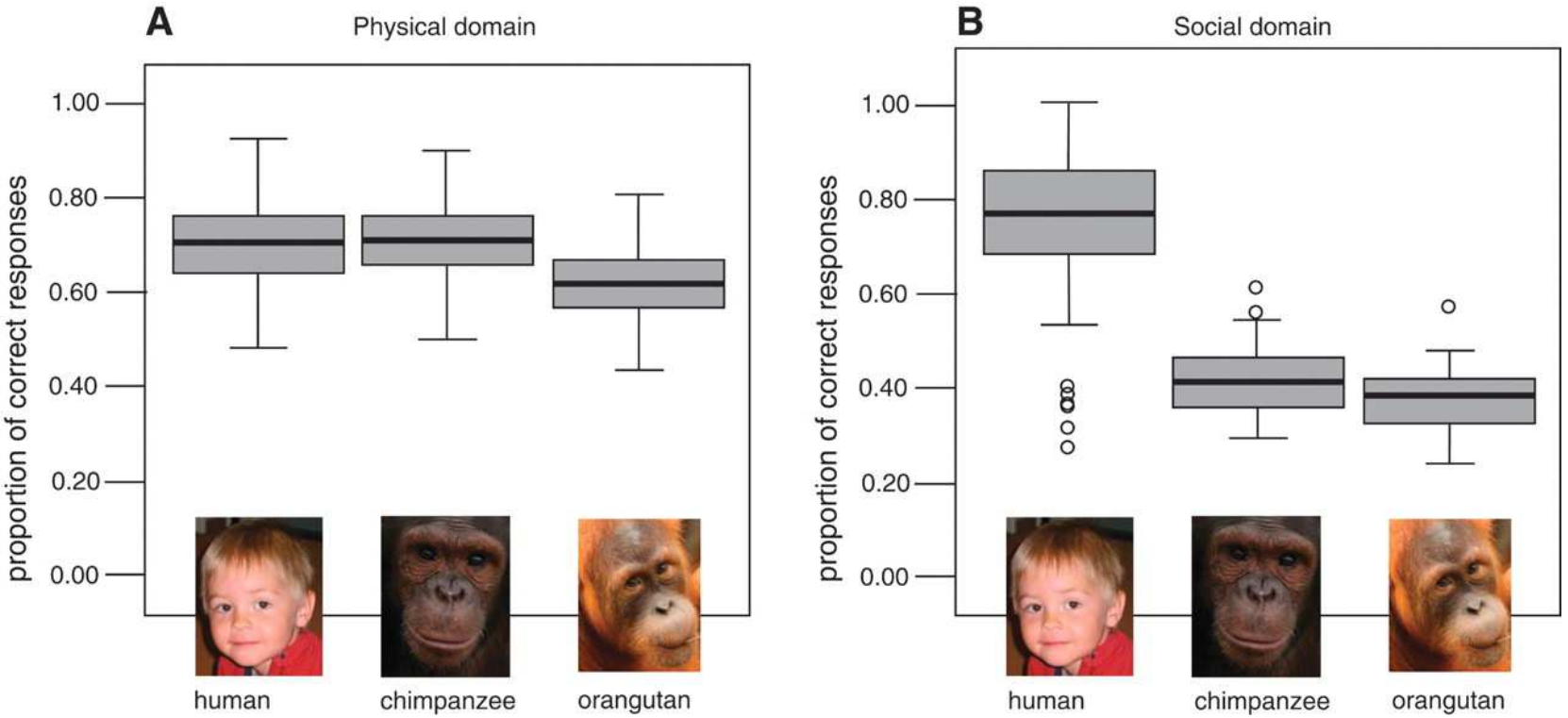
Brain Size and Intellectual Capabilities The absolute **brain size of hominids has tripled since the Pliocene** age (from an average of **450 cm³ in *Australopithecus*** to 1,345 cm³ in *H. sapiens*: Holloway, 1996)





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

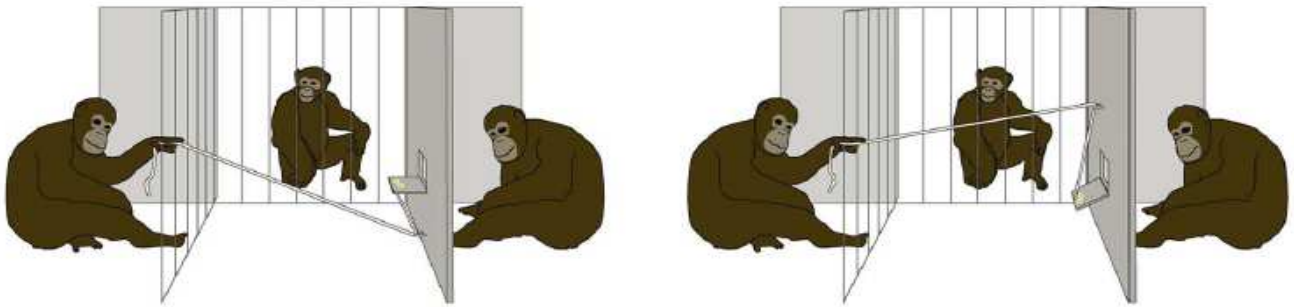


Figure. 3. Setup of the chimpanzee study. Illustration of the experimental setup for chimpanzees, viewed from the experimenter's point of view. The observed condition (pictured here) consisted of three different roles, subject (left), observer (middle) and receiver (right). In the stealing task (left),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

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

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

Published online before print May 23, 2016, doi: 10.1073/pnas.1506752113 PNAS May 23, 2016

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

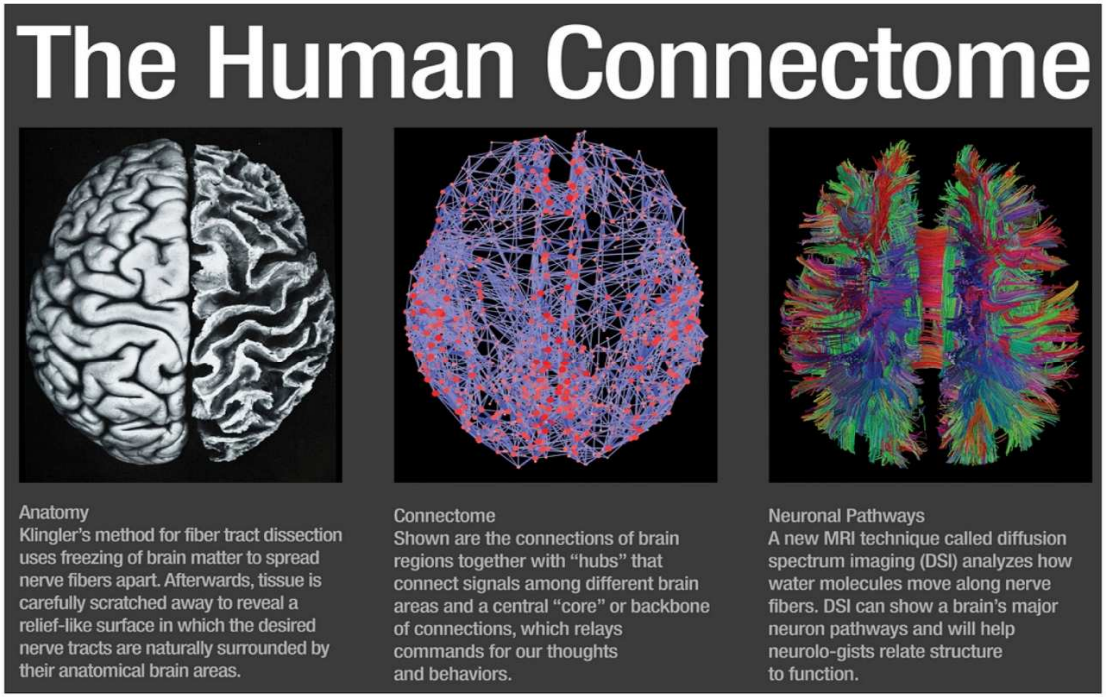
Madhura Ingalhalikar[a,1], Alex Smith[a,1], Drew Parker[a], Theodore D. Satterthwaite[b], Mark A. Elliott[c], Kosha Ruparel[b], Hakon Hakonarson[d], Raquel E. Gur[b], Ruben C. Gur[b], and Ragini Verma[a,2]

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.

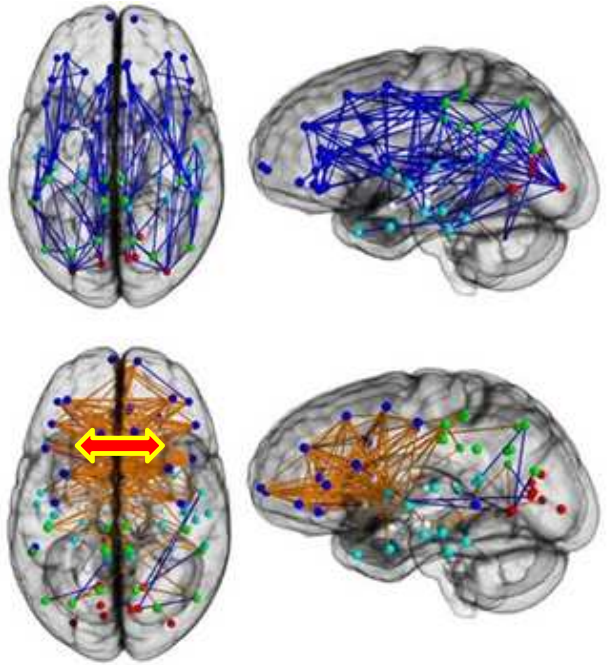
Sex differences are of high scientific and societal interes because of their **prominence in behavior of humans and nonhuman species**. This work is highly significant because it studies **a very large population of 949 youths** (8–22 y, 428 males and 521 females) **using the diffusion-based structural 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 pr
in the right auditory cortex. Functional and structural
within this neural network, however, are immature
connectivities only between the two hemispheres, cor
the adult pattern of prevalent intrahemispheric c
Thus, although the brain responds to spoken lang
at birth, thereby providing a strong biological bas
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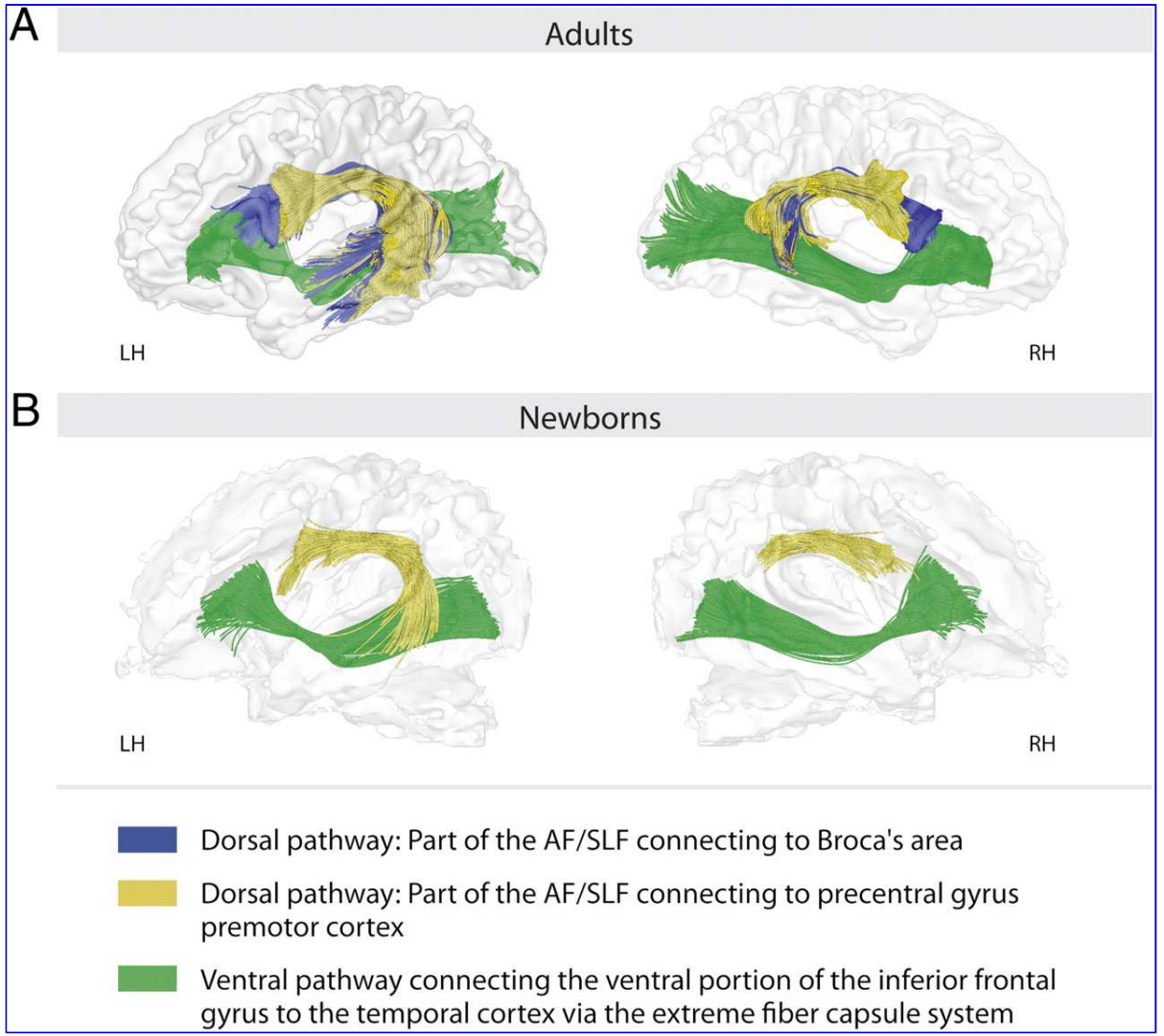
connectivity is yet to be established with language ex
brain develops.

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.



THE

EXPRESSION OF THE EMOTIONS

IN

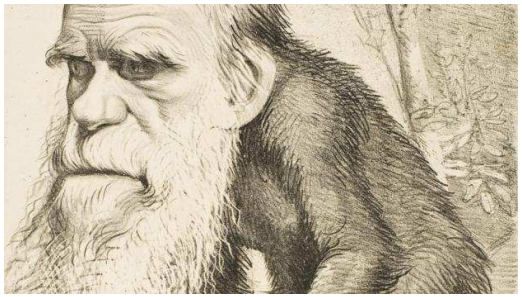
MAN AND ANIMALS.

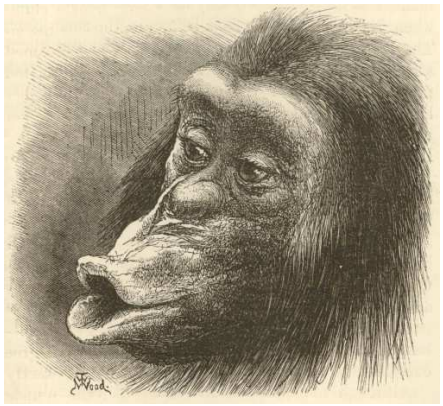
By CHARLES DARWIN, M.A., F.R.S., &c.

WITH PHOTOGRAPHIC AND OTHER ILLUSTRATIONS.

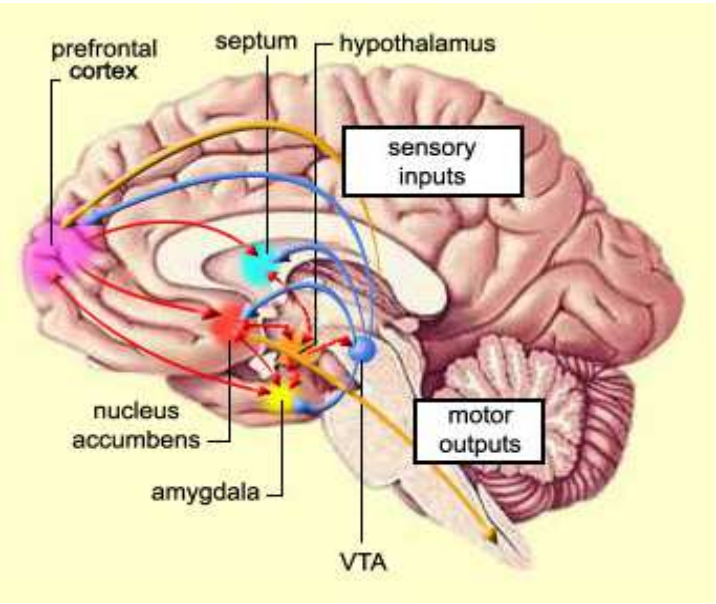
LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1872.

The ***ancestral*** **wiring 2: emotions**



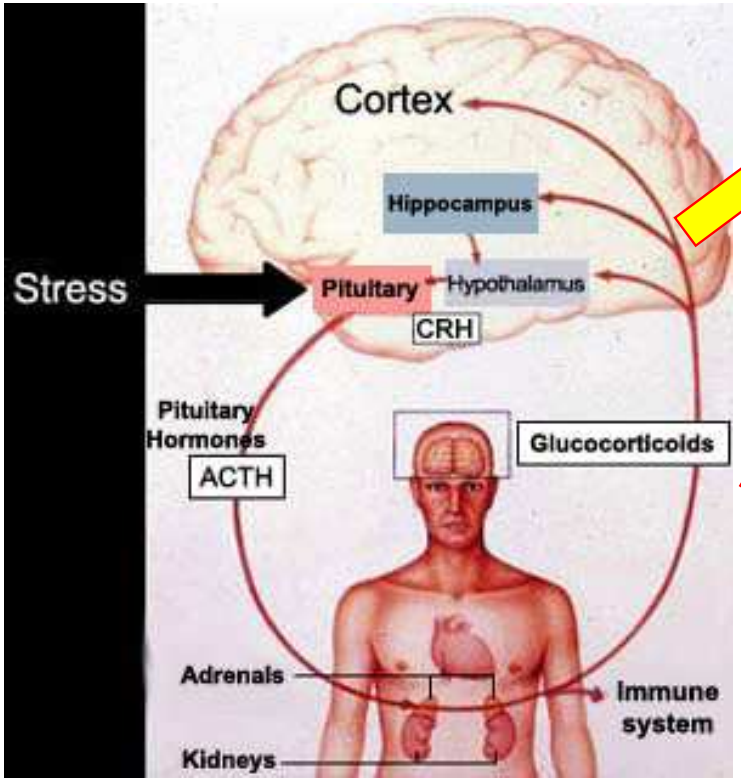


THE PLEASURE CENTRES

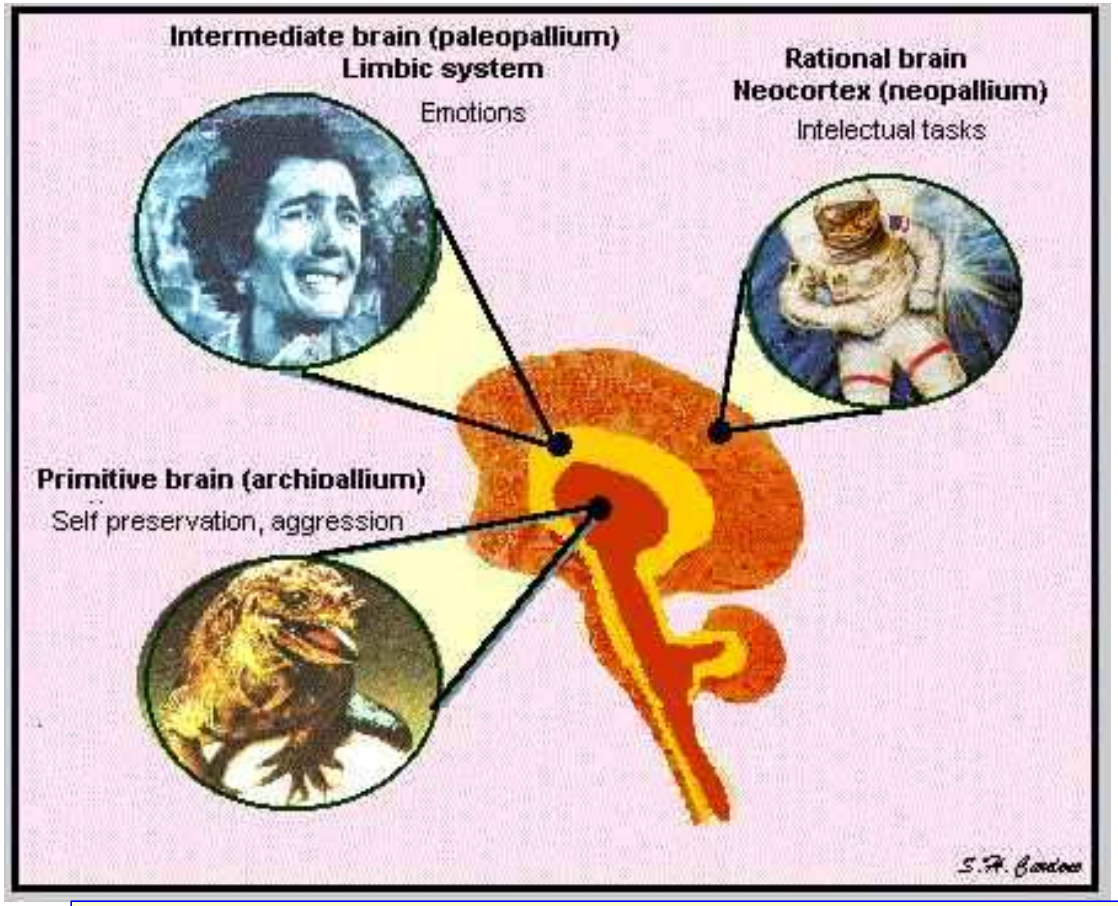


Ventral Tegmental Area

WHEN FEAR TAKES THE CONTROLS



DEPRESSION

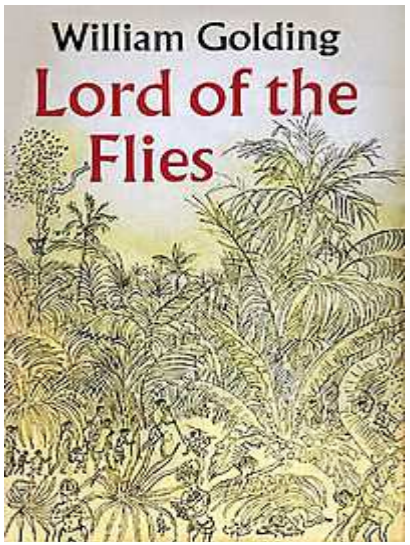


The Lucifer Principle is a book by Howard Bloom.
It sees a **social group, not an individual, as a main subject of human evolution**. It "explores the **intricate relationships among genetics, human behavior, and culture**" and argues that **"evil is a by-product of nature's strategies for creation and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

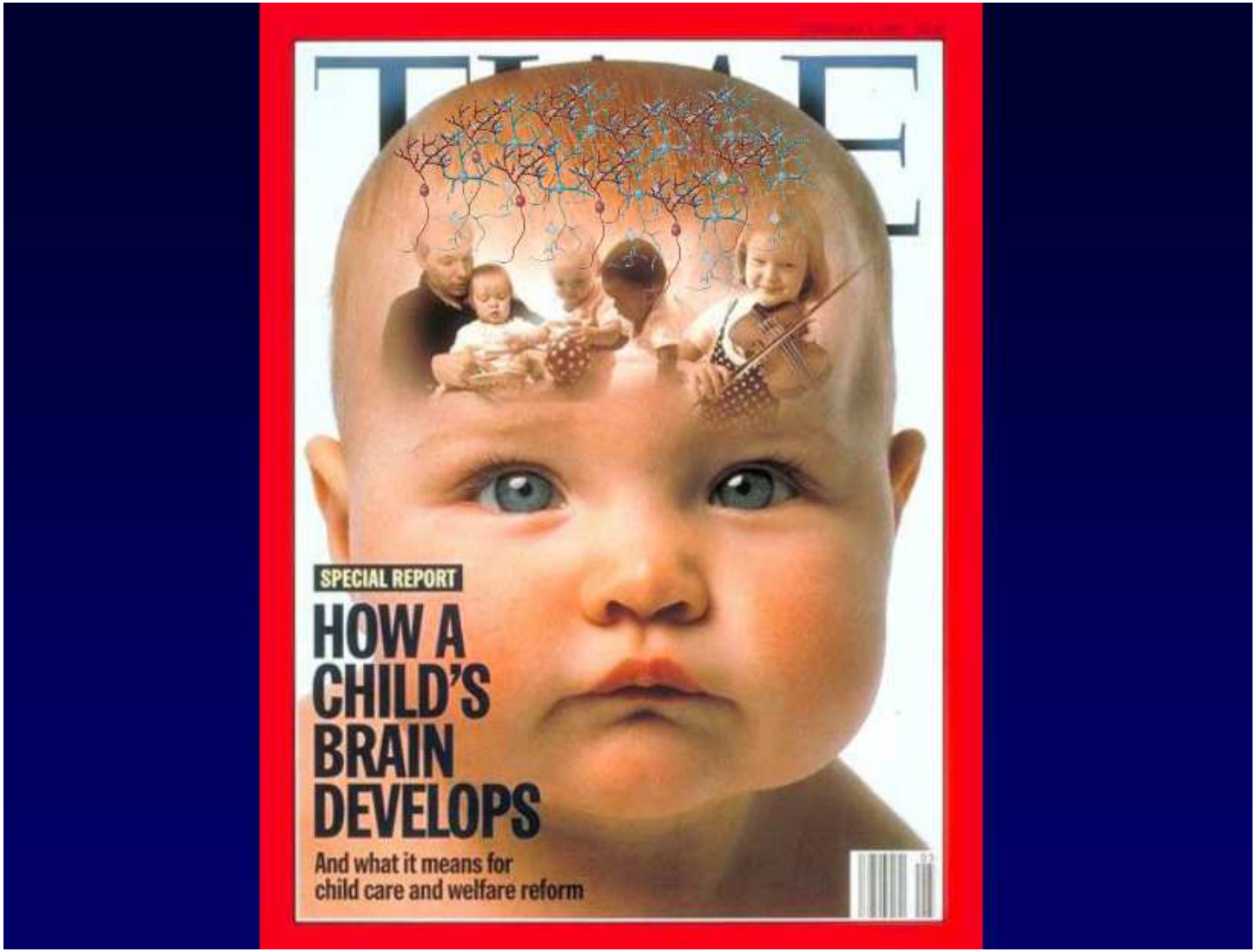
Nurture
Culture

WAR
HOLOCAUST

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



1961



Adolescenza, Stili di Vita, Psicopatologia

Giovanni Biggio

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

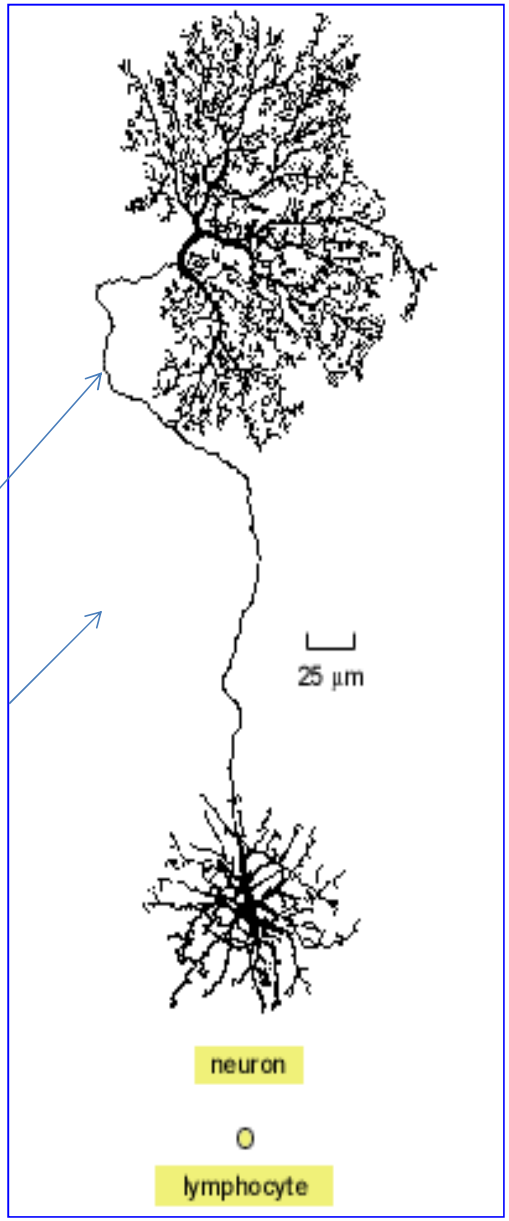
The ***Individual*** wiring

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

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

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

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



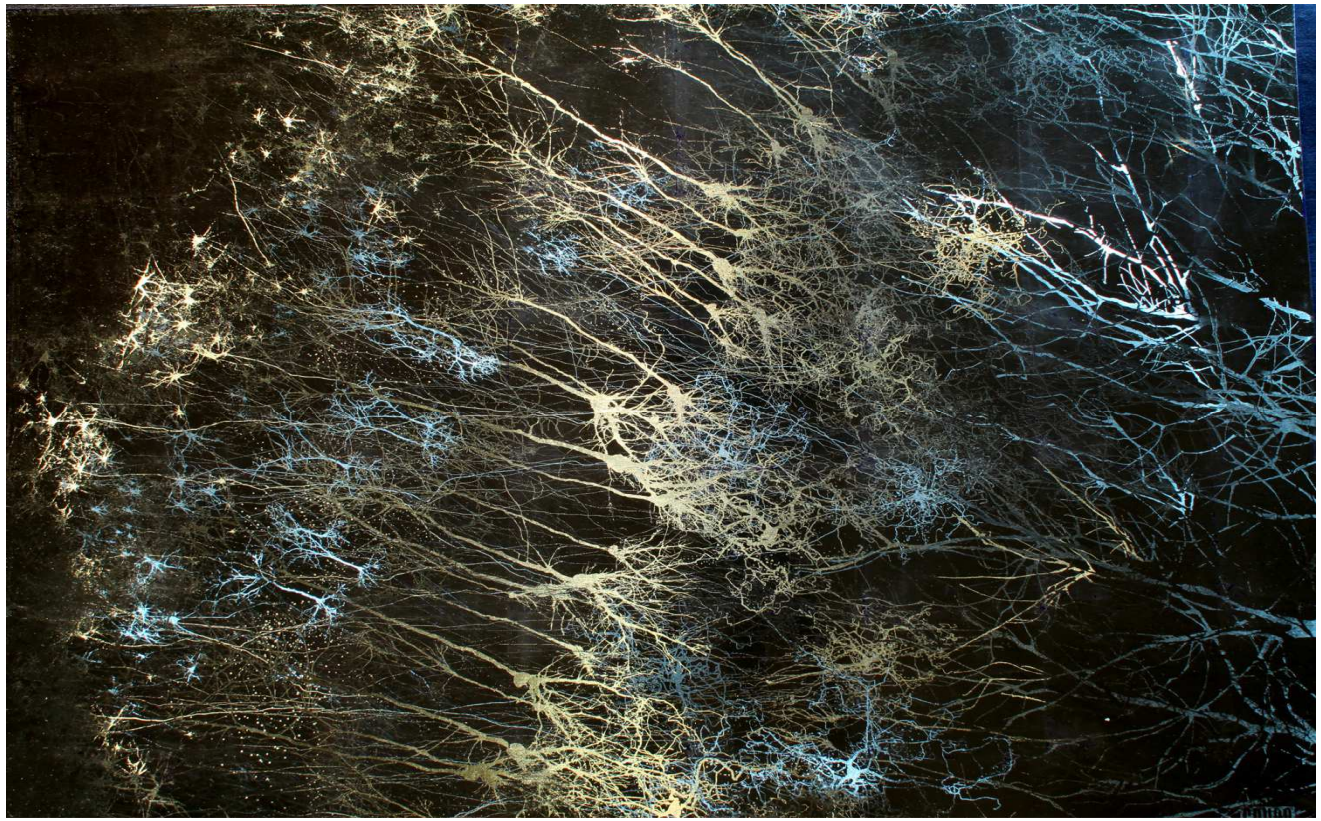
* In our species ***synaptogenesis*** begins as early as the **second month of fetal life** (in ***other mammals*** **only a few synapses are in place at birth**)

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

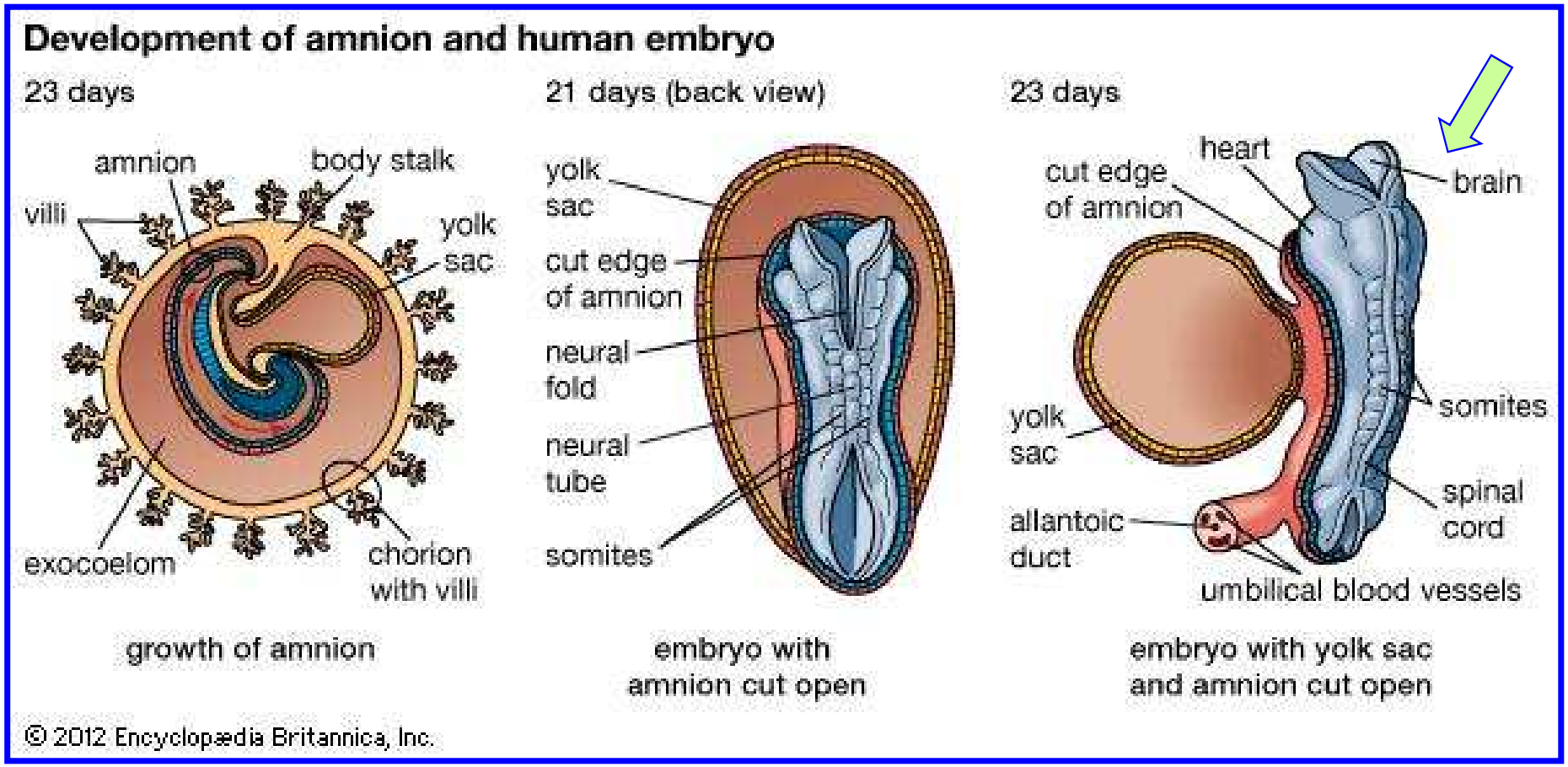
Neurons adjust…their connections (to one another) by ***strengthening*** or ***weakening*** them.

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

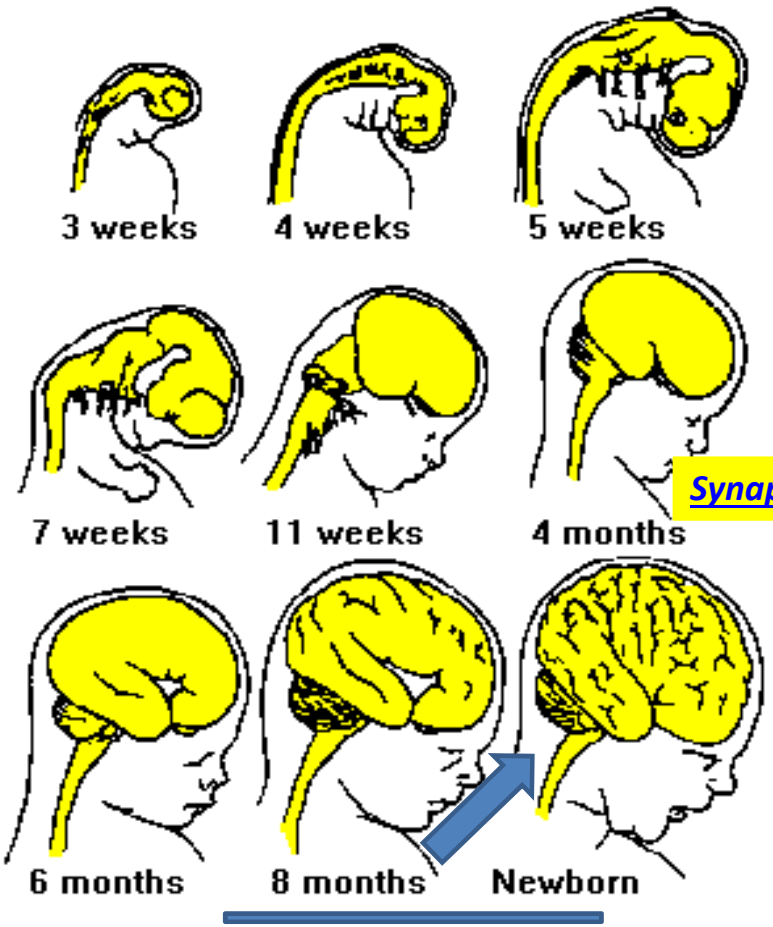
***You are more than your genes. You are your connectom* (*Sebastian Seung, MIT*).**



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

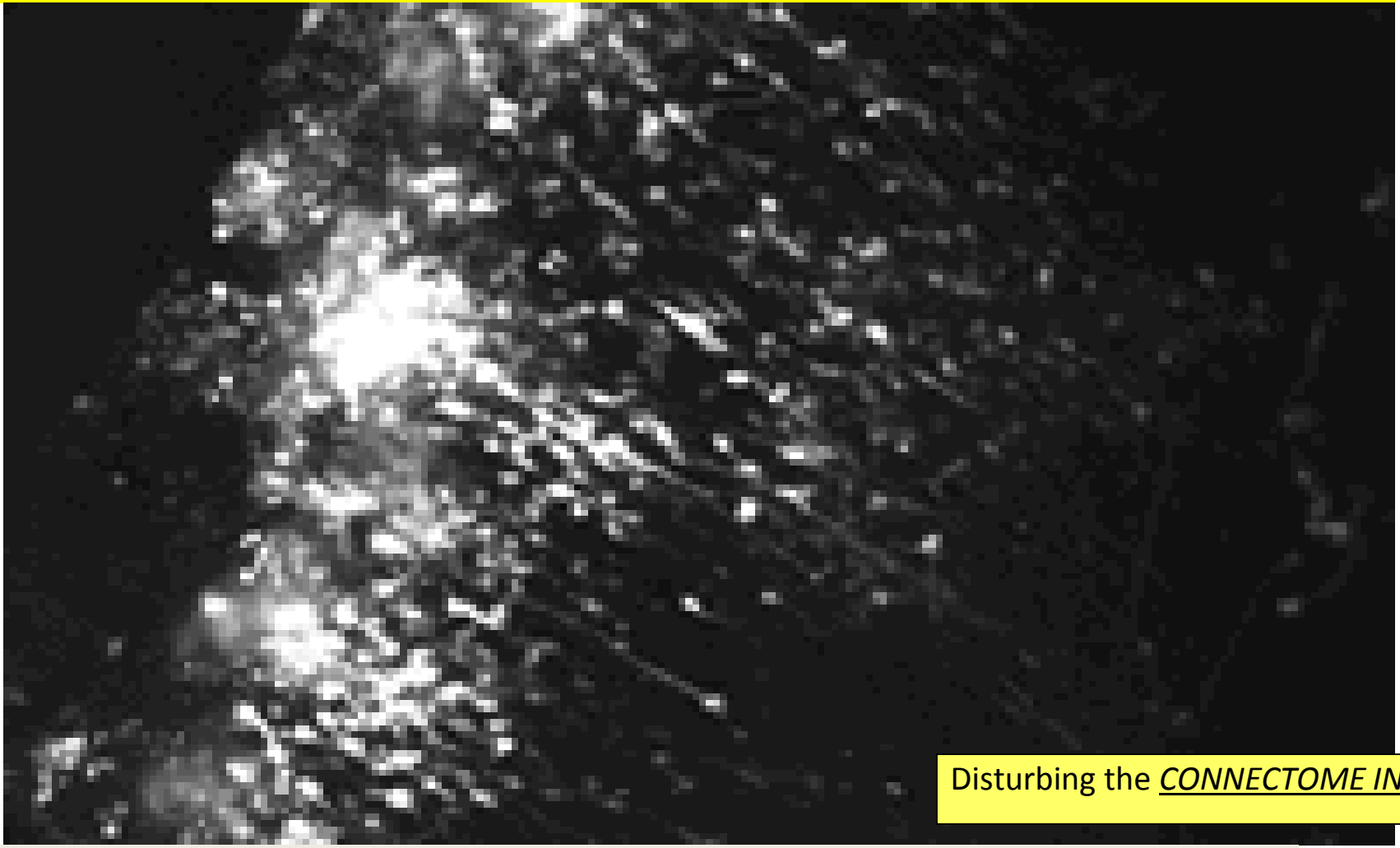
The brain grows at an amazing rate during development.
At times during brain development, **250,000 neurons are added every minute!**
At birth, almost all the neurons that the brain will ever have are present.

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*

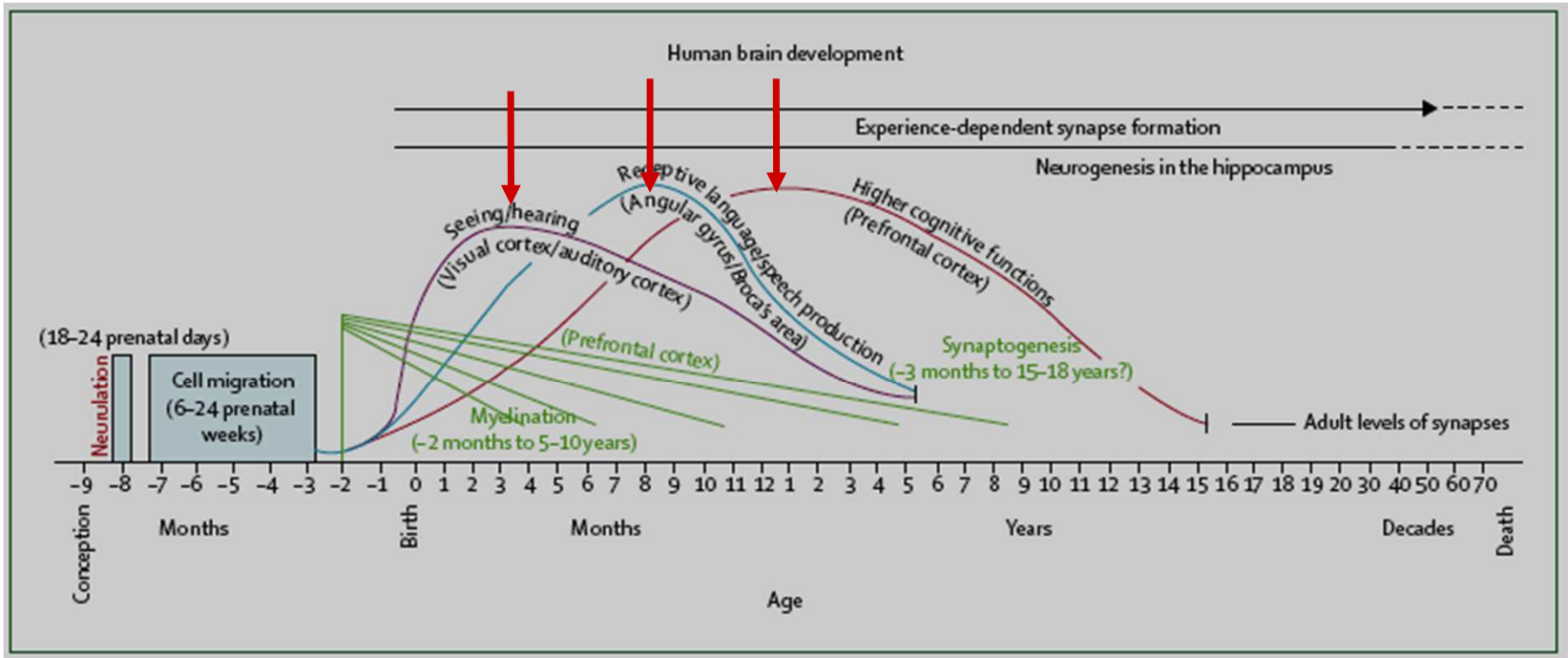


Figure 1: **Human brain development**
Reproduced with permission of authors and American Psychological Association[17] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; **56**: 5–15).

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

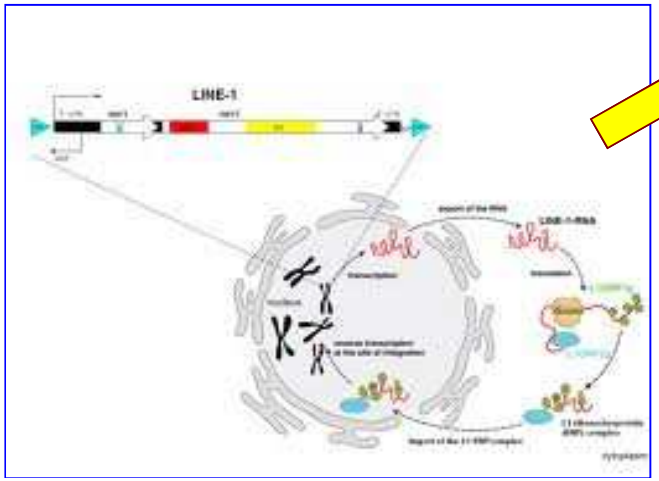
Genes we inherit and environmental factors both influence human behaviors. Scientists have recently discovered other underlying processes at work.

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.

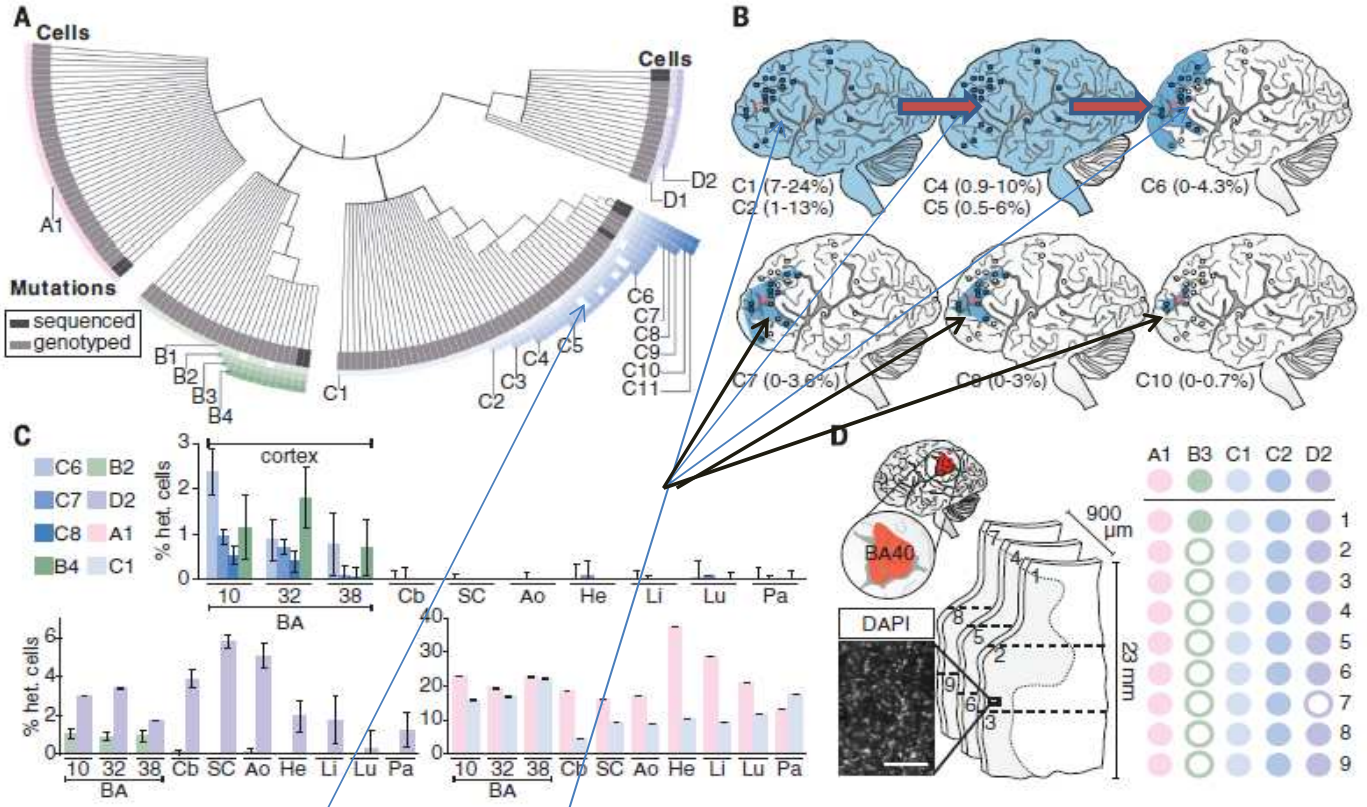


Fig. 3. Somatic mutations are shared between multiple neurons and demonstrate lineage relationships. (**A**) Lineage map of 136 human cortical neurons from brain B derived from 18 clonal somatic mutations, including SNVs, long interspersed nuclear element (LINE) insertions, and a TG-dinucleotide expansion.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

Developmental Plasticity: Synaptic Pruning

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

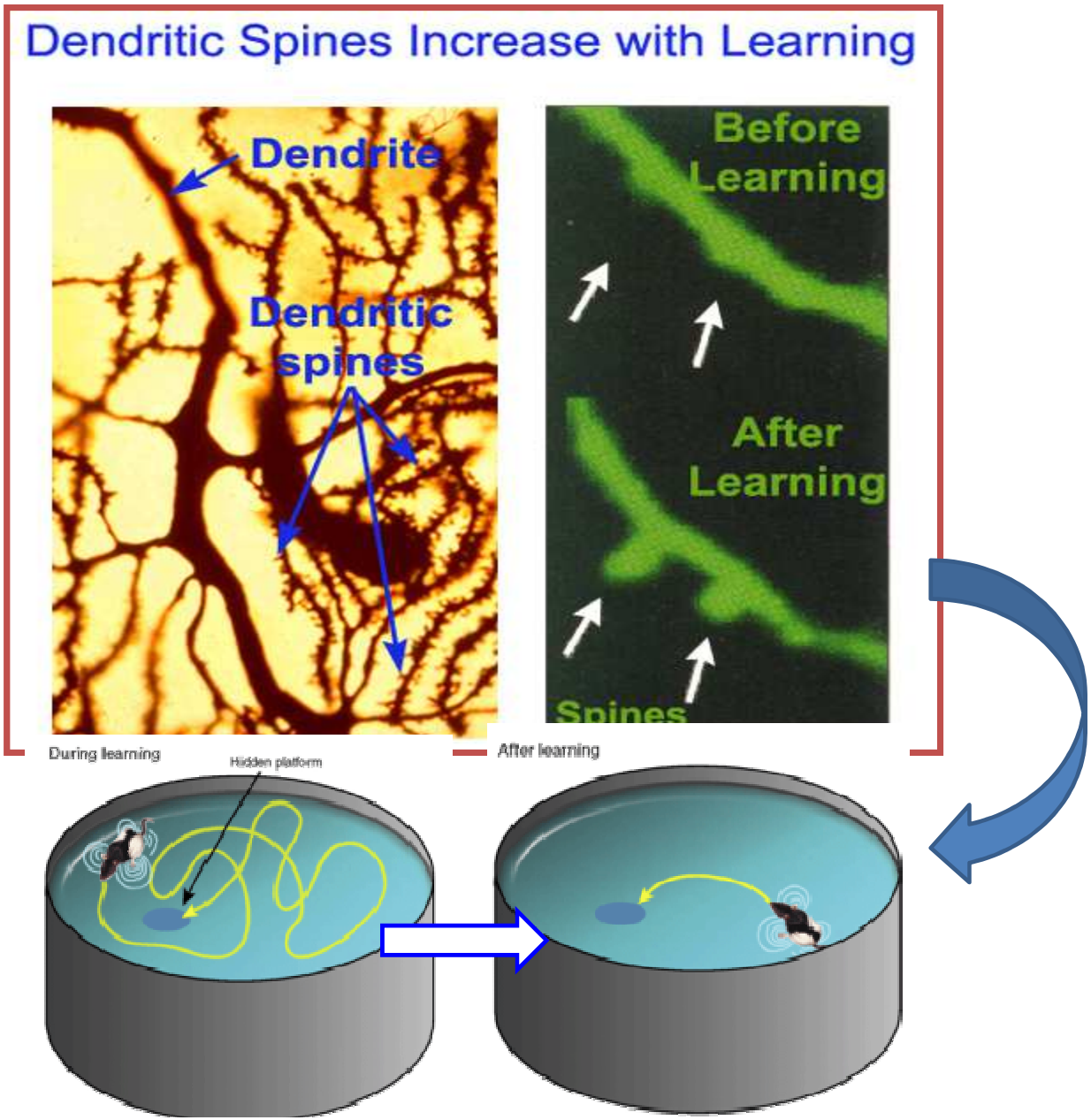
By the time an infant is **two or three years old**, the number of synapses is approximately **15,000 synapses per neuron** (Gopnick, et al., 1999). This amount is **about twice that of the average adult brain**.

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**

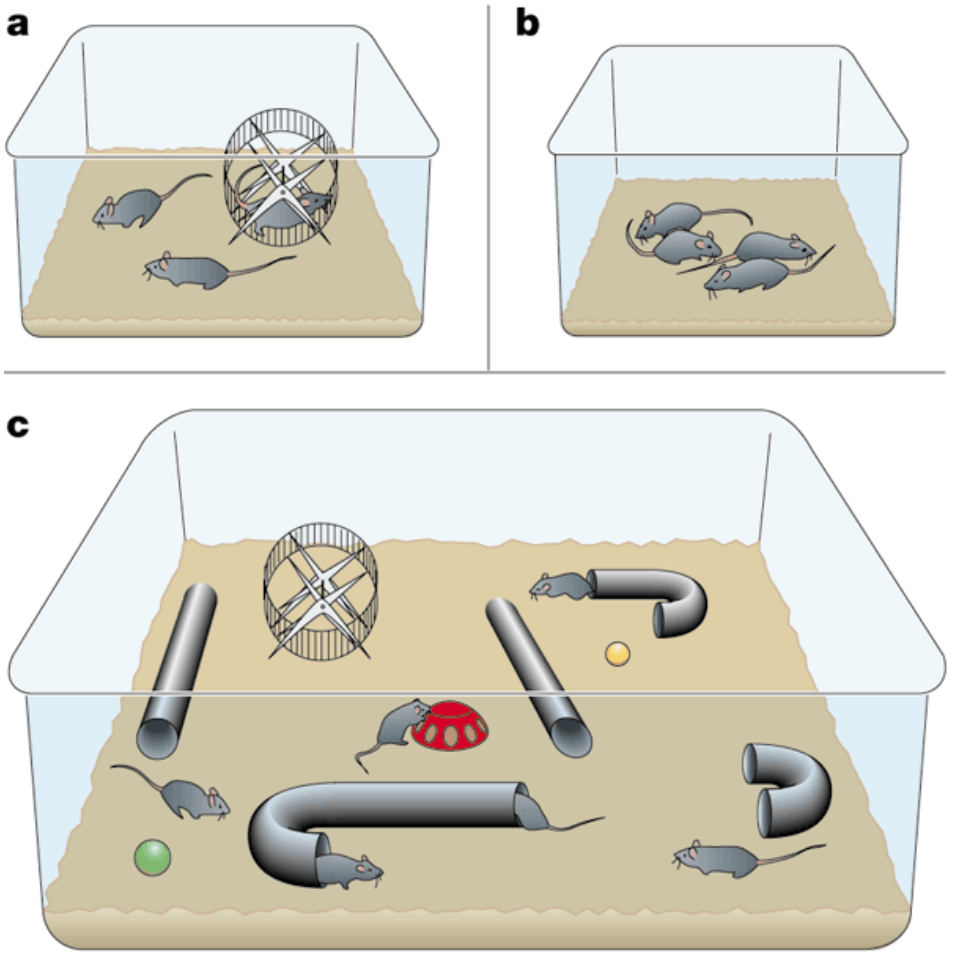
https://faculty.washington.edu/chudler/plast.html



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**.

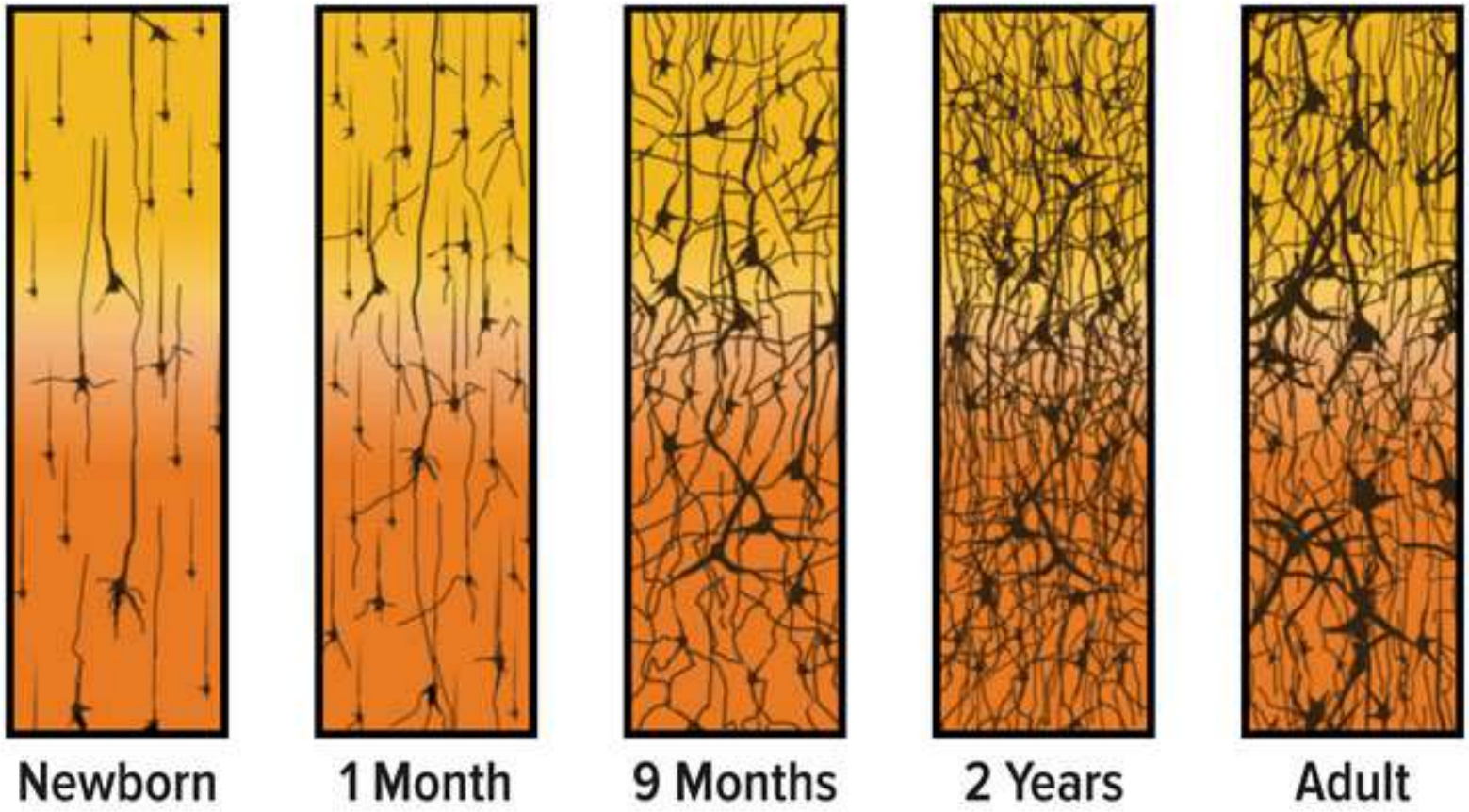
Giovanni Biggio
Centro di Eccellenza per la "Neurobiologia delle Dipendenze", Università degli Studi di Cagliari

- 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**

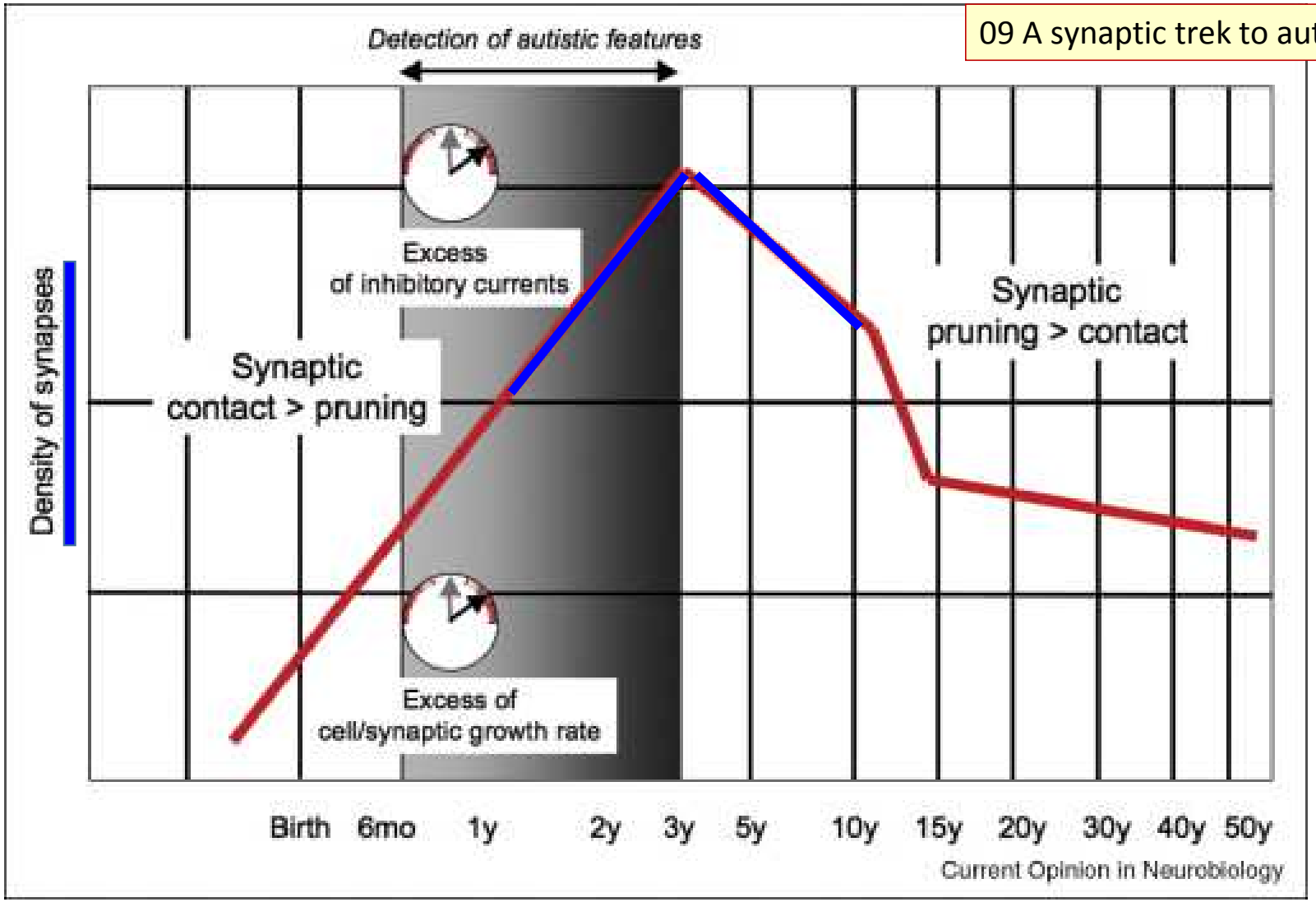


Nature Reviews | Neuroscience

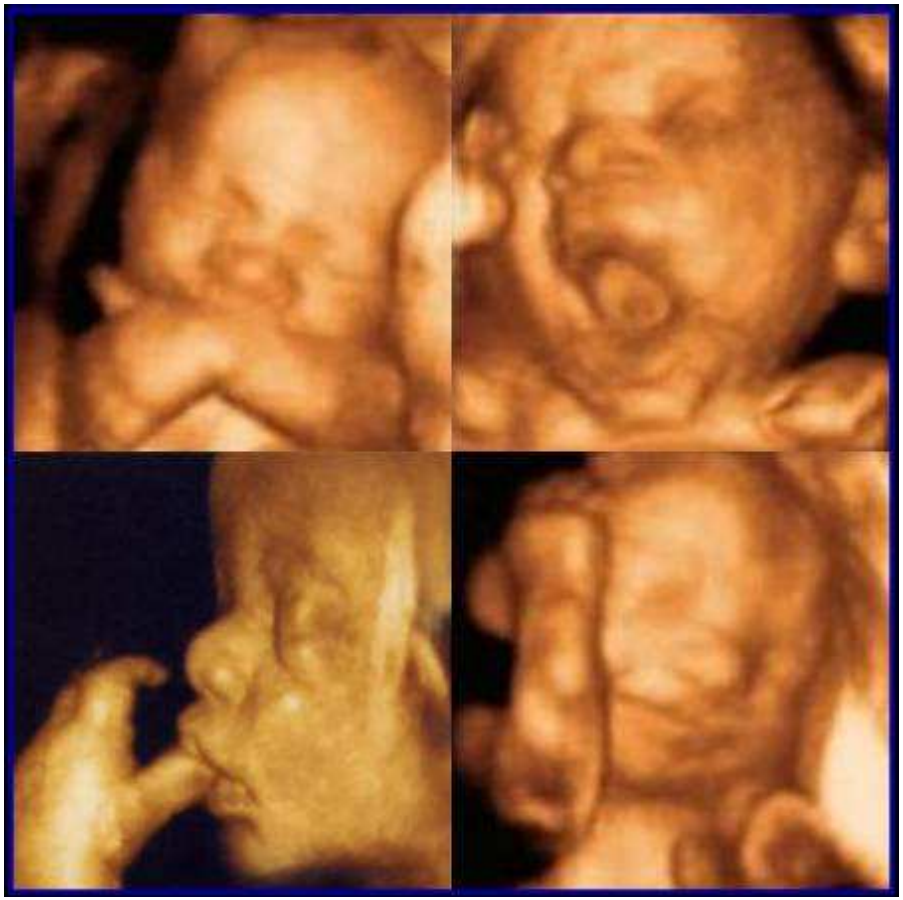
Connessioni interneurali dall'infante all'adulto umano



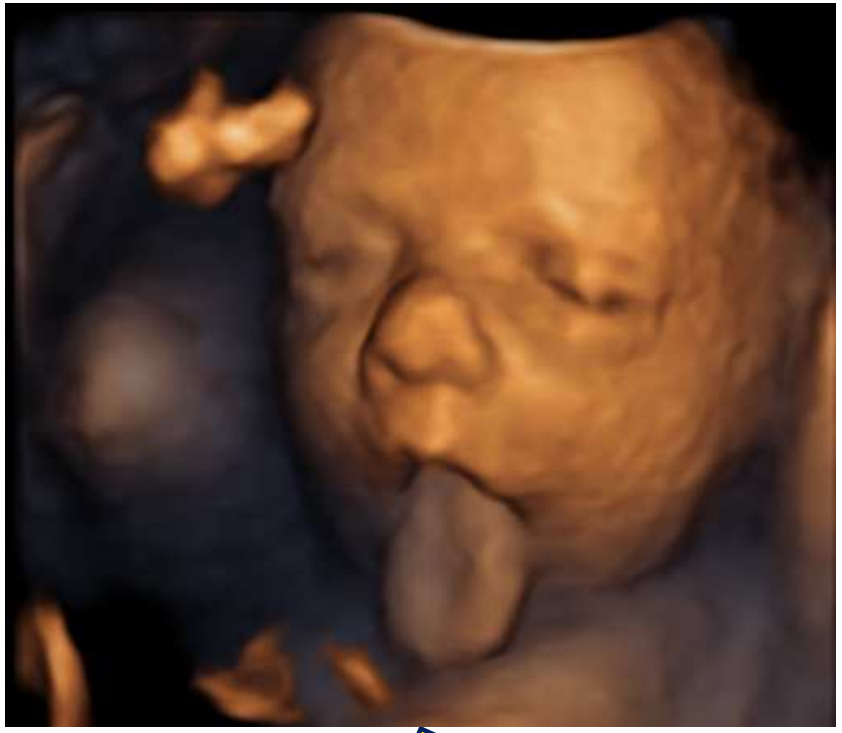
09 A synaptic trek to autism



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

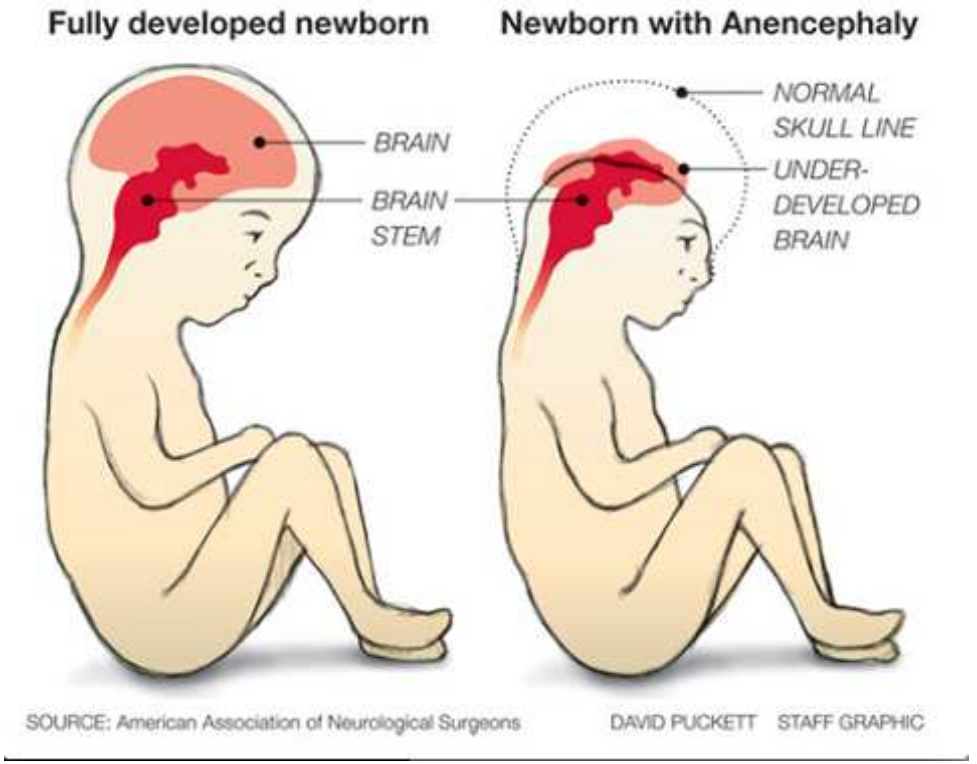


Submitted to appropriate **stimuli**, the **fetus yawns, he sneezes, he has the hiccups, he blinks**, he presents **several ancestral brain-reflex-responses (that will disappear** way, way that the brain matures)

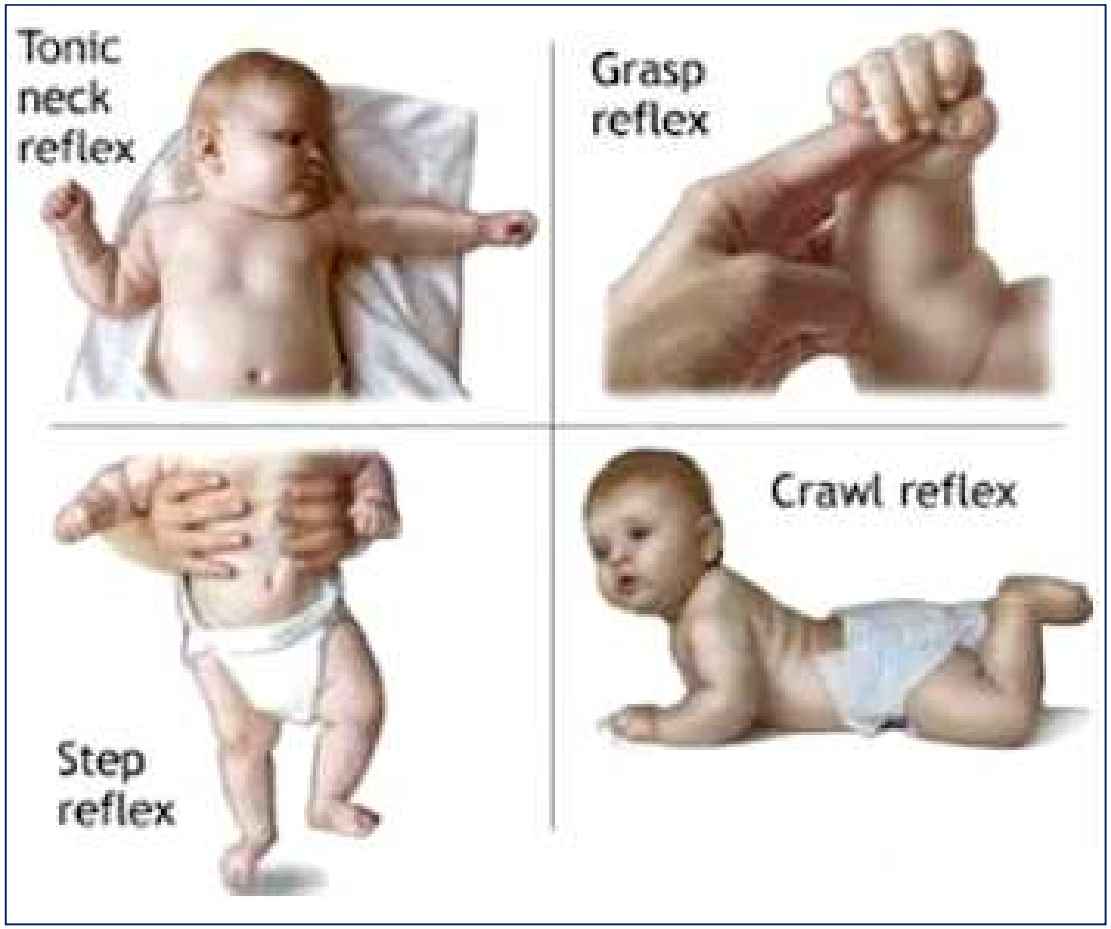
Until the **age of three months** the infant has **virtually no need, in order to survive, of the cerebral hemispheres !**

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!

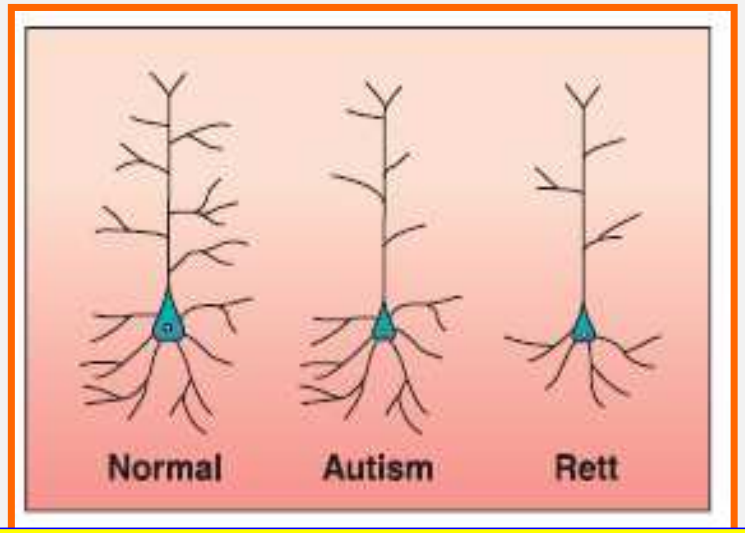


Archaic neonatal reflexes



Les réflexes archaïques néonatales

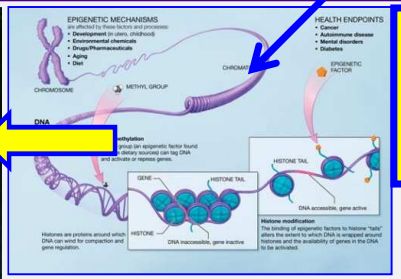
Léo Kanner



Hans Asperger

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

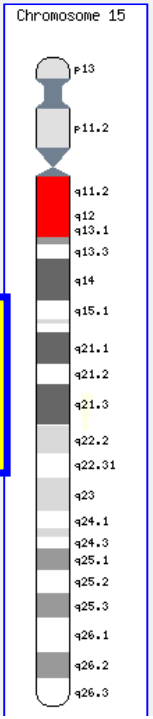
Angelman syndrome



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

ECERI
European Cancer and Environment Research Institute

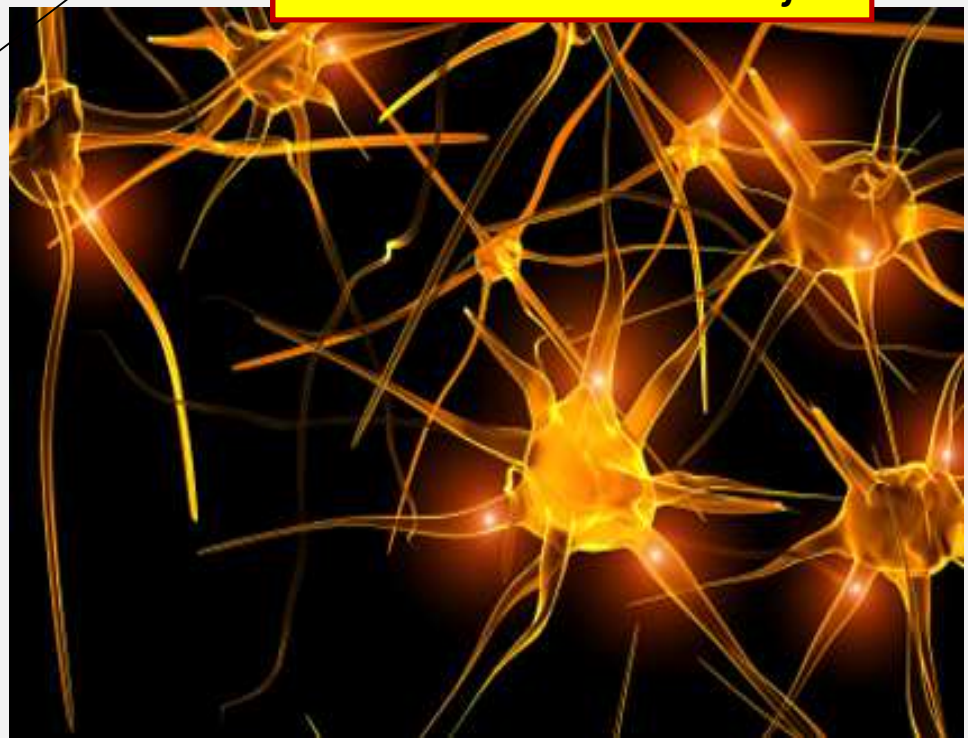
INTERNATIONAL SOCIETY OF DOCTORS FOR ENVIRONMENT
ISDE



Autism

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

*The **Human Connectome Project***



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

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

  to be damaged.

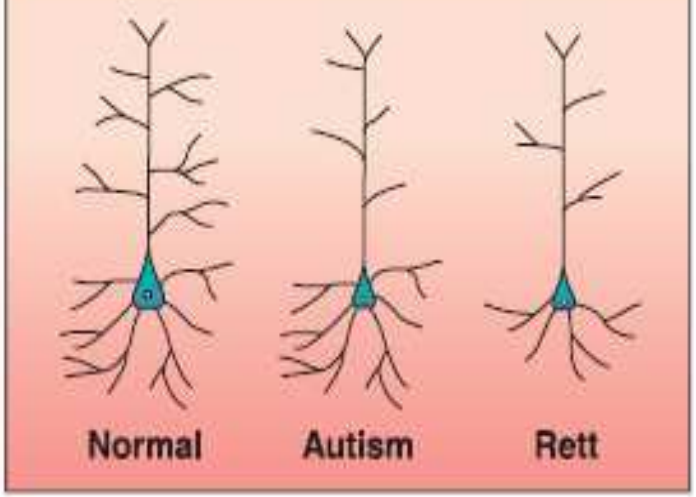


Fig. 2. Schematic representation of pyramidal neurons from control, autism, and Rett brains. In autism, the cell body is small and there is reduced dendritic branching. Similar changes occur in Rett, along with reduction in basilar dendritic branching. The reported changes are subtle and apply to a few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

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

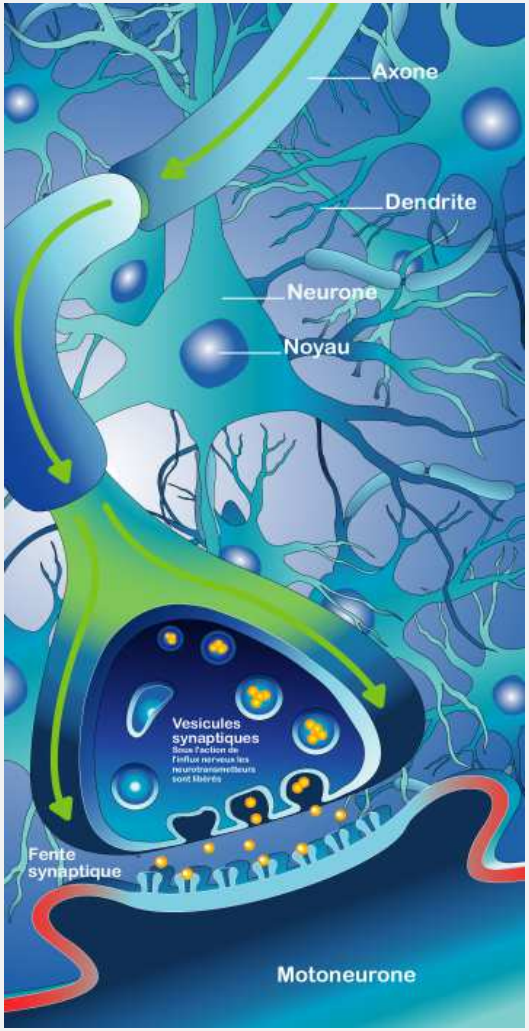
As for the **causes of autism**

many hypotheses have been advanced:

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

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

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



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

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

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

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

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

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

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

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

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

ONLINE FIRST

Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism

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

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

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

Design, Setting, and Participants: Twin pairs with

sessments (Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule) were completed on 192 twin pairs. Concordance rates were calculated and parametric models were fitted for 2 definitions, 1 narrow (strict autism) and 1 broad (ASD).

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

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

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

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

EDITORIAL

ONLINE FIRST

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

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

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

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

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

⇩

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

ORIGINAL ARTICLE

Genome-wide Epigenetic Regulation by Early-Life Trauma

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

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

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

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

gene expression profiles obtained by messenger RNA microarrays. Methylation differences between groups were validated on neuronal and nonneuronal DNA fractions isolated by fluorescence-assisted cell sorting. Functional consequences of site-specifi
tion were assessed by luciferase ass

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

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

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

Abuse Leaves Its Mark on the Brain

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

Francisco_de_Goya,_Saturno_devorando_a_su_hijo_(1819-1823)

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

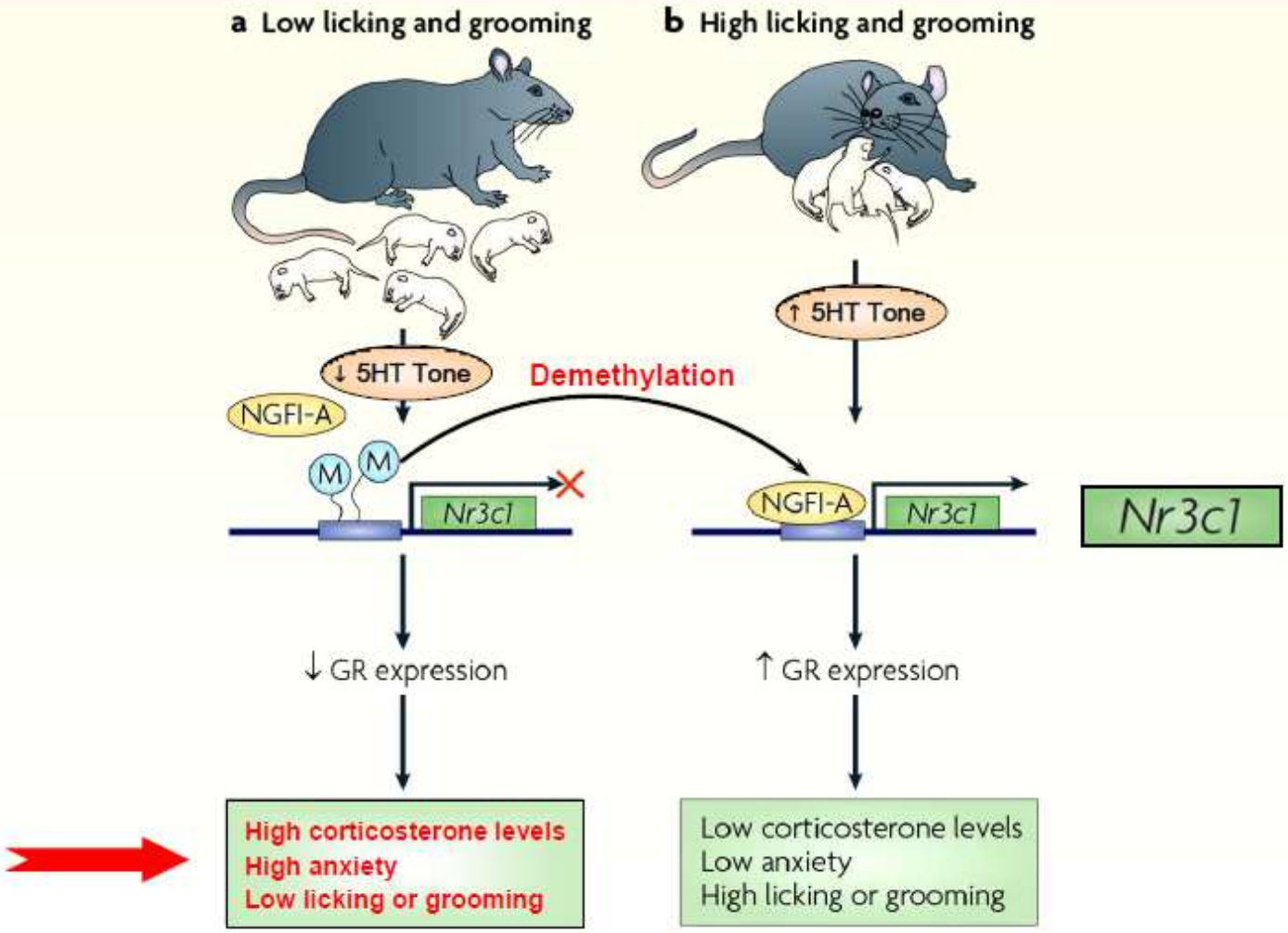
In a comparison of **suicide victims** who were abused or not, **only the abused victims had an epigenetic tag on the GR gene**

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

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

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

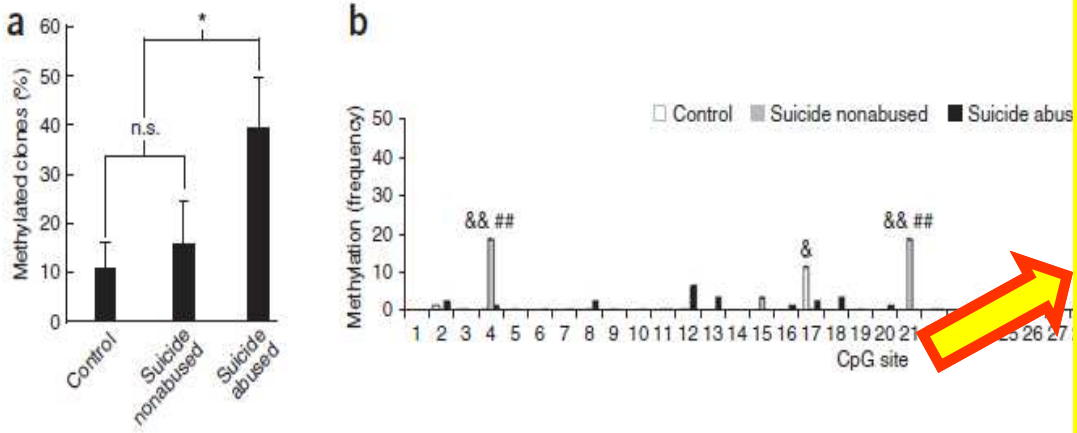


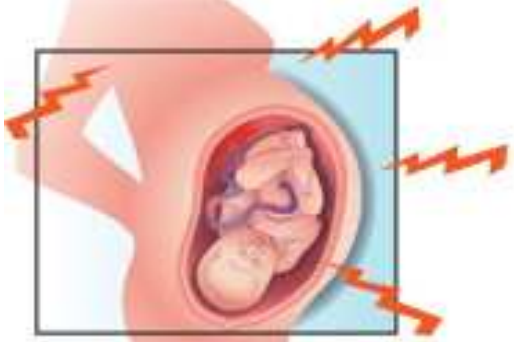
Figure 2 Methylation of the *NR3C1* promoter in the hippocampus. Twenty clones were sequenced for each subject for m
percentage of methylated clones for suicide victims with a history of childhood abuse ($n = 12$), suicide victims without a
and controls ($n = 12$). The methylation percentage was calculated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

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

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

Prenatal Stress

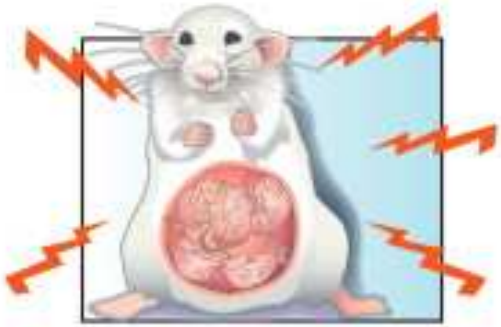
Traumatic war experiences, natural disasters, death of husband



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?

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 progr

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**

ORIGINAL ARTICLE

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

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

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

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

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

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

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

Autism Risk Across Generations

A Population-Based Study of Advancing Grandpaternal and Paternal Age

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

Importance: Advancing paternal age has been linked to autism.

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

Design: Population-based, multigenerational, case-control study

age at the time of birth of the parent was obtained for a smaller subset (5936 cases and 30 923 controls).

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

Results: A statistically significant monotonic association was found between advancing grandpaternal age at the time of birth of the parent and risk of autism in grandchildren. Men who had fathered a daughter when they were 50 years or older were 1.79 times (95% CI, 1.35-2.37; $P<.001$) more likely to have a grandchild with autism, and men who had fathered a son when they were 50 years or older were 1.67 times (95% CI, 1.35-2.37; $P<.001$) more likely to have a grandchild with autism, compared with men who had fathered children when they were 20 to 24 years old, after controlling for birth year and sex of the child, age of the spouse, family history of est family educational level, tatistically significant mono- ound between advancing pa- n in the offspring. Sensitivity se findings were not the re- data on grandparental age.

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

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

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

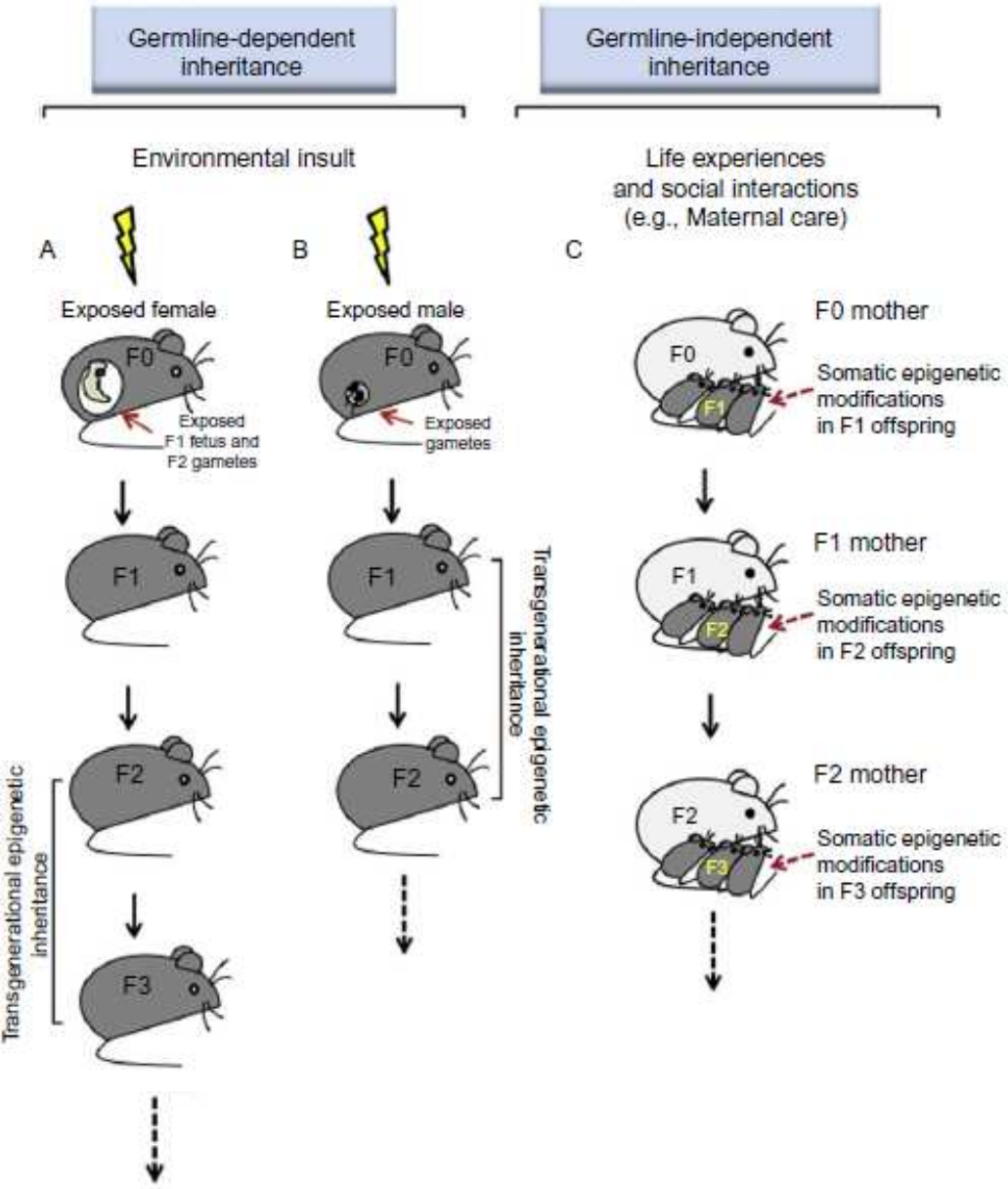


Figure 2.1 Germline-dependent versus germline-independent epigenetic inheritance.

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

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

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

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

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

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

genes

Genes 2017, 8, 150; doi:10.3390/genes8060150

MDPI

Review

Maternal Factors that Induce Epigenetic Changes Contribute to Neurological Disorders in Offspring

Avijit Banik [1], Deepika Kandilya [1], Seshadri Ramya [1], Walter Stünkel [2], Yap Seng Chong [3] and S. Thameem Dheen [1,*]

It is well established that **the regulation of epigenetic factors**, including **chromatin reorganization, histone modifications, DNA methylation, and miRNA regulation, is critical for the normal development and functioning of the human brain**.
There are a number of **maternal factors influencing epigenetic pathways such as lifestyle, including diet, alcohol consumption, and smoking**, as well as **age and infections** (viral or bacterial).

Genetic and metabolic alterations such as **obesity, gestational diabetes mellitus (GDM), and thyroidism alter epigenetic mechanisms, thereby contributing to neurodevelopmental disorders (NDs) such as embryonic neural tube defects (NTDs), autism, Down's syndrome, Rett syndrome, and later onset of neuropsychological deficits**.

This review comprehensively describes the recent findings in the epigenetic landscape contributing to altered molecular profiles resulting in NDs. Furthermore, we will discuss potential avenues for future **research to identify diagnostic markers and therapeutic epi-drugs to reverse these abnormalities in the brain as epigenetic marks are plastic and reversible in nature.**

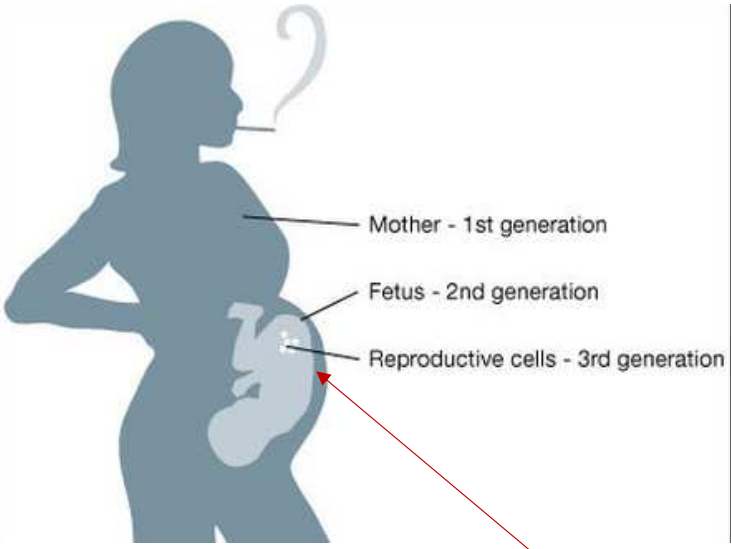
Figure 1 Smoking in mothers alters neurodevelopmental processes in the fetus. Maternal smoking alters the DNA methylation of genes involved in placental and fetal development, leading to neurodevelopmental disorders in the offspring.

Maternal Smoking

Alteration in DNA methylation pattern of fetal gene pools

- Placental Function: *LINE-1* [43], *AluYb8* [9]
- Neurodevelopment: *NR3C1* [50], *HSD11B2* [51], *GPR13, LRFN3* [53]
- Neurotransmission: *HTR2A, ADA* [47,48]
- Immune development: *ADA, PTPN22* [48]
- Transcriptome regulator: *RUNX3* [46], *PURA, GTF2H2, HKR1* [49]
- Calcium binding: *GCA* [45]
- Metabolism of aromatic hydrocarbon: *CYP1A1* [49]

- Placental abruption, Miscarriage, stillbirth, preterm delivery
- Neurobehavioral disorders: ADHD, Autism, Tourette's syndrome, Tic disorder , Obsessive-compulsive disorder



Exposure of the germline *to* ***nicotine*** *produces* ***epigenetic changes in the germline…*** *they are* ***permanent, and passed from one generation to the next***

F2 Epigenetic targets of alcohol exposure in the fetus. **Gestational alcohol exposure induces histone modification, alteration in DNA methylation pattern and miRNA targets, and expression of genes associated with fetal developmental process**, leading to neurodevelopmental disorders.

Gestational Alcohol Exposure

Susceptible targets in the fetus

1 Gene targets

- Developmental: Plunc, Neurofilament, Pale ear [68], *Hoxa1* [87]
- Cell Proliferation: *Oct4, Sox2, Nanog* [72], *Bub1, Cdc20, CcnB1, Plk1* [74]
- Cell Differentiation: *Sox1, Zic1, Cxcl12, BMP8b, Dmrt1, Meis1, Mef2c* [72], *Sh3bp2, Tnf, Adra1a, Pik3r1* [75]
- Brain development: *Pten, Otx2, Slitrk2, Nmnat1* [79]
- Imprinting: *H19* [76], *POMC* [80], *Sfmbt2, Dlk1, Ube3a* [79]
- Learning & Memory: *PNOC, PDYN* [82]

2 miRNA targets

miR-9, miR-21, miR-153, miR-335 [73]; miR-10a, miR-10b, miR-30a-3p, miR-145, miR-152, miR-29c, miR-30e-5p, miR-154, miR-200a, miR-296, miR-339, miR-362, miR-496 [87]

3 Histone modifying targets

H3K9ac [81]
H3K27me3 [82]
CBP [83]

4 DNA methylation targets

DNMT, MeCP2 [67]

Phenotypic outcomes in the offspring

Fetal alcohol spectrum disorder (FASD)

- Attention and memory deficit
- Craniofacial malformation
- Motor function abnormalities
- Auditory and language problem

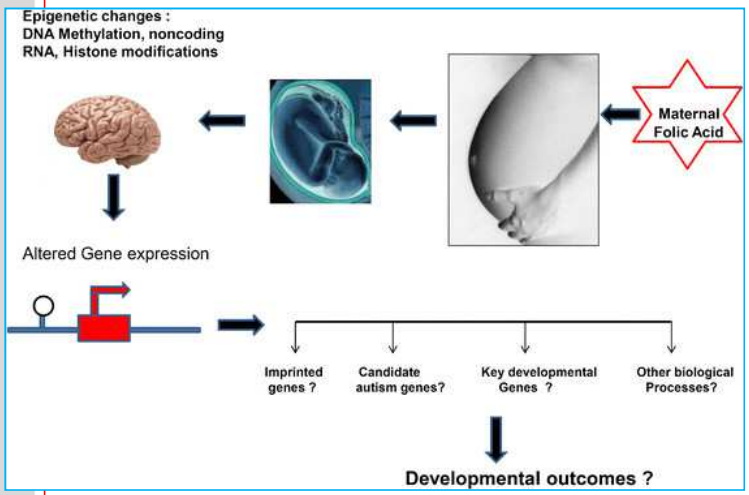
F3 Effect of **maternal dietary deficiency** on fetal development.
The absence of essential dietary supplements in maternal diet during gestation leads to a disruption in metabolic pathways and several epigenetic alterations in the fetus, triggering **abnormal uterine development** and **neurodevelopmental disorders**.

Maternal dietary deficiency

Absence of dietary methyl group donors such as folate, choline, methionine, betain and methylcobalamine

- Imbalance in folate-mediated one-carbon metabolism (FOCM) pathway [98]
- Mutation in methionine synthase reductase (*Mtrr*) gene, essential for deployment of methyl groups from the folate cycle [104]
- Down-regulation of genes related to fetal brain development: *BDNF*, *CREB*, *NGF* and *TrkB* [105]
- H3K9 and H4K20 methylation [114]
- Altered expression of miRNAs linked to FOCM pathway : miR-29c, miR-183, miR-422b, miR-189 [115]; miR-22, miR-24, miR-29b, miR-34a, miR-125, miR-344-5p/484, miR-488 [116-118]

Abnormal uterine development and congenital malformation [104]



F4 Effect of **maternal metabolic conditions** on fetal development.
Metabolic conditions at gestation such as GDM, obesity, and hypothyroidism induce epigenetic alterations in the fetus, leading to a series of **metabolic and immunogenic changes triggering neuroanatomical and neuropsychological deficits in the developing brain**.

Maternal metabolic conditions

- Gestational Diabetes Mellitus (GDM)
- Maternal Obesity
- Maternal Hypothyroidism

Trigger epigenetic imbalance in the fetus [149,150,157,158,172]

- Induces oxidative stress [148]
- ROS accumulation [148]
- Inflammatory response [155]
- Cytokine production [156]
- Decreased T3 levels [169]
- Altered levels of metabolic genes [172]

Neuroanatomical /neuropsychological deficits in developing brain

F5 Several **lifestyle-related metabolic factors and infection at gestation play a critical role in the epigenetic modification** and in turn the **altered expression of many genes associated with abnormal fetal development**. This may lead to a series of neurodevelopmental disorders in the offspring.

Maternal Factors

Life Style	Metabolic	Infection
• Smoking • Alcohol consumption • Malnutrition • High fat diet • Late parental age	• Gestational diabetes mellitus (GDM) • Thyroidism • Obesity	• Viral • Bacterial

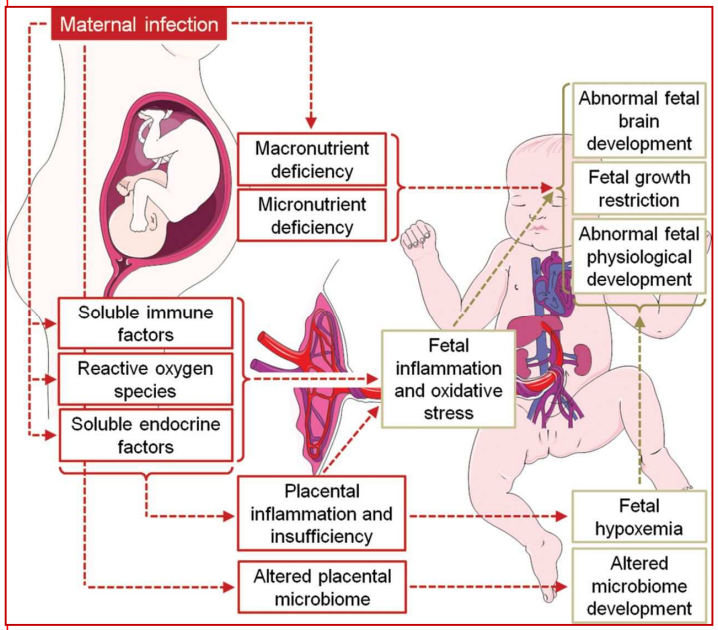
Induce imbalance in the epigenetic mechanisms in early developmental process

DNA Methylation | Histone Modification | Chromatin Remodelling | Differential expression of mi-RNAs

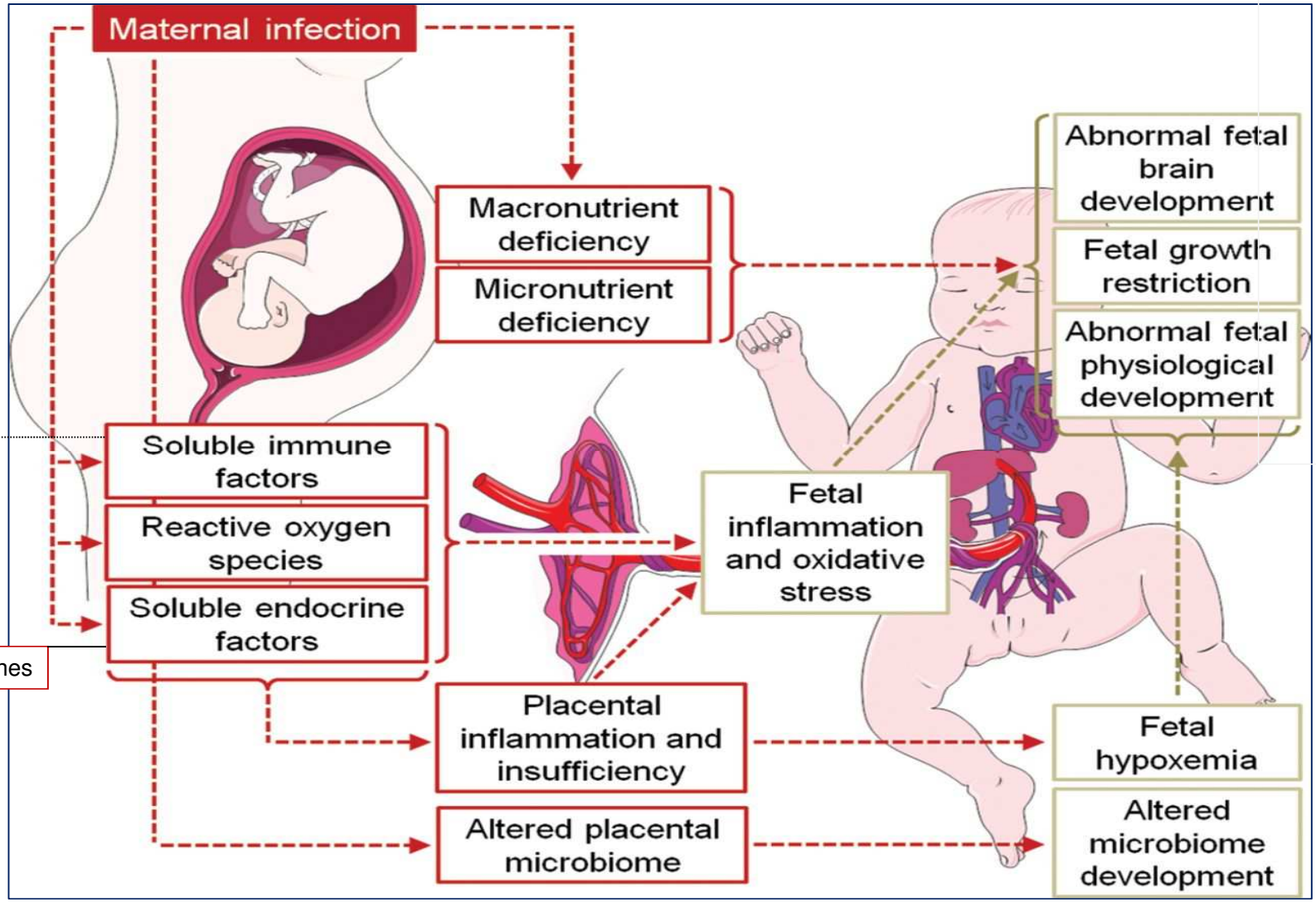
Altered expression of genes critical for normal fetal development

Neurodevelopmental Disorders

Genetic	Multifactorial
• Down's syndrome • Prader–Willi syndrome • Rett syndrome • Fragile-X syndrome • ICF syndrome	• Neural tube defects • ADHD • Autistic disorders • Epilepsy • Tourette's syndrome • Fetal alcohol syndrome • Schizophrenia



Possible mechanisms mediating the pathological effects of maternal infection on the developing organism in utero

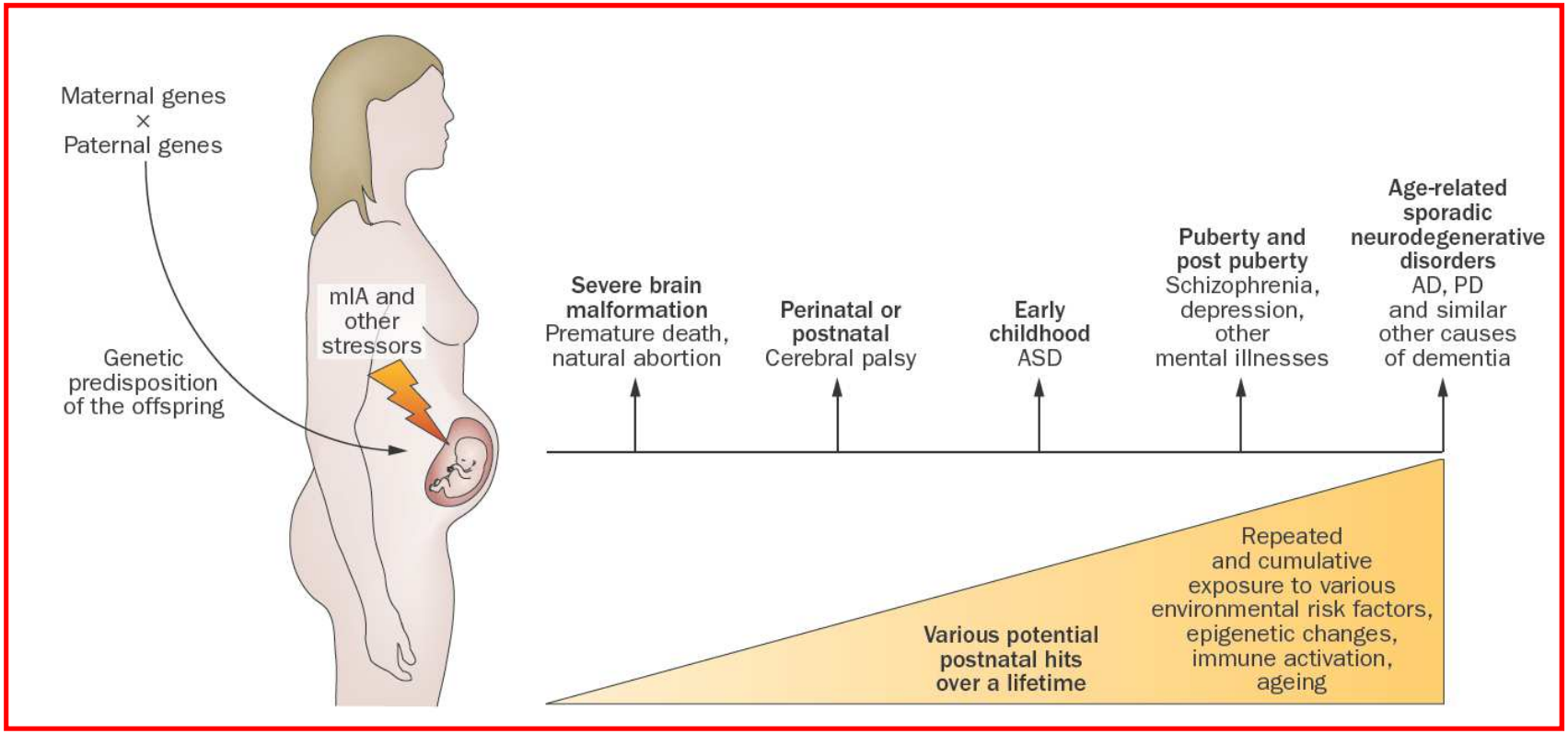


AMERICAN JOURNAL OF PHYSIOLOGY
Regulatory, Integrative and Comparative Physiology

Marie A. Labouesse et al. Am J Physiol Regul Integr Comp Physiol 2015;309:R1-R12

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**.

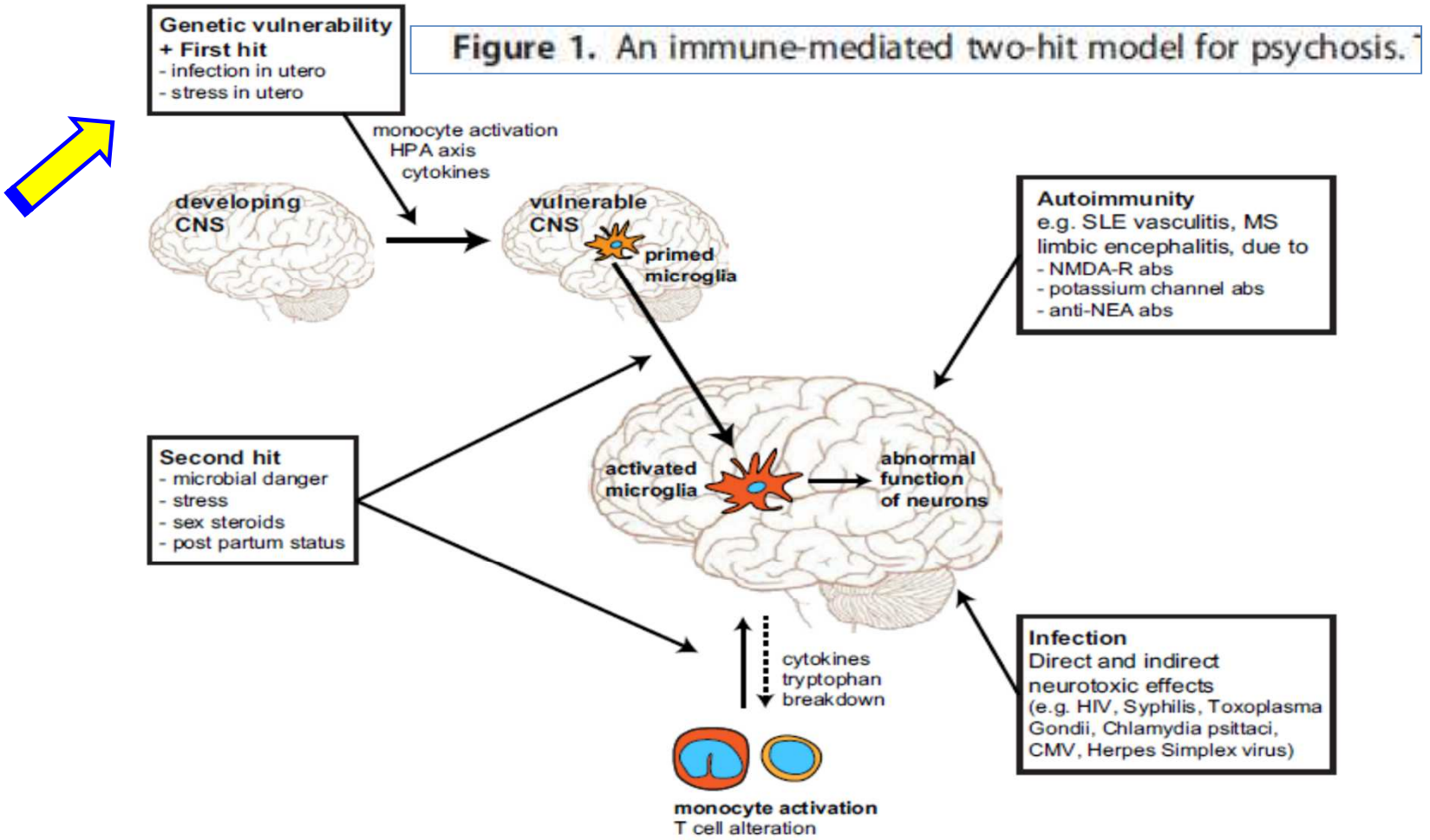


Figure 1. An immune-mediated two-hit model for psychosis.

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

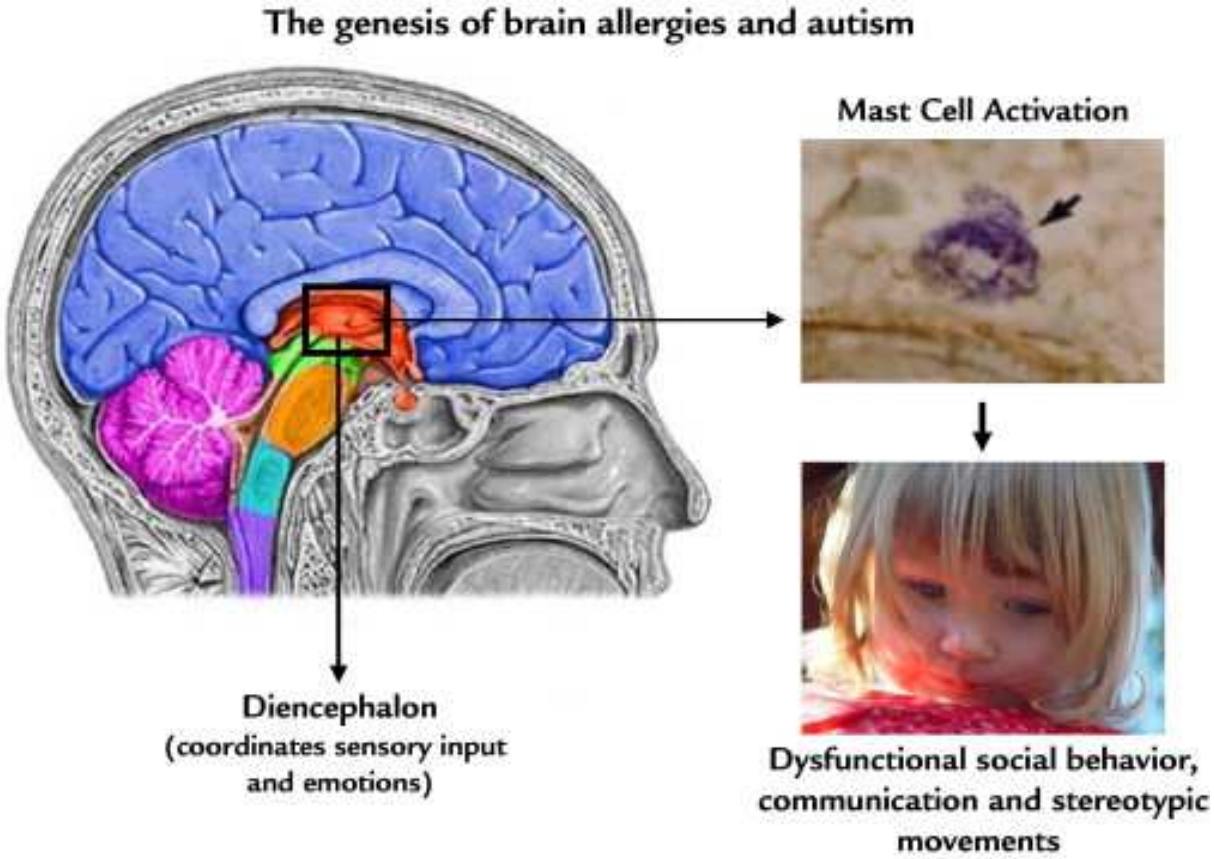
New "atopic" clinical entities in search of pathogenesis and treatment

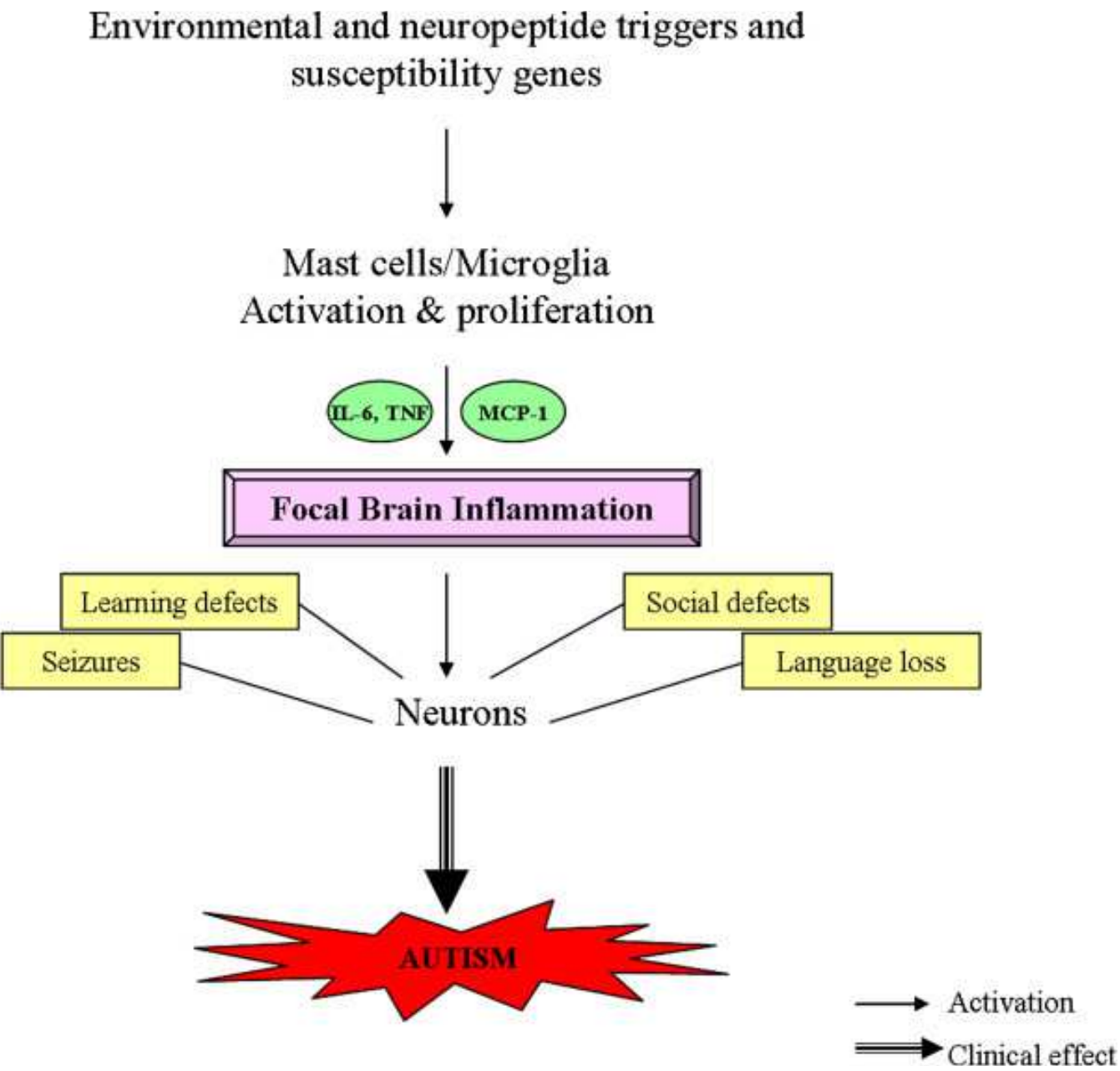
Is a Subtype of Autism an Allergy of the Brain?

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

CHEMICAL FALL OUT

1 **ENDOCRINE DISRUPTORS**
dioxin-like moleculles

2 **HEAVY METALS**

3 **ULTRAFINE PARTICLES**

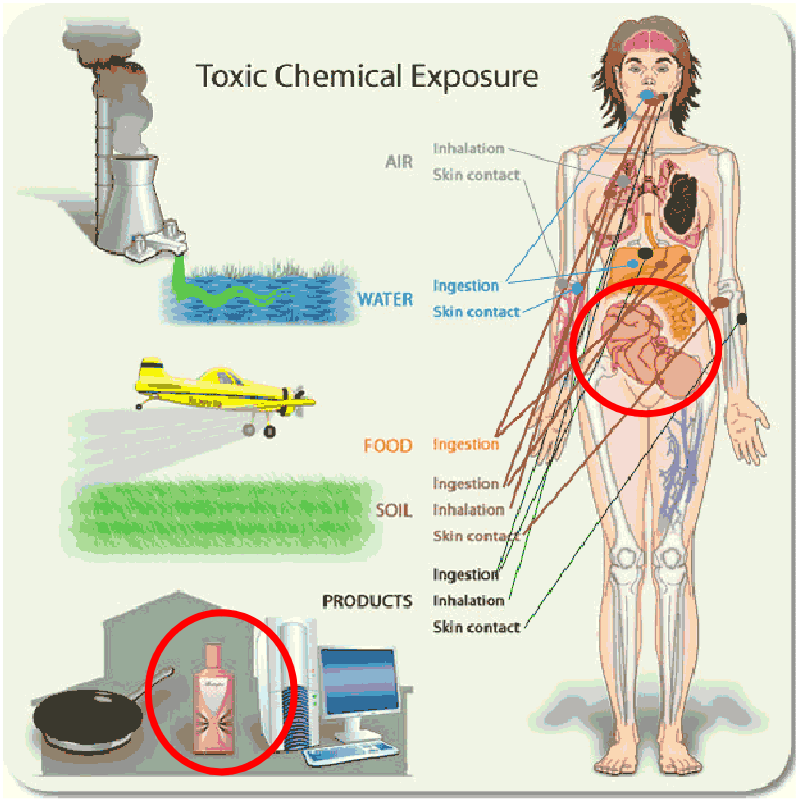
The gift our mothers never wanted to give us

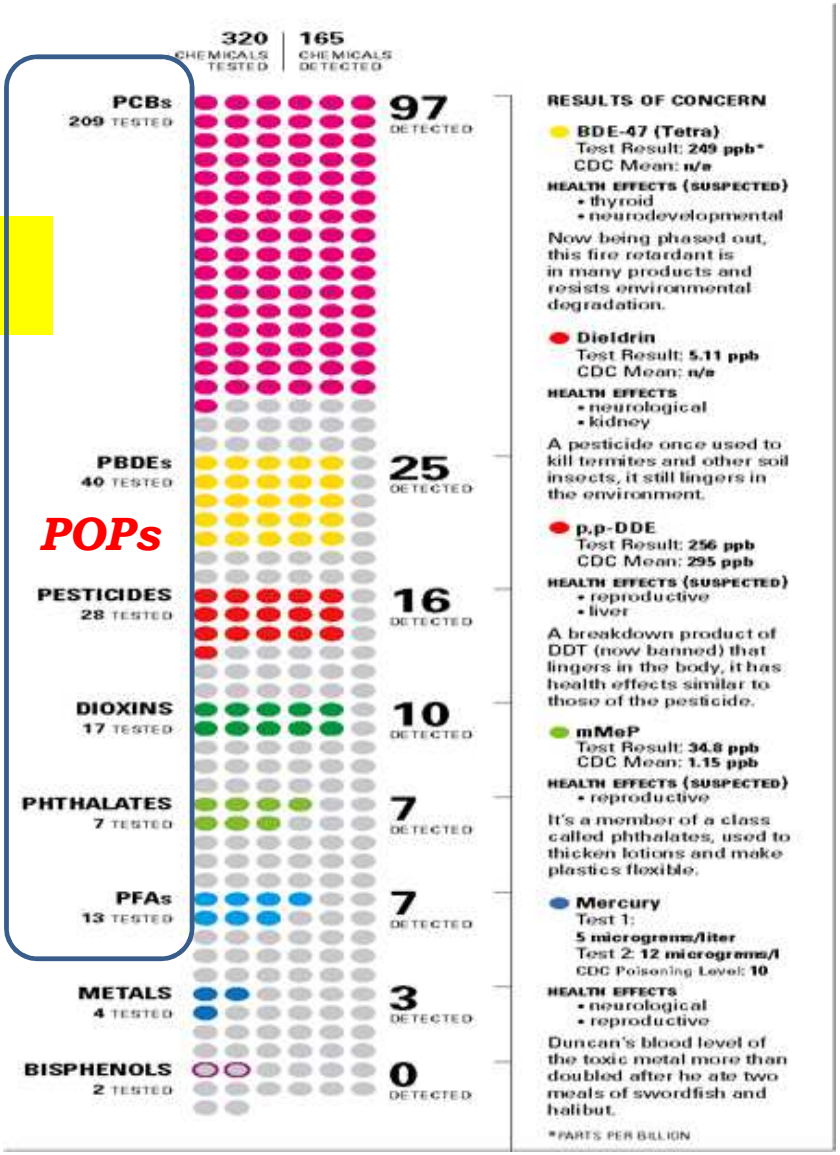
.. at present many studies in various parts of the world are evaluating the ***chemical body burden*** .. especially in women, children, embryos / fetuses, **providing dramatic results**.

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

Monitoring Body-Burdens

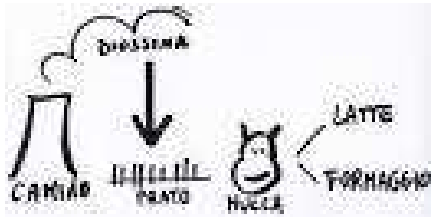
700 different synthetic chemicals or heavy metals found in human blood,





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**).

Giuseppe Giordano ISDE Palermo

L'autisme, une épidémie ?

Environmental Health

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

Review

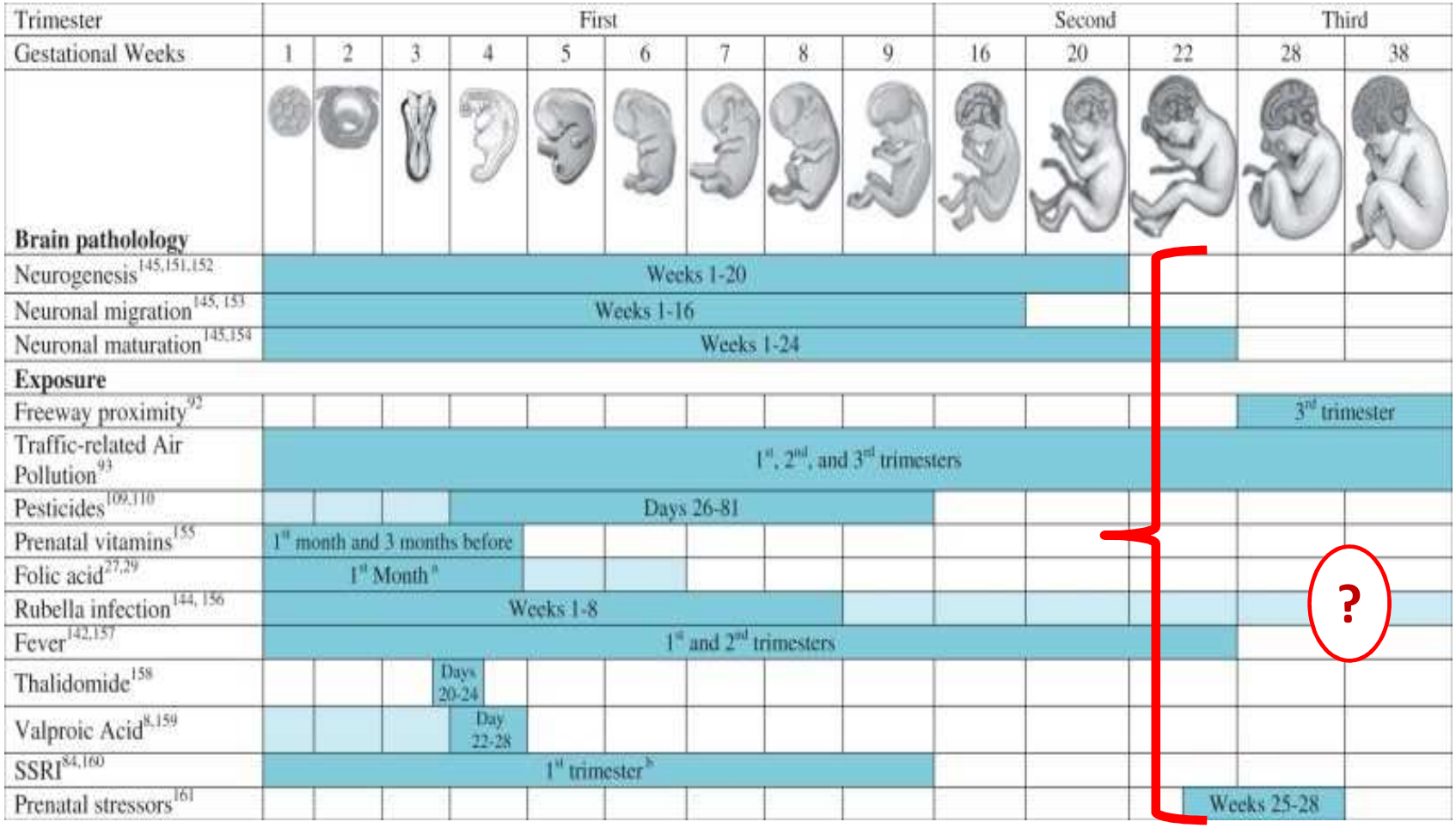
Open Access

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 ique vulnera calls for inv nties 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.

Research | Children's Health

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

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

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.

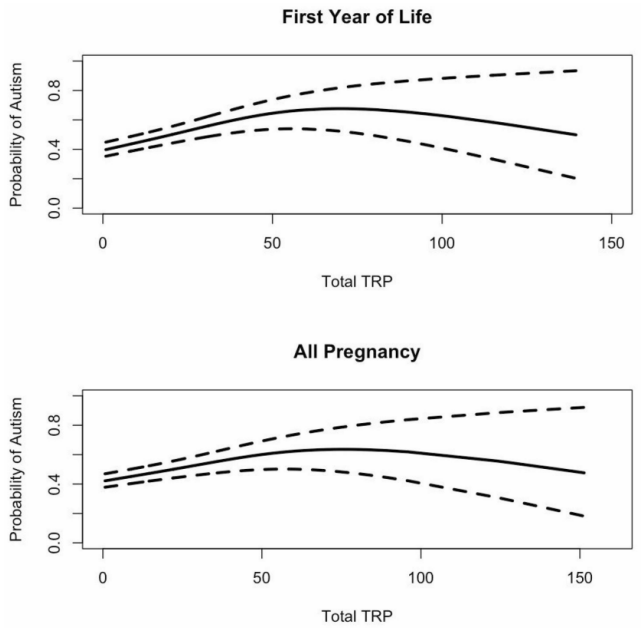
ASDs risk (OR> 50%) increased significantly among mothers exposed to fine particles (PM 2.5) and not to PM 2.5-10 especially during the **third trimester of pregnancy (Synaptogenesis!)**

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.

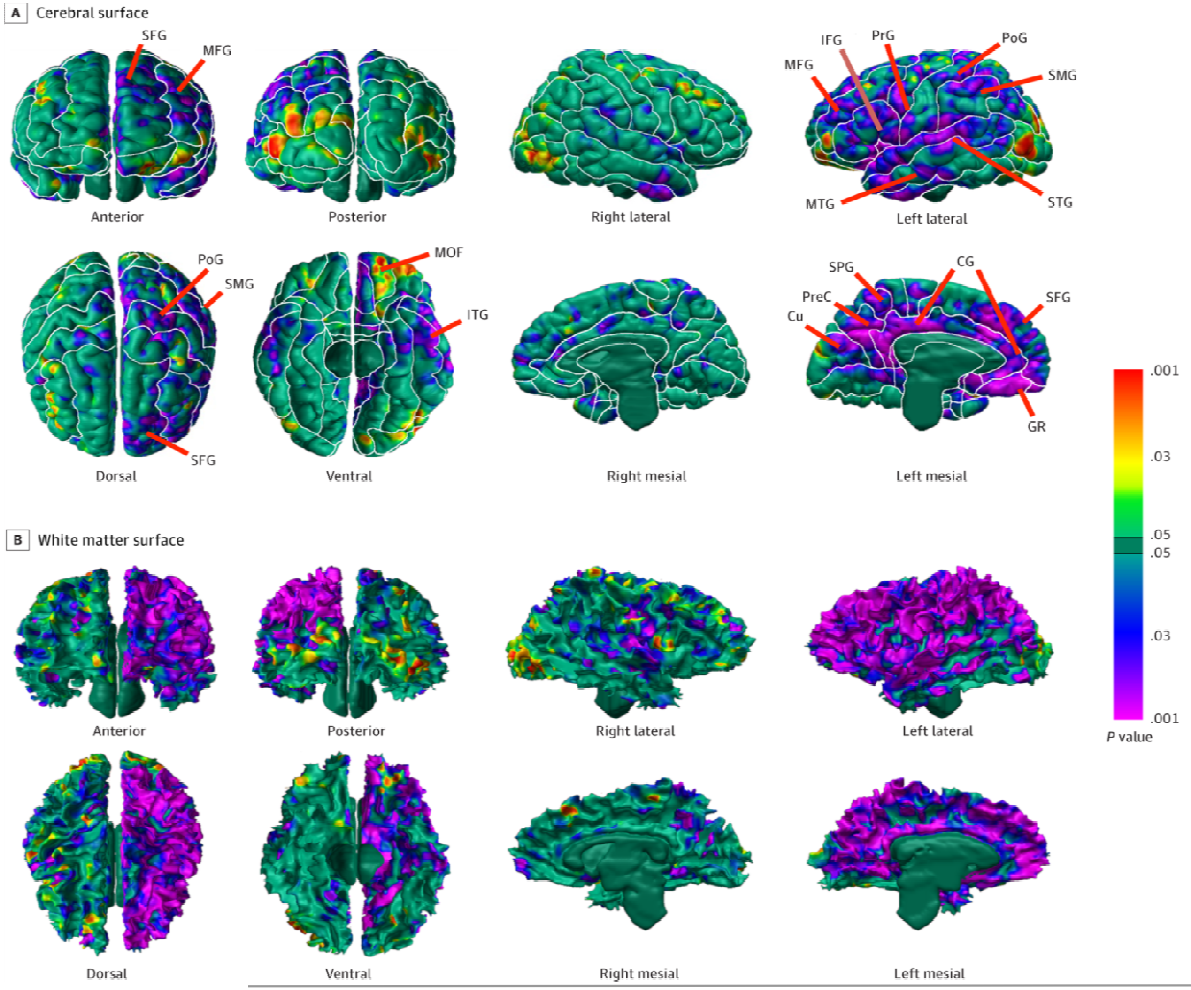
The magnitude of these **associations** appear to be **most pronounced during late gestation** (OR=1.98, 95%CI 1.20–3.31) **and early life / first year of life** (OR=1.98, 95%CI 1.20–3.31)



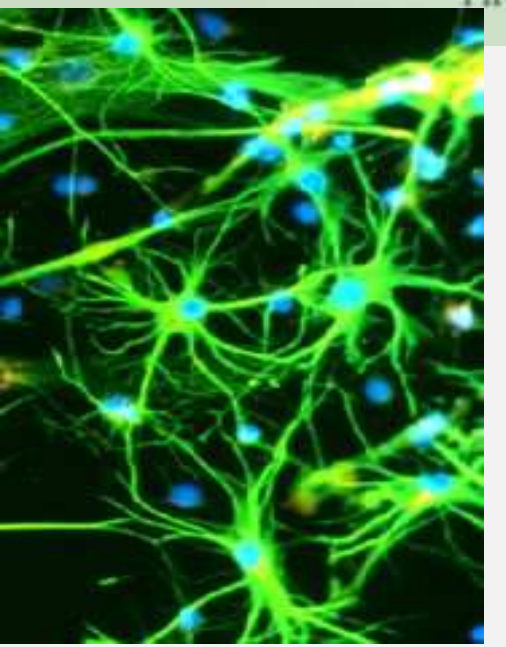
JAMA Psychiatry. 2013 January ; 70(1): 71–77.
doi:10.1001/jamapsychiatry.2013.266

From: **Effects of Prenatal Exposure to Air Pollutants (Polycyclic Aromatic Hydrocarbons) on the Development of Brain White Matter, Cognition, and Behavior in Later Childhood**

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



Tiny particles enter the brain after being inhaled

Oberdarster, G. et al. ***Translocation of inhaled ultrafine particles to the brain***. Inhalation Toxicology (Nature Jan 2004)

Brain cells that pick up smell can carry nanoparticles inside

http://**www.nature.com/news/2004/040105/pf/040105-9_pf.html**

news@nature.com
The best in science journalism

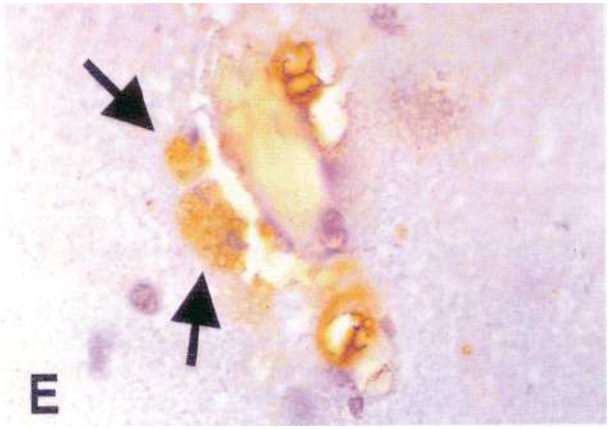
Toxicologic Pathology
http://tpx.sagepub.com

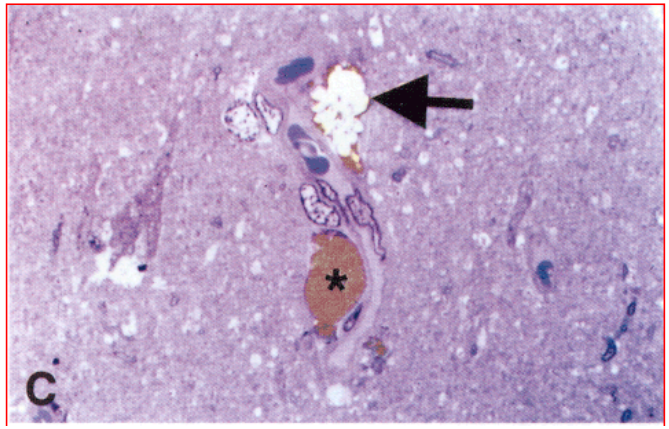
Air Pollution and Brain Damage

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.





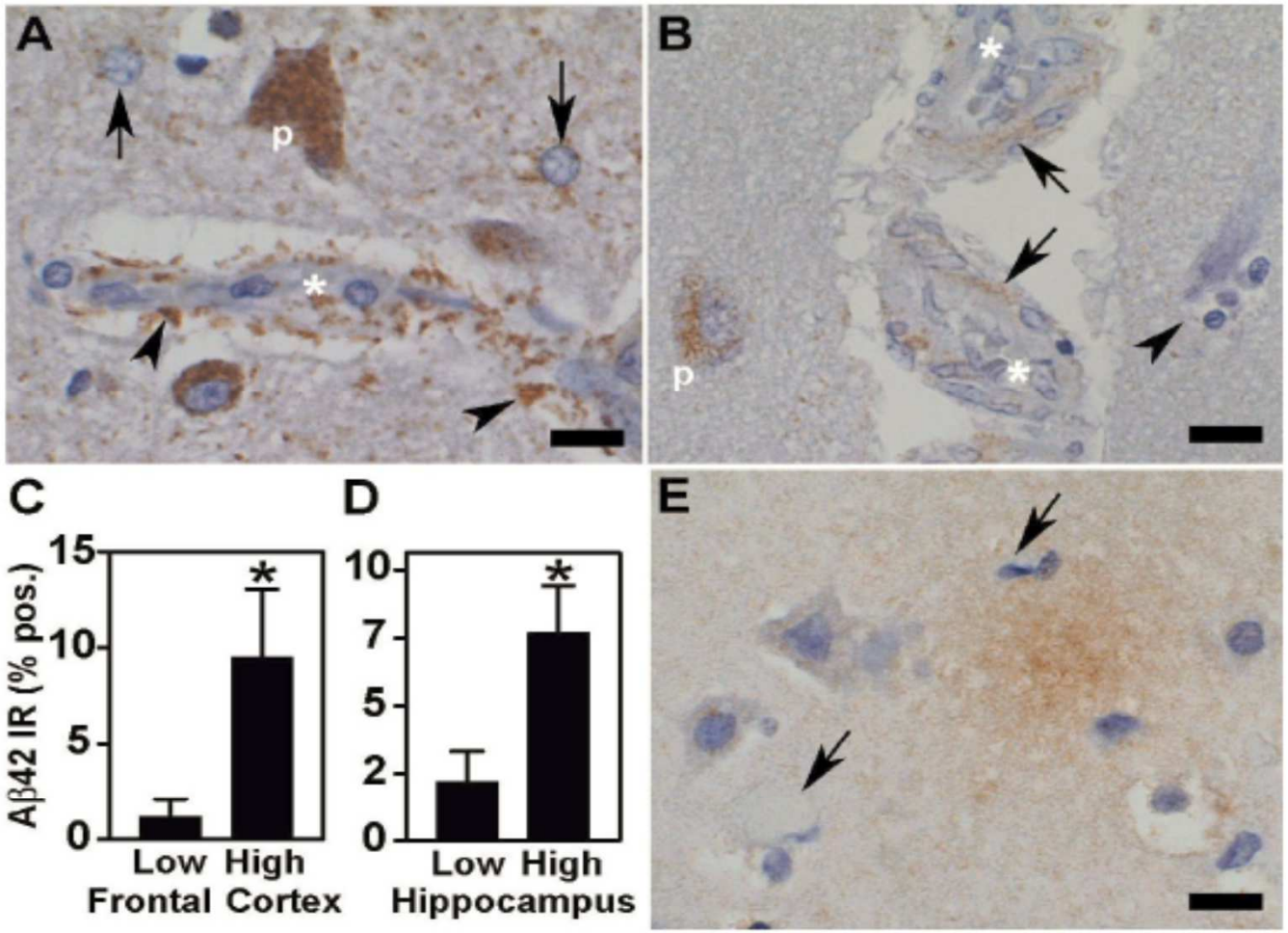


Figure 3

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

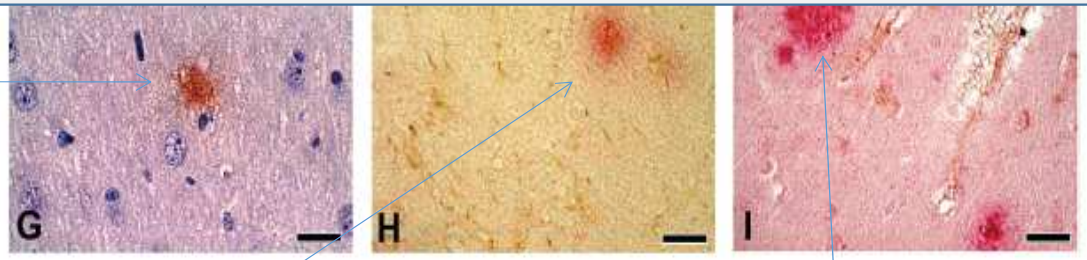
Exposures to **particulate matter and gaseous air pollutants** have been associated with **respiratory tract inflammation**, disruption of the nasal respiratory and olfactory barriers, **systemic inflammation**, production of mediators of inflammation capable of **reaching the brain and systemic circulation 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 *Aβ42 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*β42 plaques*** *(red stain) along* with GFAP-positive reactive astrocytosis

Review

Trends in Neurosciences

Cell PRESS

Air pollution: mechanisms of neuroinflammation and CNS disease

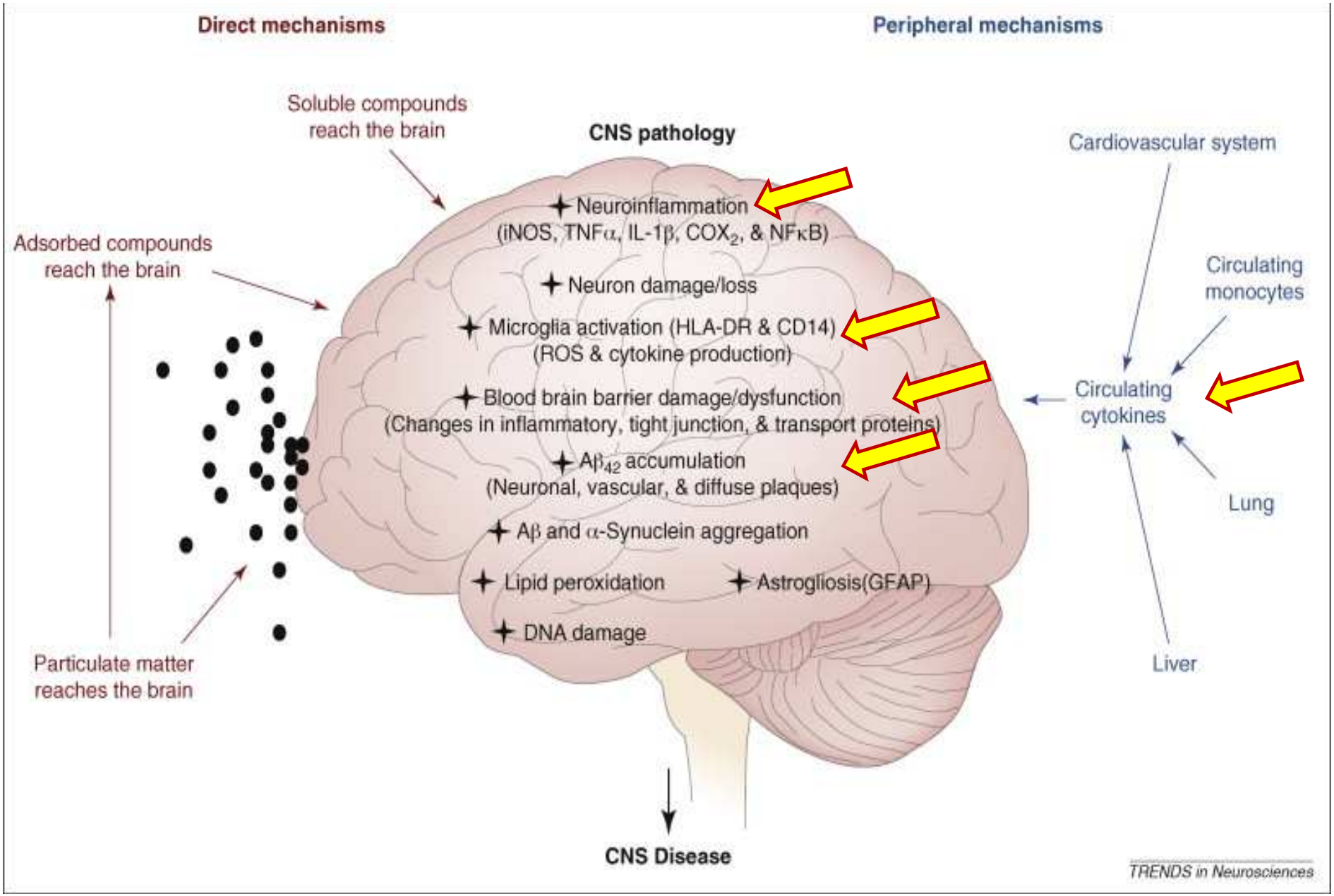
Michelle L. Block[1] and Lilian Calderón-Garcidueñas[2,3]

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.**

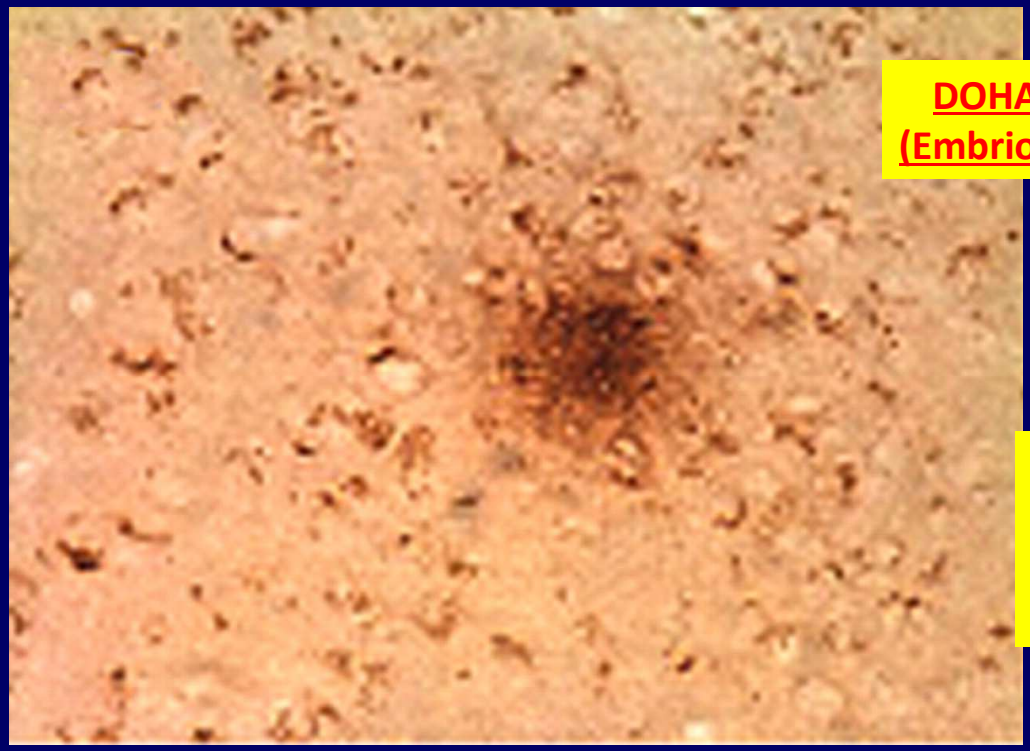
Fig 1: It is likely that CNS pathology is due to the **synergistic interactions of the multiple pathways listed here**, making air pollution a potent, biologically relevant environmental exposure and a significant challenge for mechanistic inquiry.


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

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.

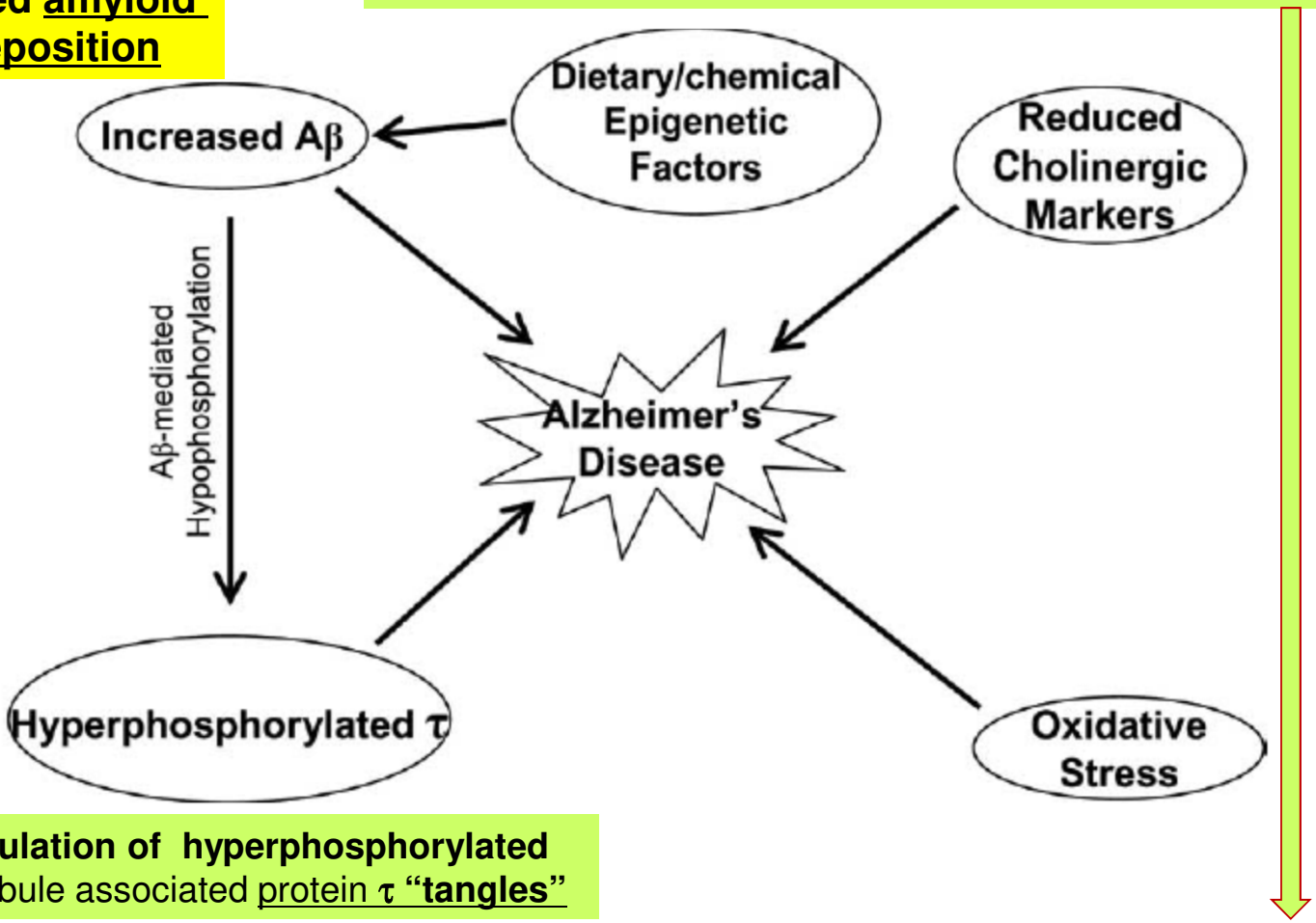
Early life exposures

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

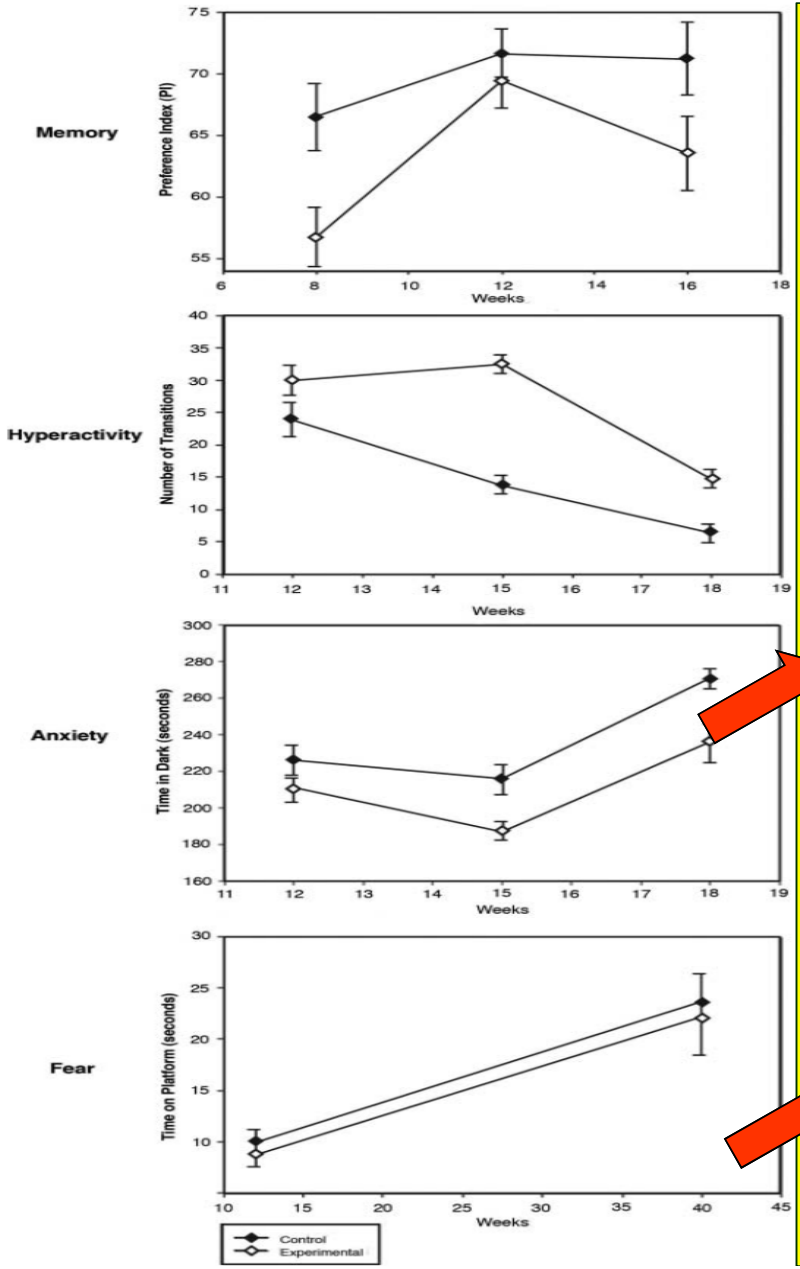
www.nature.com

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.***

http://www.bioinitiative.org/

BioInitiative 2012

A Rationale for Biologically-based Exposure Standards for Low-Intensity Electromagnetic Radiation

BIOINITIATIVE 2012 - CONCLUSIONS Table 1-1

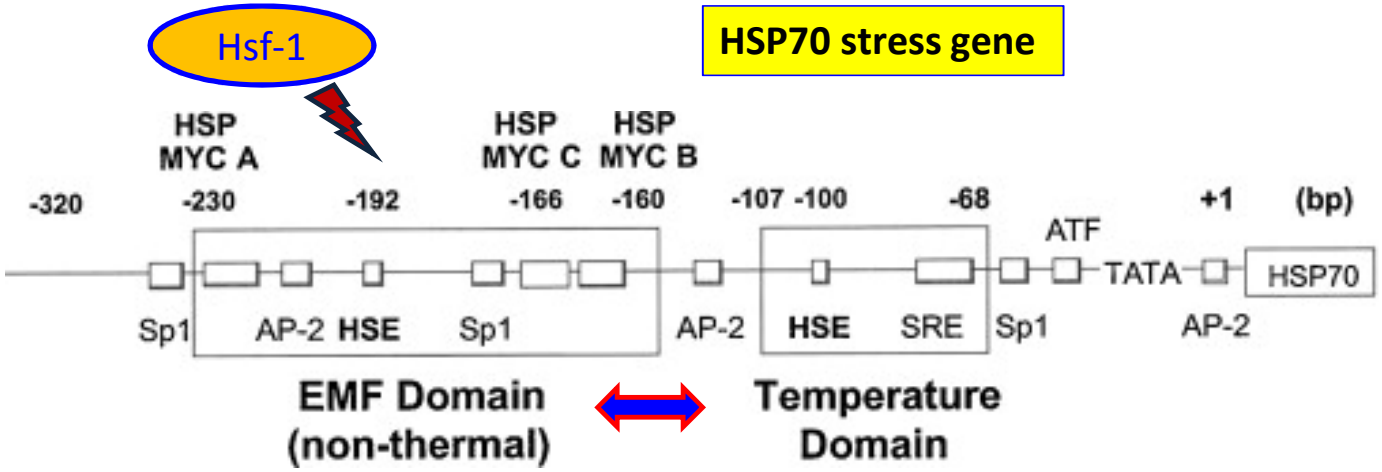
(Genetics and Neurological Effects Updated March 2014)

BIOEFFECTS ARE CLEARLY ESTABLISHED

Bioeffects are clearly established and occur at very low levels of exposure to electromagnetic fields and radiofrequency radiation. Bioeffects can occur in the first few minutes at levels associated with cell and cordless phone use. Bioeffects can also occur from just minutes of exposure to mobile phone masts (cell towers), WI-FI, and wireless utility 'smart' meters that produce whole-body exposure. Chronic base station level exposures can result in illness.

Overall, more than 1800 or so new studies report abnormal gene transcription (Section 5); genotoxicity and single-and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers - particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9), carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on offspring behavior (Section 18, 19 and 20); and effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18). This is only a snapshot of the evidence presented in the BioInitiative 2012 updated report.

Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF...



Synthesis of this stress protein is initiated in a **region of the promoter** where a transcription factor known as **Heat Shock Factor 1 (HSF-1) binds to a Heat Shock Element (HSE).**
The **EMF sensitive region on HSP70 promoter** is **upstream from the thermal domain of the promoter and is not sensitive to increased temperature**. The binding of **HSF-1** to **HSE** occurs at **–192** in the **HSP70 promoter** relative to the transcription initiation site.

The **EMF domain contains three nCTCTn myc-binding sites –230, –166 and –160 relative to the transcription initiation site and upstream of the binding sites for the heat shock (nGAAn)** and serum responsive elements…. **The electromagnetic response elements (EMREs) have also been identified on the c-*myc* promoter and are also responsive to EMF**

Pathophysiology
Volume 16, Issues 2-3, August 2009, Pages 71-78

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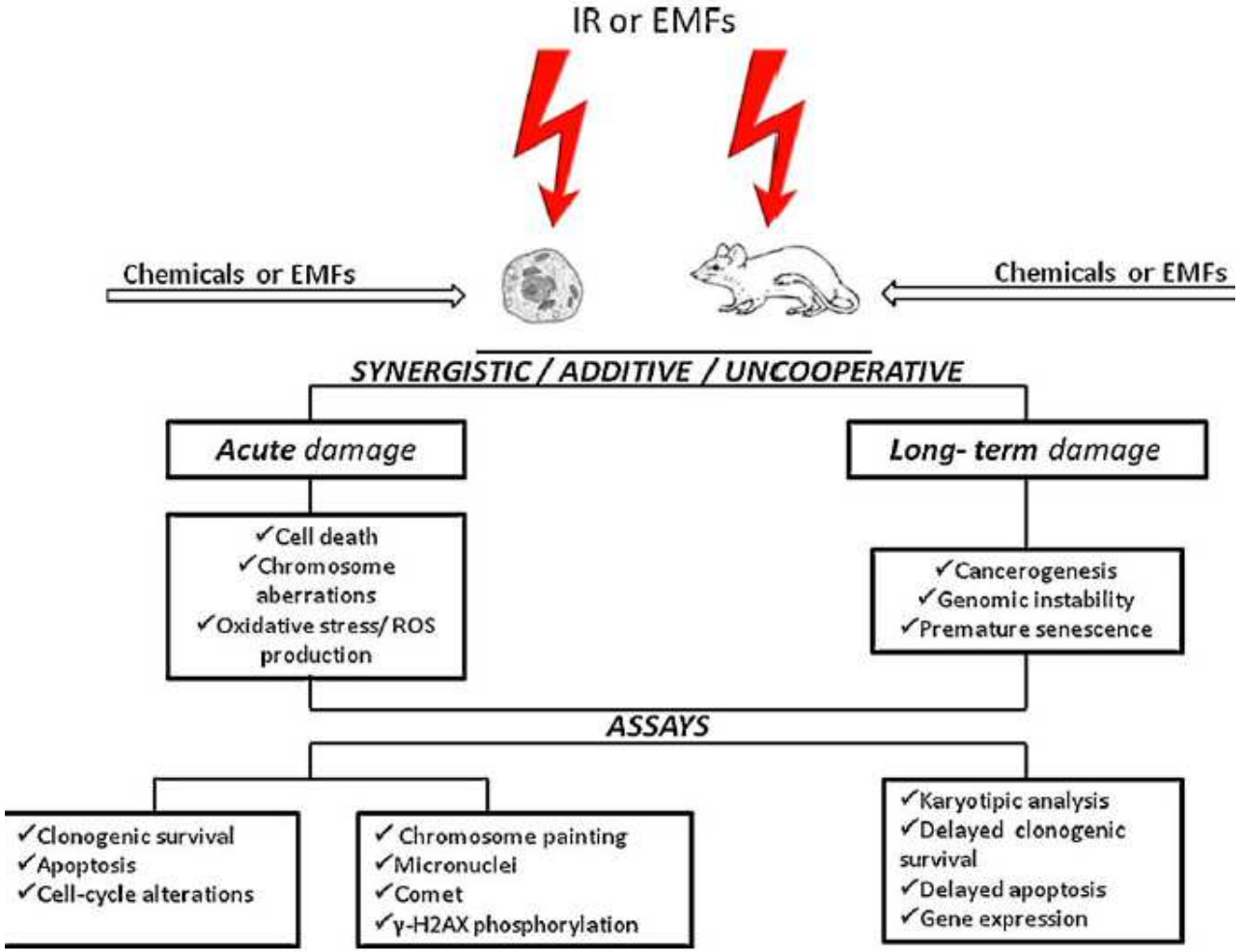
Review

Cooperative biological effects between ionizing radiation and other physical and chemical agents

Lorenzo Manti *, Annalisa D'Arco

Exposure to ionizing radiation (IR), at environmentally and therapeutically relevant doses or as a result of diagnostics or accidents, causes cyto- and genotoxic damage. However, exposure to IR alone is a rare event as it occurs in spatial and temporal combination with several physico-chemical agents. Some of these are of known noxiousness, as is the case with chemical compounds at high dose, hence additive/synergistic effects can be expected or have been demonstrated. Conversely, the cellular toxicity of other agents, such as non-ionizing electromagnetic fields (EMFs), is only presumed and their short- and long-

.. recent **data on the interaction between ELF EMFs and chemicals show delayed chromosomal instability arising in human fibroblasts** [67]. Suggestions of **long-lasting inhibition of DNA repair by UMTS/GSM signals** were made based on the observed persistence of the **reduction in 53BP1/γ-H2AX colocalized foci** [97]. Hence, **RF may epigenetically modulate genomic instability inducible by chronical chemical exposure and/or IR ...** Therefore, it is of interest **to investigate the long-term cooperative effects arising from combined exposure scenarios (Fig. 1).**



Very little data are currently available on the **cumulative effects of exposure to multiple hazardous agents that have either similar or different mechanisms of action on DNA**.. In addition to known mutagens, **presumptive DNA-damaging agents, such as EMFs fields, ought to be also considered since they may influence cellular responses to IR or chemicals, for instance by sublethal stress generation**

EVIDENCE FOR NEUROLOGICAL EFFECTS (Updated March 2014)

http://www.bioinitiative.org/

Two hundred eleven (211) new papers that report on neurological effects of RFR published between 2007 and early 2014 are profiled. Of these, 144 (68%) showed effects and 67 (32%) showed no effects.

One hundred five (105) new ELF-EMF papers (including two static field papers) that report on neurological effects of ELF-EMF published between 2007 and early 2014 are profiled. Of these, 95 (90%) show effects and 10 (10%) show no effect. (Lai, 2014 – Section 9)

..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), **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

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**

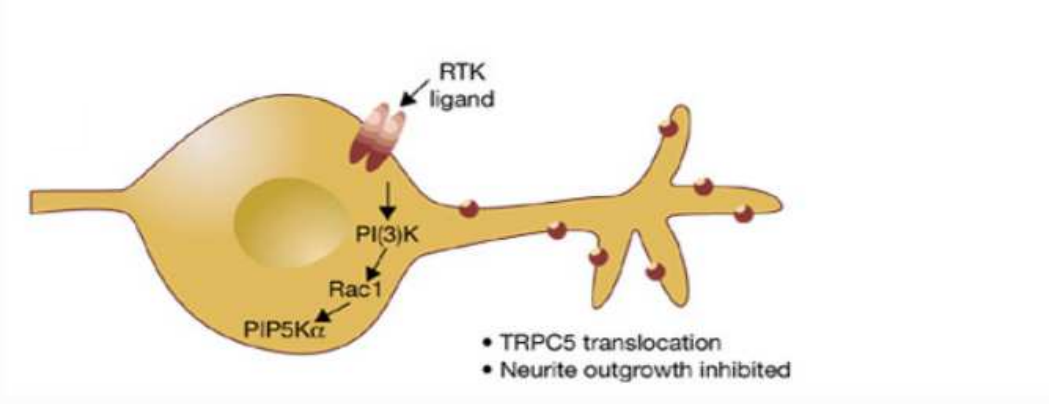
stem cells are the most relevant cellular model for validating safe mobile communication signals."

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 cy[illegible] 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*



Ma Q, Deng P, Zhu G, Liu C, Zhang L, Zhou Z, Luo X, Li M, Zhong M, Yu Z, Chen C, Zhang Y

Extremely low-frequency electromagnetic fields affect transcript levels of Neuronal differentiation-related genes in embryonic neural stem cells.

PLoS One 2014 Mar 3;9(3):e90041. doi: 10.1371/journal.pone.0090041. eCollection 2014.

Previous studies have reported that extremely low-frequency electromagnetic fields (ELF-EMF) can affect the processes of brain development, but the underlying mechanism is largely unknown. **The proliferation and differentiation of embryonic neural stem cells (eNSCs) is essential for brain development during the gestation period**. To date, there is no report about the effects of ELF-EMF on eNSCs. In this paper, we studied the effects of ELF-EMF on the proliferation and differentiation of eNSCs. Primary cultured eNSCs were treated with 50 Hz ELF EMF; various magnetic intensities and exposure times were applied.

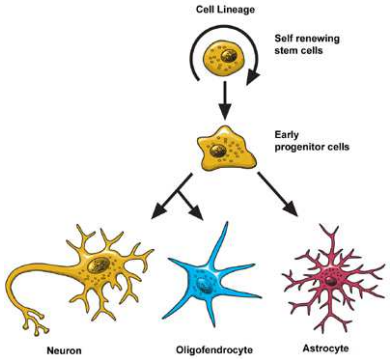
Our data showed that there was no significant change in cell proliferation, w

Disturbing the *CONNECTOME INSTRUCTION*

viability (CCK-8 assay), DNA synthesis (Edu incorporation), average diameter o

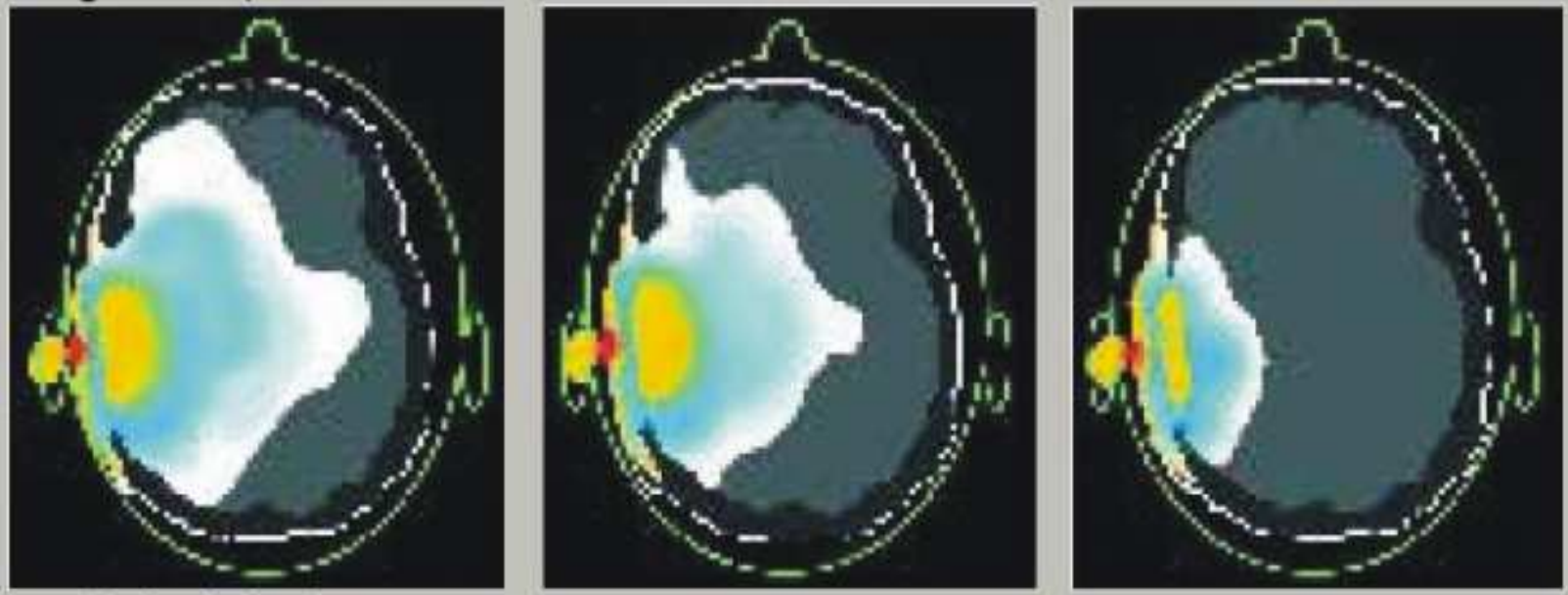
distribution (flow cytometry) and transcript levels of cell cycle related genes (P53, P21 and GADD45 detected by real-time PCR). **When eNSCs were induced to differentiation, real-time PCR results showed a down regulation of Sox2 and up-regulation of Math1, Math3, Ngn1 and Tuj1 mRNA levels after 50 Hz ELF EMF exposure (2 mT for 3 days)**, but the percentages of neurons (Tuj1 positive cells) and astrocytes (GFAP positive cells) were not altered when detected by immunofluorescence assay. Although cell proliferation and the percentages of neurons and astrocytes differentiated from eNSCs were not affected by 50 Hz ELF-EMF, **the expression of genes regulating neuronal differentiation was altered.**

In conclusion, **our results support that 50 Hz ELF-EMF induce molecular changes during eNSCs differentiation, which might be compensated by post-transcriptional mechanisms to support cellular homeostasis.**



Gandhi O.P., Lazzi G., Furse C.M. (1996 vol.44, p1884-1897) : Absorption des rayonnements électromagnétiques dans la tête et le cou humain pour les téléphones mobiles de 835MHz /1900MHz

Degré de pénétration des Radiations du Portable dans le Cerveau



Enfant de 5 ans	Enfant de 10 ans	Adulte
Taux d'absorption: 4,49W/kg	Taux d'absorption: 3,21W/kg	Taux d'absorption: 2,93W/kg

Int J Toxicol. 2015 Mar 5. pii: 1091581815574348

Cognitive Impairment and Neurogenotoxic Effects in Rats Exposed to Low-Intensity Microwave Radiation.

Deshmukh PS[1], Nasare N[2], Megha K[1], Banerjee BD[3], Ahmed RS[1], Singh D[1], Abegaonkar MP[4], Tripathi AK[1], Mediratta PK[5].

The health hazard of microwave radiation (MWR) has become a recent subject of interest as a result of the enormous increase in mobile phone usage. The present study aimed **to investigate the effects of chronic low-intensity microwave exposure on cognitive function, heat shock protein 70 (HSP70), and DNA damage in rat brain**. Experiments were performed on male Fischer rats exposed to MWR for 180 days at 3 different frequencies, namely, 900, 1800 MHz, and 2450 MHz. Animals were divided into 4 groups: group I: sham exposed; group II: exposed to MWR at 900 MHz, specific absorption rate (SAR) 5.953×10^{-4} W/kg; group III: exposed to 1800 MHz, SAR 5.835×10^{-4} W/kg; and group IV: exposed to 2450 MHz, SAR 6.672×10^{-4} W/kg. **All the rats were tested for cognitive function at the end of the exposure period and were subsequently sacrificed to collect brain**. Level of HSP70 was estimated by enzyme-linked immunotarget assay and DNA damage was assessed using alkaline comet assay in all the groups.

The results showed **declined cognitive function, elevated HSP70 level, and DNA damage in the brain of microwave-exposed animals**. The results indicated that, chronic low-intensity microwave exposure in the frequency range of 900 to 2450 MHz may cause hazardous effects on the brain.

Li HJ et al. **Alterations of cognitive function and 5HT system in rats after long term microwave exposure** Physiol Behav. 2015 Mar 1;140:236-46

The increased use of **microwaves** raises concerns about its **impact on health including cognitive function in which neurotransmitter system** plays an important role…

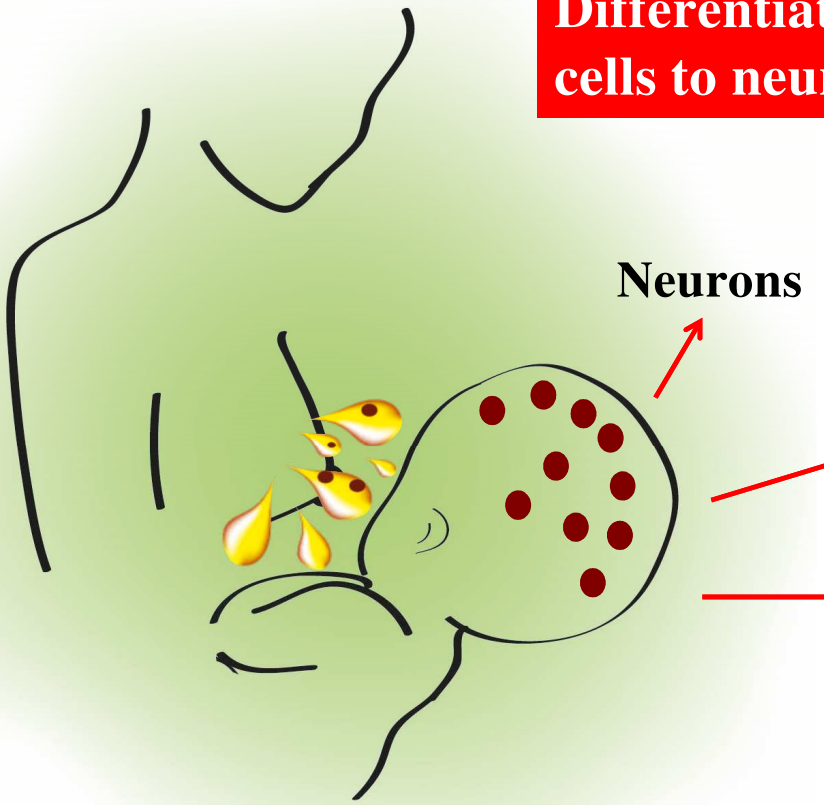
We demonstrated that **chronic exposure to microwave** (2.856GHz, with the average power density of 5, 10, 20 and 30mW/cm(2)) could induce **dose-dependent deficit of spatial learning and memory in rats accompanied with inhibition of brain electrical activity, the degeneration of hippocampus neurons, and the disturbance of neurotransmitters, among which the increase of 5-HT** occurred as the main long-term change that the decrease of its metabolism partly contributed to.

Besides, **the variations of 5-HT1AR and 5-HT2CR expressions were also indicated**.

The results suggested that **in the long-term way, chronic microwave exposure could induce cognitive deficit** and **5-HT system may be involved in it**

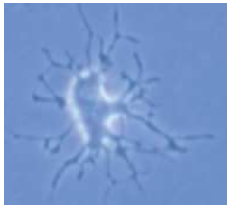
FROM BREAST MILK TO BRAIN

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



Neurons

Oligodendrocytes



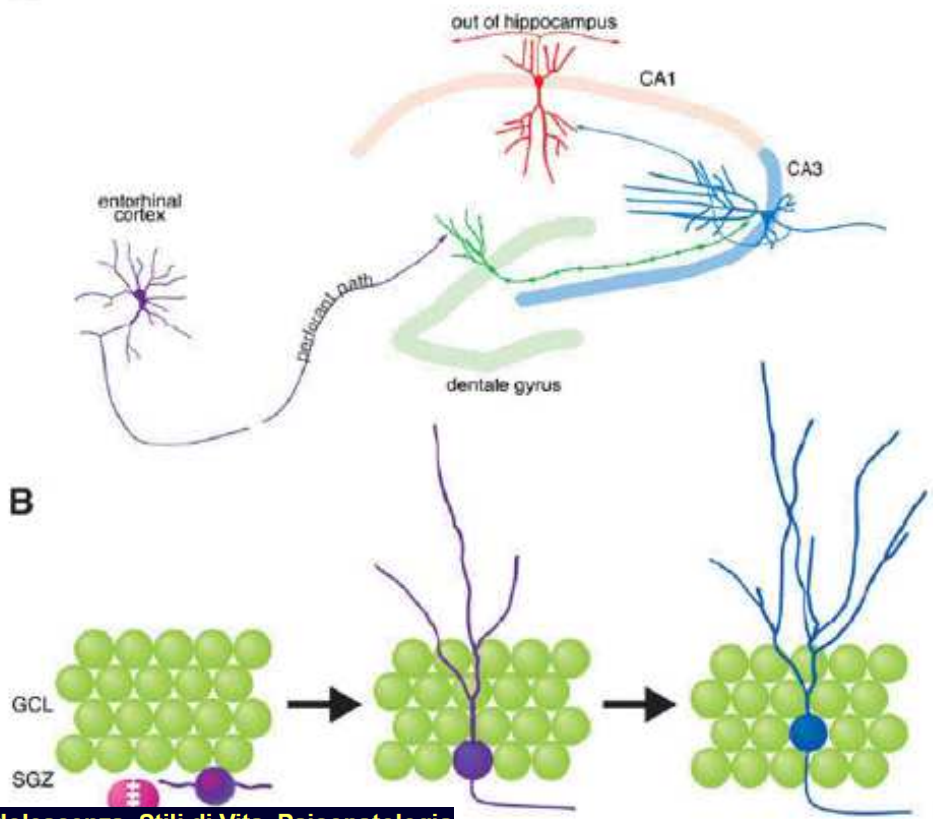
Astrocytes

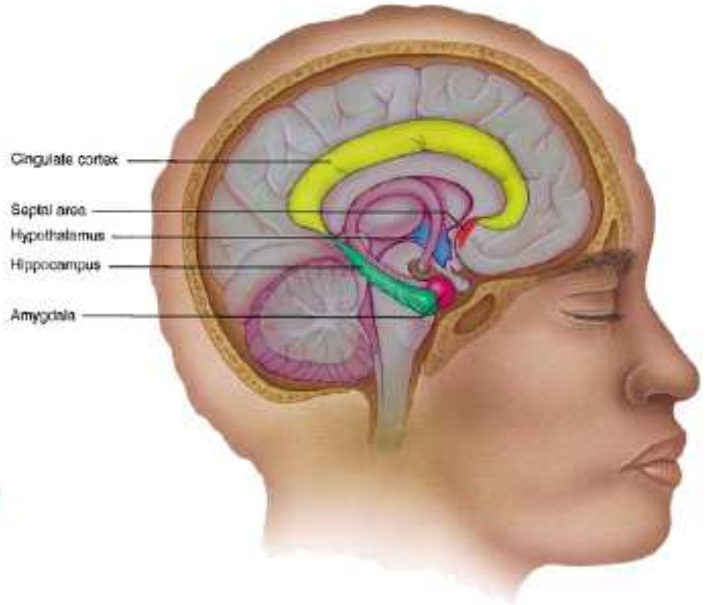
Metabolomica liquido
cellule staminali

Hosseini SM Neurol Res Int 2014

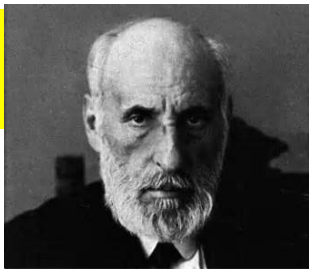
The Incredible Elastic Brain: How Neural StemCells Expand Our Minds

Neuron, 2008





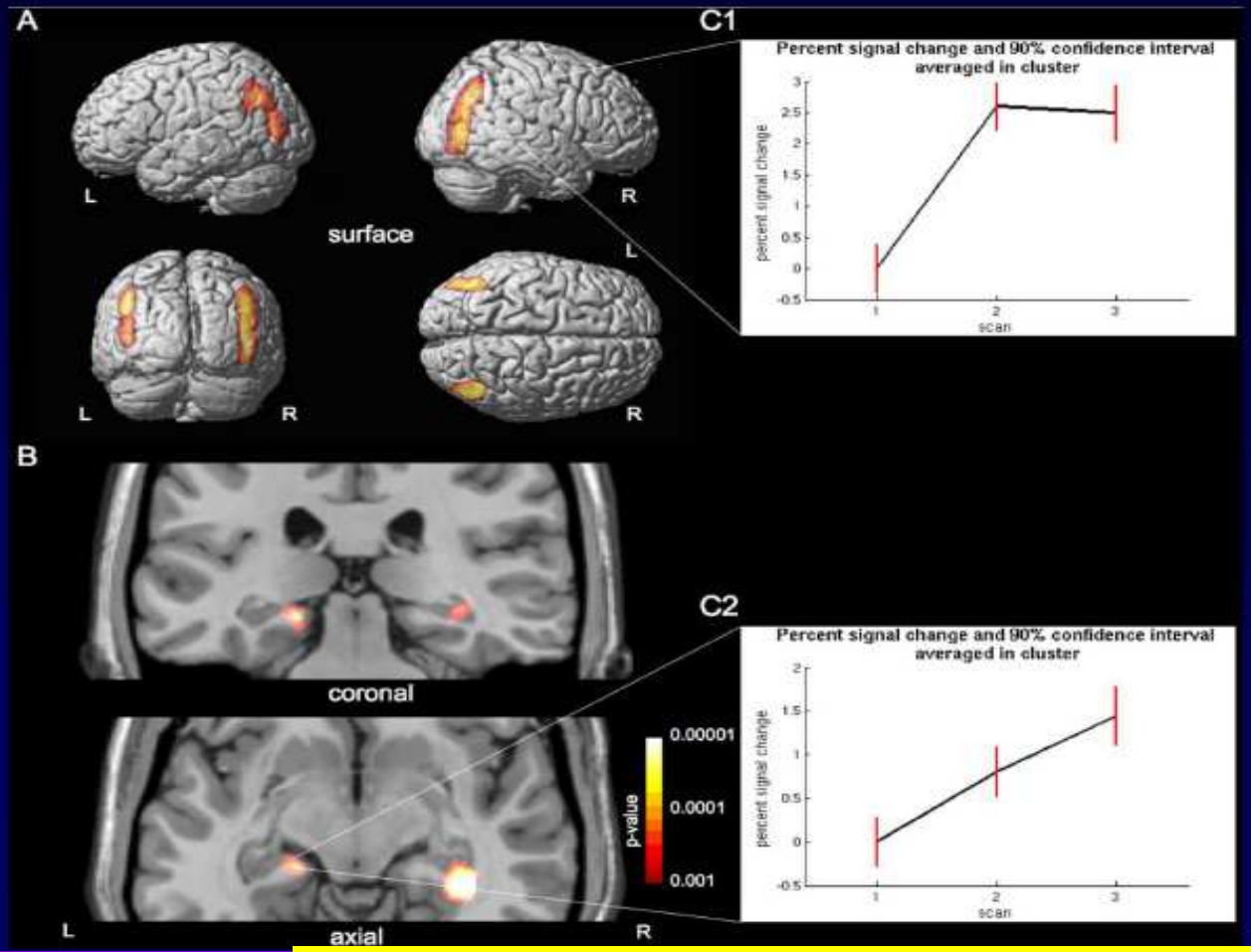
Ramón y Cajal
Death of a DOGMA



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

Temporal and Spatial Dynamics of Brain Structure Changes During Extensive Learning

Draganski B et al., J. Neurosci., 2006

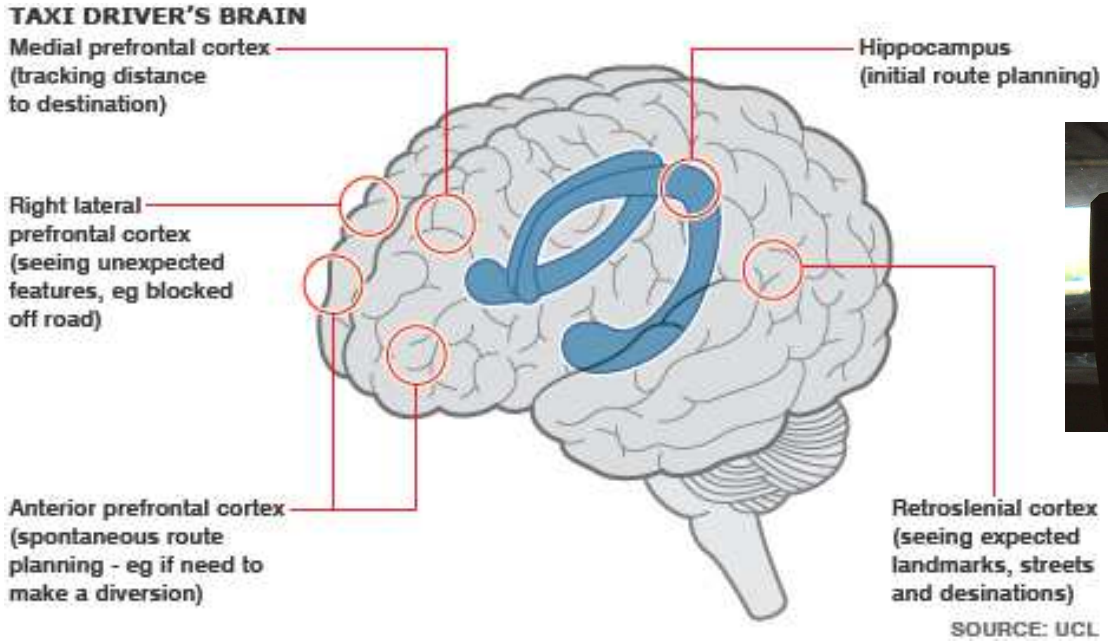


Giovanni Biggio
Centro di Eccellenza per la "Neurobiologia delle Dipendenze", Università degli Studi di Cagliari

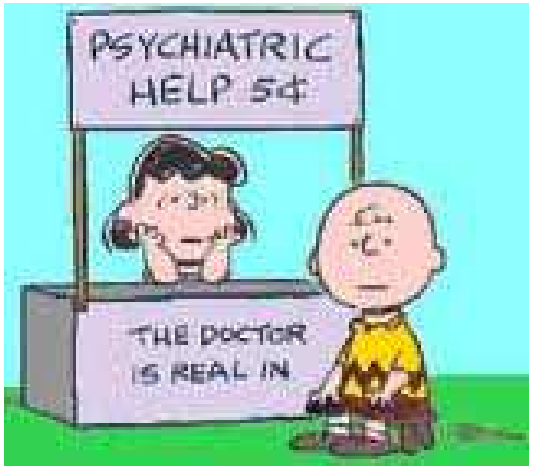
During the **learning** period, the **gray matter increased significantly in the posterior and lateral parietal cortex bilaterally**.

Navigation-related structural change in the hippocampi of taxi drivers

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)



Eleanor A. Maguire, David G. Gadian, Ingrid S. Johnsrude, Catriona D. Good, John Ashburner, Richard S. J. Frackowiak, and Christopher D. Frith ***Navigation-related structural change in the hippocampi of taxi drivers*** *PNAS 2000 97 (8) 4398-4403*



How Music shapes our Brain

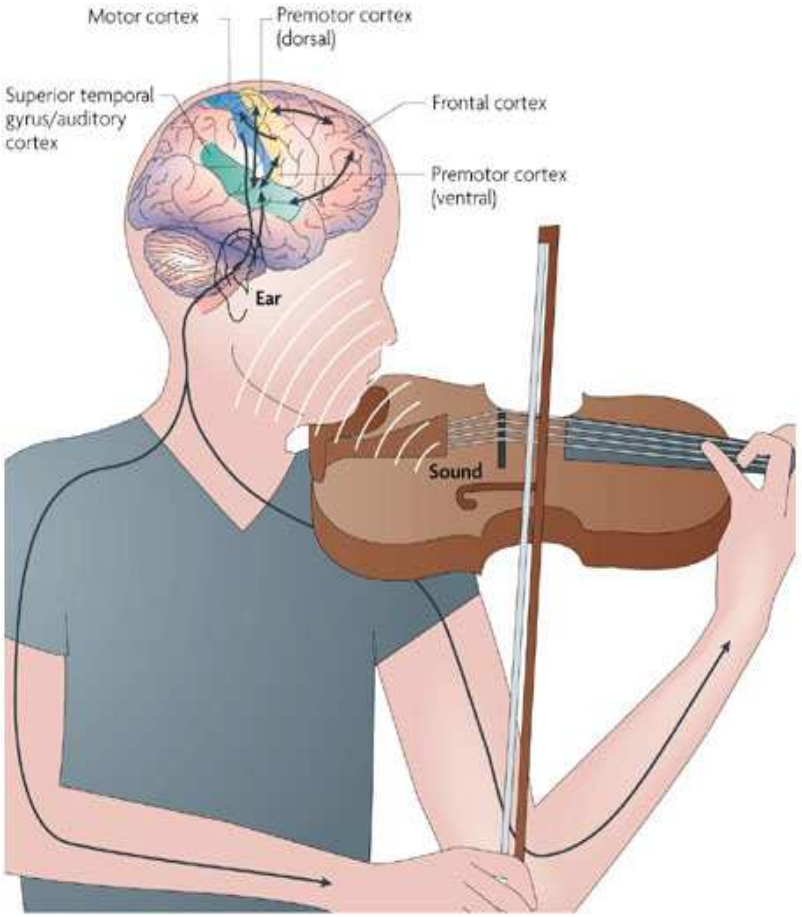
Un caso estremamente interessante è quello del **cervello del musicista** che presenta una **struttura alquanto particolare, almeno nei casi in cui lo studio della musica ha avuto inizio nelle primissime fasi della vita..**

"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.

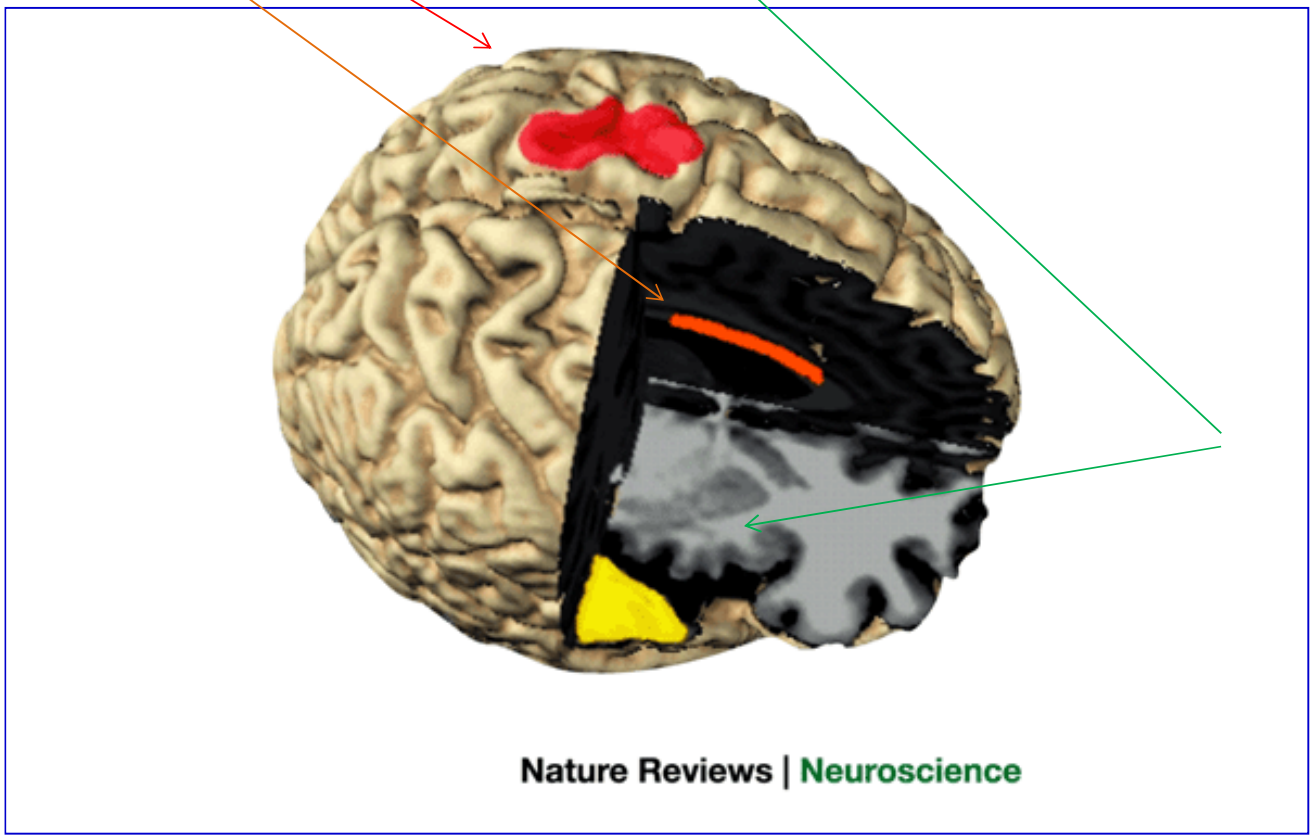
One study showed that **children who had three years or more musical instrument training performed better than those who didn't learn an instrument in auditory discrimination abilities and fine motor skills**.



Nature Reviews | Neuroscience

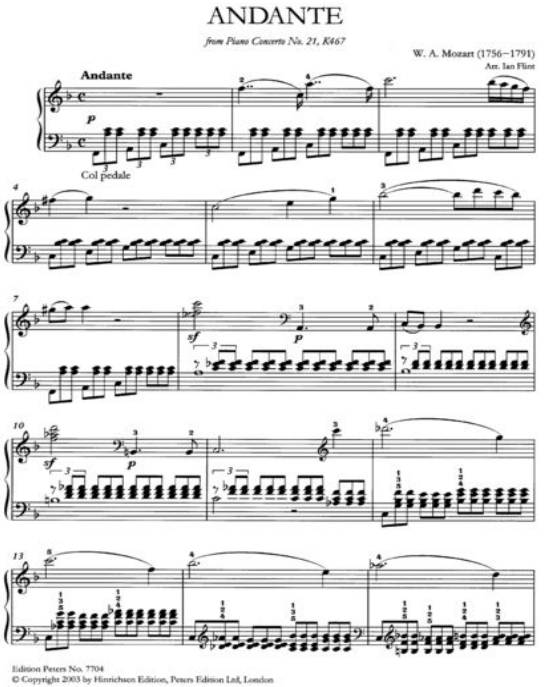
08 PLOS ONE ***Practicing a Musical Instrument in Childhood is Associated with Enhanced Verbal Ability and Nonverbal Reasoning***

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** ..



*"I just can't listen to any more **Wagner**, you know...I'm starting to get the urge to conquer **Poland**."*

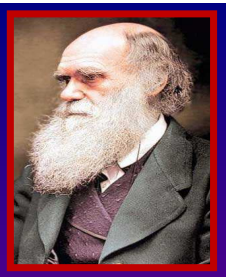

I'M LOOKING FOR THE ANSWER TO LIFE, SCHROEDER... WHAT DO YOU THINK IS THE ANSWER?
BEETHOVEN!
BEETHOVEN IS IT, CLEAR AND SIMPLE!! DO YOU UNDERSTAND?
GOOD GRIEF!

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

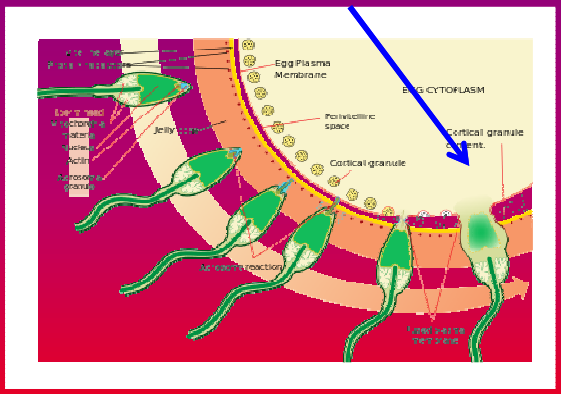
30 avril 2015

Focus sur la périconception

et la grossesse



The overlooked heritage: the genetic transmission by the father



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

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

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.**

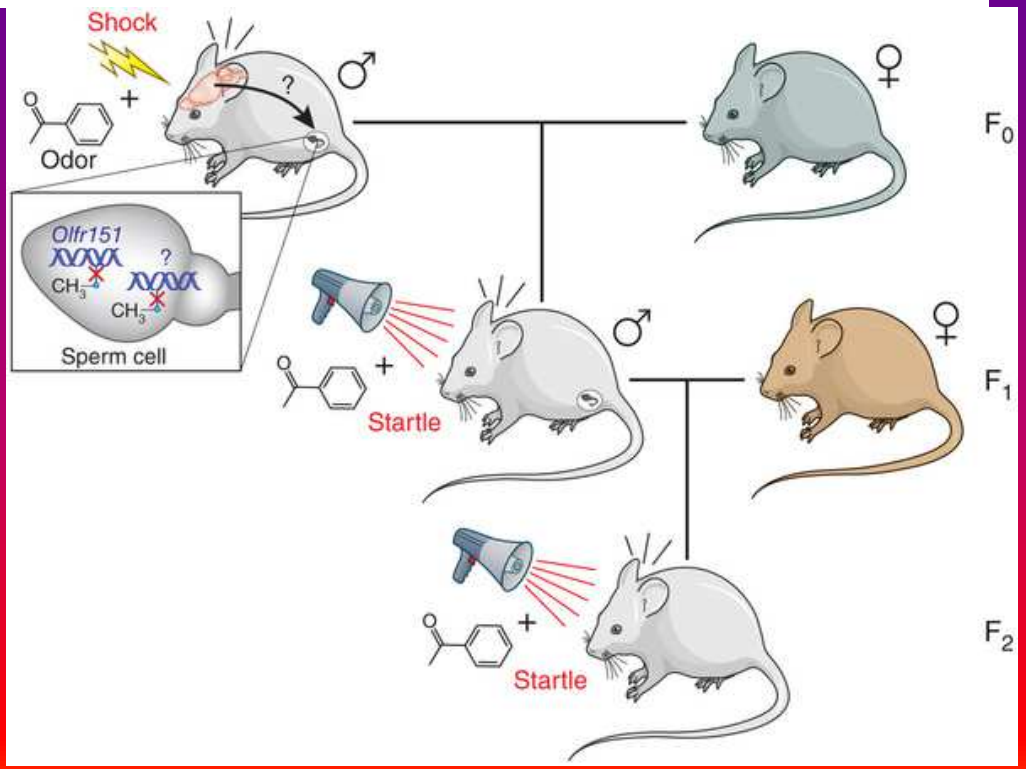
Lamarck revisited: epigenetic inheritance of ancestral odor fear conditioning

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**.

Journal of Andrology, Vol. 33, No. 3, May/June 2012

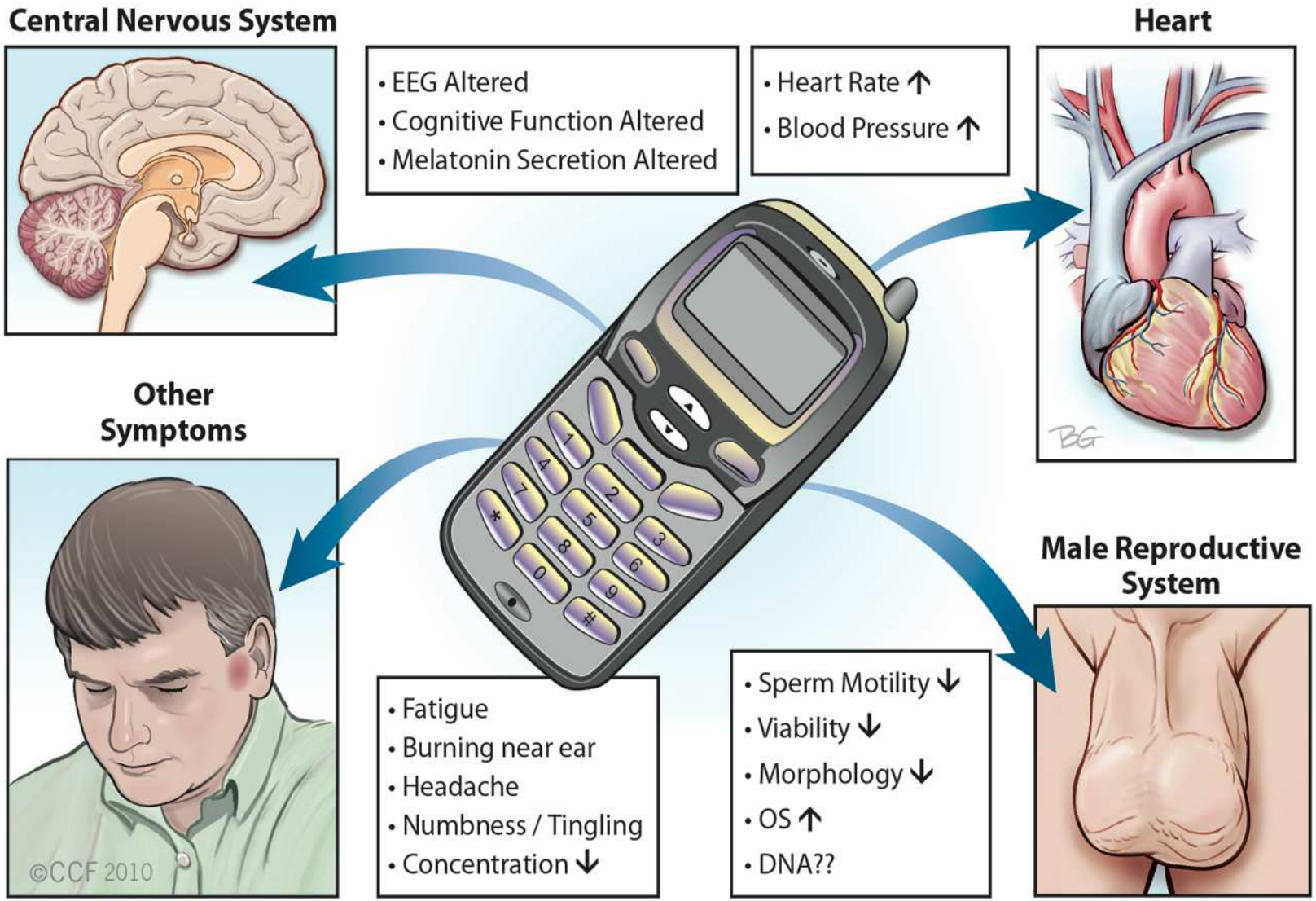
Effects of the Exposure to Mobile Phones on Male Reproduction: A Review of the Literature

SANDRO LA VIGNERA, ROSITA A. CONDORELLI, ENZO VICARI, ROSARIO D'AGATA, AND ALDO E. CALOGERO

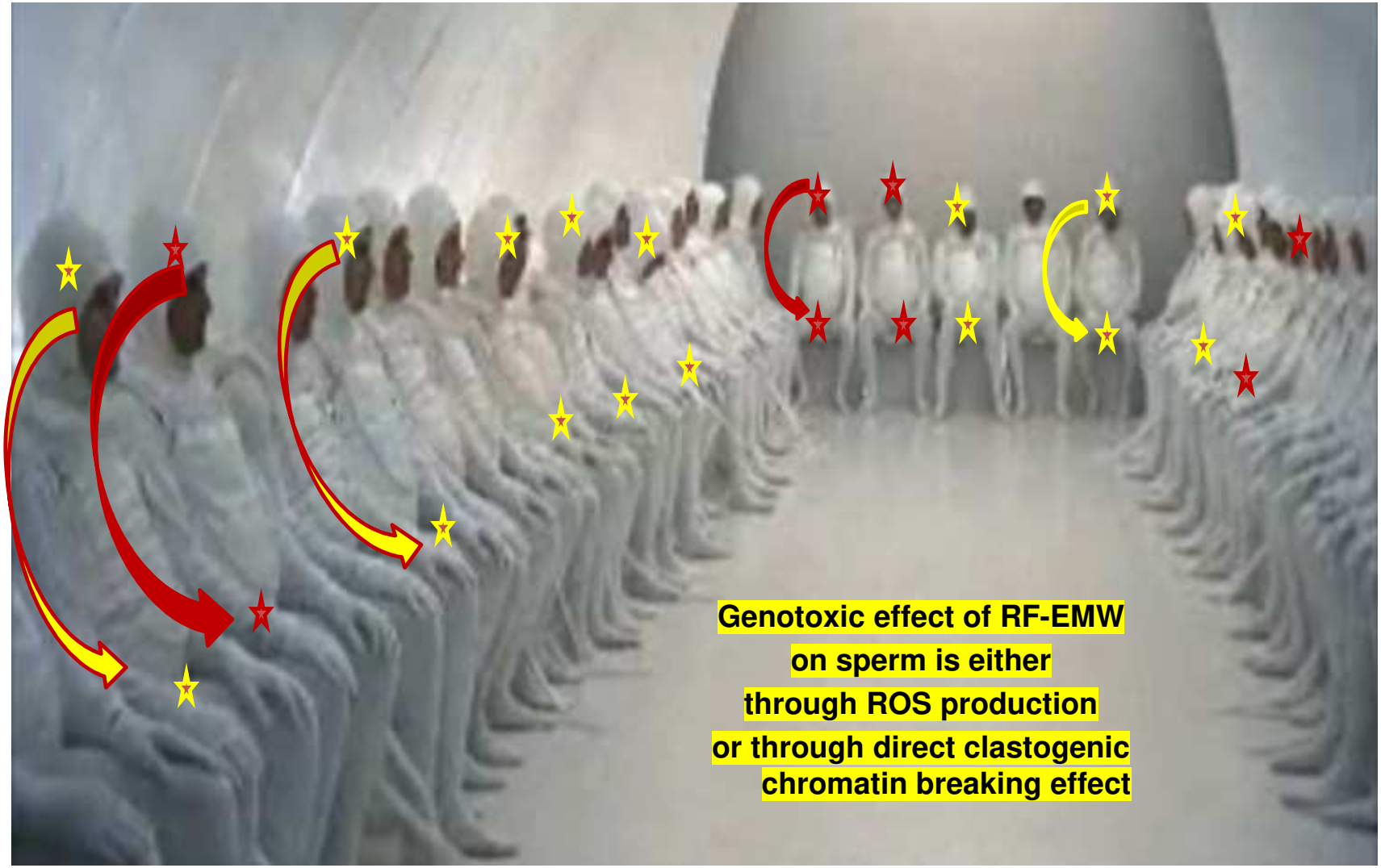
From the Section of Endocrinology, Andrology, and Internal Medicine and Master in Andrological, Human Reproduction, and Biotechnology Sciences, Department of Internal Medicine and Systemic Diseases, University of Catania, Catania, Italy.

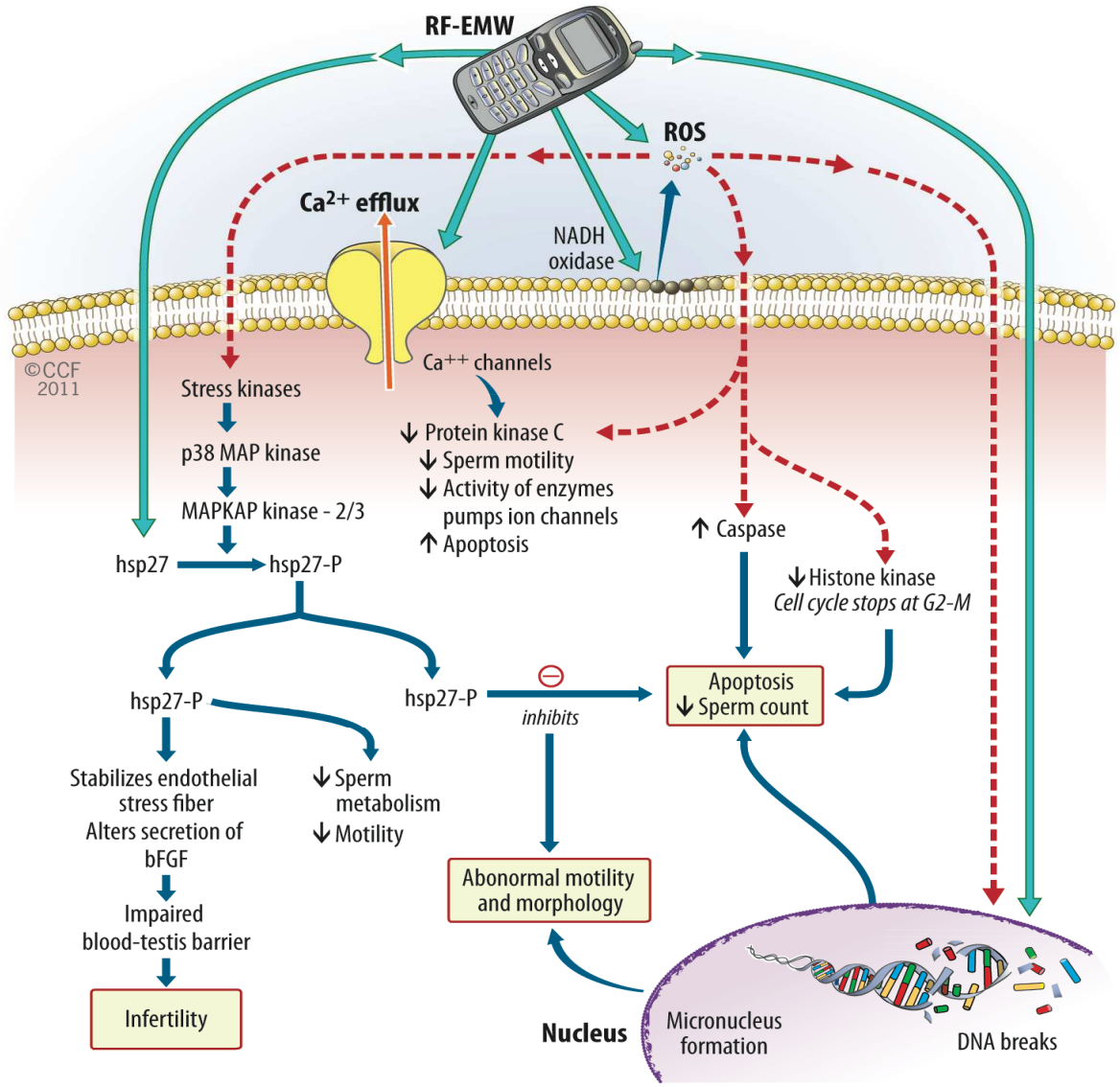
ABSTRACT: The use of mobile phones is now widespread. A great debate exists about the possible damage that the radiofrequency electromagnetic radiation (RF-EMR) emitted by mobile phones exerts on different organs and apparatuses. The aim of this article was to review the existing literature exploring the effects of RF-EMR on the male reproductive function in experimental animals and humans. Studies have been conducted in rats, mice, and rabbits using a similar design based upon mobile phone RF exposure for variable lengths of time. Together, the results of these studies have shown that RF-EMR one has explored the effects of RF-EMR directly on spermatozoa and the other has evaluated the sperm parameters in men using or not using mobile phones. The results showed that human spermatozoa exposed to RF-EMR have decreased motility, morphometric abnormalities, and increased oxidative stress, whereas men using mobile phones have decreased sperm concentration, decreased motility (particularly rapid progressive motility), normal morphology, and decreased viability. These abnormalities seem to be directly related to the duration of mobile phone use.

The aim of this article was **to review the existing literature exploring the effects of RF-EMR on the male reproductive function in experimental animals and humans**.. **human spermatozoa exposed to RF-EMR have decreased motility, morphometric abnormalities, and increased oxidative stress, whereas men using mobile phones have decreased sperm concentration, decreased motility (particularly rapid progressive motility) and decreased viability.**
These **abnormalities seem to be directly related to the duration of mobile phone use.**



Hamada JL et al. ***Cell Phones and their Impact on Male Fertility: Fact or Fiction***
The Open Reproductive Science Journal, 2011, 5, 125-137


Genotoxic effect of RF-EMW
on sperm is either
through ROS production
or through direct clastogenic
chromatin breaking effect



Hamada JL et al. ***Cell Phones and their Impact on Male Fertility: Fact or Fiction*** The Open Reproductive Science Journal, 2011, 5, 125-137

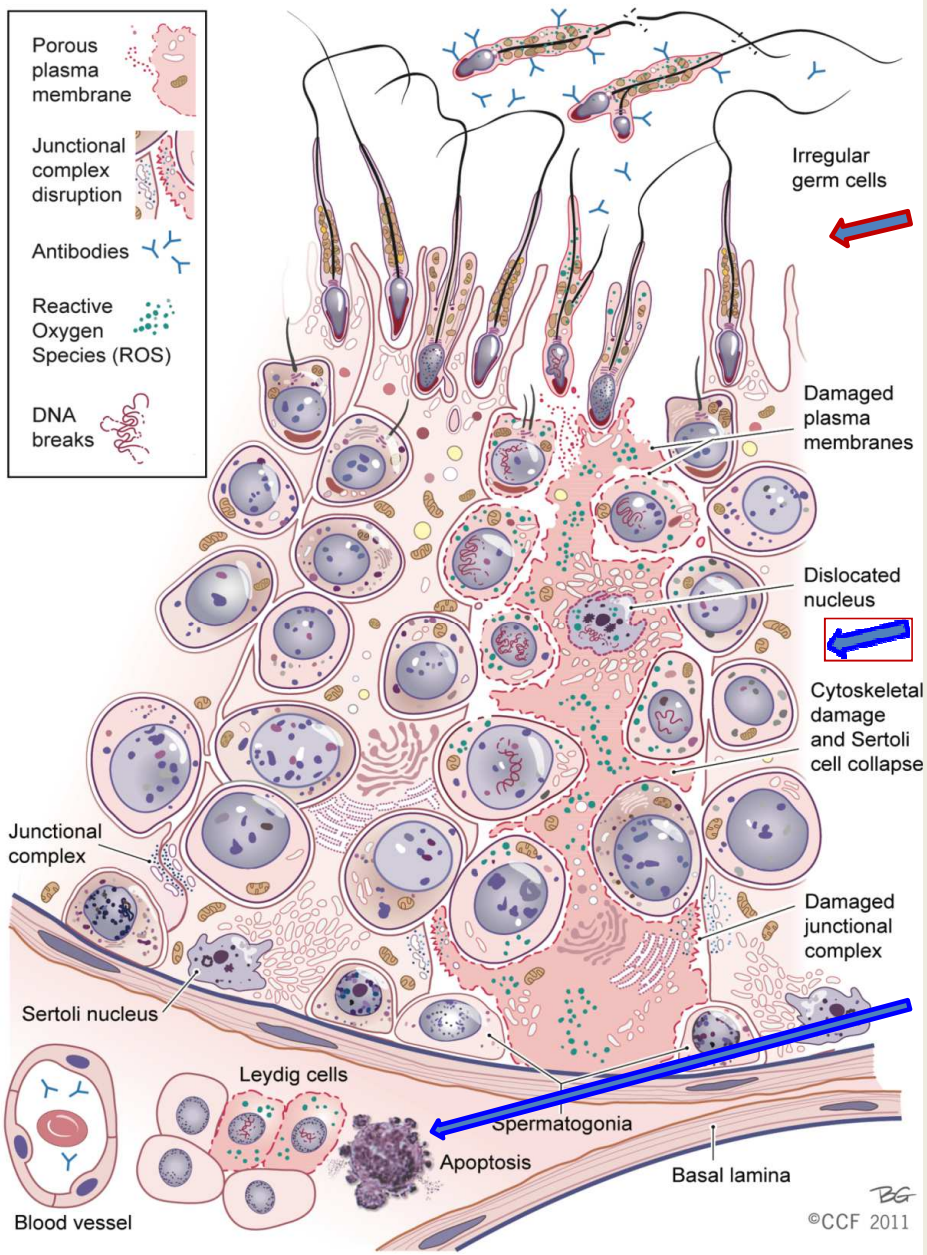
Heat shock proteins (HSPs) increase in response to **electromagnetic radiation** and **ROS.**

HSPs slows the metabolism of the sperm and impairs the blood testis barrier interfering with **apoptosis of damaged and transformed sperm**.

RF-EMW also induce ROS production through disturbance of the mitochondrial membrane bound NADH oxidase.

ROS has impact on PKC, histone kinase, heat shock protein, DNA and apoptosis.

Changed plasma membrane potential and calcium efflux with resultant calcium depletion leads to **decrease in the activity of protein kinase C (PKC).** This decrease leads to **alteration in many enzymes, ion pumps, channels and proteins** as well as **inducing apoptosis**



Cross sectional view of **testicular tissue** showing various effects of **cell phone RF-EMW** on cellular components of the testis.

In sperm: a) plasma membrane becomes leaky and porous due to EMW induced electroporation,

b) **cytoplasmic mitochondria generate excess ROS** resulting in ***oxidative stress***

c) **nuclear DNA and chromatin undergo breaks and damage**.

In **Sertoli cells**: a) **damage to plasma membrane tight junctional complexes compromises the integrity of BTB (Blood testis Barrier) and increases its permeability** resulting in exposure of sperm antigens to immune system and formation of ASA (**Antisperm ABs**),

b) **damage to cytoskeleton** results in cell collapse with

c) production of excess **ROS**, and

d) **dislocation of nucleus** to a more central position.

In **Leydig cells**: a) plasma membrane sustains damage with

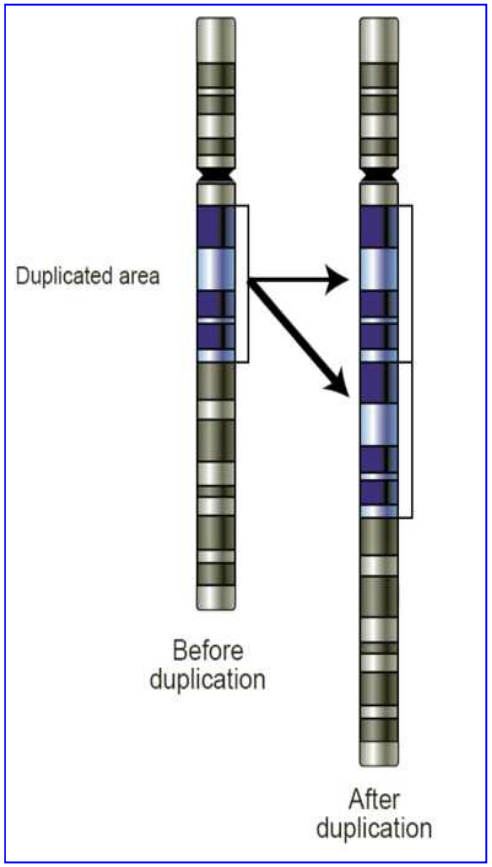
b) **++ cytoplasmic ROS generation**, and

c) **nuclear DNA damage resulting in apoptosis**.

WI-FI PRODUCED BY YOUR PC
the radiated signal exceeds 13 V / m

Dr. Fiorenzo Marinelli
Istituto di Genetica Molecolare
IGM-CNR Bologna

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

Cell PRESS

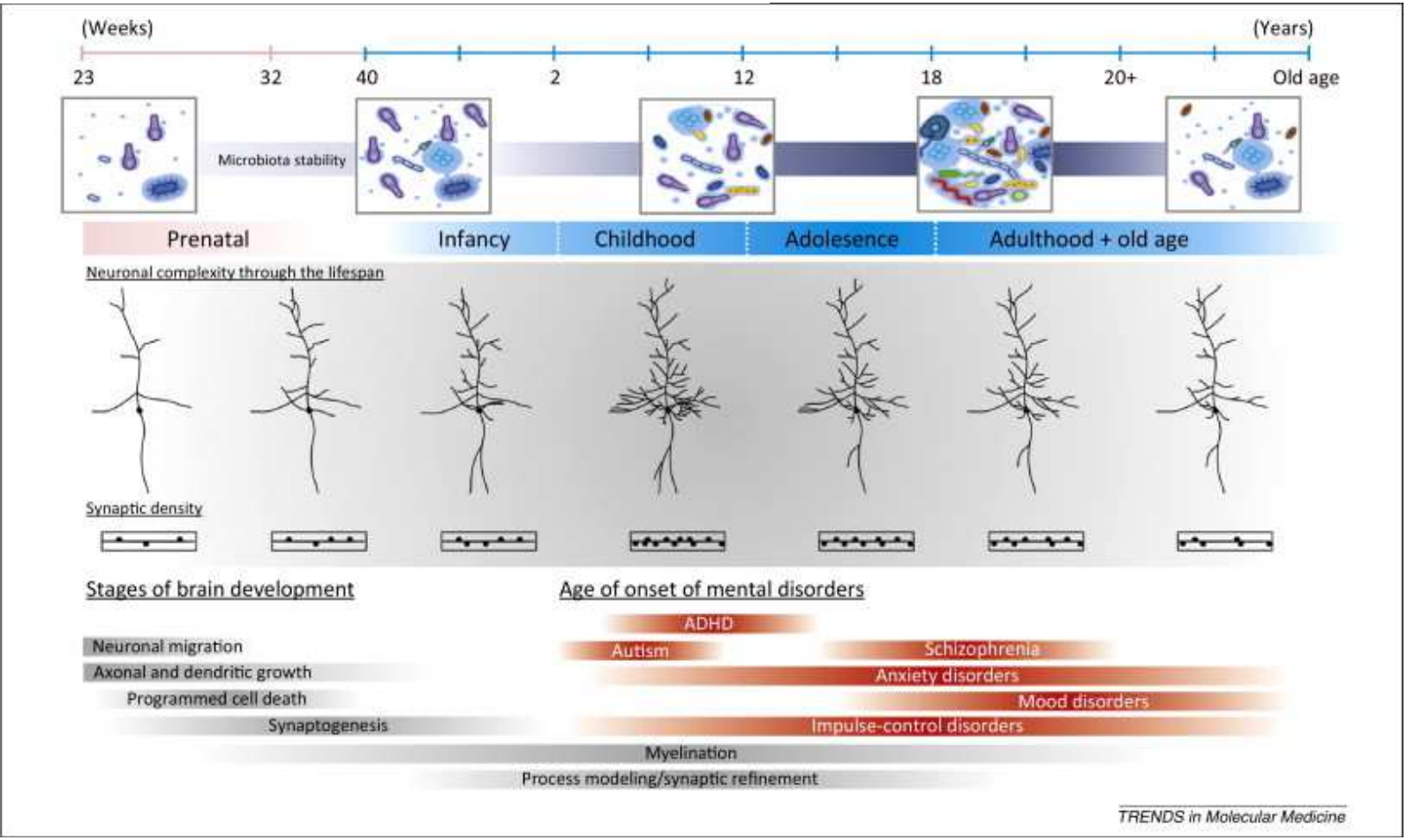
Volume 20, Issue 9, September 2014, Pages 509–518

Review

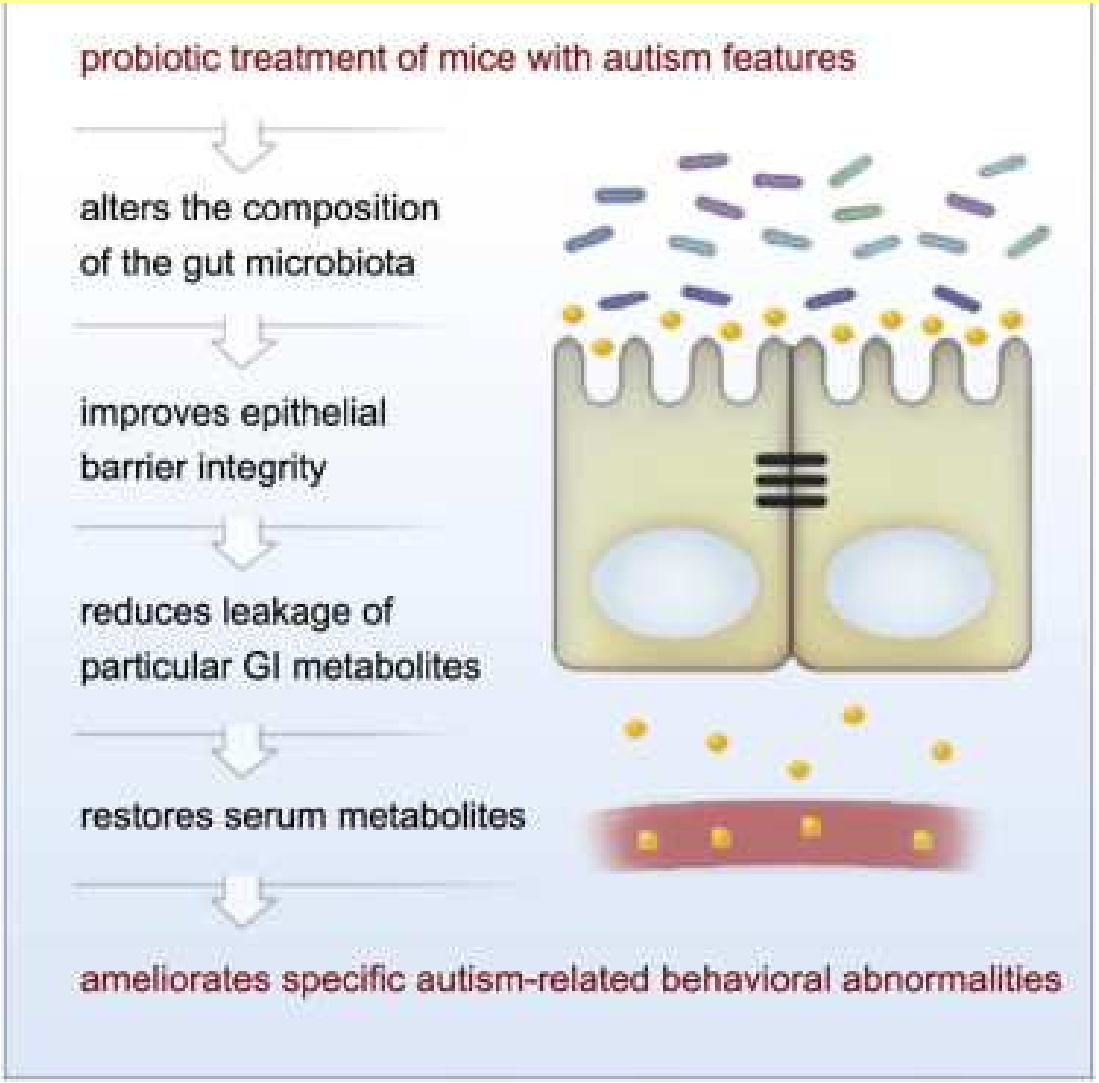
Microbiota and neurodevelopmental windows: implications for brain disorders

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

Kang *et al. Microbiome* (2017) 5:10
DOI 10.1186/s40168-016-0225-7

Microbiome

RESEARCH Open Access

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

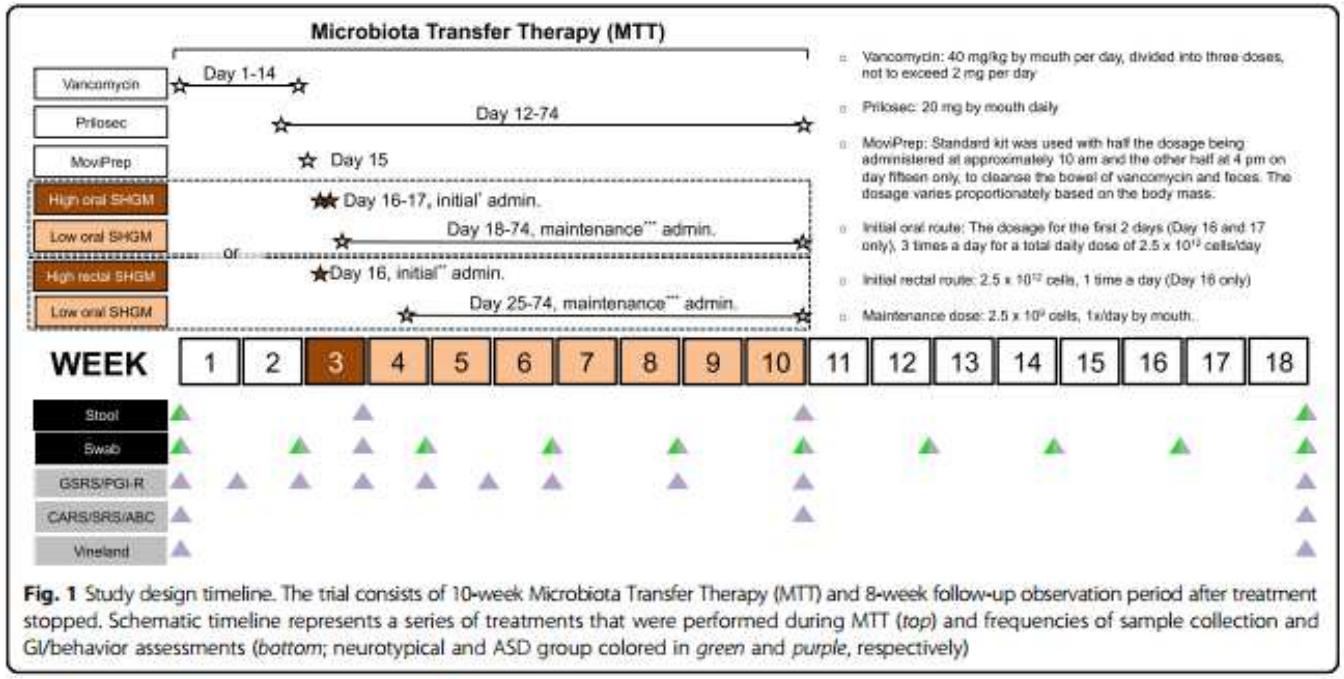
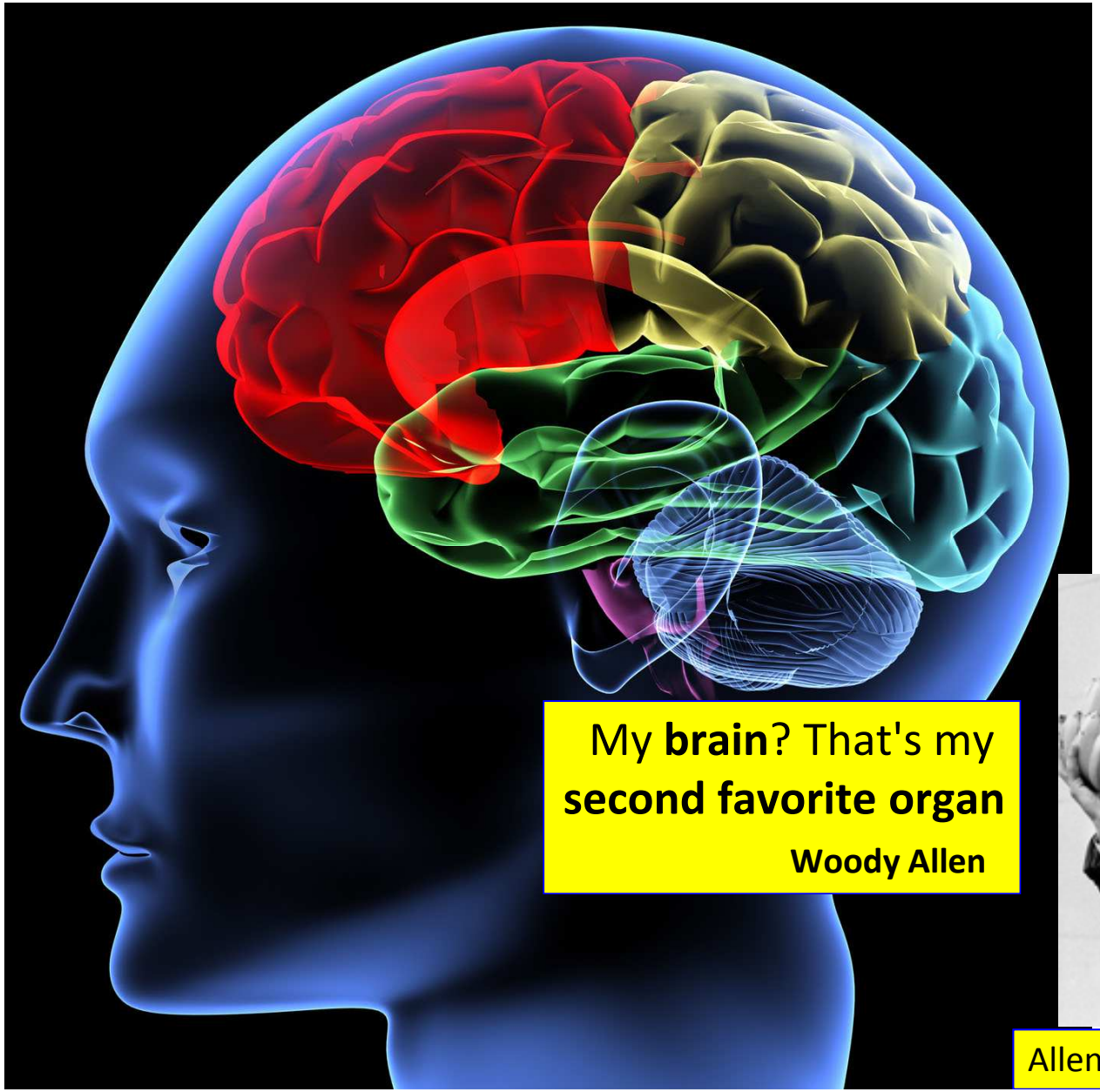


Fig. 1 Study design timeline. The trial consists of 10-week Microbiota Transfer Therapy (MTT) and 8-week follow-up observation period after treatment stopped. Schematic timeline represents a series of treatments that were performed during MTT (*top*) and frequencies of sample collection and GI/behavior assessments (*bottom*; neurotypical and ASD group colored in *green* and *purple*, respectively)

MTT involved a 2-week antibiotic treatment, a bowel cleanse, and then an extended fecal microbiota transplant (FMT) using a high initial dose followed by daily and lower maintenance doses for 7–8 weeks.

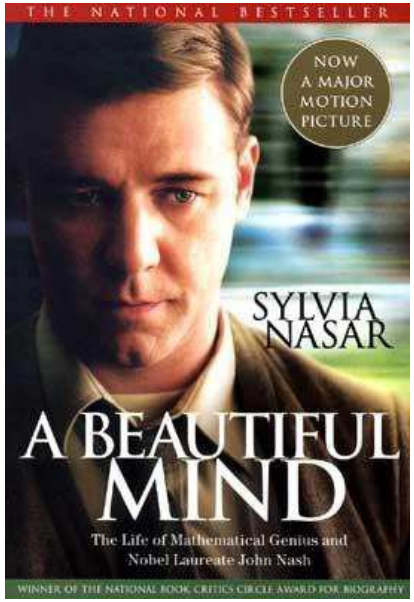
The Gastrointestinal Symptom Rating Scale revealed an approximately **80% reduction of GI symptoms at the end of treatment, including significant improvements in symptoms of constipation, diarrhea, indigestion, and abdominalpain. Improvements persisted 8 weeks after treatment.**

Similarly, clinical assessments showed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended.



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)

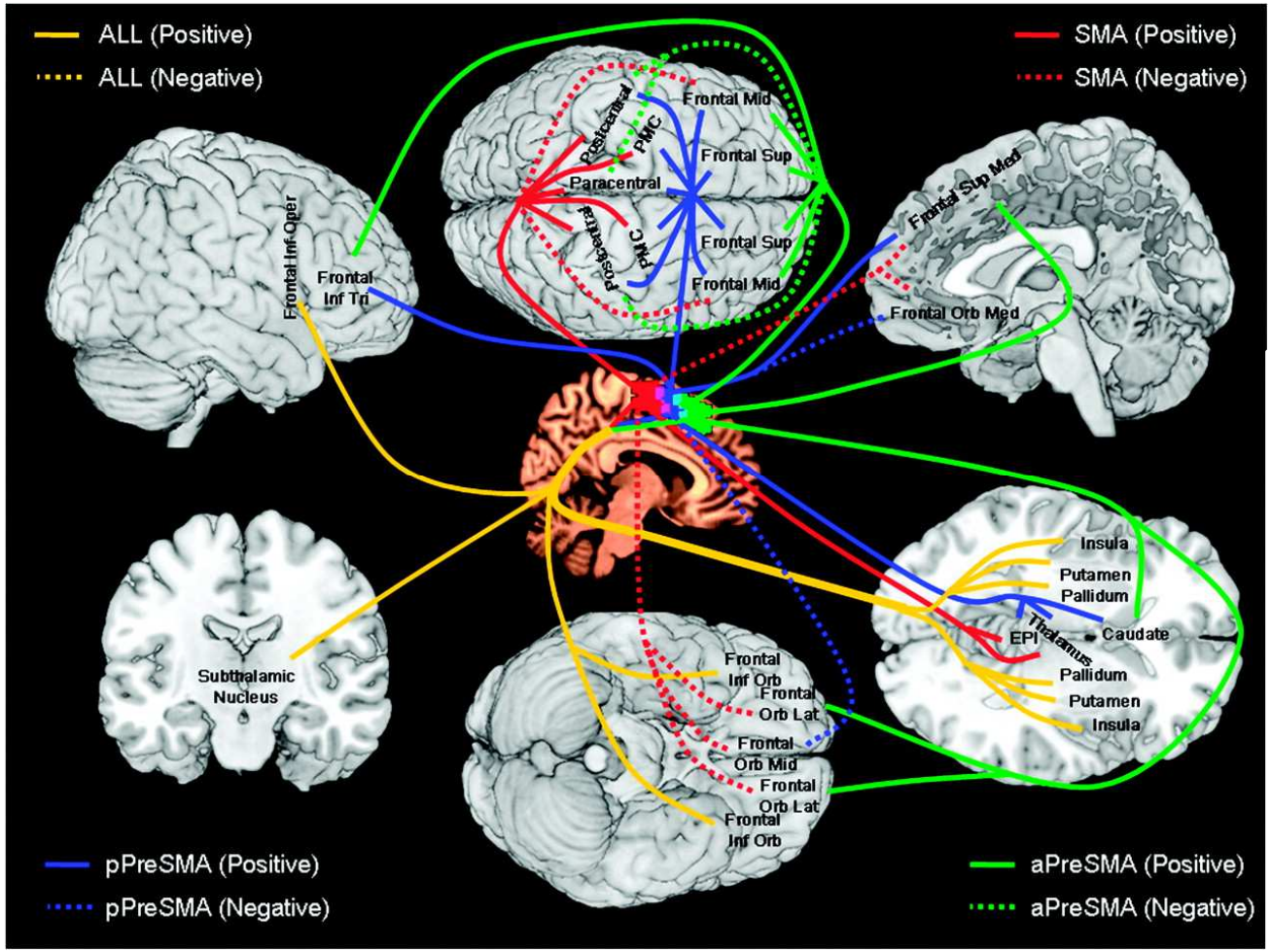
1

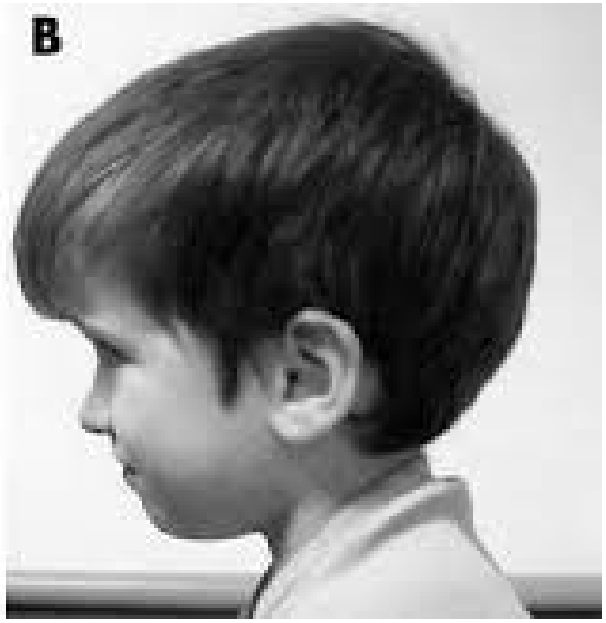
2

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**

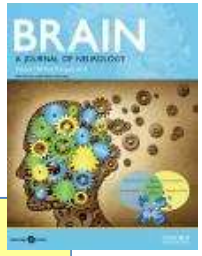
* Uddin etal., ***Reconceptualizing functional brain connectivity in autism from a developmental perspective*** (2013)

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

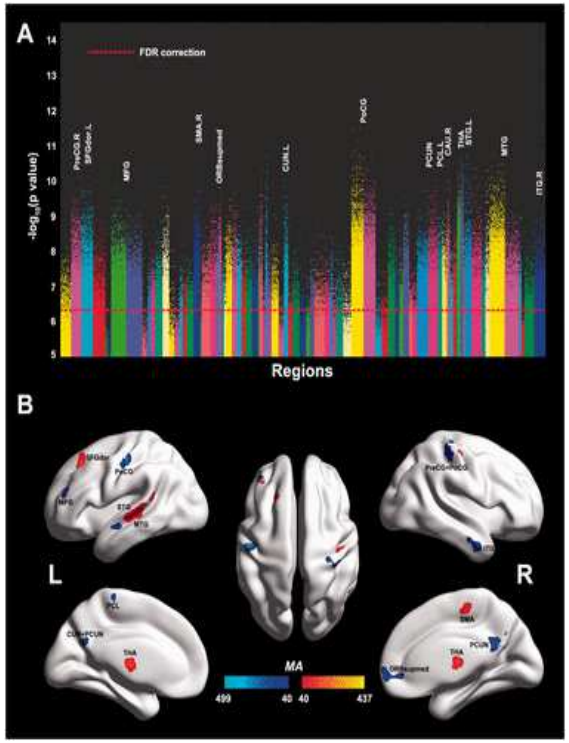
Cheng W, Rolls ET, Gu H, Zhang J, Feng J

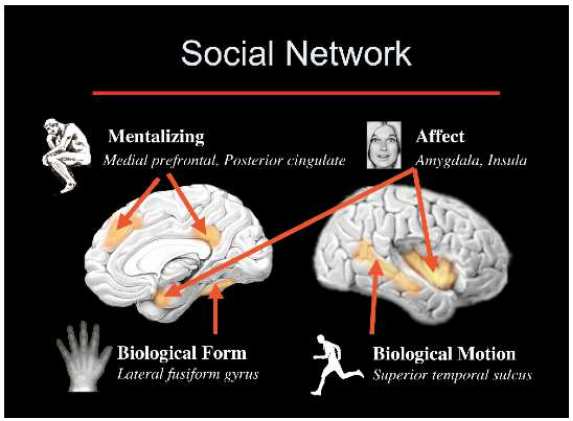
Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. Brain. 2015 May;138(Pt 5):1382-93.

..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

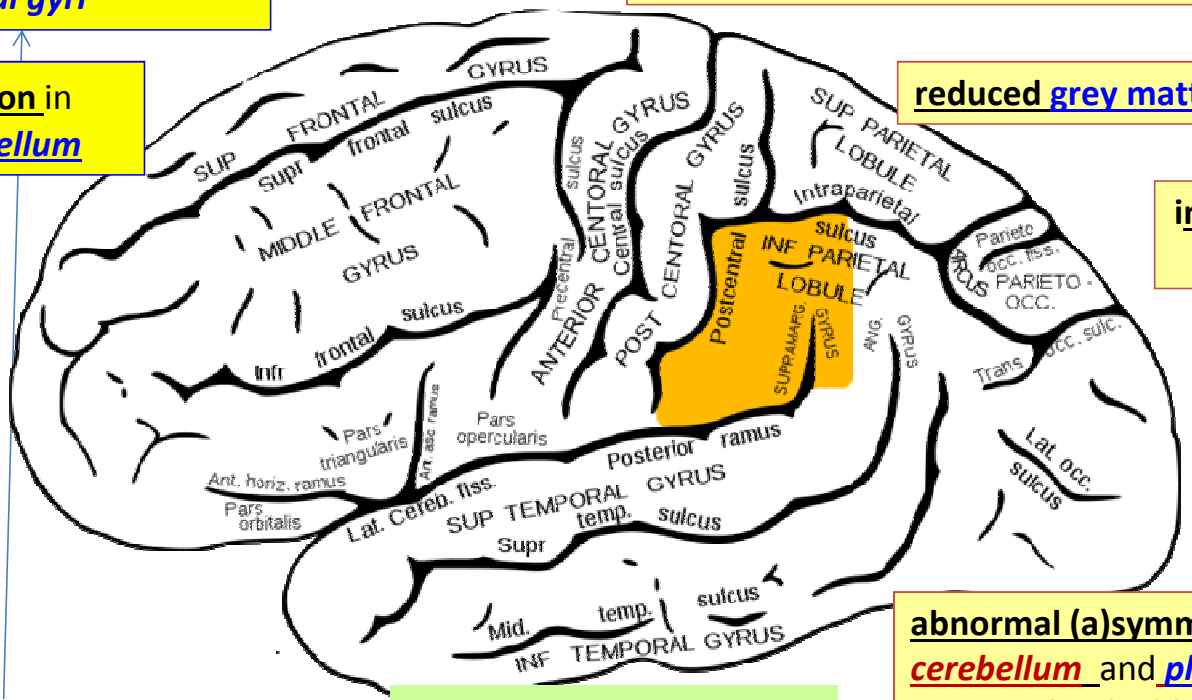
under-activations in the **left hemisphere fusiform** and ***supramarginal gyri***

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***

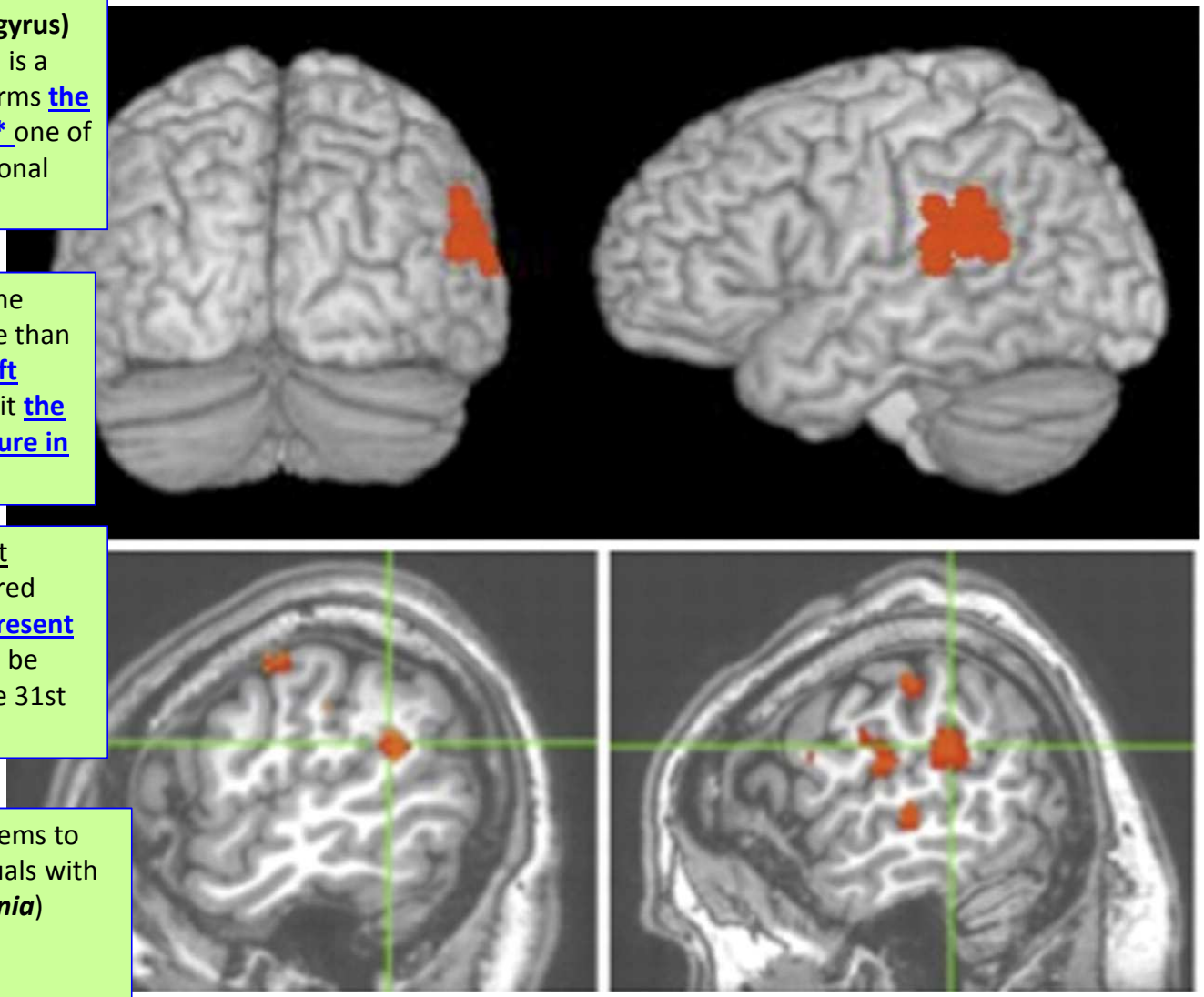
Elnakib A, Soliman A, Nitzken M, Casanova MF, Gimel'farb G, El-Baz A. ***Magnetic resonance imaging findings for dyslexia: a review.*** J Biomed Nanotechnol. **2014** Oct;10(10):2778-805.

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
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Leading Edge
Previews

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

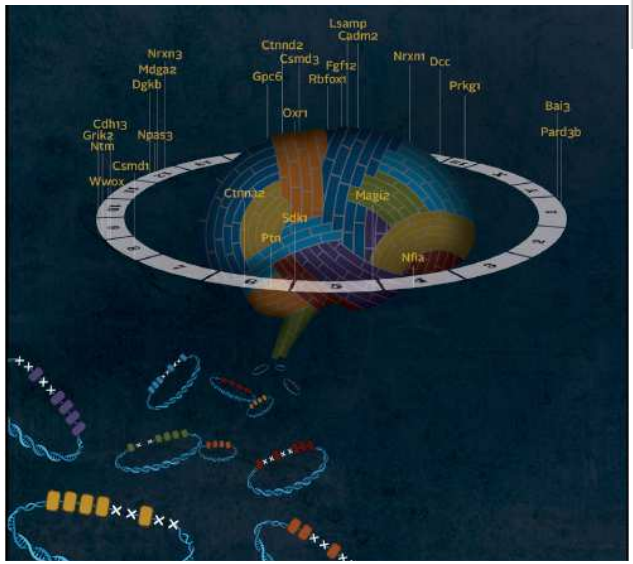
Cell

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.

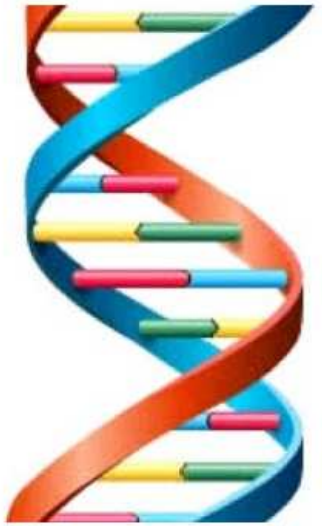
The mechanism involves direct interaction of EMF with the DNA molecule (claims that there are no known mechanisms of interaction are patently false)

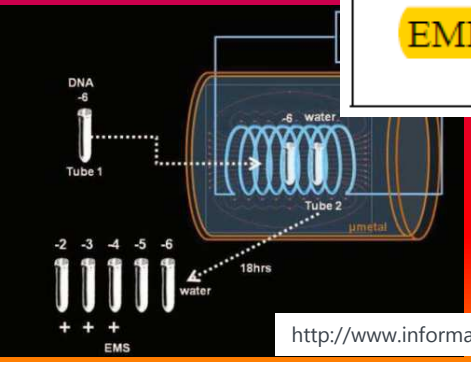
Many EMF frequencies in the environment can and do cause DNA changes.

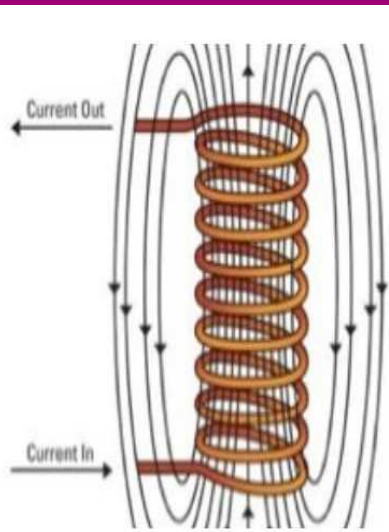
The EMF-activated cellular stress response is an effective protective mechanism for cells exposed to a wide range of EMF frequencies.

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)

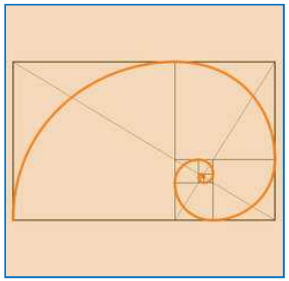


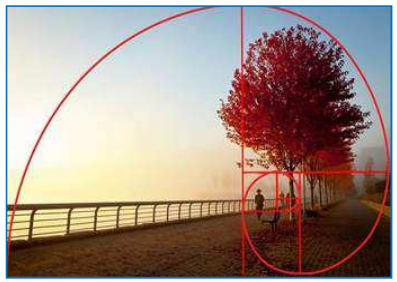


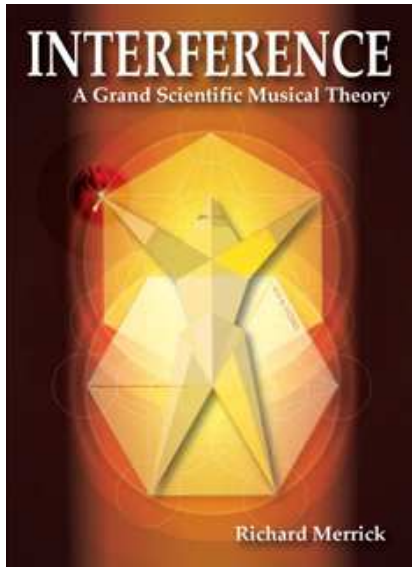


http://www.informationenergymedicine-academy.com/wp-content/uploads/coil-to-generate-7-Hz-carrier-wave-300x228.jpg 300w" sizes="(max-width: 500px) 100vw, 500px" /

Holonomic Brain Model

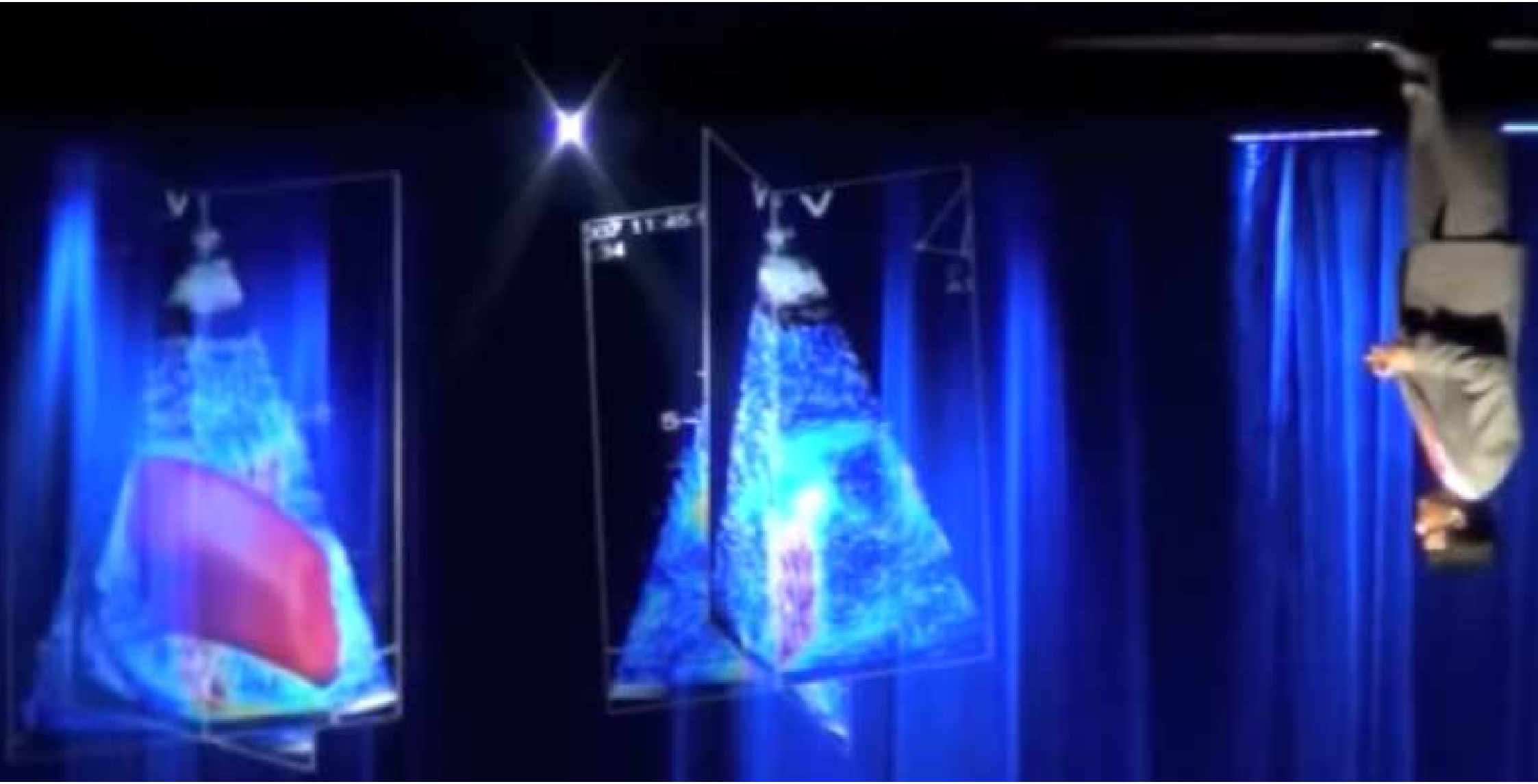


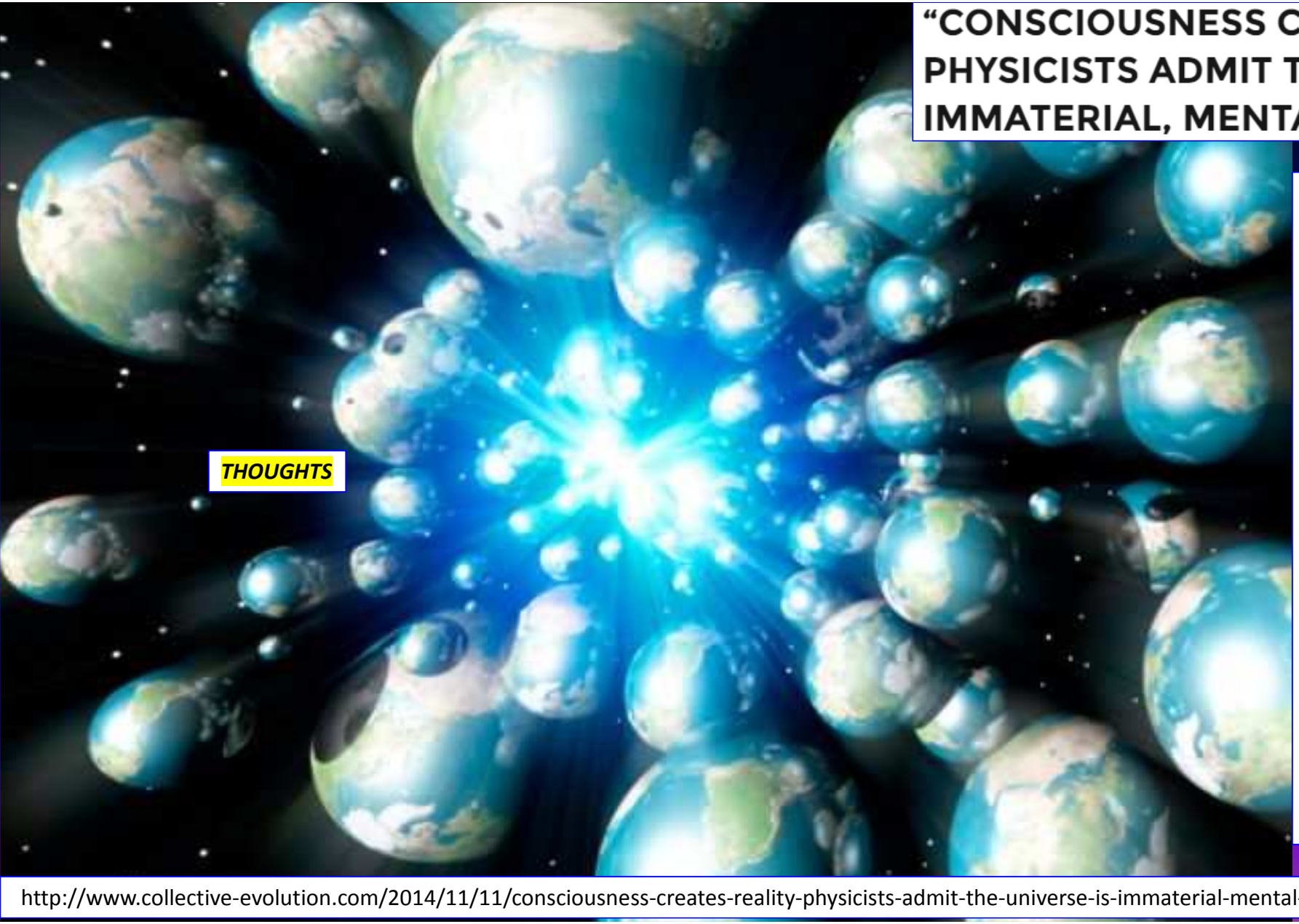




We recognize harmony and harmonics in music by pattern matching standing wave patterns against identical standing wave patterns in our brain. This is compatible with the **Pribram-Bohm holonomic brain model** whereby the **brain is described as a hologram interference pattern resulting from orthogonal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

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





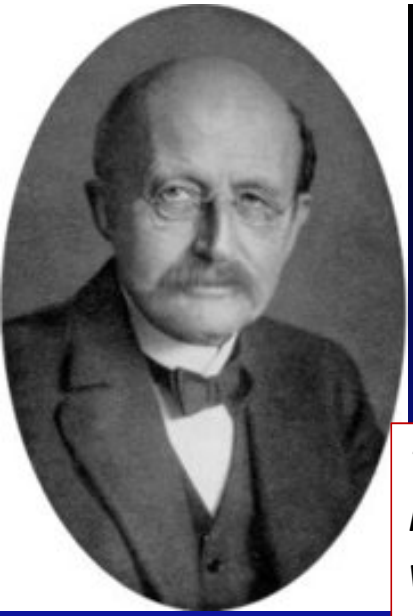
"CONSCIOUSNESS CREATES REALITY" PHYSICISTS ADMIT THE UNIVERSE IS IMMATERIAL, MENTAL & SPIRITUAL

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/

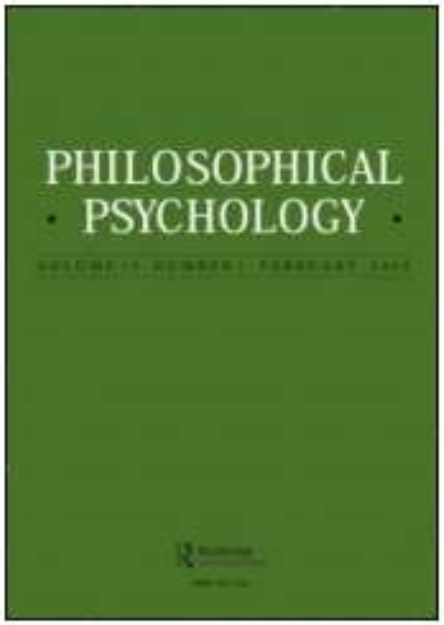


*"**All matter originates and exists only by virtue of a force** **which brings the particle of an atom to vibration** and holds this most minute solar system of the atom together.*

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)



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

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)