CORTONA FRIENDS

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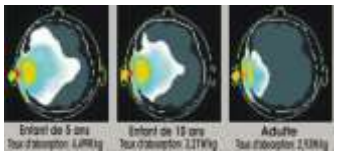
Cortona Week in Todi, 22-29 June 2019 – Being Human in a Technological World

Neurodevelopmental disorders in a hyper-tech world

ERNESTO BURGIO ECERI - European Cancer and Environment Research Institute

GIANFRANCO TAJANA UNIVERSITA' SALERNO



Giornate su
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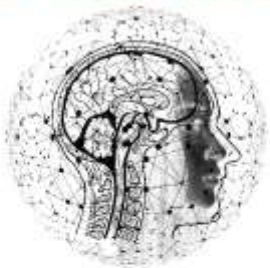

Con l'intervento di:

Ernesto Burgio - Il genoma minacciato

Carina Brochier - Cure palliative ed eutanasia

David Lana Tuñon, Fermín Jesús González Meladio, Luis Torró Ferrero - Tavola rotonda: 'Sfide attuali del transumanesimo'

Claudia Estela Vanney - Costruire una nuova cultura dall'interdisciplinarità

Brad S. Gregory - Come la rivoluzione religiosa ha secolarizzato la società

18 - 19 Ottobre 2019

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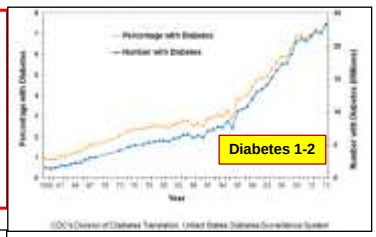
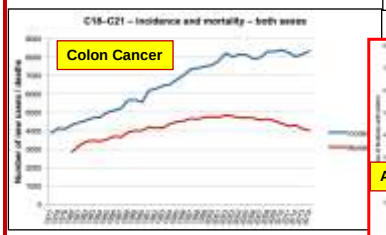
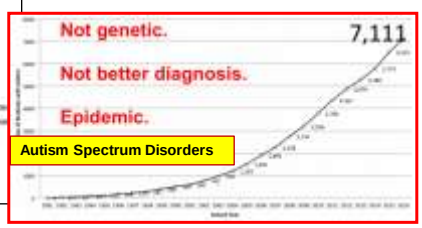
Santander

OBESITY IS NOW A GLOBAL EPIDEMIC!

Obesity

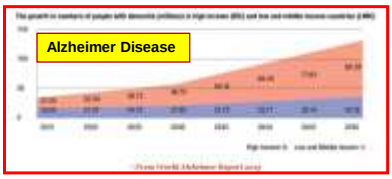






'Il genoma minacciato'

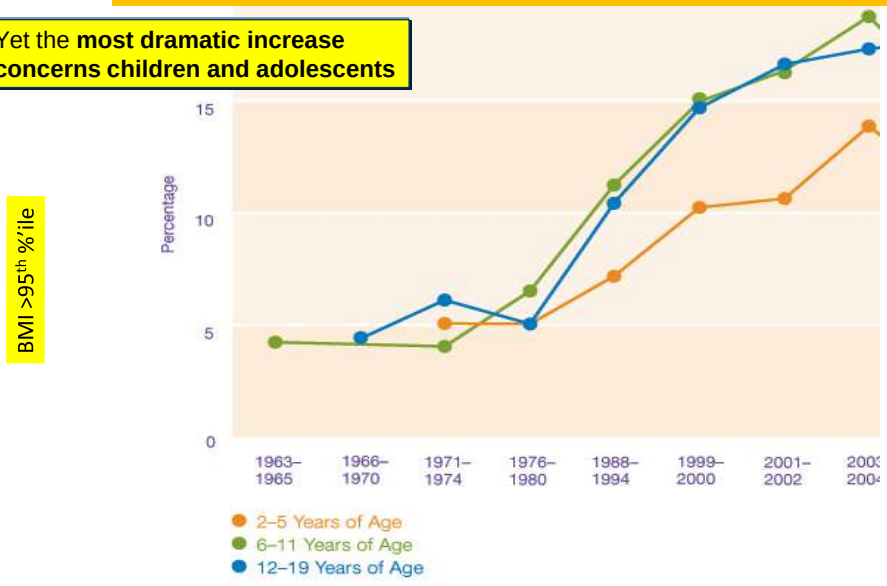
ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute



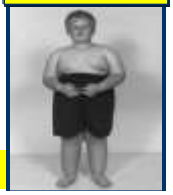
The Childhood Obesity Epidemic

Matthew W. Gillman, MD, SM

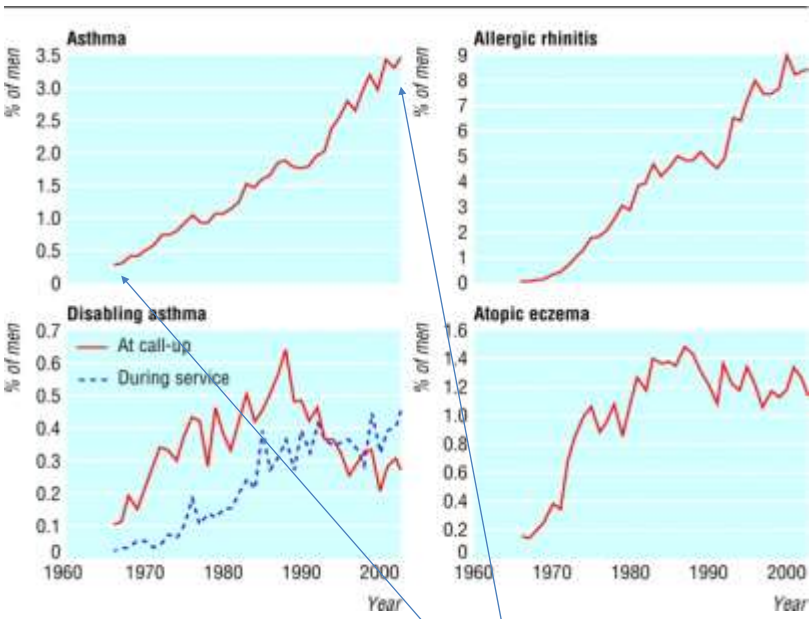
Yet the **most dramatic increase concerns children and adolescents**



in the 70s childhood obesity virtually did not exist (it was associated with **rare genetic syndromes**): since then the increase has been **rapid and relentless**

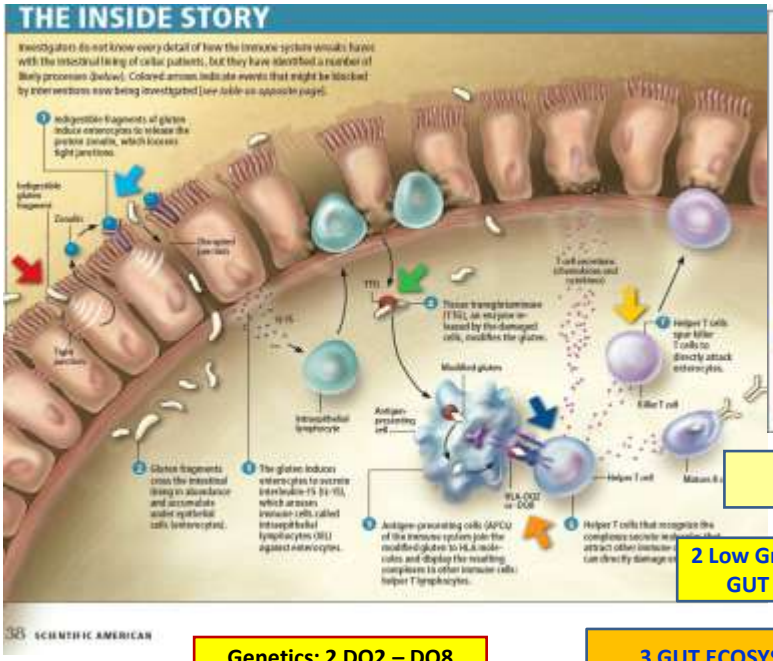


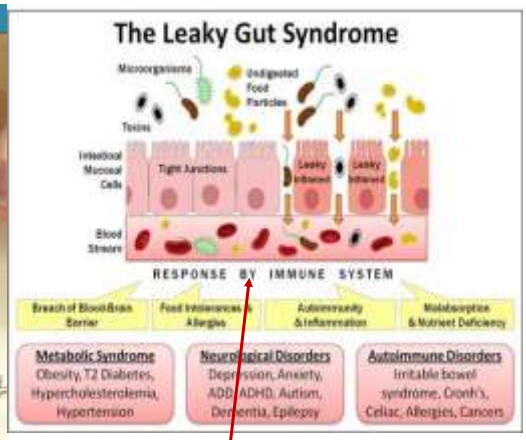
US DHHS, 2001; Hedley et al., 2004; Ogden et al., 2006, 2008



Trends in prevalence of asthma and allergy in Finnish young men
http://www.bmj.com/content/330/7501/1186

The ***prevalence*** of **asthma increased 12-fold between 1966 (0.29%) and 2003 (3.45%),** showing a continuous rising trend ... **The average annual increment** in prevalence during this period **was 0.1%.** By contrast, **the trends for indicators of disabling asthma turned downwards in 1989**





1 GLIADIN

2 Low Grade Inflammation
GUT PERMEABILITY

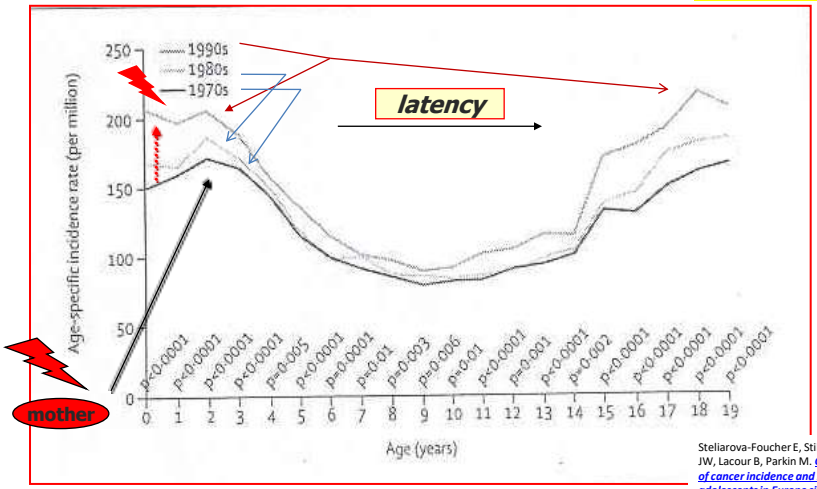
Genetics: 2 DQ2 – DQ8
(CELIAC Disease)

3 GUT ECOSYSTEM

A first draft of the report, published on ***the Lancet*** in **2004**, demonstrated an **annual increase of 1-1,5% for all cancers** (with more marked increases in **lymphomas, soft tissue sarcomas, tumours of the nervous system…**) . But the **most troubling was the increase - almost the double** - for all cancers **in the very first year of life (apparently due to transplacental or even trans-generational exposure)**

CA incidence in childhood and adolescence IN EUROPE (1970-1999)

http://www-dep.iarc.fr/accis.htm



Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, Parkin M. *Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study.* Lancet. 2004 Dec 11-17;364(9451):2097-105

Grandjean P.

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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

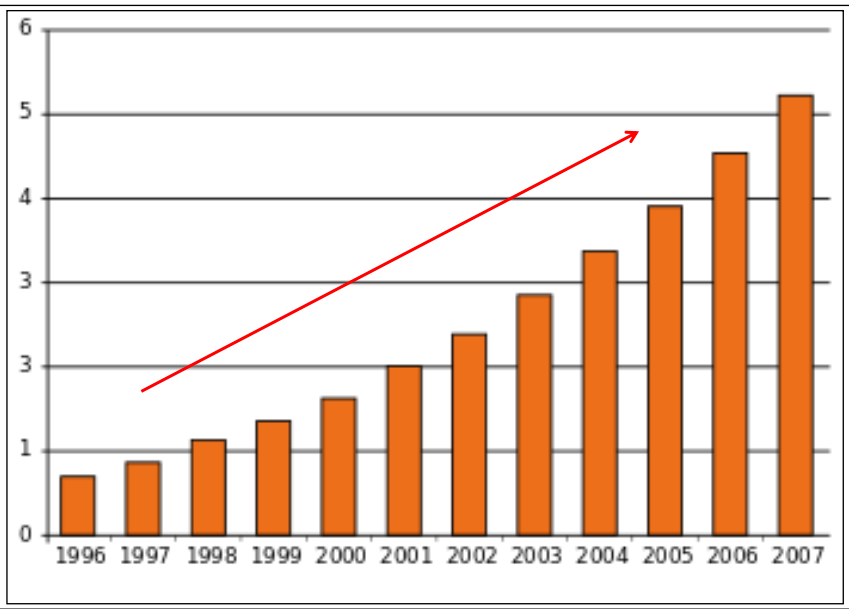
P Grandjean, PJ Landrigan

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**) were recognized causes of neurodevelopmental disorders and subclinical brain dysfunction.

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

In fact the reports of autism cases per 1,000 children had increased dramatically over the years in the U.S. from 1996 to 2007



Newschaffer CJ, Croen LA, Daniels J et al. ***The epidemiology of autism spectrum disorders*** Annu Rev Public Health. 2007;28:235–58.

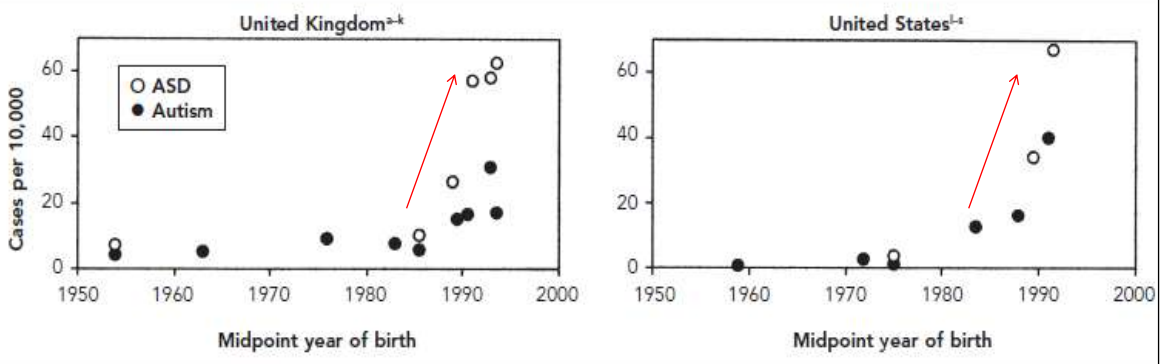
AUTISM
(ASD :Autism Spectrum Disorders)

ASD is the fastest-growing developmental disorder in the world, the prevalence of diagnosis having increased by 600% over the last 20 years. New diagnosed cases (**incidence**) in US increased **from 15,580 in 1992 to 163.773 in 2003**

The estimated **prevalence was of 8-12 cases/1000 children in 2012..**

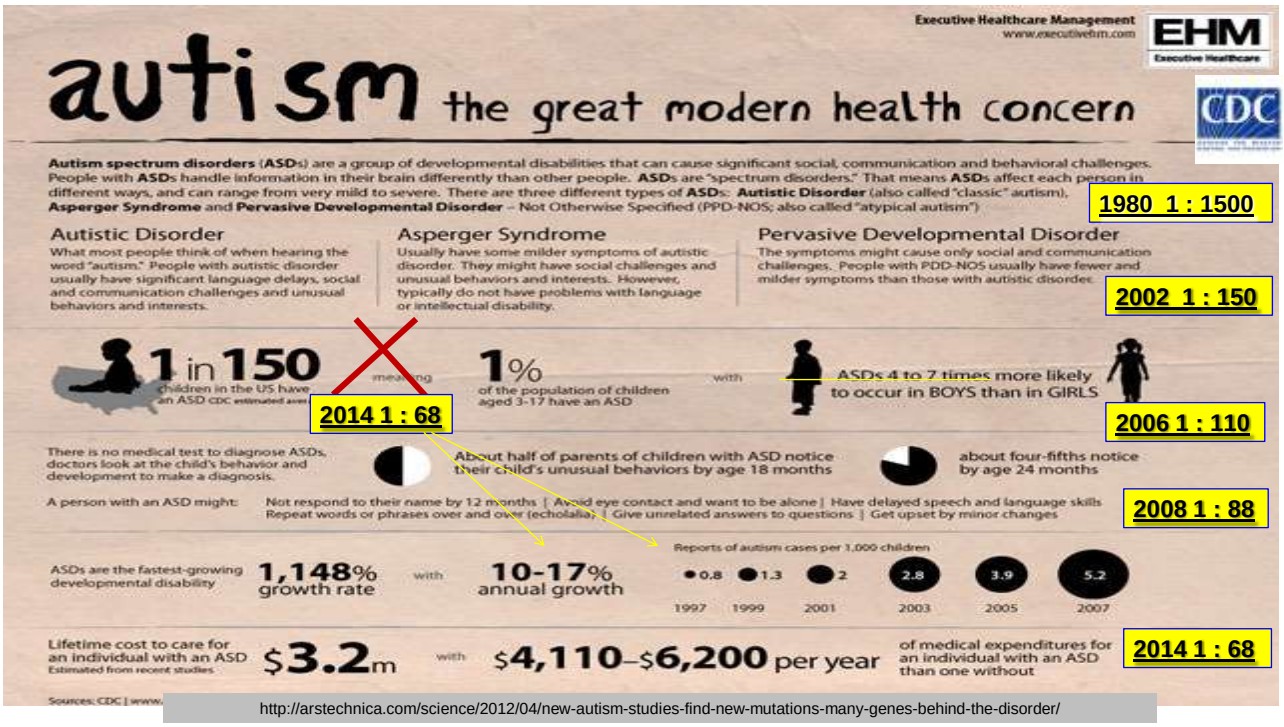
Chart showing the **increase in autism diagnosis (A)** ***versus*** **all disabilities (B)** (statistics based on data from the National Center for Health Statistics)

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]



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

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

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

Neurobehavioural effects of developmental toxicity

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.

The same two authors returned to the problem **seven years later, with a broad review published the Lancet Neurology (2014)**

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

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.**

And it is increasingly evident that **the increase continues unabated**

1:119	Finlandia	*Mattila et al., 2011*
1:87	Svezia	*Idring et al., 2012*
1:59	Gran Bretagna	Russel et al., 2014

Community Report on Autism 2018

Centers for Disease Control and Prevention

Community Report from the **Autism and Developmental Disabilities Monitoring (ADDM) Network**

ADDM Network

1.7% is the average percentage identified with ASD

1 in 59 8-year-old children were identified with ASD by ADDM in 2014

Why is this information important and how can it be used?

1. Lower the age of first evaluation by community providers; and
2. Increase awareness of ASD among black and Hispanic families, and identify and address barriers in order to ensure that all children with ASD are evaluated, diagnosed, and connected to services.

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children

Michael D. Kogan, PhD,[a] Catherine J. Vladutiu, PhD, MPH,[a] Laura A. Schieve, PhD,[b] Reem M. Ghandour, DrPH,[a] Stephen J. Blumberg, PhD,[c] Benjamin Zablotsky, PhD,[c] James M. Perrin, MD,[d] Paul Shattuck, PhD,[e] Karen A. Kuhlthau, PhD,[d] Robin L. Harwood, PhD,[a] Michael C. Lu, MD, MPH[f]

OBJECTIVES: To estimate the national prevalence of parent-reported autism spectrum disorder (ASD) diagnosis among US children aged 3 to 17 years as well as their treatment and health care experiences using the 2016 National Survey of Children's Health (NSCH).

METHODS: The 2016 NSCH is a nationally representative survey of 50 212 children focused on the health and well-being of children aged 0 to 17 years. The NSCH collected parent-reported information on whether children ever received an ASD diagnosis by a care provider, current ASD status, health care use, access and challenges, and methods of treatment. We calculated weighted prevalence estimates of ASD, compared health care experiences of children with ASD to other children, and examined factors associated with increased likelihood of medication and behavioral treatment.

RESULTS: Parents of an estimated 1.5 million US children aged 3 to 17 years (2.50%) reported that their child had ever received an ASD diagnosis and currently had the condition.

CONCLUSIONS: The estimated prevalence of US children with a parent-reported ASD diagnosis is now 1 in 40, with rates of ASD-specific treatment usage varying by children's sociodemographic and co-occurring conditions.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

New genetic risk factor for developing autism spectrum disorder identified

Date: August 31, 2017

Source: Oregon Health & Science University

Summary: A new systematic analysis has been applied to a cohort of 2,300 families who have a single child affected with autism. The study focused on identifying and characterizing low-lying genetic mutations that may have been missed in previous research, given these mutations are only present in a fraction of the bulk DNA of an individual.

tematic analysis to a cohort of 2,300 families who have a single child affected with autism. The study focused on identifying and characterizing low-lying genetic mutations that may have been missed in previous research, given these mutations are only present in a fraction of the bulk DNA of an individual.

Known as postzygotic mosaic mutations, or PMMs, these genetic changes occur after the conception of the human zygote during the development cycle of a fetus. An individual will contain a mosaic -- or assortment -- of mutated and non-mutated cells with the level of mosaicism depending on the time and location of the mutation's occurrence. This emerging class of genetic risk factors has recently been implicated in various neurologic conditions, however,

Autism risk due to unexpected mosaic mutations

.. yet many continue **to define autism (and schizophrenia) as "genetic" diseases !!??!!**

As in this case: ***The risk of autism connected to unexpected exonic mutations ...!!??!!***

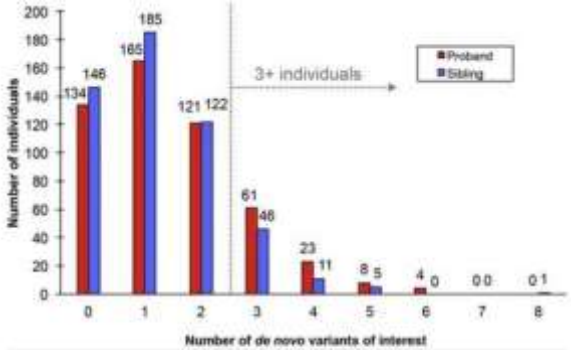
Deidre R. Krupp, Rebecca A. Barnard, Yannis Duffourd, Sara A. Evans, Ryan M. Mulqueen, Raphael Bernier, Jean-Baptiste Rivière, Eric Fombonne, Brian J. O'Roak. **Exonic Mosaic Mutations Contribute Risk for Autism Spectrum Disorder**. *The American Journal of Human Genetics*, 2017; DOI: 10.1016/j.ajhg.2017.07.016

Whole genome sequencing identifies new genetic signature for autism

Date: October 12, 2017

Source: Howard Hughes Medical Institute

Summary: An analysis of the complete genomes of 2,064 people reveals that multiple genetic variations could contribute to autism. The work suggests that scanning whole genomes may one day be useful for clinical diagnostics.



Children with autism (red bars) were significantly more likely to have three or more genetic variations than their unaffected siblings (blue bars).

..or here: **Autistic children have > 3 mutations** if compared to unaffected siblings **...!!??!!**

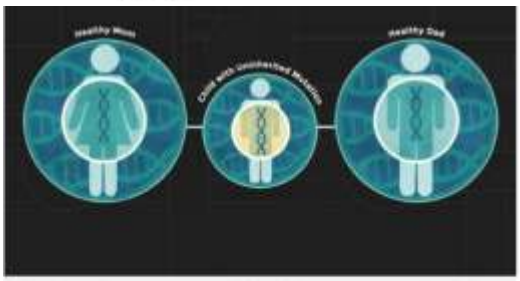
Tychele N. Turner, Bradley P. Coe, Diane E. Dickel, Kendra Hoekzema, Bradley J. Nelson, Michael C. Zody, Zev N. Kronenberg, Fereydoun Hormozdiari, Archana Raja, Len A. Pennacchio, Robert B. Darnell, Evan E. Eichler. **Genomic Patterns of De Novo Mutation in Simplex Autism**. *Cell*, 2017; DOI: 10.1016/j.cell.2017.08.047

Autism genetics study calls attention to motor skills, general cognitive impairment

Date: February 7, 2018

Source: Cold Spring Harbor Laboratory

Summary: A new study of the genetic factors involved in the causation of autism spectrum disorders (ASD) draws fresh attention to the impact these illnesses have on motor skills, and more broadly on cognitive function. Careful inference from the data suggests to researchers that the genetic factors causing ASD broadly diminish the brain's cognitive functions.



Mutations that appear in a child which are not present in either parent -- called de novo mutations -- can be important in autism. Severe, gene-disrupting de novo mutations are thought to be capable of causing the disorder in certain instances. New research shows that diminished motor skills, like low non-verbal IQ, correlate with the severity of de novo mutations. More broadly the study calls attention to role played by genetics in di-

…or in this case: **new mutations disturbing motor functions** could be important in ***autism*** **...!!??!!**

Andreas Buja, Natalia Volfovsky, Abba M. Krieger, Catherine Lord, Alex E. Lash, Michael Wigler, Ivan Iossifov. **Damaging de novo mutations diminish motor skills in children on the autism spectrum**. *Proceedings of the National Academy of Sciences*, 2018; 201715427 DOI: 10.1073/pnas.1715427115

JAMA Psychiatry | Original Investigation

Association of Genetic and Environmental Factors With Autism in a 5-Country Cohort

Dan Bai, MSc; Benjamin Hon Kei Yip, PhD; Gayle C. Windham, PhD, MSPH; Andre Sourander, PhD; Richard Francis, PhD; Rinat Yoffe, MPH; Emma Glasson, PhD; Behrang Mahjani, PhD; Auli Suominen, MSc; Helen Leonard, MBChB, MPH; Mika Gissler, PhD; Joseph D. Buxbaum, PhD; Kingsley Wong, PhD; Diana Schendel, PhD; Arad Kodesh, MD; Michaeline Bresnahan, PhD, MPH; Stephen Z. Levine, PhD; Erik T. Parner, PhD; Stefan N. Hansen, PhD; Christina Hultman, PhD; Abraham Reichenberg, PhD; Sven Sandin, PhD

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2019.1411
Published online July 17, 2019.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sven Sandin, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 6, SE-17177 Stockholm, Sweden (sven.sandin@ki.se).

IMPORTANCE The origins and development of autism spectrum disorder (ASD) remain unresolved. No individual-level study has provided estimates of additive genetic, maternal, and environmental effects in ASD across several countries.

OBJECTIVE To estimate the additive genetic, maternal, and environmental effects in ASD.

DESIGN, SETTING, AND PARTICIPANTS Population-based, multinational cohort study including full birth cohorts of children from Denmark, Finland, Sweden, Israel, and Western Australia born between January 1, 1998, and December 31, 2011, and followed up to age 16 years. Data were analyzed from September 23, 2016 through February 4, 2018.

MAIN OUTCOMES AND MEASURES Across 5 countries, models were fitted to estimate variance components describing the total variance in risk for ASD occurrence owing to additive genetics, maternal, and shared and nonshared environmental effects.

RESULTS The analytic sample included 2 001 631 individuals, of whom 1 027 546 (51.3%) were male. Among the entire sample, 22 156 were diagnosed with ASD. The median (95% CI) ASD heritability was 80.8% (73.2%-85.5%) for country-specific point estimates, ranging from 50.9% (25.1%-75.6%) (Finland) to 86.8% (69.8%-100.0%) (Israel). For the Nordic countries combined, heritability estimates ranged from 81.2% (73.9%-85.3%) to 82.7% (79.1%-86.0%). Maternal effect was estimated to range from 0.4% to 1.6%. Estimates of genetic, maternal, and environmental effects for autistic disorder were similar with ASD.

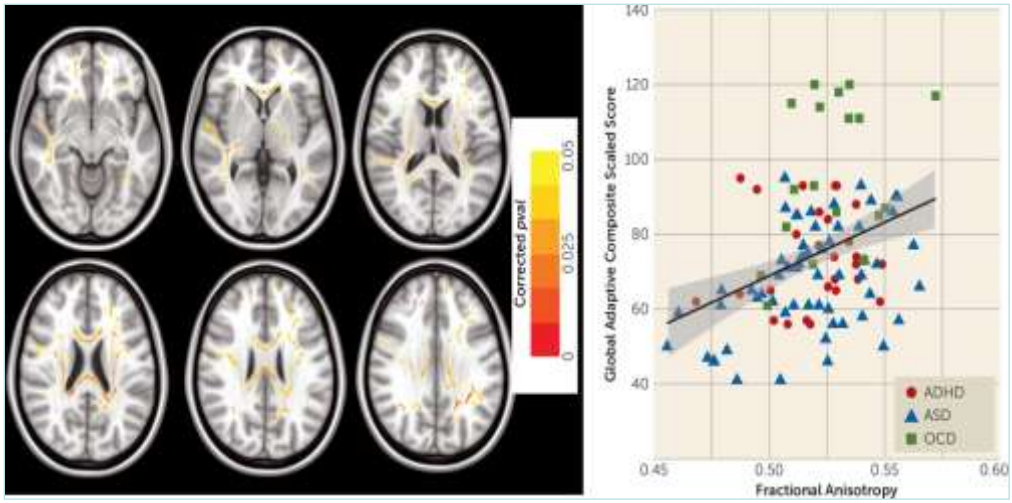
CONCLUSIONS AND RELEVANCE Based on population data from 5 countries, the heritability of ASD was estimated to be approximately 80%, indicating that the variation in ASD occurrence in the population is mostly owing to inherited genetic influences, with no support for contribution from maternal effects. The results suggest possible modest differences in the sources of ASD risk between countries.

Heritability estimates ranged from **81.2%**(73.9%-85.3%) to 82.7% (79.1%- 86.0%). ***Maternal effect*** was estimated to range from ***0.4% to 1.6%.***

Autism, ADHD and **OCD** have **common symptoms** and **are linked by some of the same genes**.

Yet they have always been considered as separate disorders

a continuum…



Children with autism and ADHD showed more severe impairments affecting more of the brain's white matter than those with OCD. This finding may reflect the fact that both autism and ADHD typically have an onset at a much younger age than OCD, and at a time when a number of different white matter tracts are going through rapid development.

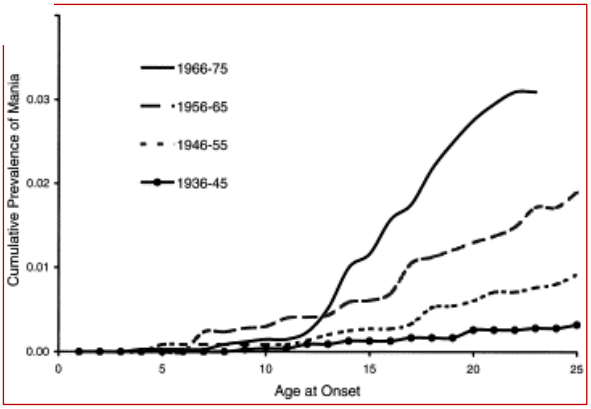
Biological Psychiatry
Volume 49, Issue 12, 15 June 2001, Pages 1002-1014

The unmet needs in diagnosis and treatment of mood disorders in children and adolescents

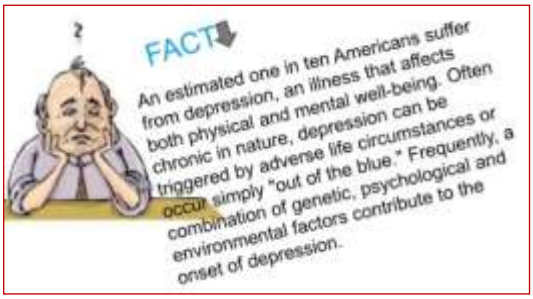
Mood disorders in children and adolescents: an epidemiologic perspective

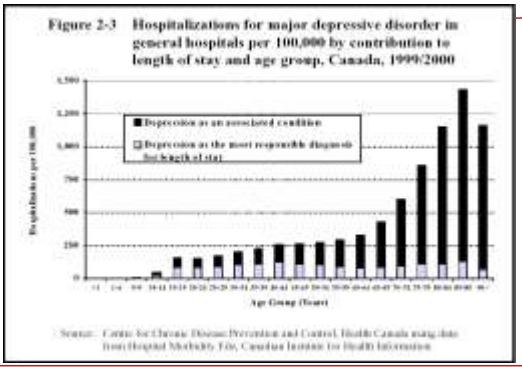
Ronald C Kessler [a,*], Shelli Avenevoli [b], Kathleen Ries Merikangas [b]

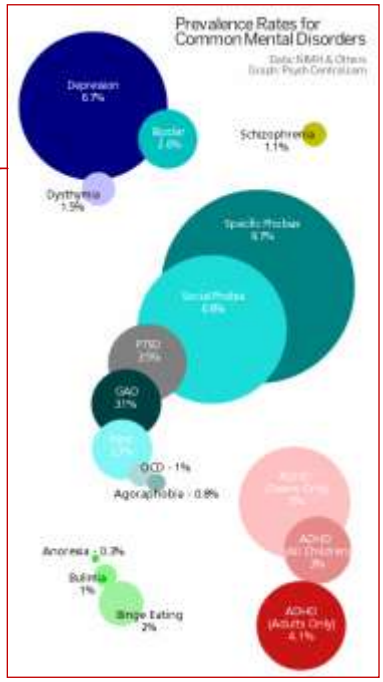
Adolescence is a time of increasing vulnerability for severe mental health disorders such as depression.
Epidemiological studies show that the **incidence of new cases of depression drastically increases with puberty..** Importantly, there is growing evidence that **sleep disturbance in adolescence may predict the development of depression**.. In addition to the increase in the prevalence of depression with the transition from childhood to adolescence, **there is also a secular trend of an increasing incidence of depression during adolescence since the 1960s**



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



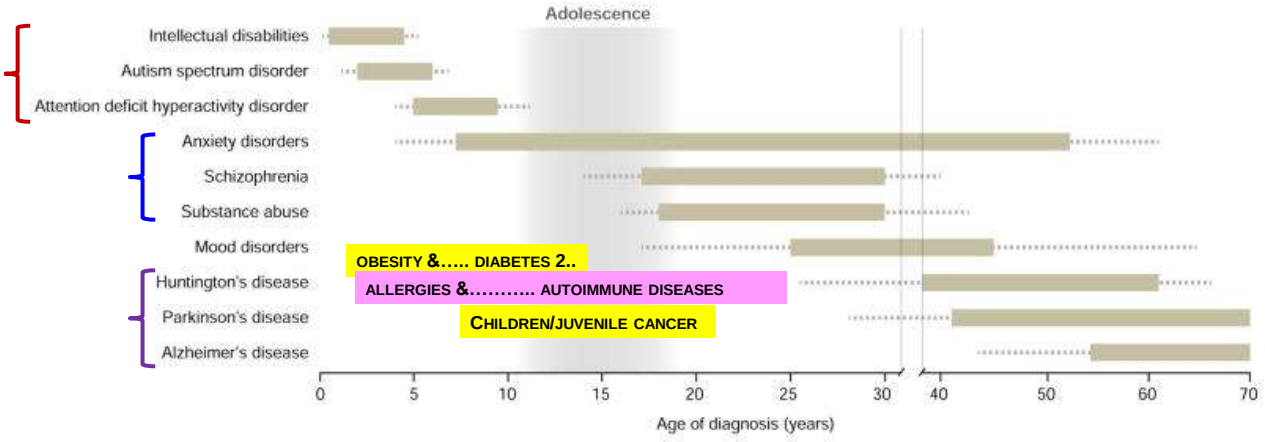




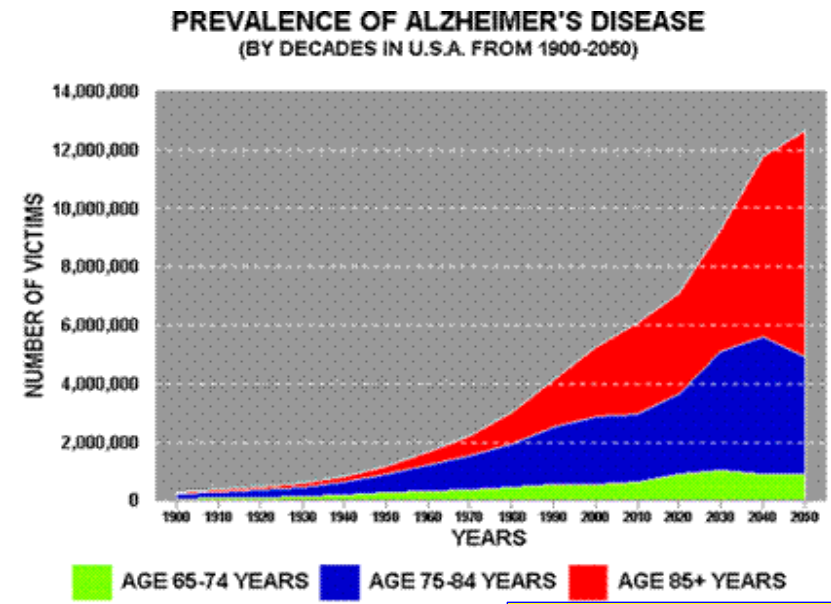
http://psychcentral.com/blog/archives/2009/10/05/prevalence-of-common-mental-disorders/

Psychiatric and Neurological disorders Have Discrete Ages of Onset (but represent a *continuum*)..
the most interesting and mysterious aspect of the DOHaD model is that their origin is during the fetal-embryo period (*fetal programming*) as for all other chronic diseases that are dramatically increasing in the world (Obesity & Diabetes 2.. Allergies & Autoimmune diseases.. Cancer..) ... which means: *EPIGENETICS > GENETICS*

*….it's almost like **a time bomb** ..*



Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. ***The Cellular and Molecular Landscapes of the Developing Human Central Nervous System***. Neuron. 2016;89(2):248–268. doi:10.1016/j.neuron.2015.12.008

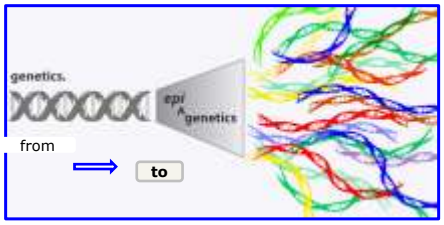


This graph portrays how many Americans over the age
Alzheimer's, and a projection of how many more will b

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

Evolution of DOHaD: the impact of environmental hazards on the origins of current "pandemics"



ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute

ECERI
European Cancer and Environment Research Institute

It has been well known for many years that **prenatal life is not fully protected** in the uterine microenvironment. **But only over the last decade** we have been focusing on mechanisms and modalities of **maternal and foetal exposure** to an impressive range of chemicals (eg .: endocrine disruptors) , physical factors (eg .:EMFs) and biological agents (eg .: viruses) **able to induce potentially adaptive and predictive epigenetic changes in the embryo-fetal genome, thus interfering with the programming of tissues and organs in an often irreversible way.**

www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2015;4(2):e040237
doi: 10.7363/040237
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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***

CHEMICAL FALL OUT

ENDOCRINE DISRUPTORS 1 | 2 HEAVY METALS | 3 ULTRAFINE PARTICLES

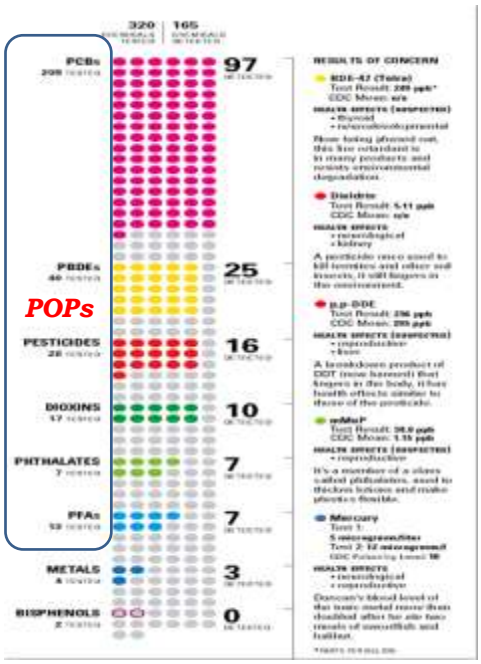
The gift our mothers never wanted to give us

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

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

Monitoring Body-Burdens

> 700 different synthetic chemicals or heavy metals are found in the cord blood and in the placenta.



Giuseppe Giordano

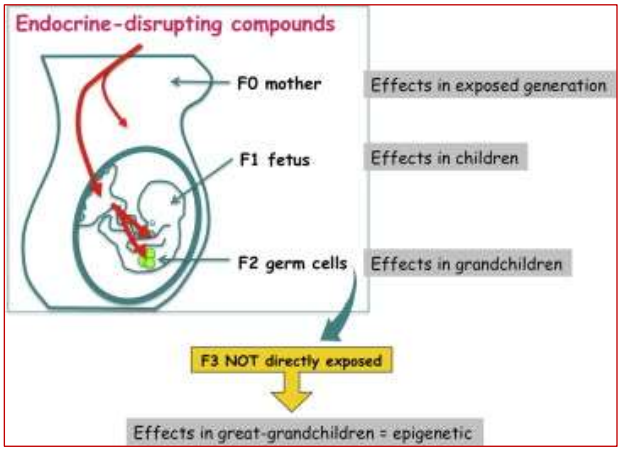
ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute

A significant, dramatic case: for some years I have been invited to Martinique, a small paradise in the Atlantic Ocean, to investigate **the origins of the continuous increase of Cancer** (in Martinique there is **the world record of prostate CA**) and **Autism in children**…

Last year, at the **last congress,** I asked **three questions:**

Question 1

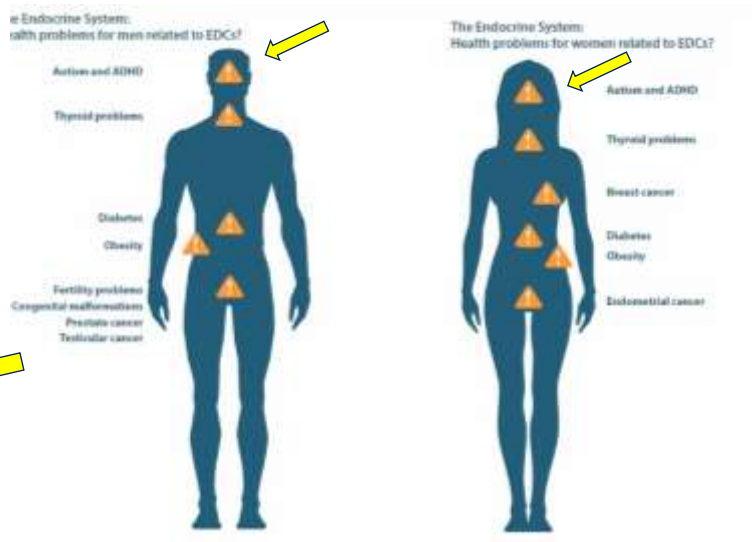
- To what extent the **exposure of moms and fetuses to endocrine disruptors and other epigenotoxic molecules that interfere with *fetal programming*** represents a **serious threat** to the **health of children and *future generations*** ?



https://www.sciencedirect.com/science/article/pii/S0303720711006356

Question 2

What is the role of the ever increasing exposure of moms and fetuses to epi-genotoxic molecules in the genesis of the current ***Epidemiological Transition***: Pandemics of ***obesity*** and ***juvenile diabetes 2*** , continuous increase in ***allergic and autoimmune diseases***, ***neuro-developmental disorders***, ***neurodegenerative diseases*** and ***cancer*** (especially in infants and young people)?

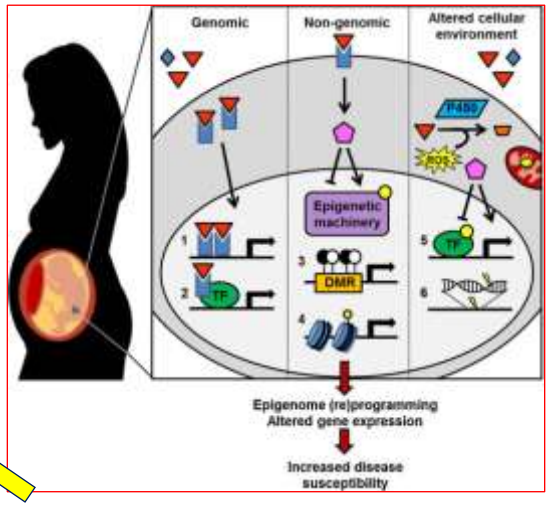


http://www.env-health.org/news/latest-news/article/health-costs-in-the-eu-how-much-is

Question 3

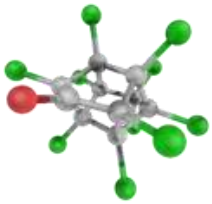
Can we still doubt that **the presence for many years** of **epi-genotoxic molecules** such as ***dioxin*** in Seveso or Taranto and ***chlordecone*** in Martinique and Guadeloupe..

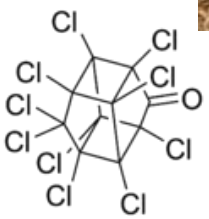
in the **food chains** and **aquifers** of a country and therefore in the organisms of **young people at the age of procreating and in their *gametes*** is a **primary cause of *poor fetal tissue and organ programming*** **and thus of increasing tumors' rates** (especially ***prostate cancer***) and ***neurodevelopmental disorders***?



https://www.sciencedirect.com/science/article/pii/S1084952115001056

- ***Kepone (Chlordecone)*** is an obsolete **insecticide related to Mirex and DDT: Martinique is heavily contaminated, following years of its unrestricted use** in the banana plantations
- It is a known ***Persistent Organic Pollutant (POP),*** classified among the "***dirty dozen***": its use was so disastrous that it is now **banned in the Western World by the Stockholm Convention** on Persistent Organic Pollutants (2011) but only after many millions of kilograms had been produced
- Kepone **bio-accumulates in animals and food-chains by factors up to a million-fold**
- Workers with repeated exposure suffer severe convulsions resulting from degradation of the synaptic junctions.





https://cordis.europa.eu/result/rcn/84240_fr.html

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ACTUALITÉS ET ÉVÈNEMENTS | PROJETS ET RÉSULTATS | MAGAZINES RESEARCH*EU

DE EN ES IT PL

PLUTOCRACY — Résultat en bref

Project ID: QLK4-CT-2000-00279
Financé au titre de: FP5-LIFE QUALITY

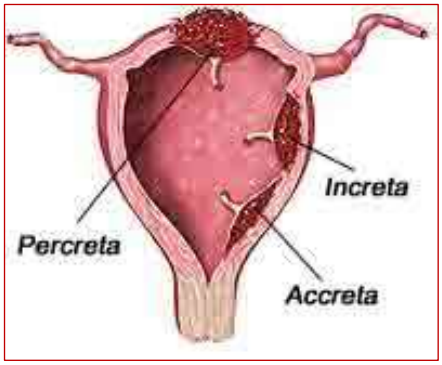
Le placenta transmet les pesticides au fœtus

L'incidence des allergies comme l'asthme a augmenté au cours des dernières décennies. Dans le cadre des efforts menés pour en trouver la raison, les scientifiques ont étudié le transport des composés chimiques à travers le placenta, du milieu environnant vers le fœtus.

This is an **official website of the European Community** that lists many studies related to the problem of **maternal-fetal exposure to pollutants** and **toxics** (in particular to ***pesticides***): scientists found that **all xenobiotics cross the placental barrier by passive diffusion and reach the fetus**..... In the main fetal organs (especially in the blood, spleen, bone marrow, brain and liver) **the concentration of these pesticides is higher than in the corresponding maternal organs**. The implications are of great significance: the **accumulation of these compounds in the fetal tissues will have an impact on the development of the child's immune and nervous systems**

1 In fact **placental alterations** are more and more frequent

The ***placenta accreta*** is an insertion/invasion of/by the placenta **into maternal tissues**: there are three types according to the **insertion depth into the endo/myometrium**
- the proper placenta accreta : the villi penetrate more or less deeply into the myometrium;
- the placenta ***increta***: the villi invade the whole myometrium;
- the placenta ***percreta***: the villi go beyond the myometrium, sometimes **invading neighboring organs (bladder)** ...



... it is, in fact, ***as if the (immunological) mechanisms of maternal-fetal tolerance were weakening !***
... we must not forget that the placenta is largely **an embryo-fetal organ** (that the **embryo** himself produces **to connect** to the mother to get oxygen, nutrition, **information**... certainly not to invade her)

(***evolutionary mechanisms*** that are **millions of years old**)

Choriocarcinoma

2 ... even more common all over the world has become **prematurity (today one child out of 10 is born prematurely** ... which represents **an increase of 30% over the last 35 years** ....) .. **another symptom of growing maternal-fetal intolerance** that should not be underestimated..

L'INSERM today defines different stages of prematurity:
extremely preterm (less than 28 weeks)
very preterm (28 to 32 weeks)
moderate to late preterm (32 to 37 weeks).

Épidémiologie [modifier | modifier le code]

En 2012, plus d'un bébé sur dix naît prématurément dans le monde[5] sans évidence de décroissance avec le temps[6].

Les naissances prématurées concernent 11 à 13 % des naissances aux États-Unis, soit près du double du taux des autres pays industrialisés et une augmentation de 30 % par rapport à 1981[7]. Plus du quart des décès néonataux seraient la conséquence de la prématurité[8].

Les données sont probablement assez solides et permettent d'avoir aujourd'hui un aperçu évolutif concernant les trois dernières décennies en France.

Évolution des taux d'incidence de la prématurité en France

	1972	1981	1988	1995	2003
Très grande prématurité (de 22 à 27 SA)	-	-	-	0,4 %	0,5 %
Grande prématurité (de 28 à 32 SA)	1,3 %	-	1 %	1,2 %	1,3 %
Prématurité (de 33 à 37 SA)	8,2 %	5,7 %	4,8 %	5,9 %	7,2 %

L'incidence est donc en augmentation, ce que confirme les chiffres d'autres pays, en particulier américains[7].

OXFORD ACADEMIC

American Journal of Epidemiology

Chlordecone Exposure, Length of Gestation, and Risk of Preterm Birth

Philippe Kadhel, Christine Monfort, Nathalie Costet, Florence Rouget, Jean-Pierre Thomé, Luc Multigner, Sylvaine Cordier

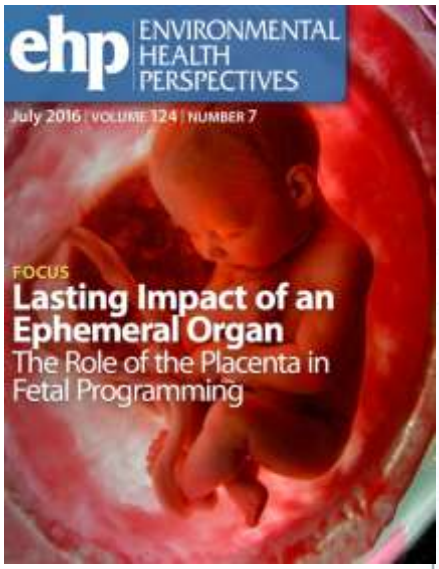
American Journal of Epidemiology, Volume 179, Issue 5, 1 March 2014, Pages 536–544, https://doi.org/10.1093/aje/kwt313

Volume 179, Issue 5

1 March 2014

Chlordecone is an organochlorine pesticide that has been widely used ... in the French West Indies. Data from the ***Timoun Mother-Child Cohort Study*** conducted in Guadeloupe between 2004 and 2007 examined **combinations of chlordecone concentrations in maternal plasma with gestational duration and preterm birth rate in 818 pregnant women** ... 1-log10 **increase in chlordecone concentration was associated with decreased duration of pregnancy** (-0.27 weeks, 95% confidence interval: -0.50, -0.03) and **increased risk premature labor** (60%; 130). ... These results are relevant to public health because of the **prolonged persistence of Chlordecone in the environment and the high rate of preterm birth** in this population.

In such a context, the organ that acquires a **truly extraordinary importance is the PLACENTA**: an organ that has been **poorly studied** until a few years ago and that emerges as a sort of **"*Black Box*" for epigenetically programming fetal tissues** and organs



HHS Public Access

Author manuscript

Am J Obstet Gynecol. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Am J Obstet Gynecol. 2015 October ; 213(4 0): S14–S20. doi:10.1016/j.ajog.2015.08.030.

THE PLACENTA IS THE CENTER OF THE CHRONIC DISEASE UNIVERSE

Kent L. Thornburg[1,2,3] and Nicole Marshall[2,3]

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[3]Department of Obstetrics & Gynecology, Oregon Health & Science University Portland, Oregon 97239

Abstract

Over the past quarter century it has become clear that adult onset chronic diseases like heart disease and type 2 diabetes have their roots in early development. The report by David Barker and colleagues showing an inverse relationship between birthweight and mortality from ischemic heart disease was the first clear-cut demonstration of fetal programming. Because fetal growth depends upon the placental capacity to transport nutrients from maternal blood, it has been a suspected causative agent since the original Barker reports. Epidemiological studies have shown that placental size and shape have powerful associations with offspring disease. More recent studies have shown that maternal phenotypic characteristics, such as body mass index and height, interact with placental size and shape to predict disease with much more precision than does birthweight alone. For example, among people in the Helsinki Birth Cohort, who were born during 1924–1944, the risk for acquiring colorectal cancer increased as the placental surface became longer and more oval. Among people in whom the difference between the length and breadth of the surface exceeded 6 cm, the hazard ratio for the cancer was 2.5 (95% CI 1.2–4.7, p=0.003) compared with those in whom there was no difference. Among Finnish men, the hazard ratio for coronary heart disease was 1.07 (1.02–1.13, P=0.01) per 1% increase in the placental weight/birthweight ratio. Thus, it appears that the ratio of birthweight to placental weight, known as placental efficiency, predicts cardiovascular risk as well. Babies born with placentas at the extremes of efficiency are more vulnerable for adult onset chronic diseases. Recent evidence suggests that placental growth patterns are sex specific. Boys' placentas are, in general, more efficient than those made by girls. Another recent discovery is that the size, shape and efficiencies of the placenta can change over years of time with very narrow confidence limits. This suggests that the growth of the placenta within a population of women is strongly affected by their nutritional environment. Even though it

PROGRAMMA CCM 2017– PROGETTI ESECUTIVI IN ORDINE DECRESCENTE DI PUNTEGGIO DI VALUTAZIONE				
N.	TITOLO	ENTE PARTNER	ID	IMPORTO
1	URBAN HEALTH: BUONE PRATICHE PER LA VALUTAZIONE DI IMPATTO SULLA SALUTE DEGLI INTERVENTI DI RIQUALIFICAZIONE E RIGENERAZIONE URBANA E AMBIENTALE	LOMBARDIA	4	€ 450.000,00
2	SCEGLIERE LE PRIORITÀ DI SALUTE E SELEZIONARE GLI INTERVENTI EFFICACI PER PREVENIRE IL CARICO DELLE MALATTIE CRONICHE NON TRASMISSIBILI	PIEMONTE	6	€ 449.250,00
3	SVILUPPO E VALIDAZIONE DI UN SISTEMA DI MONITORAGGIO EPIDEMIOLOGICO DELLE DEMENZE BASATO SUI DATI DEI SISTEMI INFORMATIVI SANITARI	CAMPANIA	5	€ 450.000,00
4	AMBIENTE, PROGRAMMAZIONE EPIGENETICA FETALE E PREVENZIONE DELLE PATOLOGIE CRONICHE	SARDEGNA	9	€ 448.000,00

For all these reasons we've got **an important funding from the Italian Ministry of Health** for a major project to study the **placentas (especially from Taranto**, the city with the largest iron and steel plant in Europe):

- ***Mass spectrometry*** (IZS - Bologna)
- ***Immunohistochemistry*** (University of Cagliari)
- ***Epigenetics*** (University of Pisa)
- ***Mitochondria*** (University of Milan)
- ***Metabolomics*** (University of Cagliari)
- ***follow-up* of children at risk by the *Italian Federation of Pediatricians* (*FIMP*): - early diagnosis !! - personalized treatment !!**

But **most importantly**, it is becoming increasingly obvious that **the most serious consequences of the increasing embryo-foetal exposure to toxics will become evident after decades** (and sometimes only in the **following generations**)

Conséquences à long terme

Le tableau ci-dessous offre une vision gl

(reconnaissables dans les premières années de la vie)

Données générales chez les nourrissons de moins de 32 SA et/ou moins de 1 500 g (en %)

	Séquelles majeures	Séquelles mineures	Total
Psychomotrices	17	28	45
Visuelles	2	26	28
Respiratoires	1	26	27
Langage	20	20	40
Auditive	2	4	6

Les données de l'étude épidémiologique française ÉPIPAGE sur les petits âges gestationnels permettent de déceler un lien évident entre la survenue d'un handicap et l'importanc de la prématurité. Près de 40 % des grands prématurés présentent des séquelles - troubles moteurs, sensoriels ou cognitifs - à l'âge de 5 ans, sévères dans 5 % des cas, modérées pour 9 % des enfants, légères pour les autres[22]. Ces données sont cohérentes avec celles issues d'autres études d'autres pays[23].

The Barker Hypothesis
Fetal Origins of Adult Disease

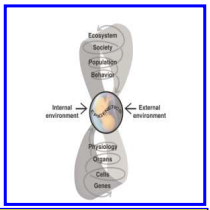
Adverse intrauterine events permanently "program" postnatal structure/function/homeostasis

"Adapted Birth Phenotype"

- Better chance of fetal survival
- Increased risk of adult disease

.. since every intrauterine adverse events might **interfere permanently with the epigenetic programming** of organs and tissues (***DOHaD theory***)

The 7 keywords: from genetics to *epigenetics*



3

Fetal programming

2

Environment

The ***environment*** should be considered as a **continuous flow of information** coming from outside and reaching the epigenome, **causing it to activate and to continuously change** its molecular **three-dimensional structure** (Chromatin)

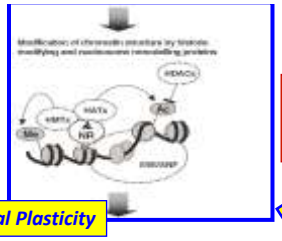
1

From Genetics to Epigenetics

Ontogeny*

4

Developmental Plasticity



Phylogeny*

Evolutionary Medicine

5

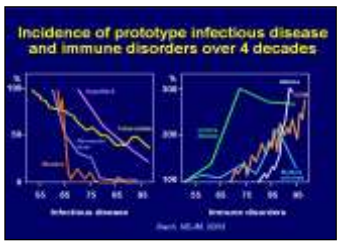
According to the ***Lamarckian paradigm***, the **environment not only selects, but also actively induces the main changes that shape the evolution of living beings** ..

Devo → Evo

Epi-genetic Mismatch DOHA

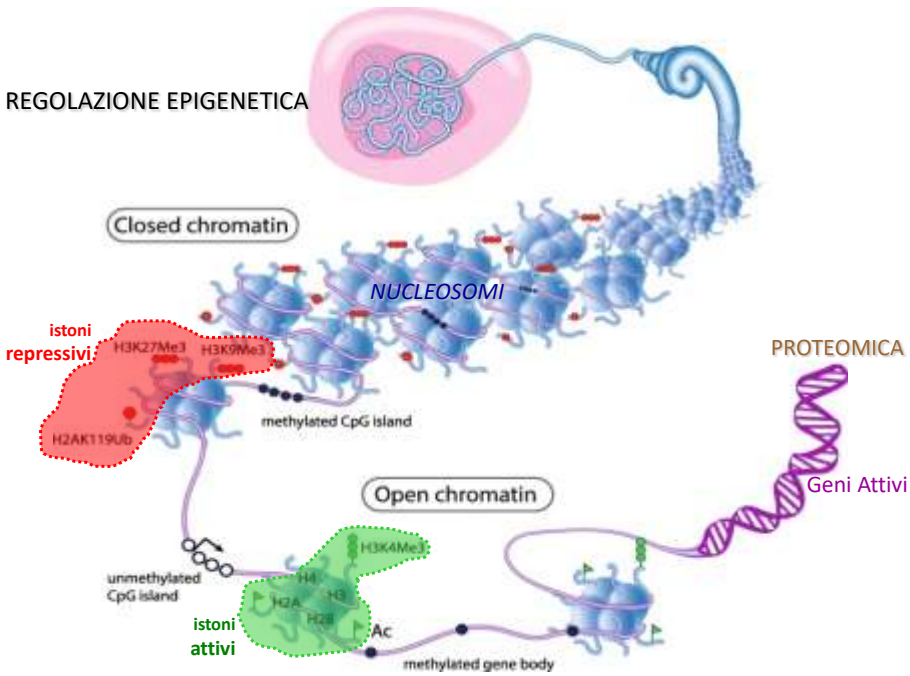
6

7

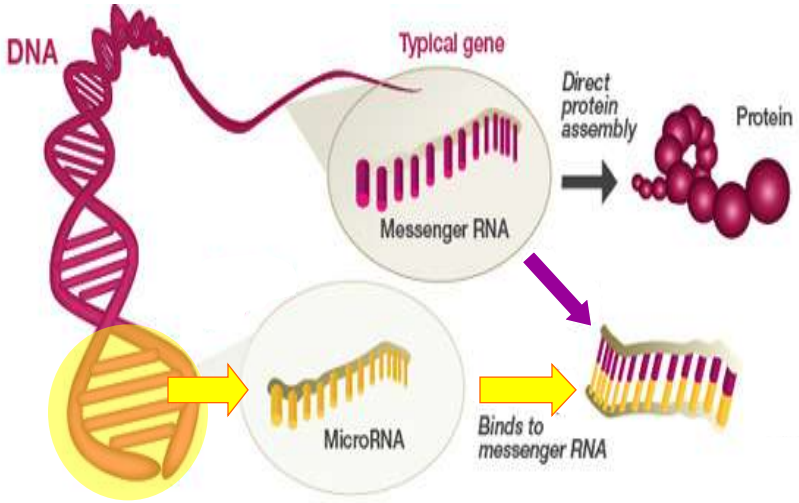


XXI Century Epidemiological Transition

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



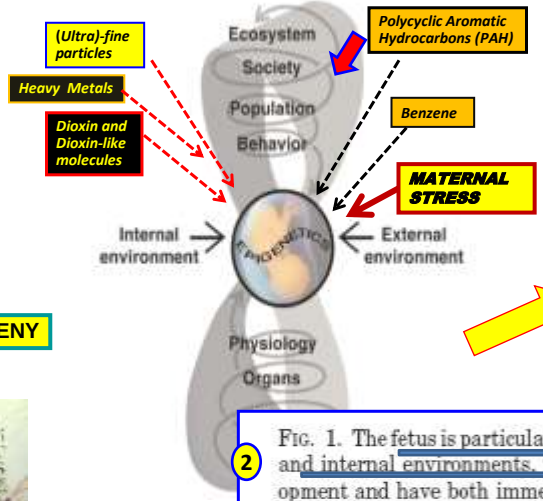
I **microRNA (miRNA) comprendono una specie di RNA corto non codificante che regola l'espressione genica a livello *post-trascrizionale***



1,5-2%

90 %

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..

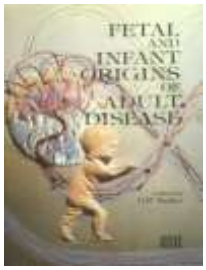


FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular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

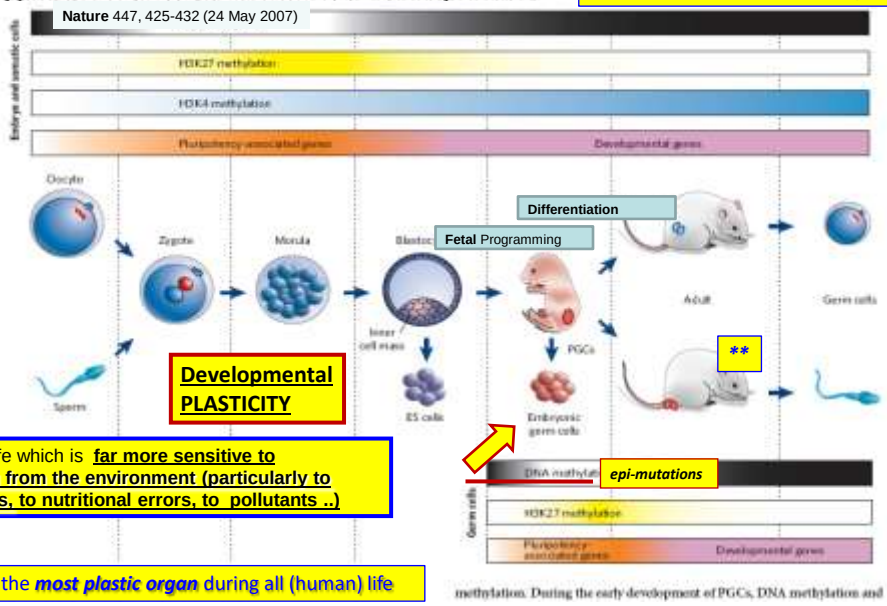
The actual genetic program of a single multicellular organism is the product of nine months of epigenetic adaptive-predictive "formatting" of trillions of cells)

1 ⇩ 2

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) ..**

Stability and flexibility of epigenetic gene regulation in mammalian development

Nature 447, 425-432 (24 May 2007)



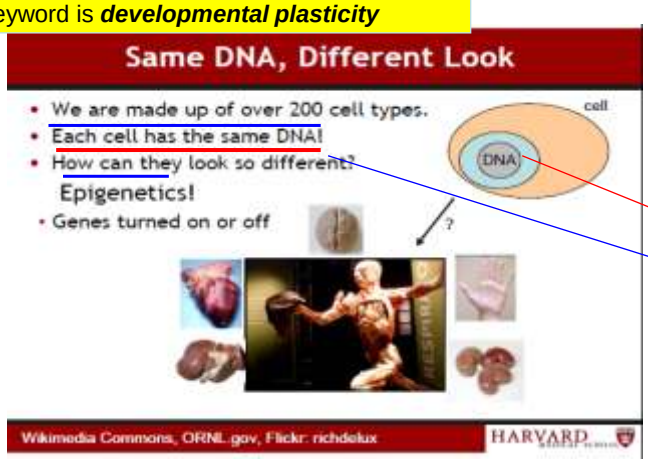
methylation. During the early development of PGCs, DNA methylation and

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

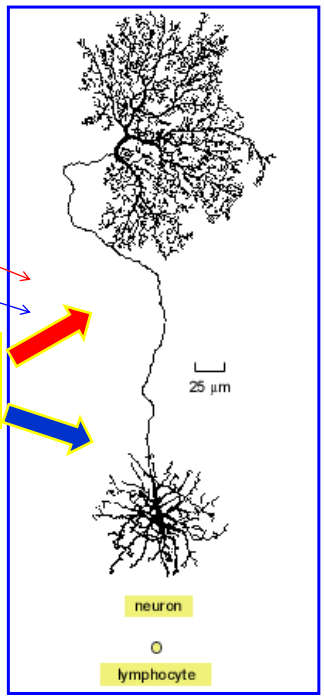
The **fourth** keyword is ***developmental plasticity***



Committed Cells

Neuroblasto

Linfoblasto

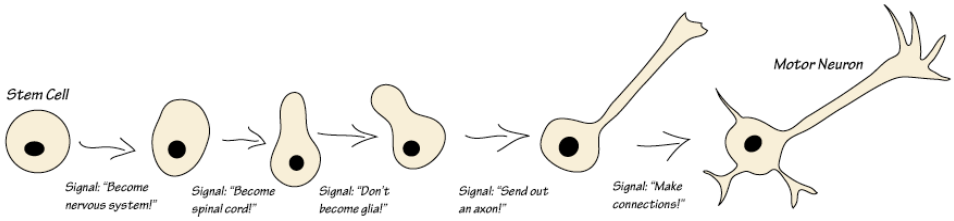


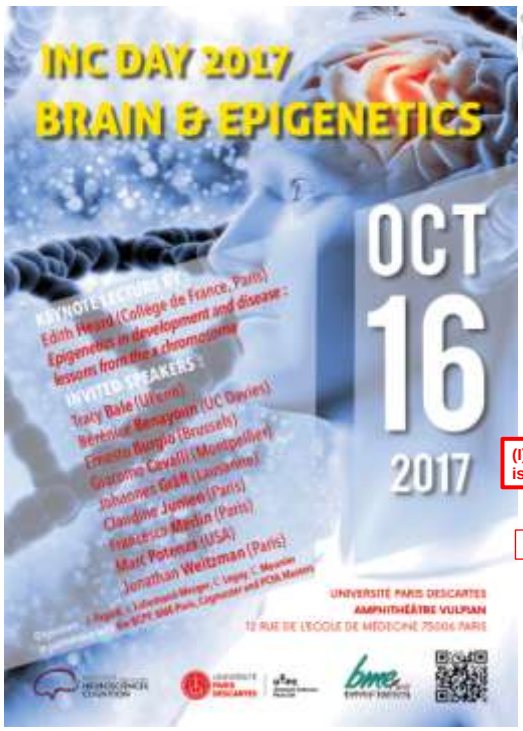
This image clearly shows the **"power" of the epigenome** and the **predominant role of environmental information in the phenotypic shaping of cells, tissues , organisms** .. the **huge phenotypic (morpho- functional) difference** between a *lymphocyte* and a *neuron* **is not due to DNA, which is virtually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

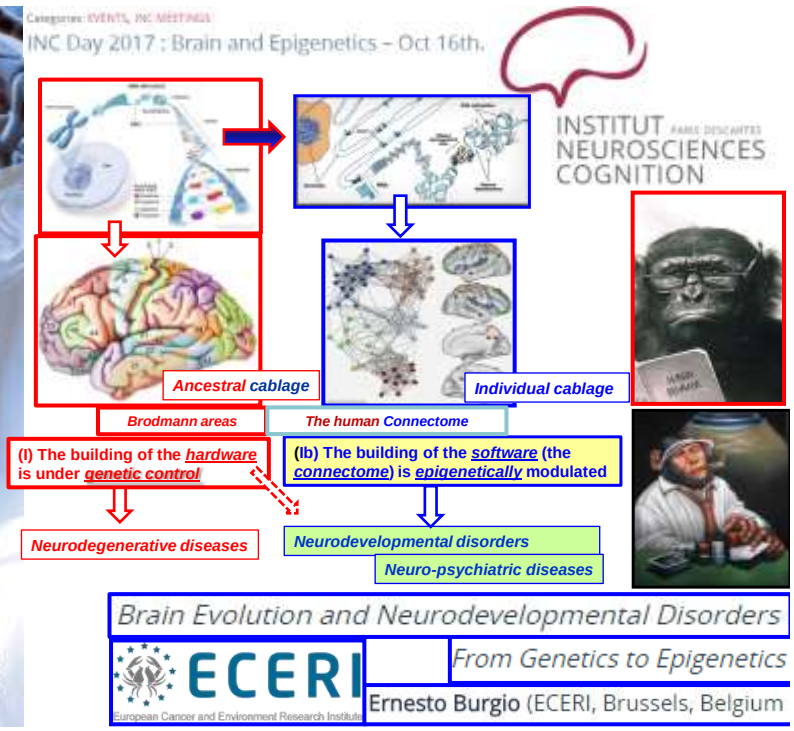
http://learn.genetics.utah.edu/content/epigenetics/epi_learns/

The Epigenome learns from its experiences

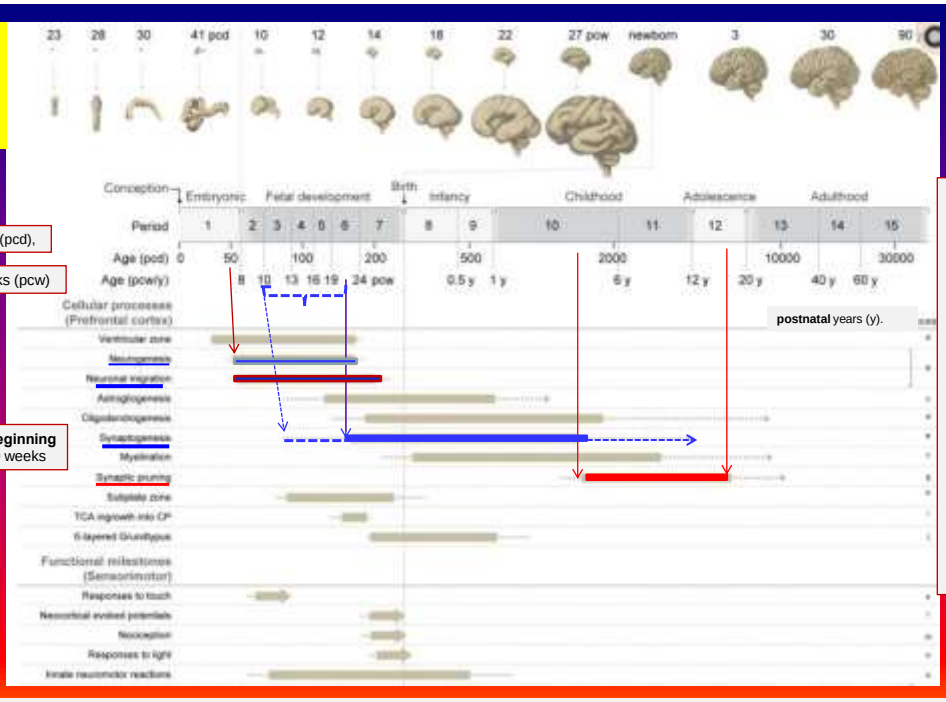
- **Epigenetic tags act as a kind of cellular memory.**
- **A cell's epigenetic profile -- a collection of tags that tell genes whether to be on or off -- is the sum of the signals it has received during its lifetime**







Timeline of Key Human Neurodevelopmental Processes and Functional Milestones **



Post-conceptional days (pcd),

Post-**conceptional** weeks (pcw)

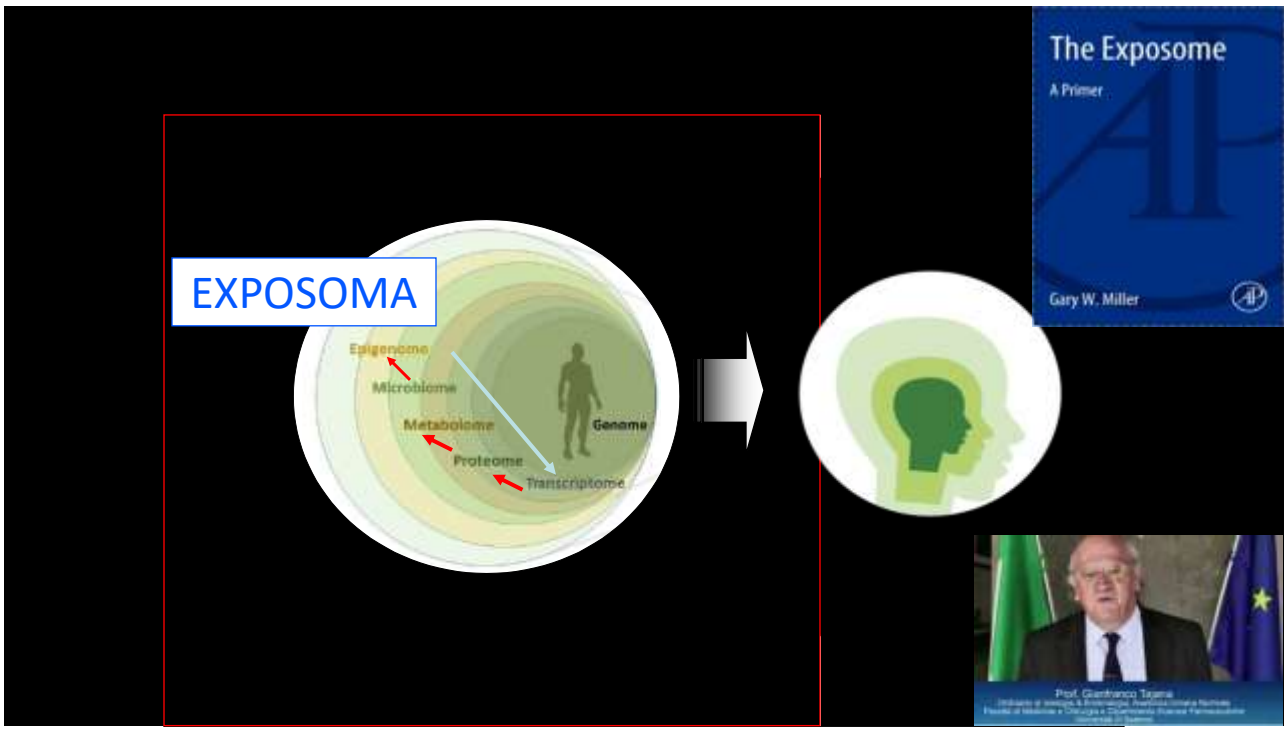
postnatal years (y).

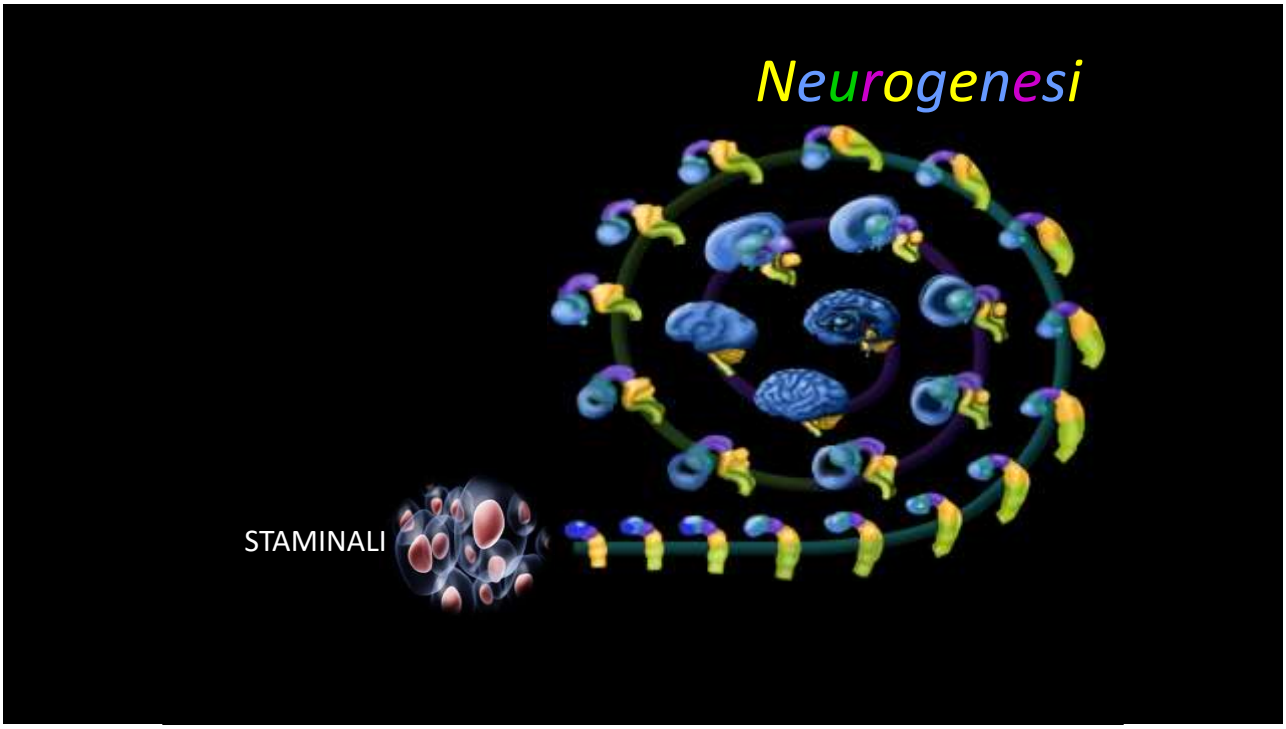
Synaptogenesis' beginning between 10 and 20 weeks

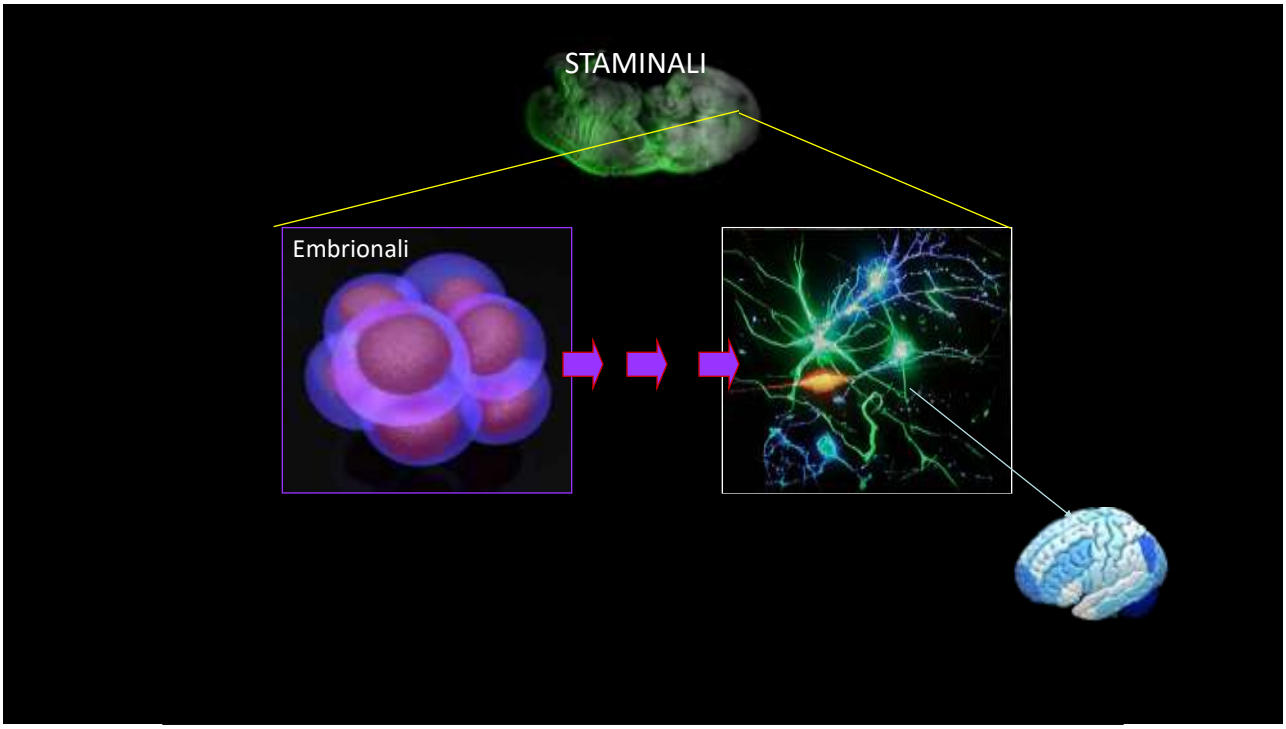
Cfr slide 117 **

.. Most of the *neuronogenesis* of the central nervous system (about 86.1 billion neurons) occurs in 781 days, from 32nd to 813th day from conception [234 prenatal + 547 postnatal days: up to the 18th post-natal month] which means **about 4.6 million neurons generated every hour ..**

Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. ***The Cellular and Molecular Landscapes of the Developing Human Central Nervous System***. Neuron. 2016;89(2):248–268. doi:10.1016/j.neuron.2015.12.008



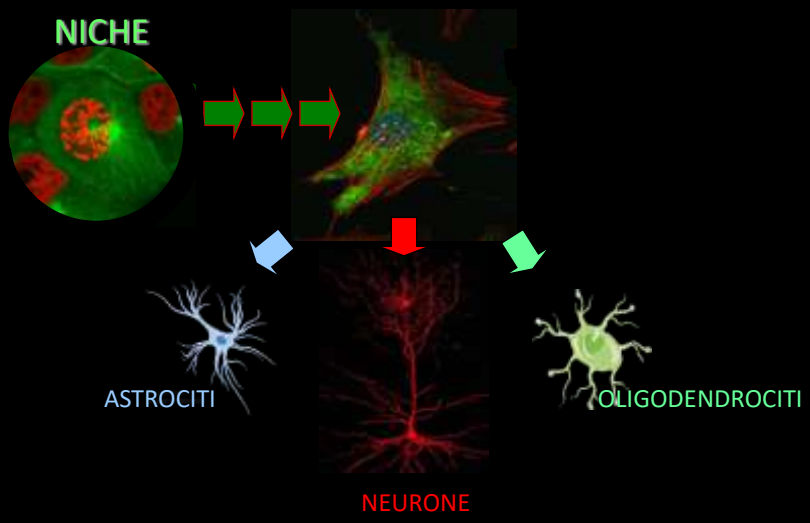

Neurogenesi
STAMINALI


STAMINALI
Embrionali

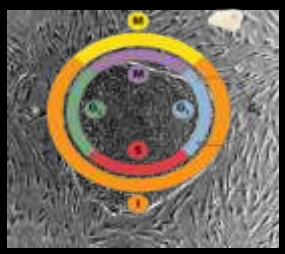
Arch Biochem Biophys. 2013 Jun;534(1-2):71-87.

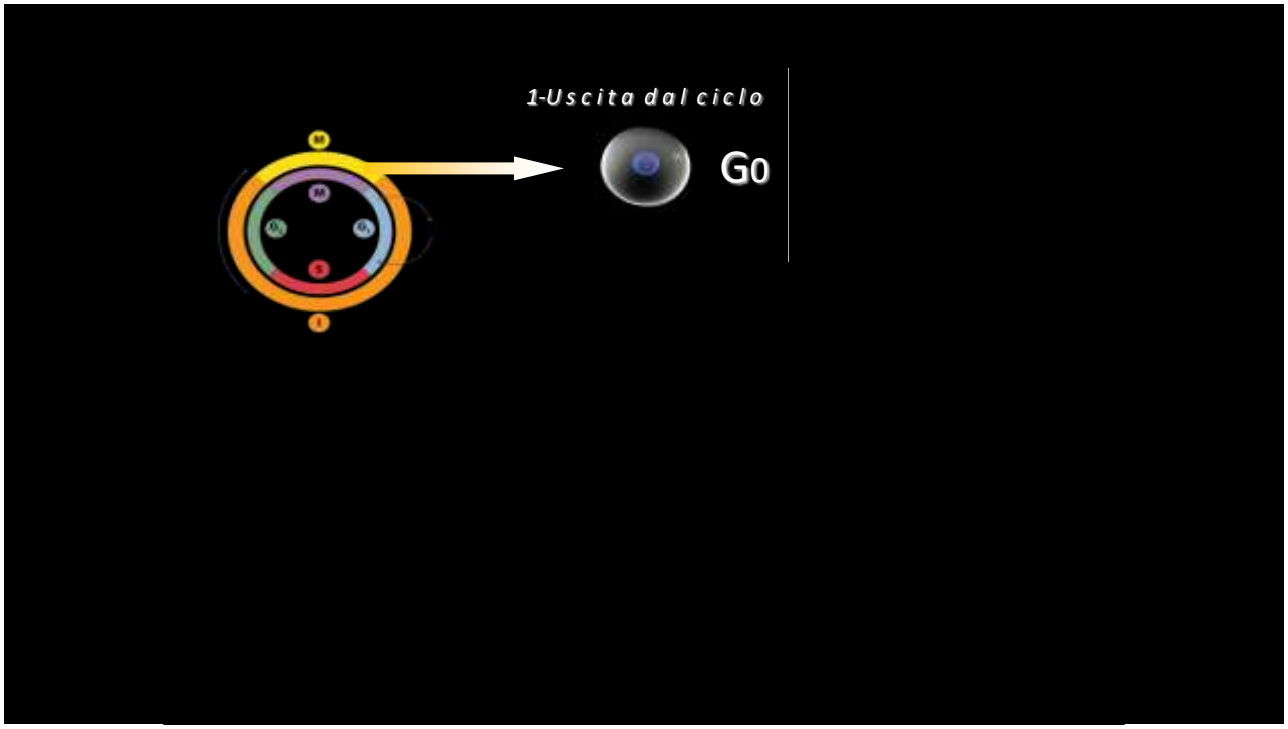
Neural stem cell survival factors.

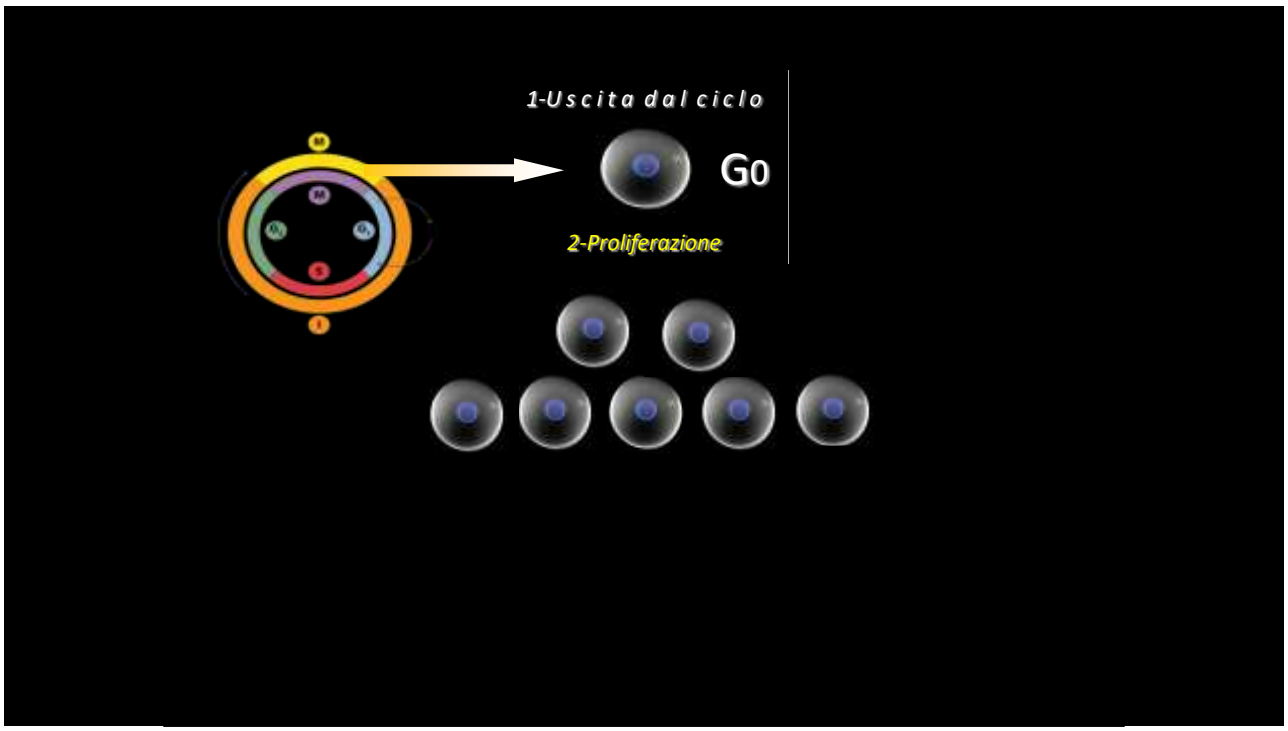
Ramasamy S et al.

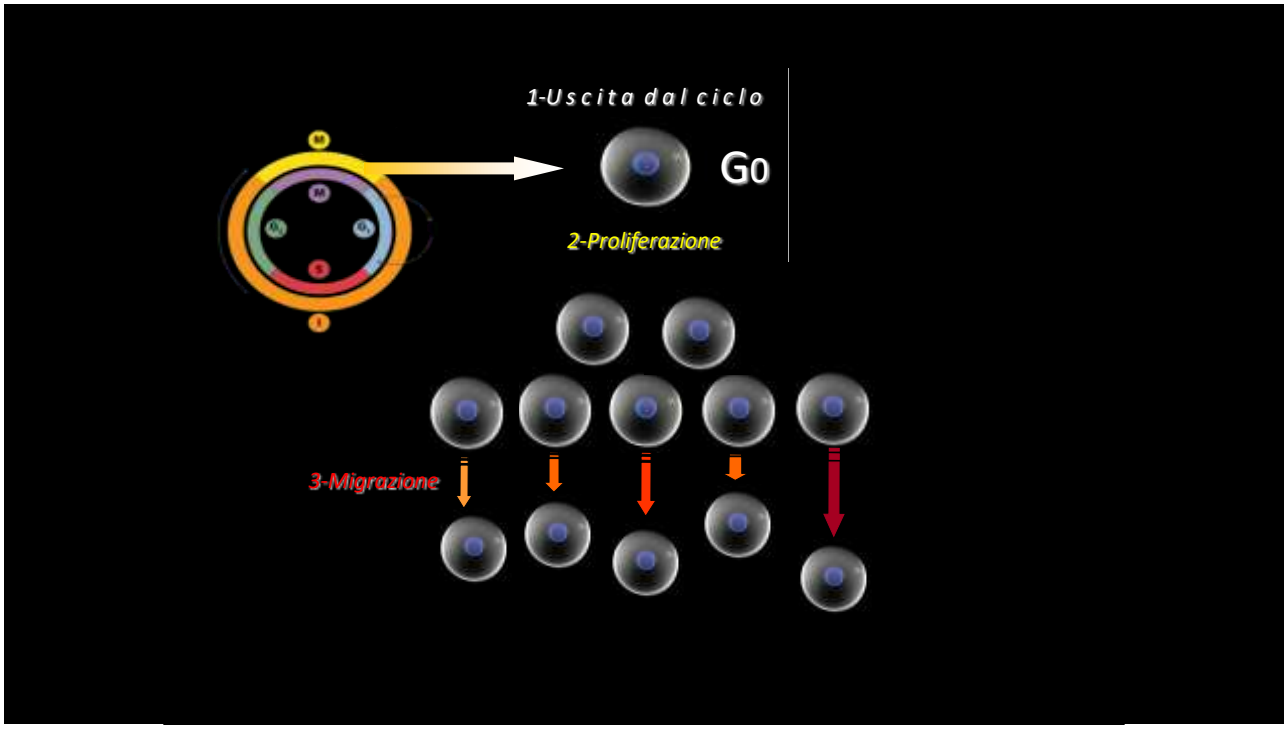


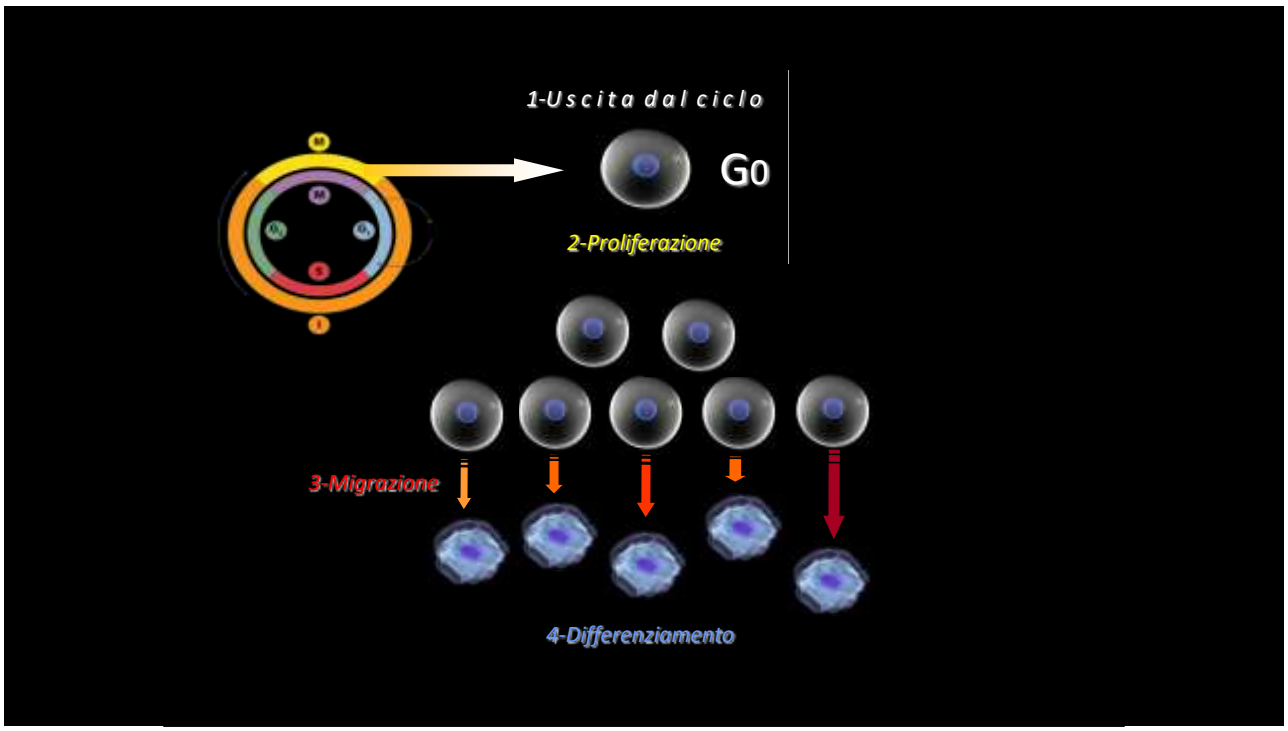
STEM CELL NICHE

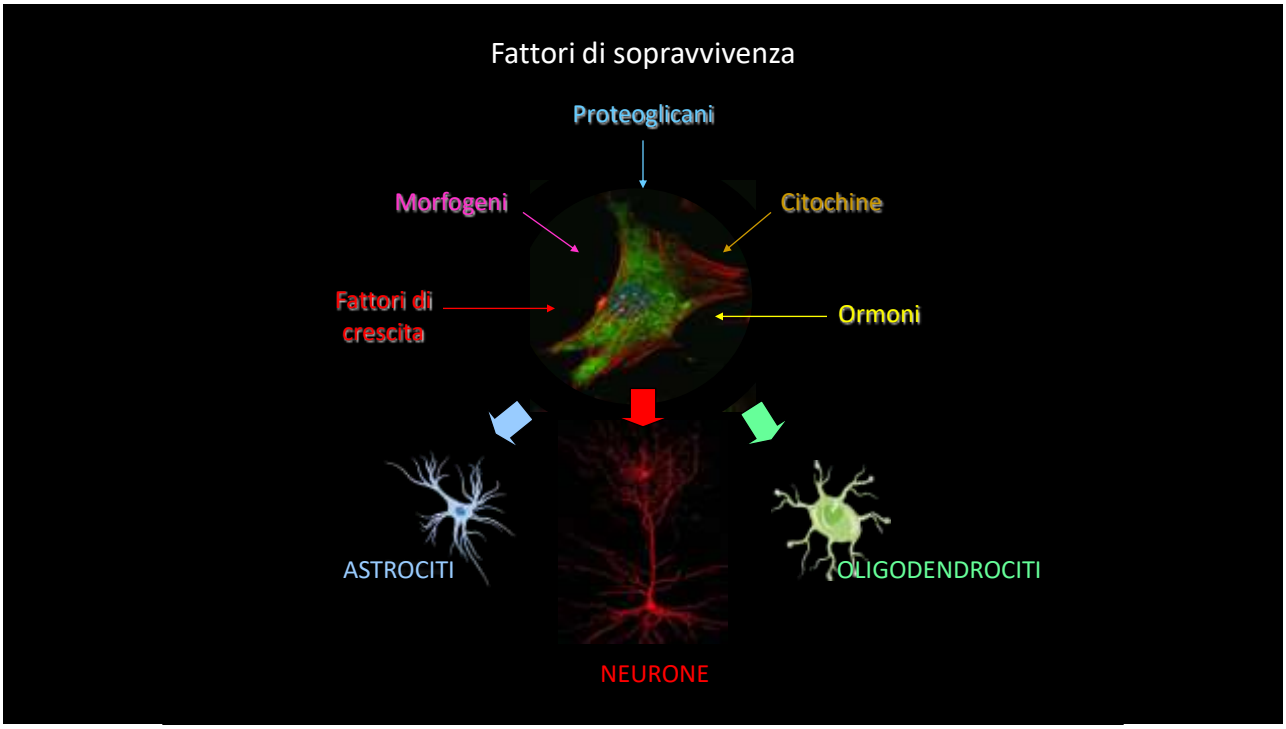


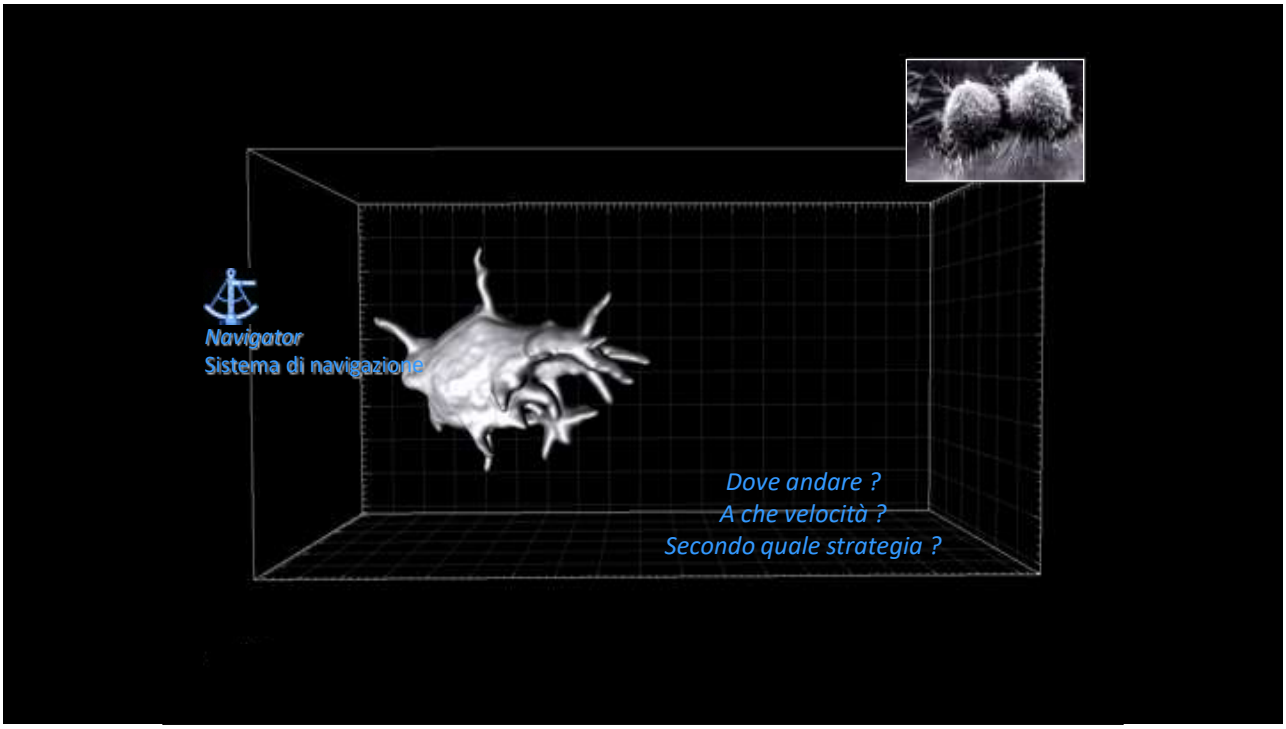

1-Uscita dal ciclo
G0

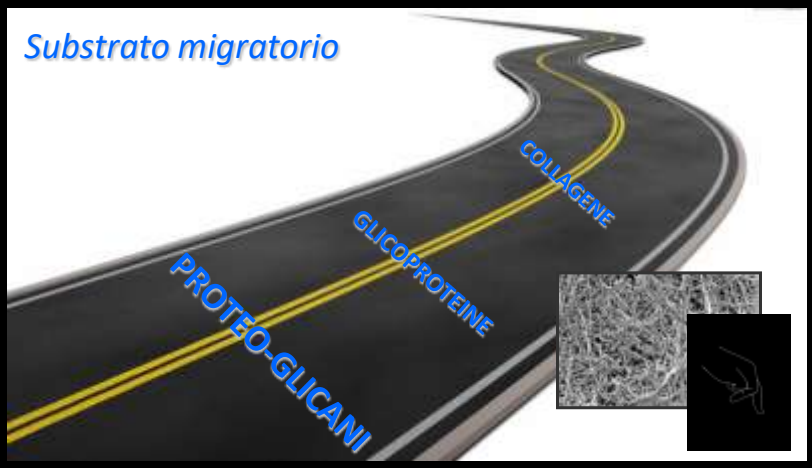

1-Uscita dal ciclo
G0
2-Proliferazione

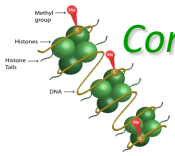

1-Uscita dal ciclo
G0
2-Proliferazione
3-Migrazione


1-Uscita dal ciclo
G0
2-Proliferazione
3-Migrazione
4-Differenziamento

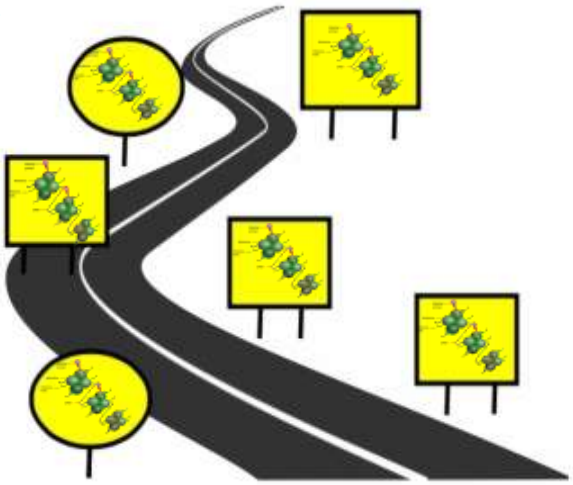

Fattori di sopravvivenza
Proteoglicani
Morfogeni
Citochine
Fattori di crescita
Ormoni
ASTROCITI
OLIGODENDROCITI
NEURONE


Navigator
Sistema di navigazione
Dove andare ?
A che velocità ?
Secondo quale strategia ?





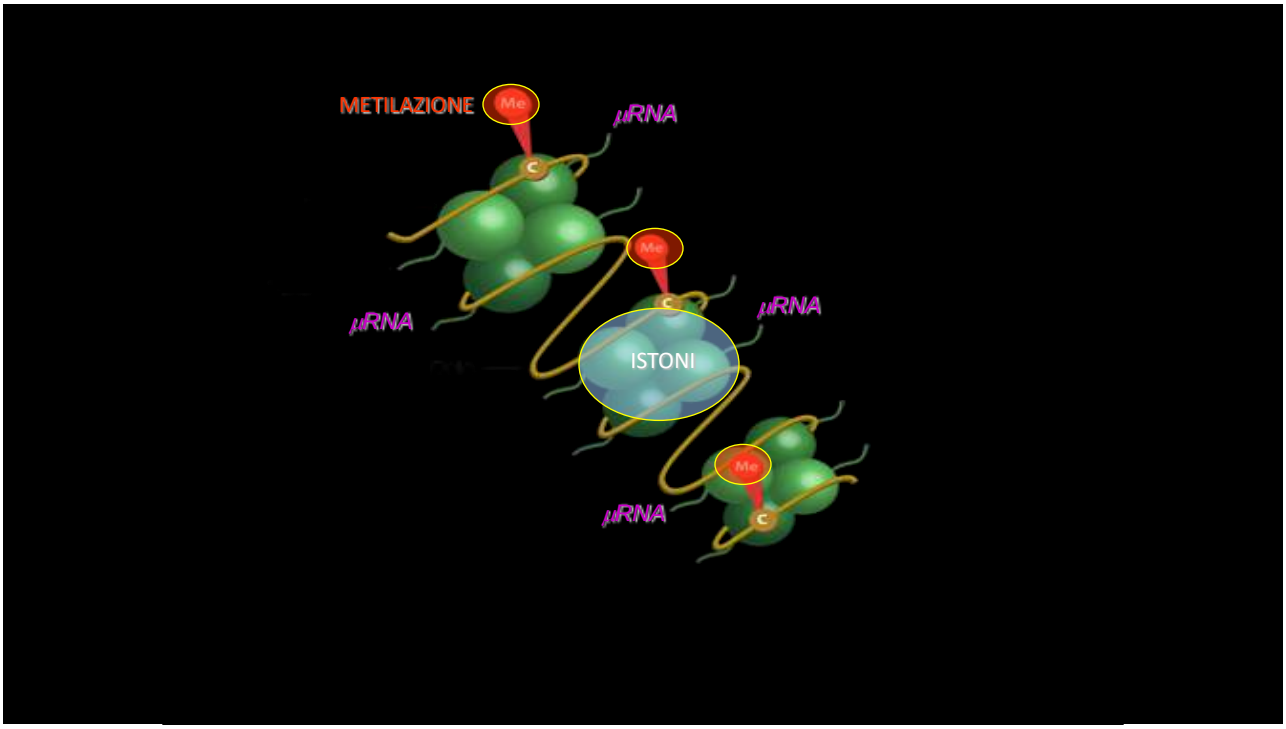
Controlli EPIGENETICI



Neurosci Res. 2014 Sep;86:3-13.

50 years of research on the phenomena and epigenetic mechanism of neurogenesis.

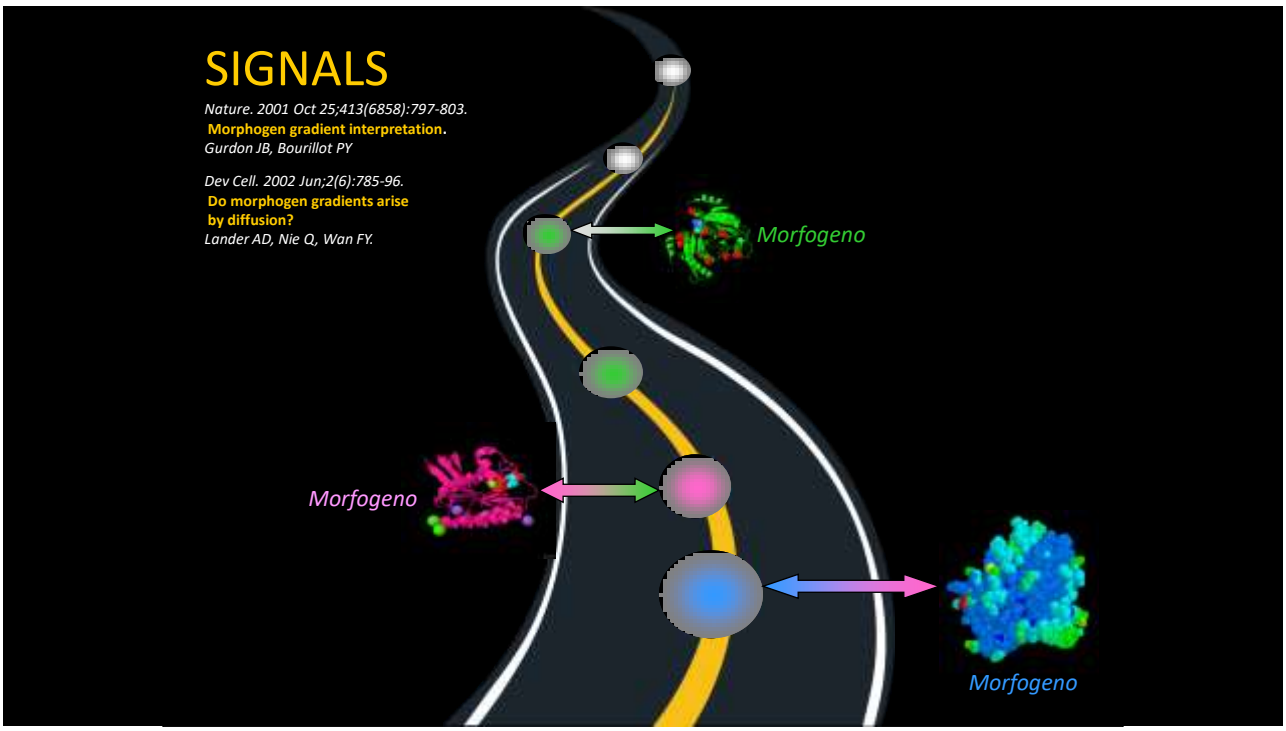
Fujita S. In 1960s,



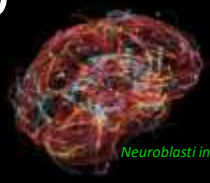
SIGNALS

Nature. 2001 Oct 25;413(6858):797-803.
Morphogen gradient interpretation.
Gurdon JB, Bourillot PY

Dev Cell. 2002 Jun;2(6):785-96.
Do morphogen gradients arise by diffusion?
Lander AD, Nie Q, Wan FY.



10^{18}

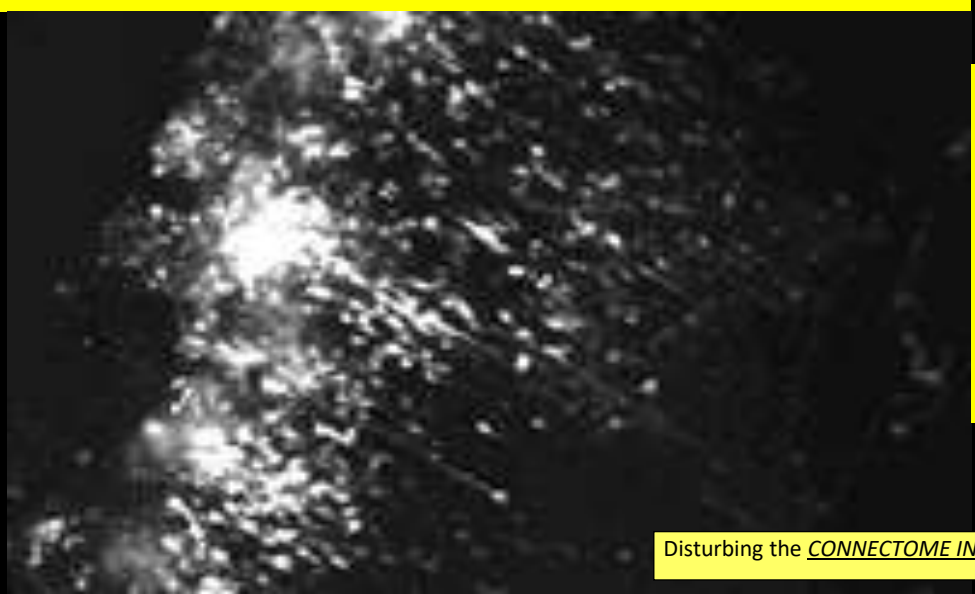


Neuroblasti in migrazione

Un milardo di miliardi

Brain plasticity and modulation of its structure and its functions

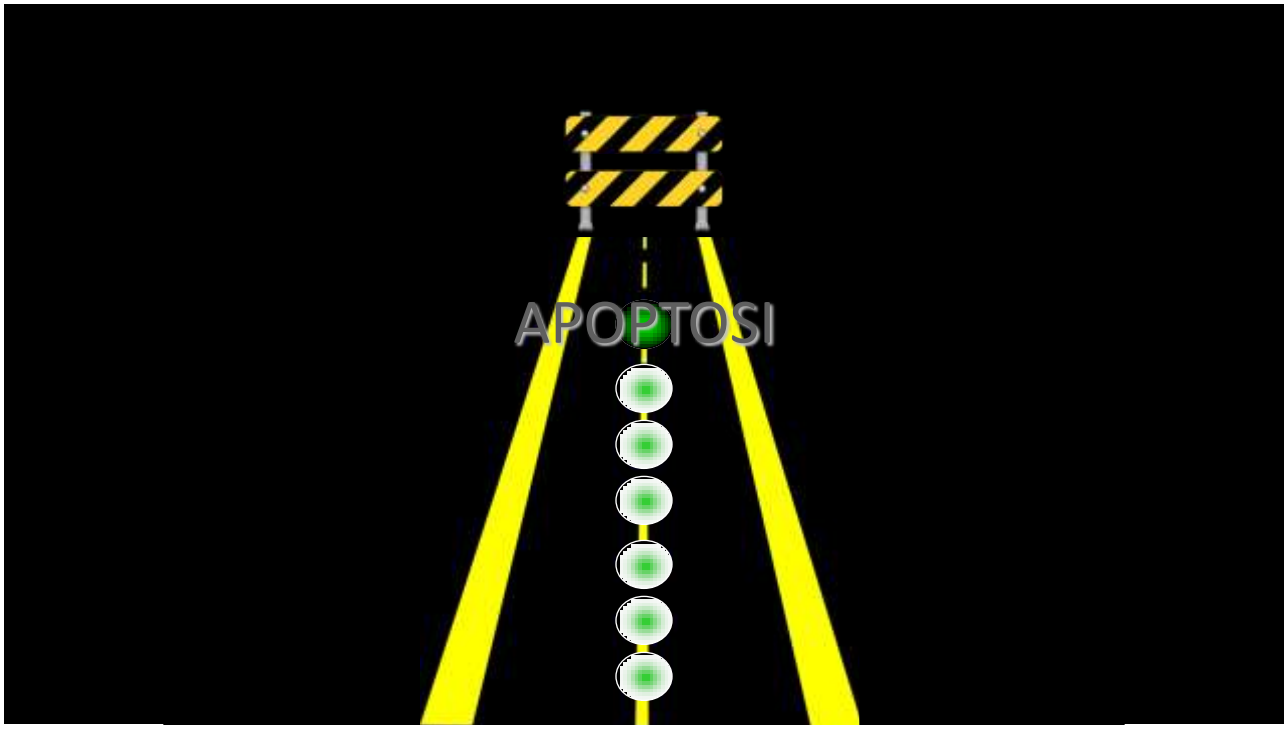
The ***Individual*** wiri



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.



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

The ***Individual*** wirin

Formation of new synapses following stimulation..

Disturbing the *CONNECTOME INSTRUCTION*

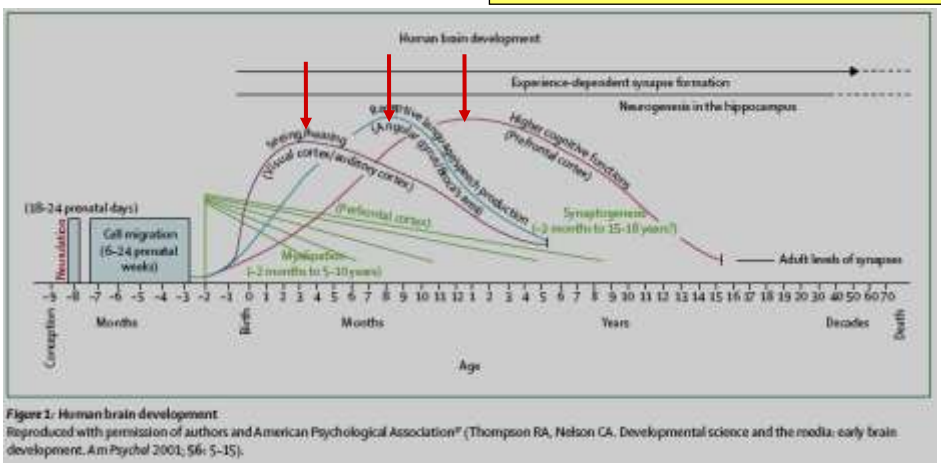
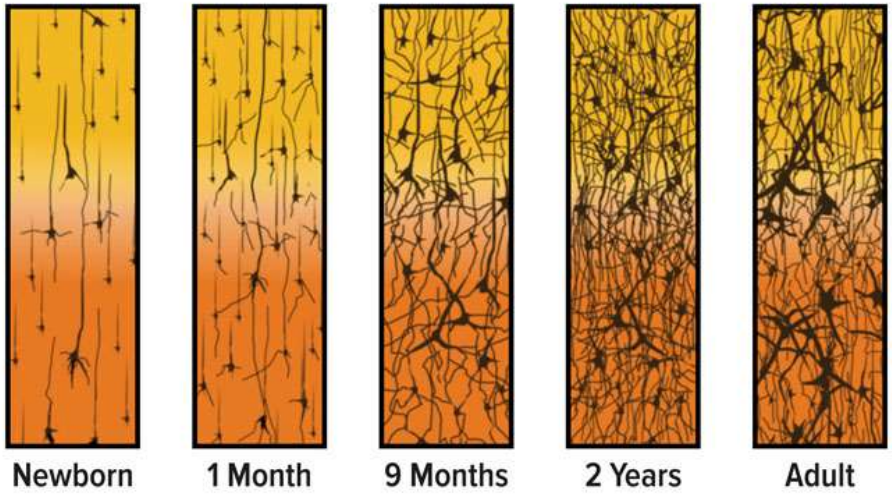
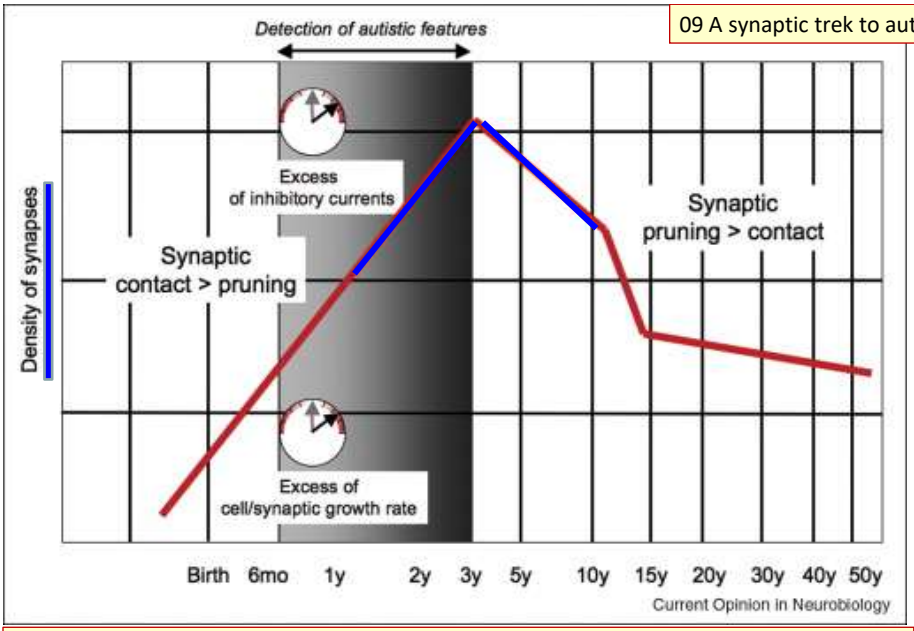


Figure 1: Human brain development
Reproduced with permission of authors and American Psychological Association® (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; 56: 5–15).

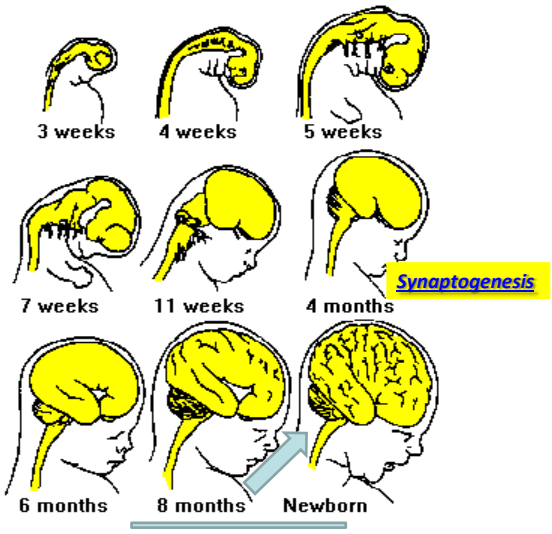
Connessioni interneurali dall'infante all'adulto umano



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.**



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.

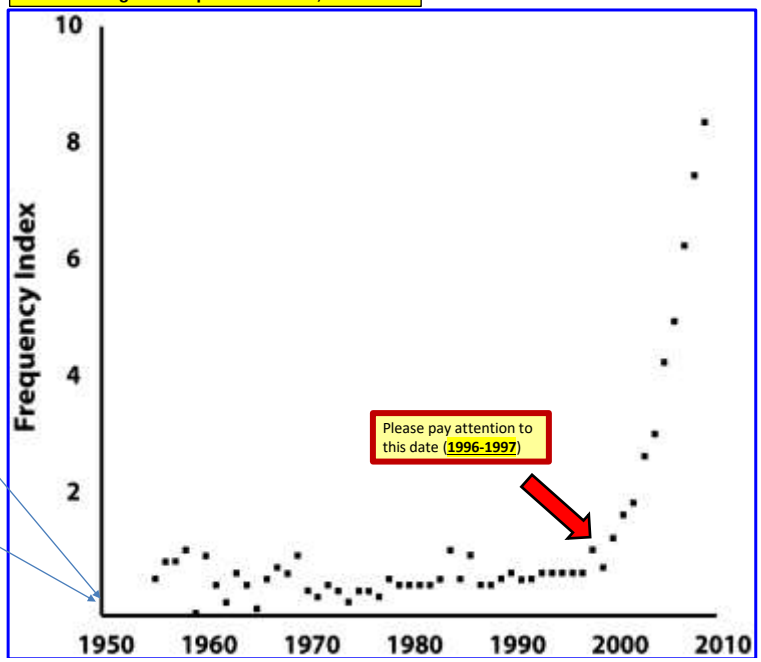
By the age of 2 years old, the brain is about **80% of the adult size**

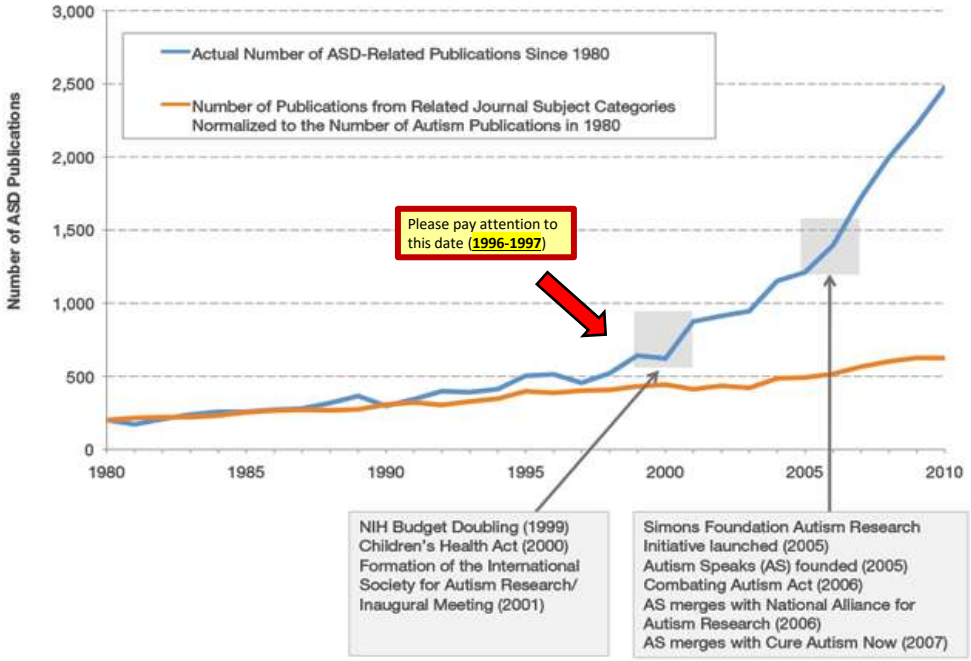
A **stegosaurus dinosaur weighed approximately 1,600 kg but had a brain that weighed only approximately 70 grams (0.07 kg).** Therefore, **the brain was only 0.004% of its total body** weight. In contrast, an adult human weighs approximately 70 kg and has a brain that weighs approximately 1.4 kg. Therefore, **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**

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

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

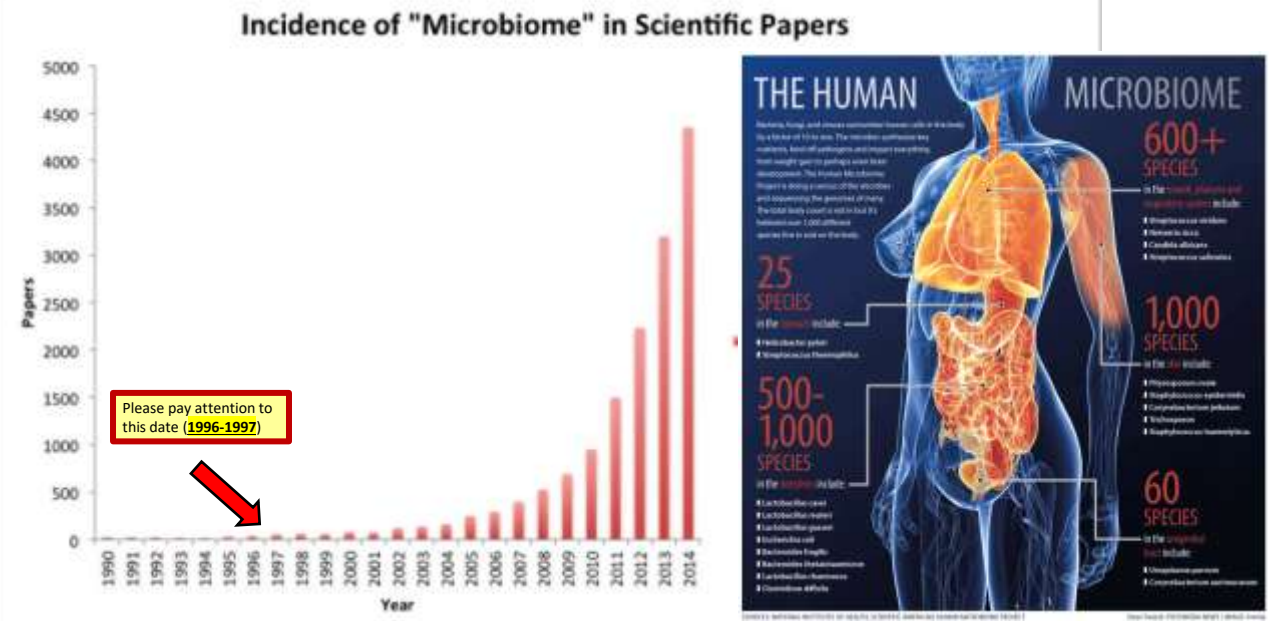
International Journal of Epidemiology



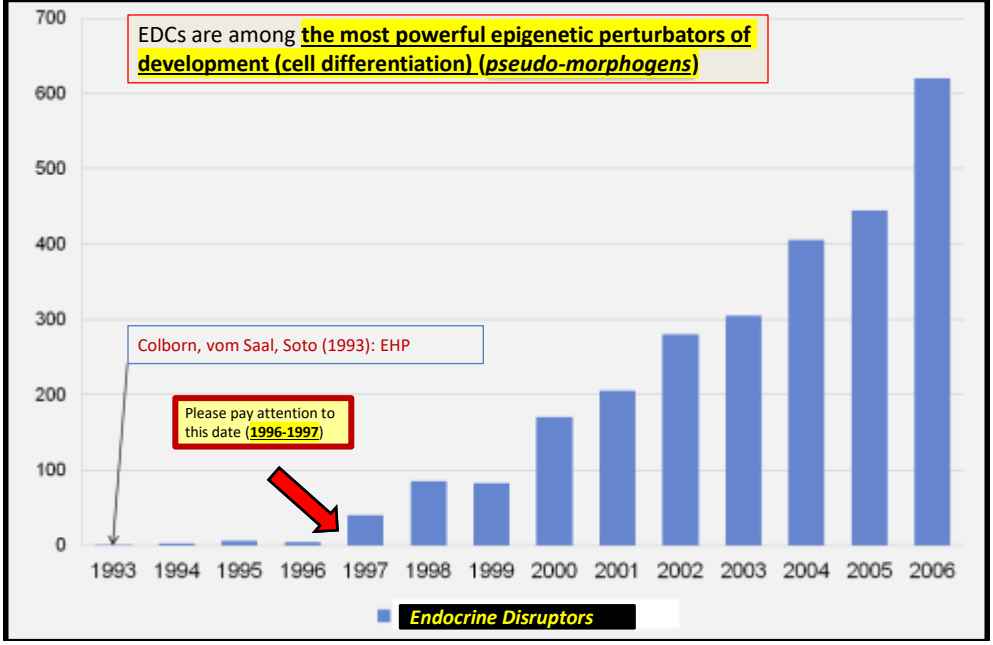


The microbiome is the most powerful "epigenetic internal modulator" of early childhood

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



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



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.**

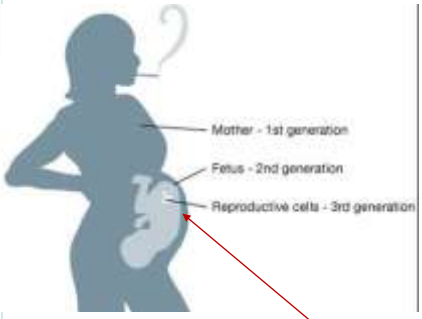
Figure 1 Smoking in mothers alters neurodevelopmental processes in the fetus. Maternal smoking alters the DNA methylation of genes involved in placental and fetal development, leading to neurodevelopmental disorders in the offspring.

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		2 miRNA targets	3 Histone modifying targets	4 DNA methylation targets
• Developmental:	Plunc, Neurofilament, Pale ear [68], *Hoxa1* [87]	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]	H3K9ac [81] H3K27me3 [82] CBP [83]	DNMT, MeCP2 [67]
• 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]			

Phenotypic outcomes in the offspring

Fetal alcohol spectrum disorder (FASD)

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

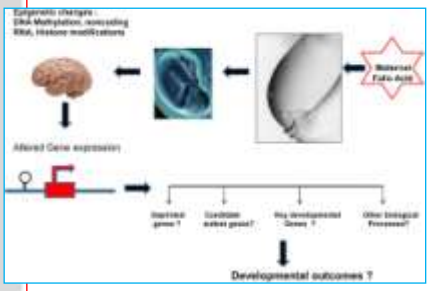
F3 Effect of **maternal dietary deficiency** on fetal development.
The absence of essential dietary supplements in maternal diet during gestation leads to a disruption in metabolic pathways and several epigenetic alterations in the fetus, triggering **abnormal uterine development** and **neurodevelopmental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

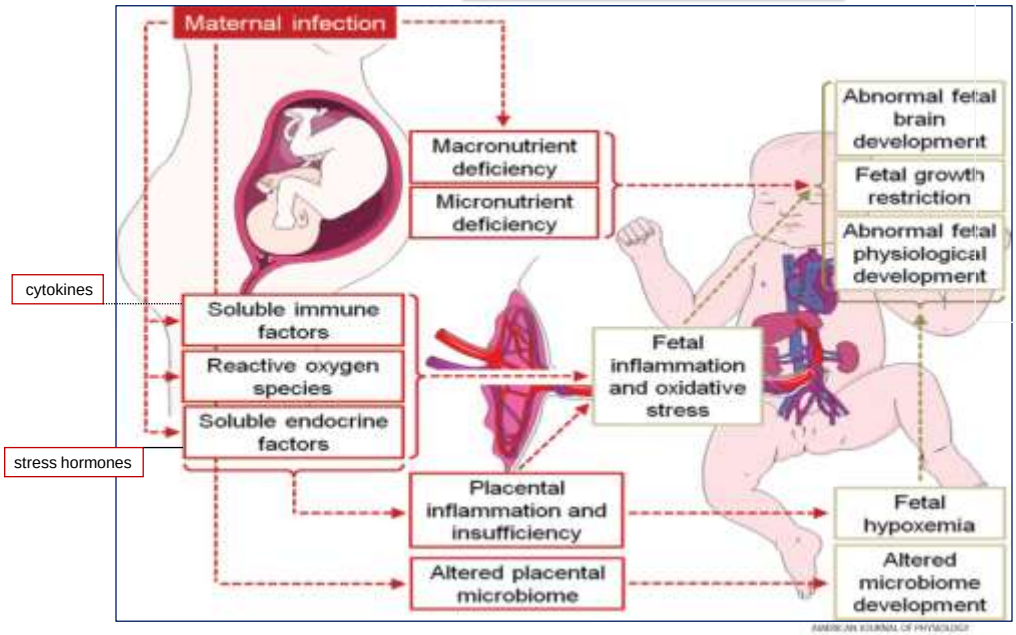
- Gestational Diabetes Mellitus (GDM)
- Maternal Obesity
- Maternal Hypothyroidism

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

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



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

Regulatory, Integrative and Comparative Physiology

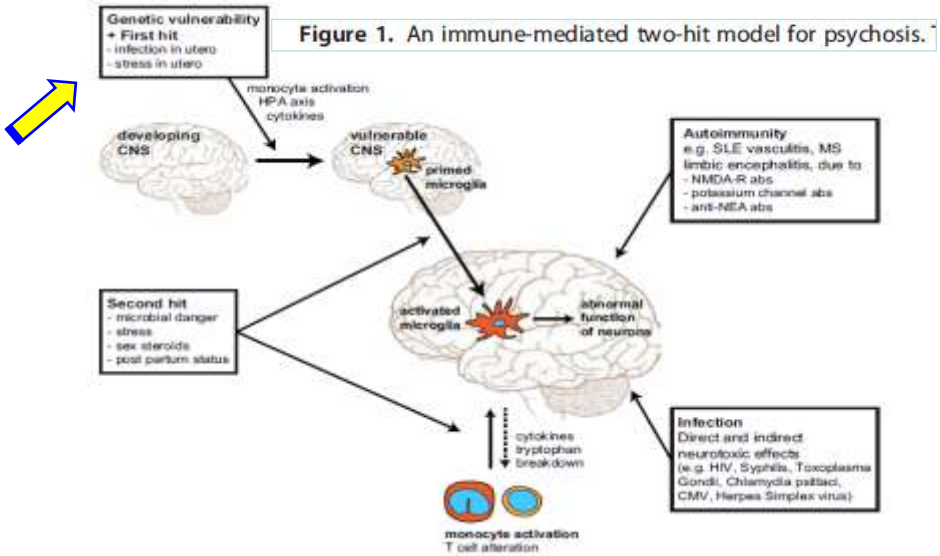
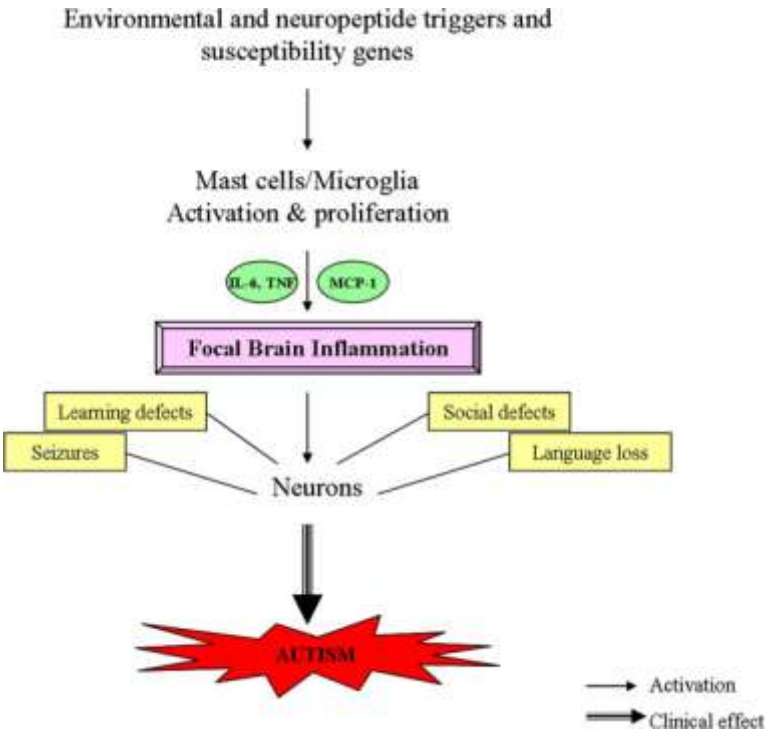


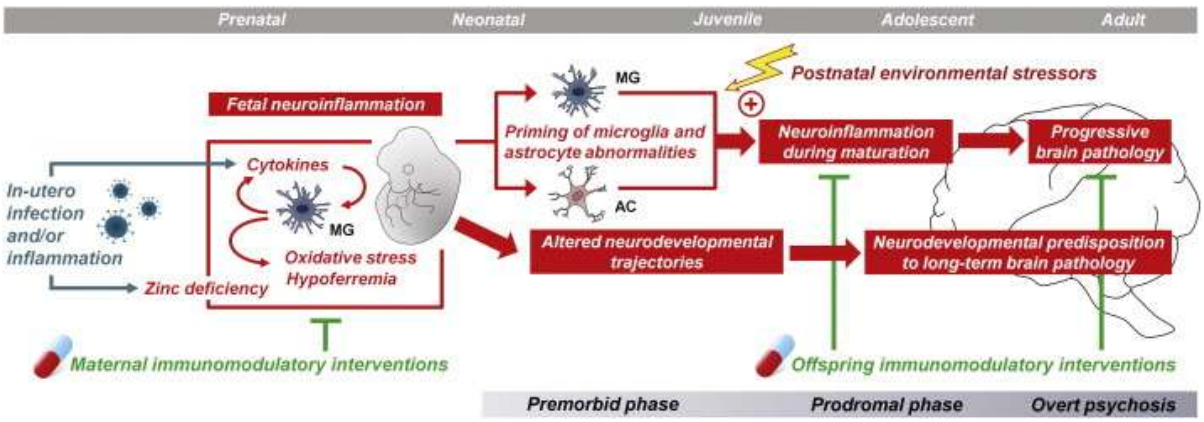
Figure 1. An immune-mediated two-hit model for psychosis.

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**



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



Urs Meyer

Developmental neuroinflammation and schizophrenia

Progress in Neuro-Psychopharmacology and Biological Psychiatry, Volume 42, 2013, 20–34

http://dx.doi.org/10.1016/j.pnpbp.2011.11.003

Pregnancy risk factors related to autism: an Italian case–control study in mothers of children with autism spectrum disorders (ASD), their siblings and of typically developing children

E. Grossi[1], L. Migliore[2] and F. Muratori[3,4]

Journal of Developmental Origins of Health and Disease

cambridge.org/doh

Original Article

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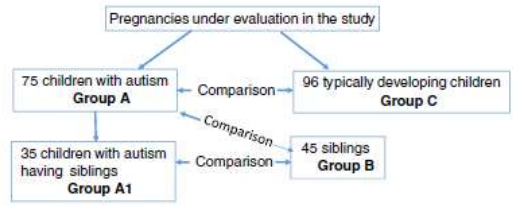
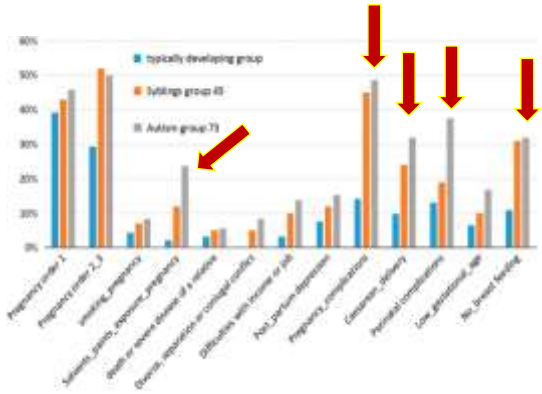


Fig. 1. Study diagram.

Demographics	Abuses or violences
Pregnancy order 1	Job strain
Pregnancy order 2–3	Average number of stressful events
Pregnancy order >3	Health problems during pregnancy
Father age at conception	Fever
Mother age at conception	Use of drugs
Behavior/environment	Pregnancy complications
Smoking at conception	Delivery problems
Smoking during pregnancy	Dystocic delivery
Alcohol during pregnancy	Cesarean section
Occupational exposure to solvents/paints	Perinatal complications
Drinking tap water	Postpartum
PVC flooring at home	Low gestational age
Stressful events	Breastfeeding
Death or severe disease of a relative	Early antibiotic therapy
Divorce, separation or conjugal conflict	Postpartum depression
Loss of house, evicted or relocation	

La **Fig. 3 mostra la mappa di connettività semantica dei fattori in studio ottenuti con la rete neurale Auto-CM** dai dati utilizzati per generare la Tabella 2 . **Il nodo di autismo, alla varianza del nodo tipico, funge da hub (variabile con tre o più collegamenti) che riceve la convergenza da più fattori, suggerendo l'esistenza di un effetto cumulativo multi-causale**.

	Autism group (73)	Typically group (90)	Odds ratio	P value	95% CI
Pregnancy order 1	45.03%	36.13%	1.31	0.300	0.7-2.45
Pregnancy order 2-3	50.00%	29.35%	2.4	0.010	1.28-4.50
Pregnancy order >3	4.17%	0.80%	n.d.	n.d.	
Father age >40 at conception	9.72%	7.61%	1.31	0.630	0.43-3.91
Mother age >40 at conception	2.78%	1.09%	2.6	0.440	0.23-29.29
Smoking at conception	10.23%	15.23%	1.59	0.250	0.51-3.32
Smoking pregnancy	8.33%	4.35%	2.01	0.300	0.54-7.37
Alcohol pregnancy	2.78%	2.17%	1.28	0.900	0.17-9.35
Solvents/paints exposure pregnancy	15.62%	2.17%	14.91	0.001	3.09-62.52
PVC flooring	10.06%	20.80%	0.66	0.230	0.3-1.41
Tap water pregnancy	15.01%	18.48%	1.58	0.410	0.63-2.9
Number of stressful events per mother	0.44	0.13	t-test	0.003	
Death or severe disease of a relative	5.56%	3.26%	1.74	0.470	0.37-8.05
Divorce, separation or conjugal conflict	8.33%	0.80%	n.d.	n.d.	
Loss of house, eviction or relocation	11.11%	3.26%	3.7	0.060	0.94-14.52
Abuses or violences	1.39%	0.80%	n.d.	n.d.	
Difficulties with income or job	13.89%	3.26%	4.78	0.020	1.26-18.09
Postpartum depression	15.28%	7.61%	2.19	0.120	0.8-5.97
Fever pregnancy	11.11%	10.87%	1.02	0.960	0.36-2.74
Use of drugs pregnancy	0.00%	2.17%	n.d.	n.d.	
Pregnancy complications	48.61%	14.13%	5.75	<0.0001	2.72-12.01
Dystocic delivery	5.56%	3.26%	1.74	0.470	0.37-8.05
Cesarean delivery	31.94%	9.78%	4.32	0.001	1.95-10.1
Perinatal complications	27.38%	13.04%	4	0.006	1.65-9.65
Low gestational age	16.67%	6.52%	2.87	0.040	1.02-8.06
No breastfeeding	31.94%	10.87%	3.85	0.001	1.59-9.76
Early antibiotic therapy	16.67%	7.61%	2.43	0.08	0.9-6.52



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.

Giuseppe Giordano ISDE Palermo

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

"Tobacco smoke is without a doubt the most significant environmental contaminant to which children are exposed indoors"

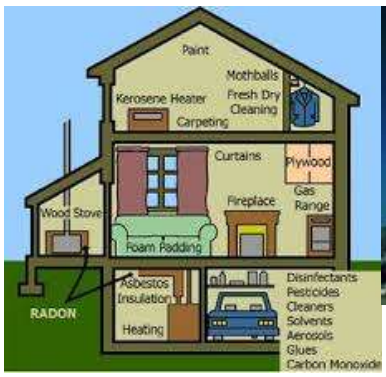
Children whose mothers smoke:

- **70%** more respiratory problems
- Pneumonia and hospitalization in year 1 is **38%** higher
- Infant mortality is **80%** higher
- **20%** of all infant deaths could be avoided if all pregnant smokers stopped by the 16th week of gestation

Environmental tobacco smoke (ETS)

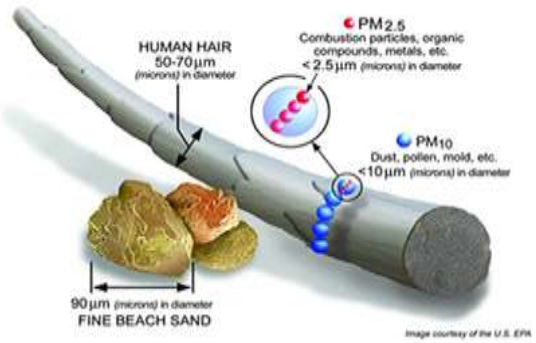
- Sudden infant death syndrome
- Lower respiratory tract illness
- Middle ear disease
- Asthma
- 12 million children exposed to secondhand smoke in homes

- Exposure to environmental tobacco smoke (ETS) causes more than 35,000 deaths annually among non-smokers.
- Smoking by pregnant women is responsible for about 1000 infant deaths each year in the U.S.
- Children exposed to ETS suffer higher rates of asthma, bronchitis, and pneumonia.
- Smokeless tobacco use has tripled since 1972, and cigar use has increased 50% since 1993.



House dust mites

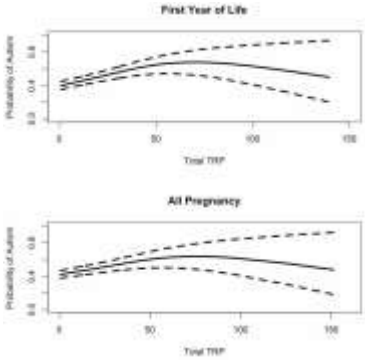
- House dust mites produce *Der p I* allergen, a potent sensitizer
- Good evidence of increased risk of sensitization with increasing allergen exposure, but this does not necessarily lead to asthma
- Small reductions in exposure will not necessarily lead to reduced incidence and/or symptoms
- Indoor humidity is important



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.

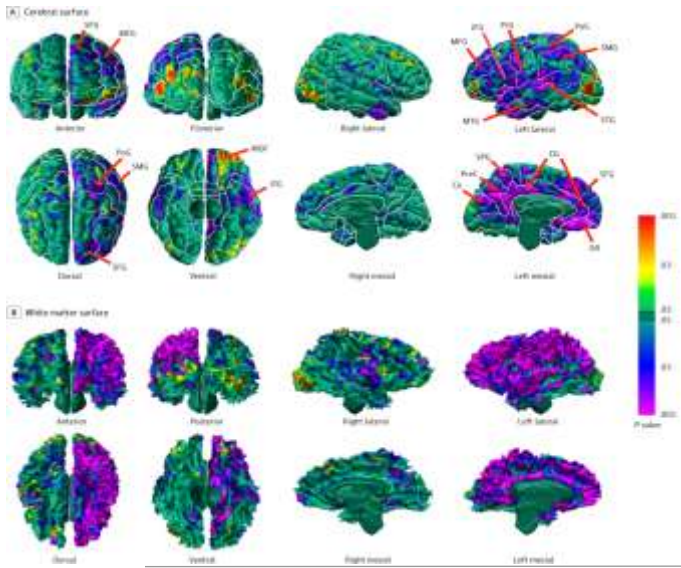
The magnitude of these **associations** appear to be **most pronounced during late gestation** (OR=1.98, 95%CI 1.20–3.31) **and early life / first year of life** (OR=1.98, 95%CI 1.20–3.31)



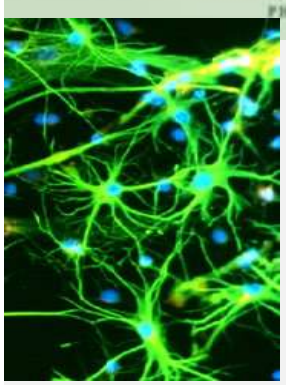
JAMA Psychiatry. 2013 January ; 70(1): 71–77. doi:10.1001/jamapsychiatry.2013.266

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 (UPs 0,1 μ) 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

UPs pass easily through the olfactory nerve and the BBB into the brain

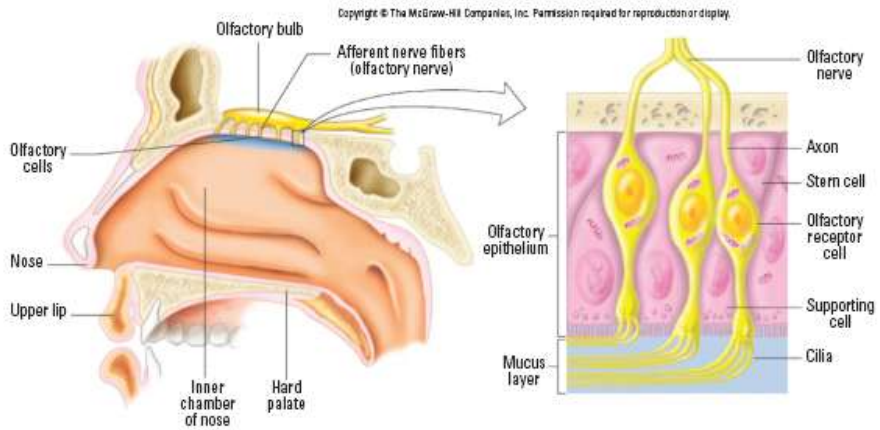


Figure 12. Close proximity of olfactory mucosa to olfactory bulb of the CNS. Inhaled NSP[s], especially below 10 nm, deposit efficiently on the olfactory mucosa by diffusion, similar to airborne "smell" molecules which deposit in this area of olfactory dendritic cilia. Subsequent uptake and translocation of solid NSP[s] along axons of the olfactory nerve has been demonstrated in non-human primates and rodents. Surface chemistry of the particles may influence their neuronal translocation. Copyright © the McGraw-Hill Companies, Inc. Reproduced from Widmaier et al. (2004) with permission from McGraw-Hill.

Environmental Health Perspectives • VOLUME 113 | NUMBER 7 | July 2005

In the most polluted cities **even dogs have Alzheimer's disease**

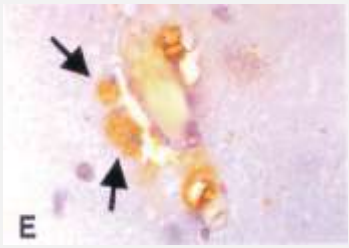
Toxicologic Pathology
http://tpx.sagepub.com

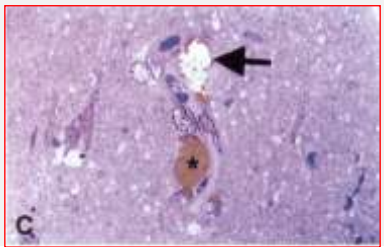
Air Pollution and Brain Damage

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.





And **a similar condition has been documented in the brain of young people dead for accidental causes..**

Toxicologic Pathology
http://tpx.sagepub.com

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

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

Toxicol Pathol 2007; 35: 154

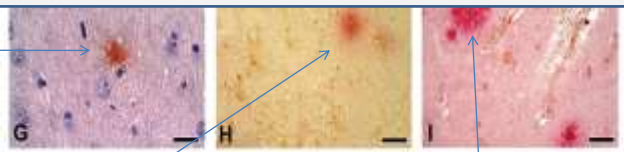
Exposures to **particulate matter and gaseous air pollutants** have been associated with **respiratory tract inflammation**, disruption of the nasal respiratory and olfactory barriers, **systemic inflammation**, production of mediators of inflammation capable of **reaching the brain and systemic circulation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

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

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

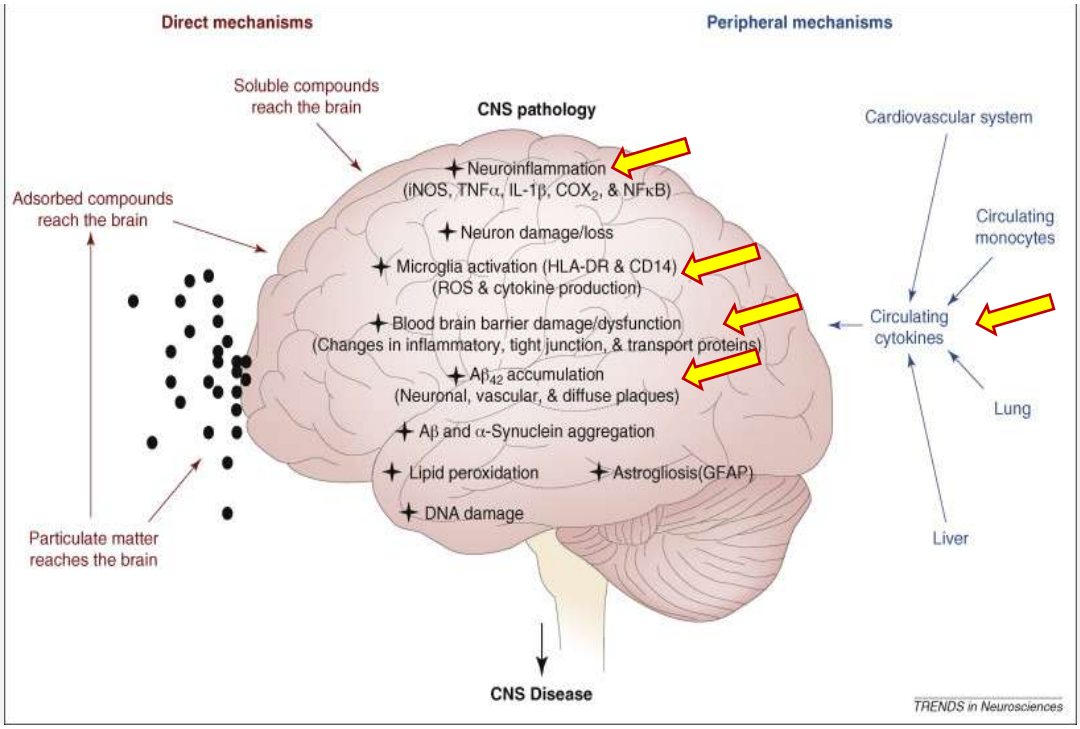
Our findings of nasal barrier disruption, systemic inflammation, and the upregulation of COX2 and IL-1*β* expression and A*β*42 accumulation in brain suggests that sustained exposures to significant concentrations of air pollutants such as particulate matter could be a risk factor for AD and other neurodegenerative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

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



The frontal cortex of a **17-year-old MC boy**… shows **a diffuse *Aβ42 plaque*** *(red product) and GFAP-negative astrocytes*

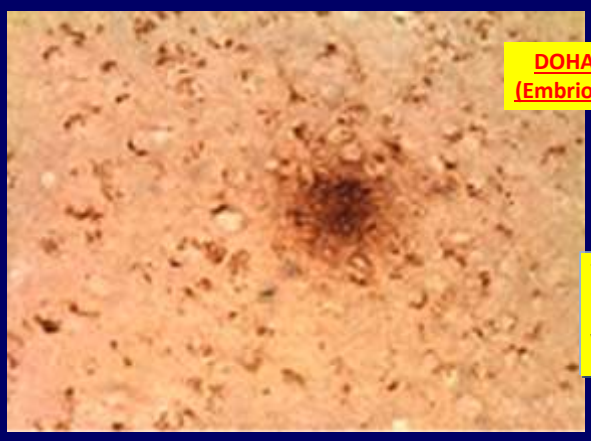
The **frontal cortex of a 36-year-old MC male** with an E3/E4 ApoE genotype .. shows **abundant mature and diffuse *Aβ42 plaques*** *(red stain) along* with GFAP-positive reactive astrocytosis



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

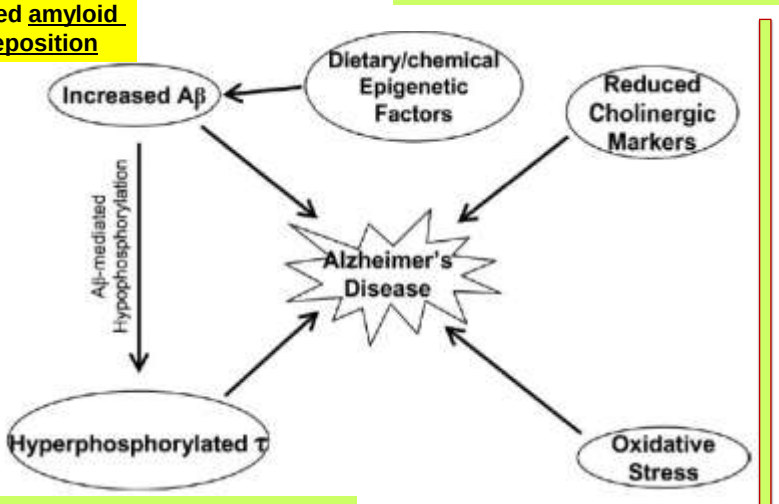
The **cause for most Alzheimer's cases is still *essentially unknown*** (except for 1**% to 5% of cases where genetic differences** have been identified)……

The Journal of Neuroscience

Even Alzheimer's Disease has early, fetal or infantile origins

(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"**

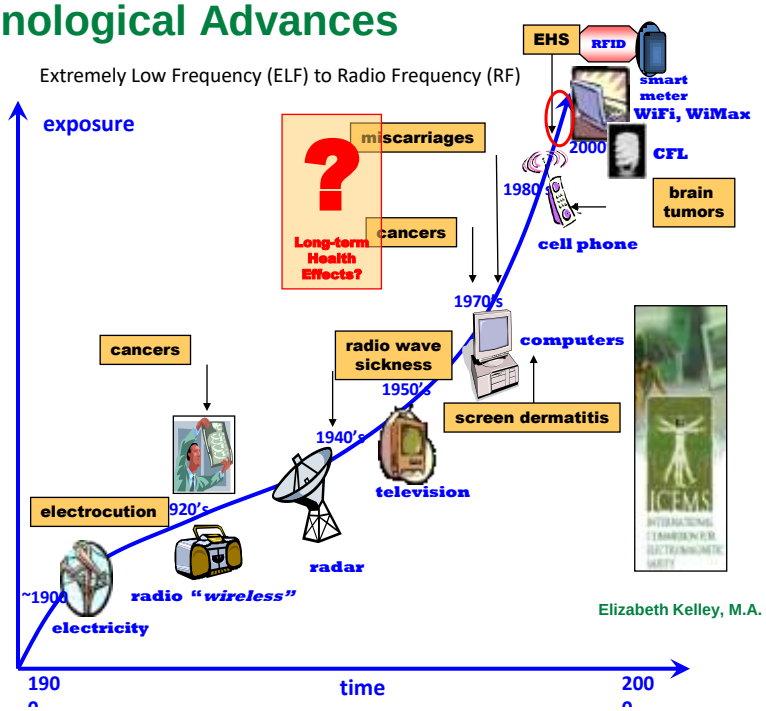
Per la prima volta* dopo milioni di anni dalla presenza dei primati sulla terra, saremo **tutti esposti*** a questi FATTORI ESOGENI (i CEM), che disturbano la vita delle **cellule** e addirittura le **bio-molecole**, il **genoma** *in primis*, determinando modifiche inedite e pericolose nell'espressione e programmazione del DNA, della segnaletica inter e intracellulare, del *folding* proteico... Siamo di fronte alla deliberata esposizione (questo è innegabile e andrebbe sottolineato) **di tutta la popolazione mondiale *** (**donne incinte, embrioni, feti, bambini, adolescenti e gameti/generazioni future inclusi**) ad un **POSSIBILE CANCEROGENO** (**classificazione IARC: 2B**).

NOTA: L'esposizione globale * rende praticamente impossibili le valutazioni epidemiologiche del rischio/danno

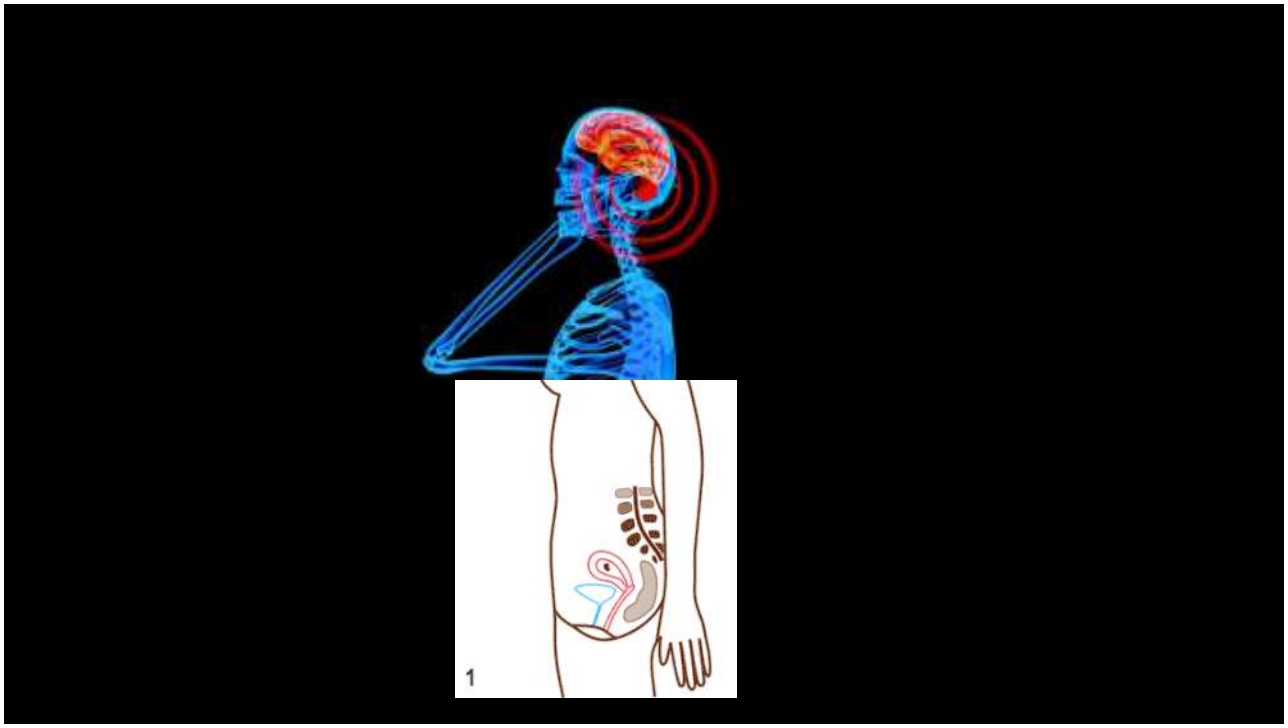
https://www.pandoratv.it/5g-grande-minaccia-p-02-lidea-piu-stupida-nella-storia-dellumanita/

PANDORA TV
UN'ALTRA VISIONE DEL MONDO

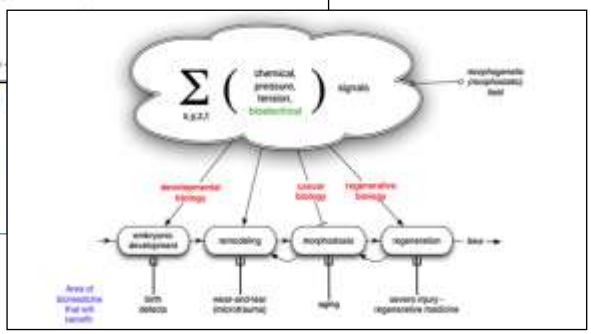
Technological Advances



Elizabeth Kelley, M.A.



Normalmente si considerano i CEM come **fattori ESOGENI**, ma ci si dimentica di un fatto fondamentale ed estremamente significativo: **l'esistenza di CEM ENDOGENI, cioè di segnali/impulsi elettromagnetici grazie ai quali le cellule comunicano tra loro per: proliferare, migrare, differenziarsi (e in particolare, nelle diverse fasi dello sviluppo embrio-fetale, per determinare la corretta formazione di organi e tessuti).**



Published in final edited form as:
Bioessays. 2012 March ; 34(3): 205–217. doi:10.1002/bies.201100136.

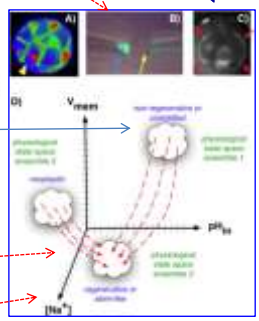
Molecular bioelectricity in developmental biology: New tools and recent discoveries:

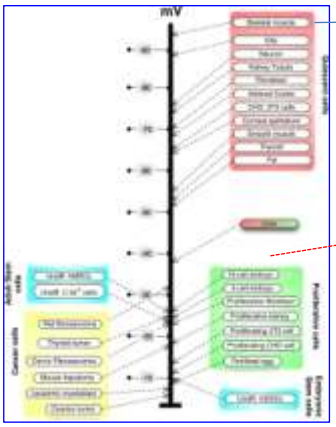
Control of cell behavior and pattern formation by transmembrane potential gradients

Michael Levin
Department of Biology, and Center for Regenerative and Developmental Biology Tufts University, Medford, MA, USA

3 **Gradienti di potenziale transmembrana delimitano importanti domini tissutali,** come la regione depolarizzata poco dopo l'amputazione della coda in *Xenopus*

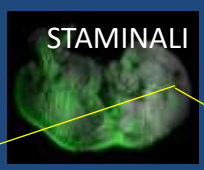
I **domini iperpolarizzati** (punte di freccia rosse) presagiscono **l'espressione di geni regolatori come *Frizzled* durante lo sviluppo craniofacciale dell'embrione**

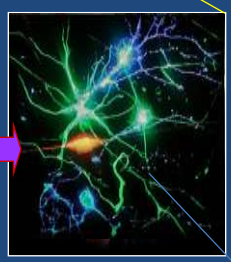




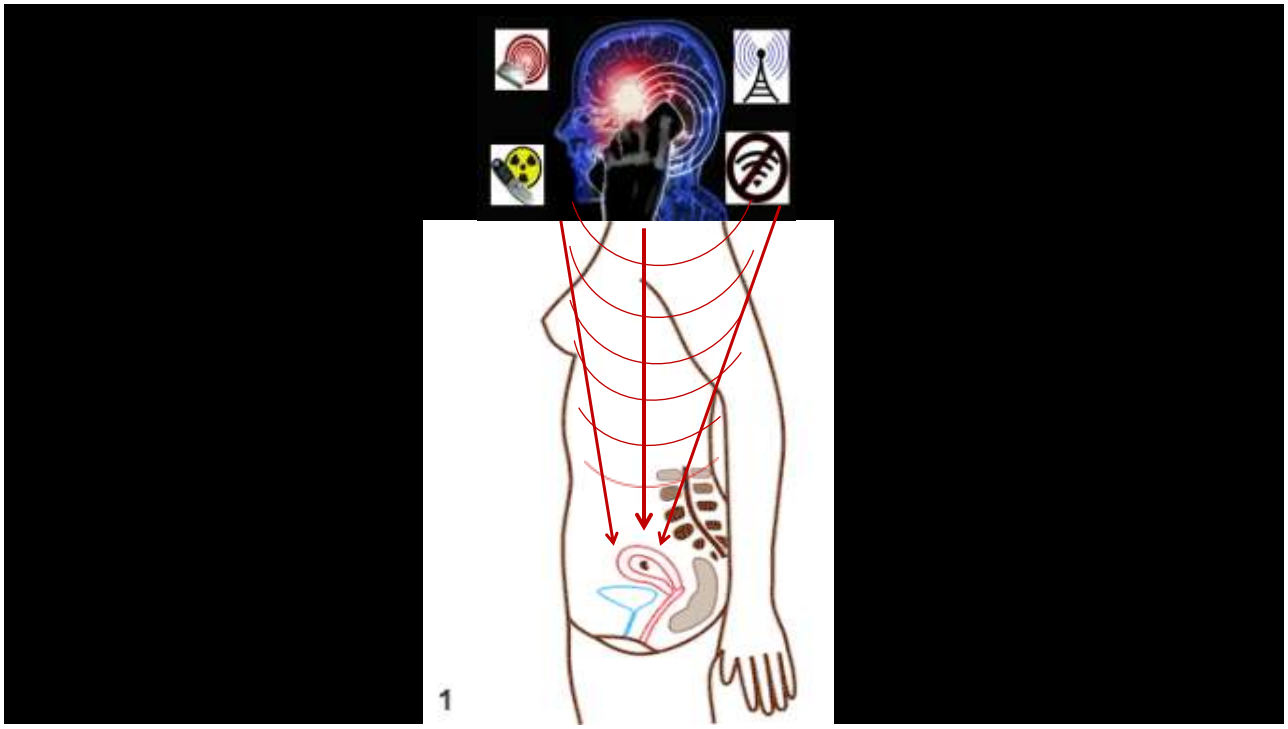
2 Controllo dello stato cellulare mediante potenziale transmembrana...le **cellule quiescenti, differenziate, tendono ad essere fortemente polarizzate**, mentre **le cellule staminali, embrionali e tumorali sono relativamente depolarizzate**

1 **I segnali bioelettrici controllano il comportamento delle cellule (regolazione della migrazione, della differenziazione e della proliferazione cellulare..).** È **interessante notare che i segnali elettrici possono superare i segnali biochimici concorrenti;** ad esempio, **la depolarizzazione supera l'induzione della differenziazione da parte dell'insulina + desametasone nelle cellule staminali** mesenchimali





I **segnali bioelettrici** stanno diventando sempre più un importante **regolatori del comportamento cellulare**, controllando il numero di cellule (**proliferazione** e **apoptosi**), la posizione (**migrazione** e **orientamento**) e l'identità (**traiettorie di differenziazione**)
Bioessays. 2012 March ; 34(3): 205–217. doi:10.1002/bies.201100136.



CHILD DEVELOPMENT

Child Dev. 2018 Jan;89(1):129-136. doi: 10.1111/cdev.12824

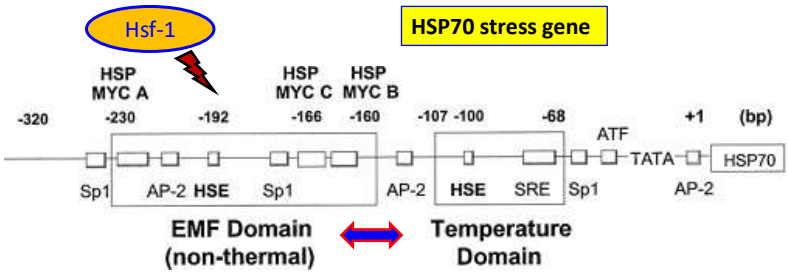
Electromagnetic Fields, Pulsed Radiofrequency Radiation, and Epigenetics: How Wireless Technologies May Affect Childhood Development

Cindy Sage
Sage Associates

Ernesto Burgio
International Society of Doctors for Environment (ISDE) Scientific Office

Mobile phones and other wireless devices that produce electromagnetic fields (EMF) and pulsed radiofrequency radiation (RFR) are widely documented to cause potentially harmful health impacts that can be detrimental to young people. New epigenetic studies are profiled in this review to account for some neurodevelopmental and neurobehavioral changes due to exposure to wireless technologies. Symptoms of retarded memory, learning, cognition, attention, and behavioral problems have been reported in numerous studies and are similarly manifested in autism and attention deficit hyperactivity disorders, as a result of EMF and RFR exposures where both epigenetic drivers and genetic (DNA) damage are likely contributors. Technology benefits can be realized by adopting wired devices for education to avoid health risk and promote academic achievement.

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

Sci Rep. **2019 Feb** 4;9(1):1333. doi: 10.1038/s41598-018-37372-2.

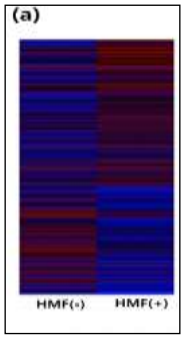
SCIENTIFIC REPORTS

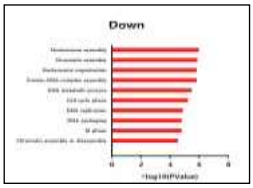
Published online: 04 February 2019

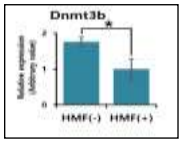
Effects of a hypomagnetic field on DNA methylation during the differentiation of embryonic stem cells

Soonbong Baek[1], Hwan Choi[2], Hanseul Park[2], Byunguk Cho[1], Siyoung Kim[3] & Jongpil Kim[1,2]

It has been reported that hypomagnetic fields (HMFs) have a negative influence on mammalian physiological functions. We previously reported that HMFs were detrimental to cell fate changes during reprogramming into pluripotency. These studies led us to investigate whether HMFs affect cell fate determination during direct differentiation. Here, we found that an HMF environment attenuates differentiation capacity and is detrimental to cell fate changes during the in vitro differentiation of embryonic stem cells (ESCs). Moreover, HMF conditions cause abnormal DNA methylation through the dysregulation of DNA methyltransferase3b (Dnmt3b) expression, eventually resulting in incomplete DNA methylation during differentiation. Taken together, these results suggest that an appropriate electromagnetic field (EMF) environment may be essential for favorable epigenetic remodeling during cell fate determination via differentiation.







…campi ipomagnetici (HMF) influenzano la determinazione del destino cellulare… interferendo sulla **differenziazione in vitro delle cellule staminali embrionali (ESC).**
…attraverso la **disregolazione dell'espressione di *DNA metiltransferasi 3b (Dnmt3b),***
con conseguente **metilazione incompleta del DNA**

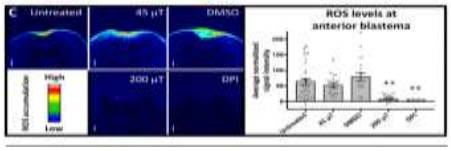
SCIENCE ADVANCES | RESEARCH ARTICLE Sci Adv. 2019 Jan 30;5(1):eaau7201. doi: 10.1126/sciadv.aau7201.

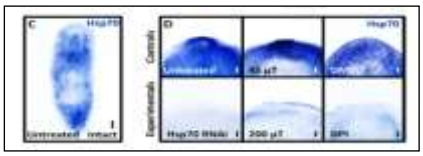
BIOPHYSICS

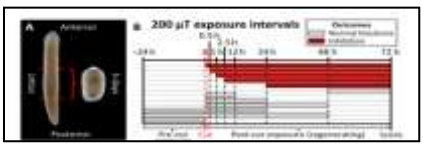
Weak magnetic fields alter stem cell–mediated growth

Alanna V. Van Huizen[1], Jacob M. Morton[1], Luke J. Kinsey[1], Donald G. Von Kannon[1], Marwa A. Saad[1], Taylor R. Birkholz[1], Jordan M. Czajka[1], Julian Cyrus[2], Frank S. Barnes[2], Wendy S. Beane[1]*

Biological systems are constantly exposed to electromagnetic fields (EMFs) in the form of natural geomagnetic fields and EMFs emitted from technology. While strong magnetic fields are known to change chemical reaction rates and free radical concentrations, the debate remains about whether static weak magnetic fields (WMFs; <1 mT) also produce biological effects. Using the planarian regeneration model, we show that WMFs altered stem cell proliferation and subsequent differentiation via changes in reactive oxygen species (ROS) accumulation and downstream heat shock protein 70 (Hsp70) expression. These data reveal that on the basis of field strength, WMF exposure can increase or decrease new tissue formation in vivo, suggesting WMFs as a potential therapeutic tool to manipulate mitotic activity.







Campi magnetici statici deboli (WMF <1 mT) producono **alterazioni della proliferazione delle cellule staminali e della successiva differenziazione** attraverso cambiamenti nell'**accumulo di specie reattive dell'ossigeno (ROS)** e nell'**espressione della proteina di shock termico 70 (Hsp70)**.

Questi dati rivelano che sulla base della forza del campo, l'esposizione al WMF può aumentare o diminuire la **formazione di nuovo tessuto *in vivo*...**

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

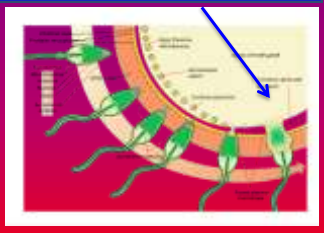
30 avril 2015

Focus sur la périconception

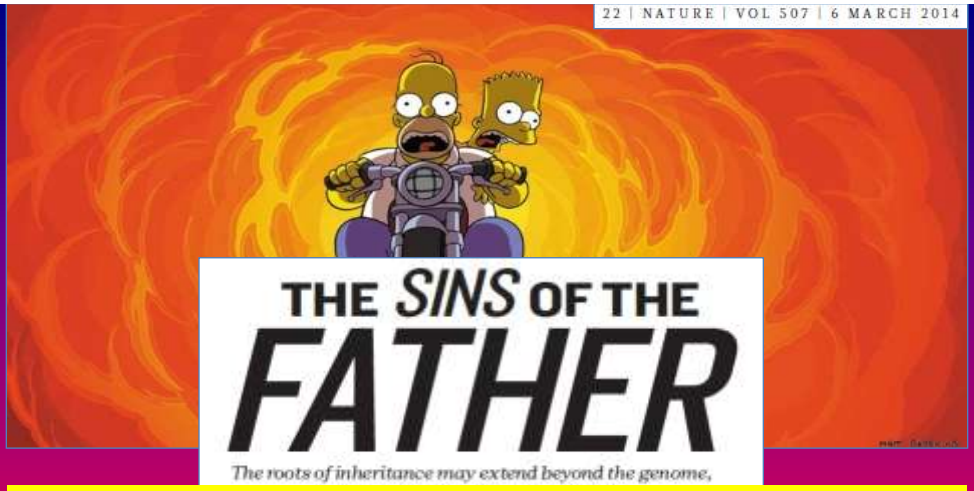
et la grossesse

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

The overlooked heritage: the genetic transmission by the father

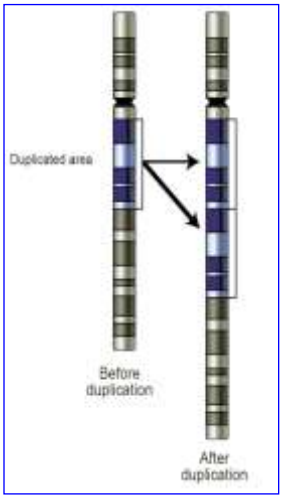


ERNESTO BURGIO
ECERI - European Cancer and Environment Research Institute
ISDE Scientific Committee



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.**

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);

Science
AAAS

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.*

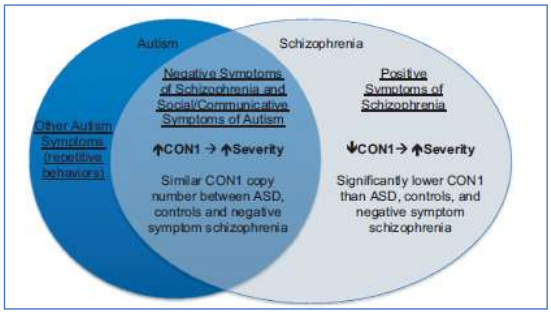
Science **320**, 539 (2008);

Science

AAAS

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.

DUF1220 CNVs.. Neural stem cells proliferation.. Human Brain Evolution.. Autism & Schizofrenia



DUF1220 copy number associations support autism and schizophrenia being related disorders. CON1 associations with negative symptoms in schizophrenic males, and with social/ communicative symptoms in ASD, suggest these phenotypes overlap between the disorders. The inverse association between CON1 and positive symptoms suggest that positive symptoms could be considered as an opposing phenotype to ASD. ASD, autism spectrum disorder.

DUF1220 protein domains drive proliferation in human neural stem cells and are associated with increased cortical volume in anthropoid primates

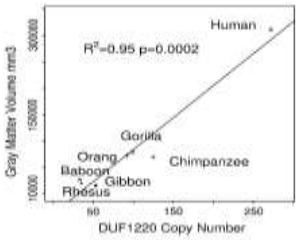
Brain Struct Funct (2015) 220:3053–3060
J. G. Keeney · J. M. Davis · J. Siegenthaler ·

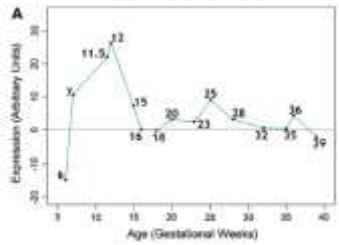
Replicated linear association between DUF1220 copy number and severity of social impairment in autism

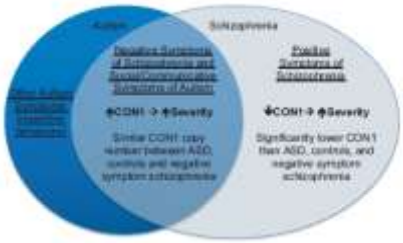
J. M. Davis · V. B. Searles Quick · J. M. Sikela
Hum Genet (2015) 134:569–575

DUF1220 copy number is associated with schizophrenia risk and severity: implications for understanding autism and schizophrenia as related diseases

www.nature.com/tp
VB Searles Quick[1], JM Davis[2], A Olincy[2] and JM Sikela[1]
Transl Psychiatry (2015) 5, e697; doi:10.1038/tp.2015.192



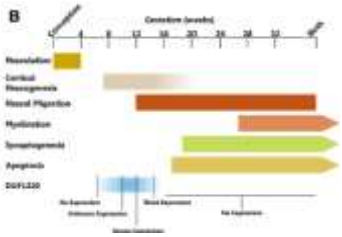




Autism and **Schizophrenia** exhibit both opposing and partially overlapping phenotypes and may represent **a disease continuum**

Variation in DUF1220 copy number contributes to both Autism and Schizophrenia disease risk and to the severity of both disorders,

Schizophrenia and autism may be, in part, a harmful by-product of the rapid and extreme evolutionary increase in DUF1220 copy number in the human species



Abuse Leaves Its Mark on the Brain

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

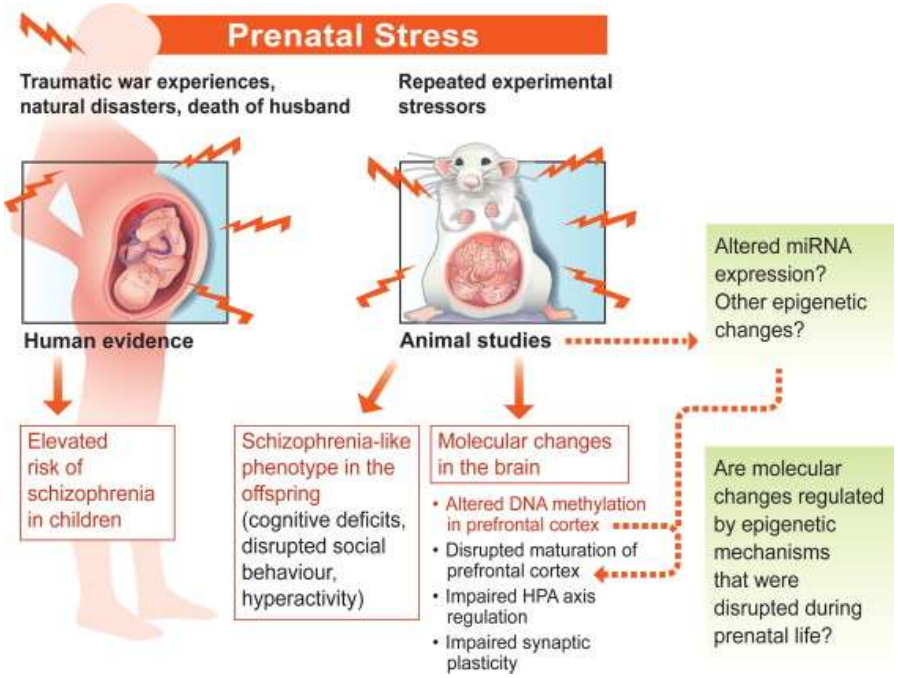
Francisco_de_Goya,_Saturno_devorando_a_su_hijo_(1819-1823)

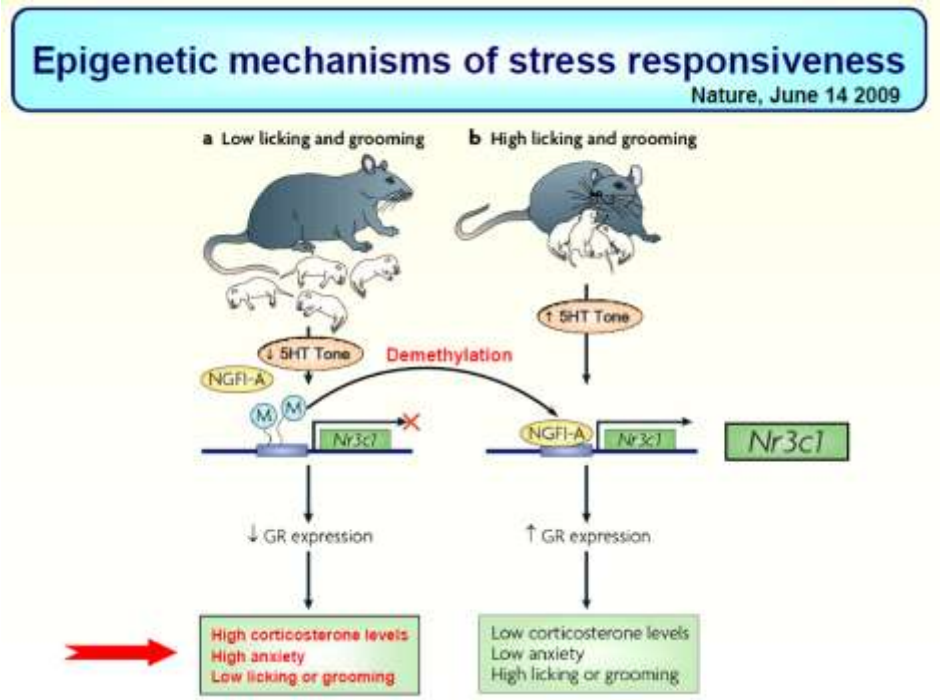
Child abuse is an environmental factor that **leaves an epigenetic mark on the brain**

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/


Prenatal Stress
Traumatic war experiences, natural disasters, death of husband
Repeated experimental stressors
Human evidence
Animal studies
Altered miRNA expression? Other epigenetic changes?
Elevated risk of schizophrenia in children
Schizophrenia-like phenotype in the offspring (cognitive deficits, disrupted social behaviour, hyperactivity)
Molecular changes in the brain
• Altered DNA methylation in prefrontal cortex
• Disrupted maturation of prefrontal cortex
• Impaired HPA axis regulation
• Impaired synaptic plasticity
Are molecular changes regulated by epigenetic mechanisms that were disrupted during prenatal life?


Epigenetic mechanisms of stress responsiveness
Nature, June 14 2009
a Low licking and grooming
b High licking and grooming
↑ 5HT Tone
↓ 5HT Tone
Demethylation
NGFI-A
M
Nr3c1
↓ GR expression
↑ GR expression
High corticosterone levels
High anxiety
Low licking or grooming
Low corticosterone levels
Low anxiety
High licking or grooming

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 of glucocorticoid receptor expression. In humans, childhood abuse alters HPA stress responses and increases the risk of suicide. We examined epigenetic differences in a neuron-specific glucocorticoid receptor (*NR3C1*) promoter between postmortem hippocampus obtained from suicide victims with a history of childhood abuse and those from either suicide victims with no childhood abuse or controls. We found decreased levels of glucocorticoid receptor mRNA, as well as mRNA transcripts bearing th glucocorticoid receptor 1_F splice variant and increased cytosine methylation of an *NR3C1* promoter. Patch-methylated *NR3C1* promoter constructs that mimicked the methylation state in samples from abused suicide victims showed decreased NGFI-A transcription factor binding and NGFI-A–inducible gene transcription. These findings translate previous results from rat to human and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression.

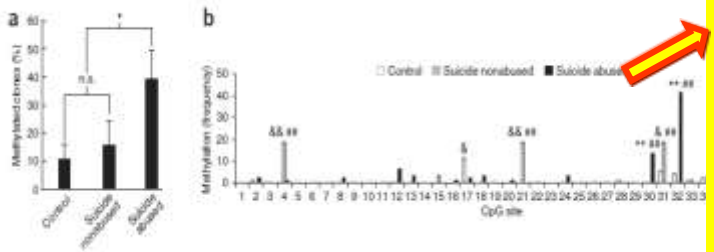


Figure 2 Methylation of the *NR3C1* promoter in the hippocampus. Twenty clones were sequenced for each subject for methylation mapc percentage of methylated clones for suicide victims with a history of childhood abuse ($n = 12$), suicide victims without a history of child and controls ($n = 12$). The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

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 **e (Nurses 'Health Study II)**

Isr J Psychiatry Relat Sci - Vol. 50 - No 1 (2013)

Epigenetic Transmission of Holocaust Trauma: Can Nightmares Be Inherited?

Natan P.F. Kellermann

AMCHA, the National Israeli Center for Psychosocial Support of Survivors of the Holocaust and the Second Generation, Jerusalem, Israel

The Holocaust left its visible and invisible marks not only on the survivors, but also on their children. Instead of numbers tattooed on their forearms, however, they may have been marked epigenetically with a chemical coating upon their chromosomes, which would represent a kind of biological memory of what the parents experienced. As a result, some suffer from a general vulnerability to stress while others are more resilient. Previous research assumed that such transmission was caused by environmental factors, such as the parents' child-rearing behavior. New research, however, indicates that these transgenerational effects may have been also (epi) genetically transmitted to their children. Integrating both hereditary and environmental factors, epigenetics adds a new and more comprehensive psychobiological dimension to the explanation of transgenerational transmission of trauma. Specifically, epigenetics may explain why latent transmission becomes manifest under stress. A general theoretical overview of epigenetics and its relevance to research on trauma transmission is presented.

The **Holocaust** left its **visible and invisible marks** not only on the survivors, but also on their **children**. Instead of **numbers tattooed on their forearms**, however, they may have been **marked epigenetically with a chemical coating upon their chromosomes**, which would represent a kind of biological memory of what the parents experienced.

Biological Psychiatry

Holocaust Exposure and Intergenerational *FKBP5* Methylation

Childhood Adversity Effects on FKBP5 Intron 7 Methylation in Offspring

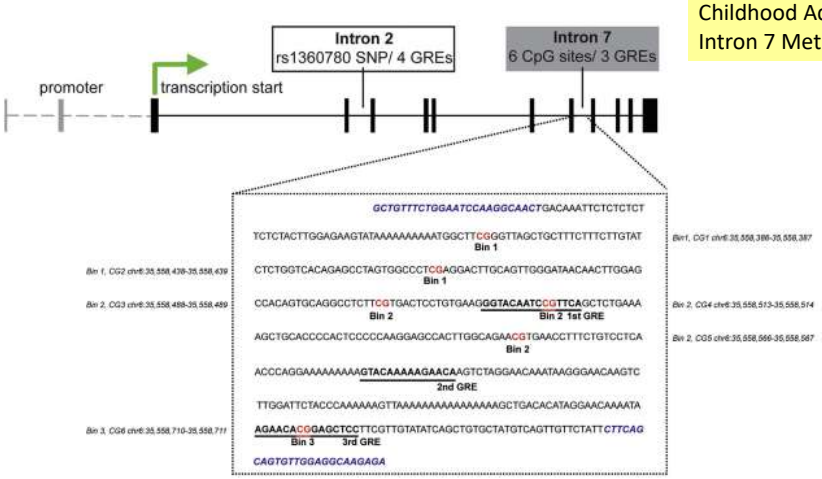


Figure 1. Schematic representation of the human *FKBP5* locus with intron 7 glucocorticoid receptor binding sequence investigated in this study. The upper panel depicts the *FKBP5* locus in 5'-3' orientation. Black bars represent the 11 exons. The transcription start site is highlighted in green. The lower panel represents the intron 7 amplicon (476 base pair) chosen for DNA methylation analysis (primer sequence dark blue/italicized). Since pyrosequencing can only reliably generate short reads, the six cytosine-phosphate-guanine (CpG) sites (red) analyzed in three bins based on the proximity to three consensus glucocorticoid response elements (GREs) are represented in bold/underlined [pyrosequencing primers are described in Klengel *et al.* (38)]. The two CpGs of bin 1 were upstream of all GREs, the three CpGs of bin 2 are surrounding the first GRE, and bin 3 represents the CpG within the third GRE. The chromosomal position (hg19) of the CpG sites is indicated on the left and the right of the lower panel. SNP, single nucleotide polymorphism.

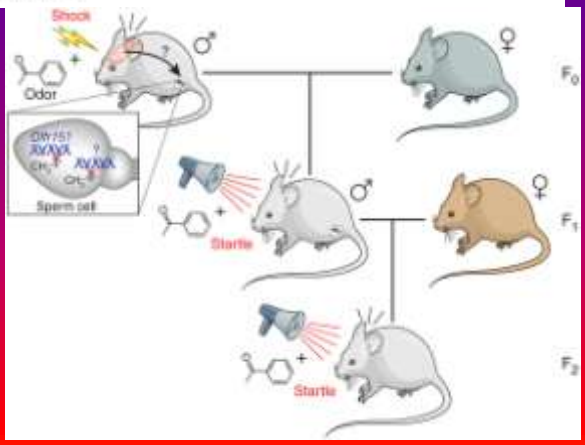
Lamarck revisited: epigenetic inheritance of ancestral odor fear conditioning

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**



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**

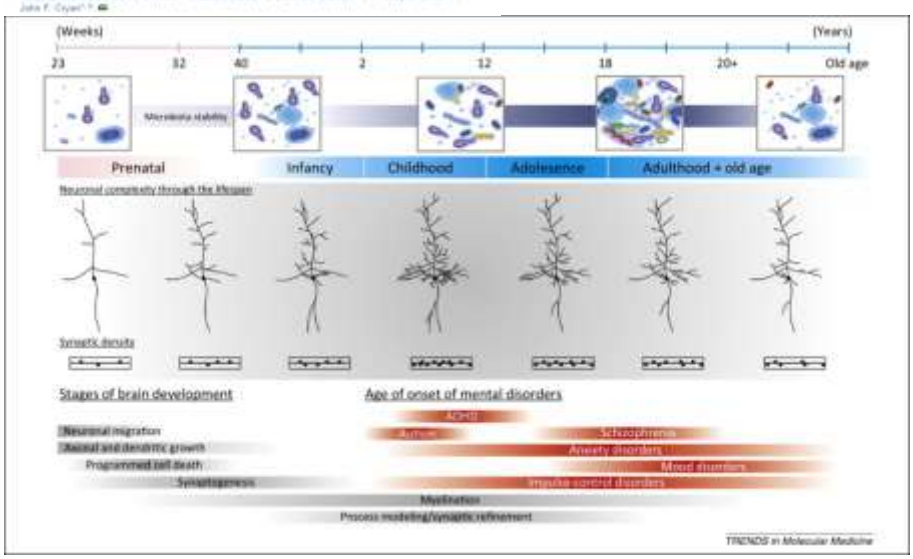
When raised this way, **male offspring showed depressive behaviours and tended to underestimate risk**, the study found. Their **sperm also showed abnormally high expression of five microRNAs**. One of these, **miR-375, has been linked to stress and regulation of metabolism.**

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.**

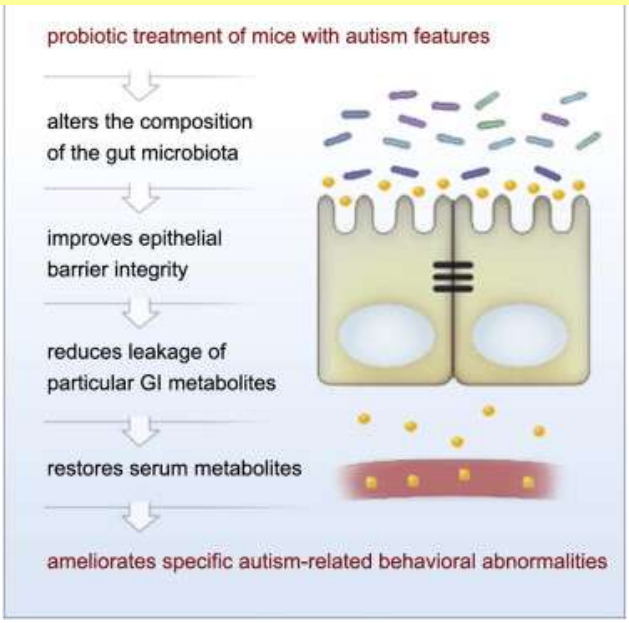
The researchers also collected **RNA from the F1 males' sperm and injected it into freshly fertilized eggs from untraumatized mice**. This resulted in mice with comparable depressive behaviours and metabolic symptoms — and **the depressive behaviours were passed, in turn, to the next generation**.

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)..**

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

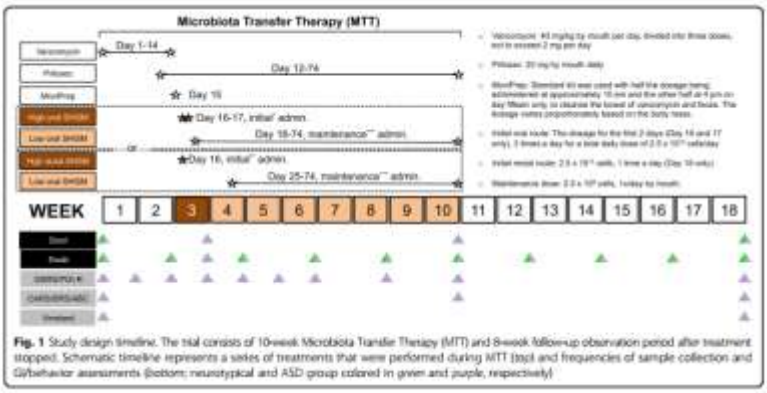


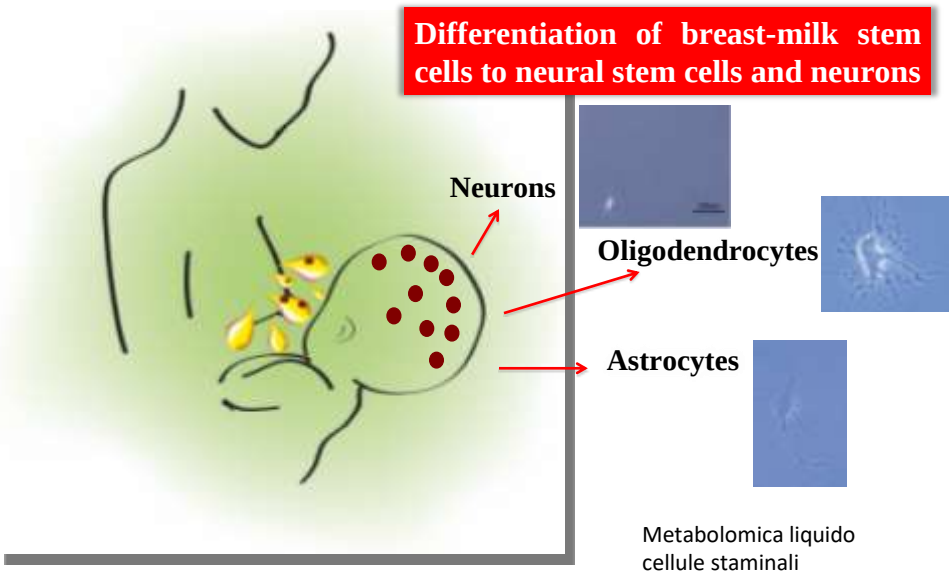
Fig. 1 Study design timeline. The trial consists of 10-week Microbiota Transfer Therapy (MTT) and 8-week follow-up observation period after treatment stopped. Schematic timeline represents a series of treatments that were performed during MTT (top) and frequencies of sample collection and GI/behavior 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.

FROM BREAST MILK TO BRAIN



Metabolomica liquido cellule staminali

Hosseini SM Neurol Res Int 2014

The raise of Neurodevelopmental Disorders (NDS): from genetics to epigenetics

Ernesto Burgio, ECERI European Cancer and Environment Research Institute, Bruxelles
e mail erburg@libero.it

The NDS are a set of conditions with **onset in the early stages** of development and variously associated with cognitive and psychiatric dysfunction. The **high heritability** of these conditions argues in favor of a **genetic component**. On the other hand, **the impressive increase of NDS calls into question environmental factors and epigenetic mechanisms.**

From a neurobiological point of view **autism** involves **early brain overgrowth and dysfunction** that may be related to **abnormal laminar development and cortical disorganization of neurons, in prefrontal and temporal cortical areas, where social, emotional, communication and language functions** are located.

*The **Human Connectome Project***

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

"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."

Cereb Cortex. 2017 Dec 1;27(12):5739-5754.

Dysregulation of Cortical Neuron DNA Methylation Profile in Autism Spectrum Disorder.

Nardone S et al.

Bar Ilan University Faculty of Medicine, Israel.

Department of Twin Research and Genetic Epidemiology, King's College London,

Campioni di cervello congelato da 15 casi di ASD e 16 controlli

Banca del cervello di Harvard

Banca autismo Britannica

Illumina Infinium
HumanMethlation27
BeadChip
target> 450.000 siti di metilazione.

Misura dei livelli di metilazione a 27.578 dinucleotidi CpG in 14.495 geni.

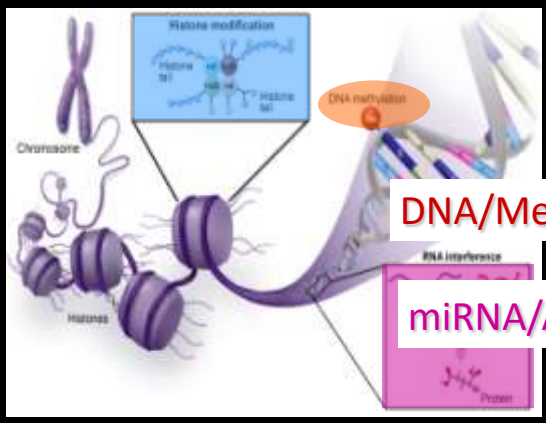
Usando il 450 K BeadArray

Sono state identificate
58 regioni differenzialmente metilate
che includevano loci associati ai geni del sistema GABAergic

ABAT e GABBR1
e MicroRNA specifici del cervello.

01.08.18

PubMed *06.09.18*



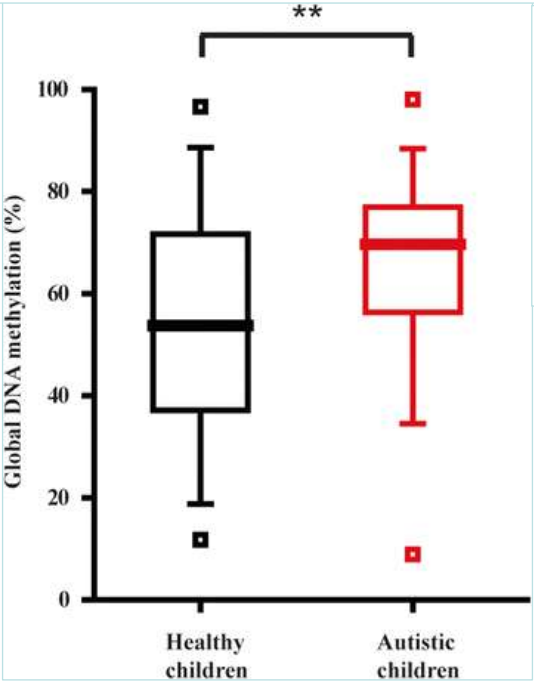
Histone/Autism: **297** →**323**

DNA/Methylation/Autism:350 →**373**

miRNA/Autism/: **149** → **158**

Markers clinici

Variation of global DNA methylation in autistic children.

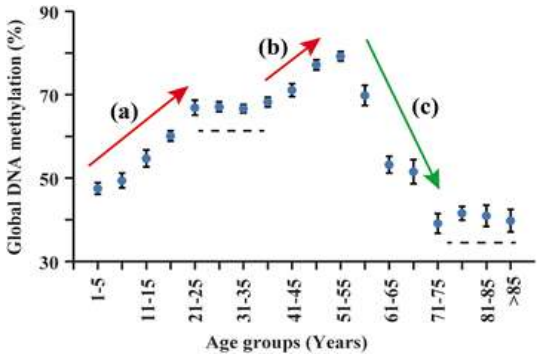


The *box plot* shows methylation levels in healthy children (*black*) and autistic children (*red*). ..

Here, we have demonstrated that **the global methylation in autistic children was increased compared to healthy children...**

Moreover, in comparison with the time profile for methylation, **the higher methylation level is that expected of young to middle-aged adults and this could be interpreted to suggest an abnormally advanced methylome in autistic children**.

This is reflected in that **no significant difference in methylation was found between autistic children and their parents**.

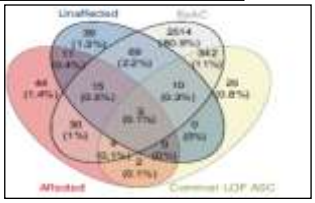


LETTERS
https://doi.org/10.1038/s41588-019-0433-8
nature genetics

Recessive gene disruptions in autism spectrum disorder

Nat ure Genetics | VOL 51 1092 | JULY 2019 | 1092–1098 | www.nature.com/naturegenetics

Autism spectrum disorder (ASD) affects up to 1 in 59 individuals[1]. Genome-wide association and large-scale sequencing studies strongly implicate both common variants[2–4] and rare de novo variants[5–10] in ASD. Recessive mutations have also been implicated[11–16] but their contribution remains less well defined. Here we demonstrate an excess of biallelic loss-of-function and damaging missense mutations in a large ASD cohort, corresponding to approximately 5% of total cases, including 10% of females, consistent with a female protective effect. We document biallelic disruption of known or emerging recessive neurodevelopmental genes (*CA2, DDHD1, NSUN2, PAH, RARB, ROGDI, SLC1A1, USH2A*) as well as other genes not previously implicated in ASD including *FEV* (FEV transcription factor, ETS family member), which encodes a key regulator of the serotonergic circuitry. Our data refine estimates of the contribution of recessive mutation to ASD and suggest new paths for illuminating previously unknown biological pathways responsible for this condition.

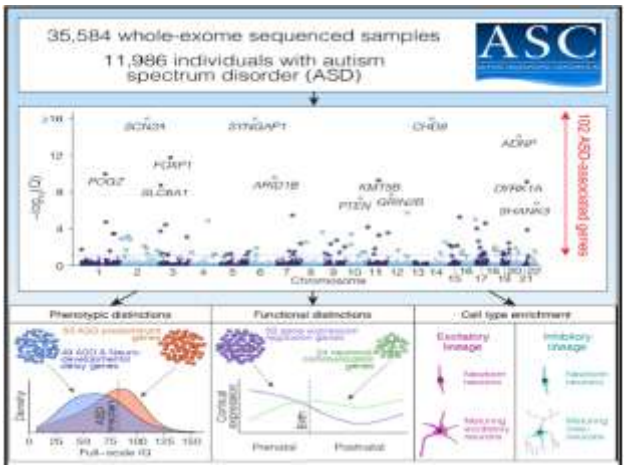


Documentiamo un eccesso di **mutazioni dannose (missenso e con perdita biallelica di-funzione)** in un'ampia coorte ASD, presenti **nel 5% del totale dei casi (10% nelle femmine,** coerentemente con un effetto protettivo del sesso femminile). Documentiamo **mutazioni bialleliche di geni noti o emergenti recessivi implicati nel neurosviluppo (CA2, DDHD1, NSUN2, PAH, RARB, ROGDI, SLC1A1, USH2A)** e di altri geni non precedentemente implicati, incluso **FEV (fattore di trascrizione, membro della famiglia ETS),** che codifica per una proteina che ha un ruolo di regolazione nei **circuiti serotoninergici**. I nostri dati perfezionano le stime del **contributo di mutazioni recessive in ASDs** e suggeriscono nuovi percorsi per illuminare le *pathways* neuro-biologiche implicate e tuttora ignote

Cell

Satterstrom et al., 2020, Cell 180, 1–17

Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism



Highlights

- 102 genes implicated in risk for autism spectrum disorder (ASD genes, FDR ≤ 0.1)
- Most are expressed and enriched early in excitatory and inhibitory neuronal lineages
- Most affect synapses or regulate other genes; how these roles dovetail is unknown
- Some ASD genes alter early development broadly, others appear more specific to ASD

102 geni implicati nel rischio di disturbo dello spettro autistico (geni ASD, FDR ≤ 0,1)

La maggior parte viene espressa e incrementata nelle prime fasi delle linee neuronali (sia eccitatorie, sia inibitorie)

La **maggior parte influenza le sinapsi o regola altri geni**; le interconnessioni non sono ancora chiare

Alcuni alterano ampiamente lo sviluppo iniziale, altri sembrano più specifici dell'ASD

Per la gran parte si tratterebbe di **mutazioni *DE NOVO***

Published: January 23, 2020DOI:https://doi.org/10.1016/j.cell.2019.12.036

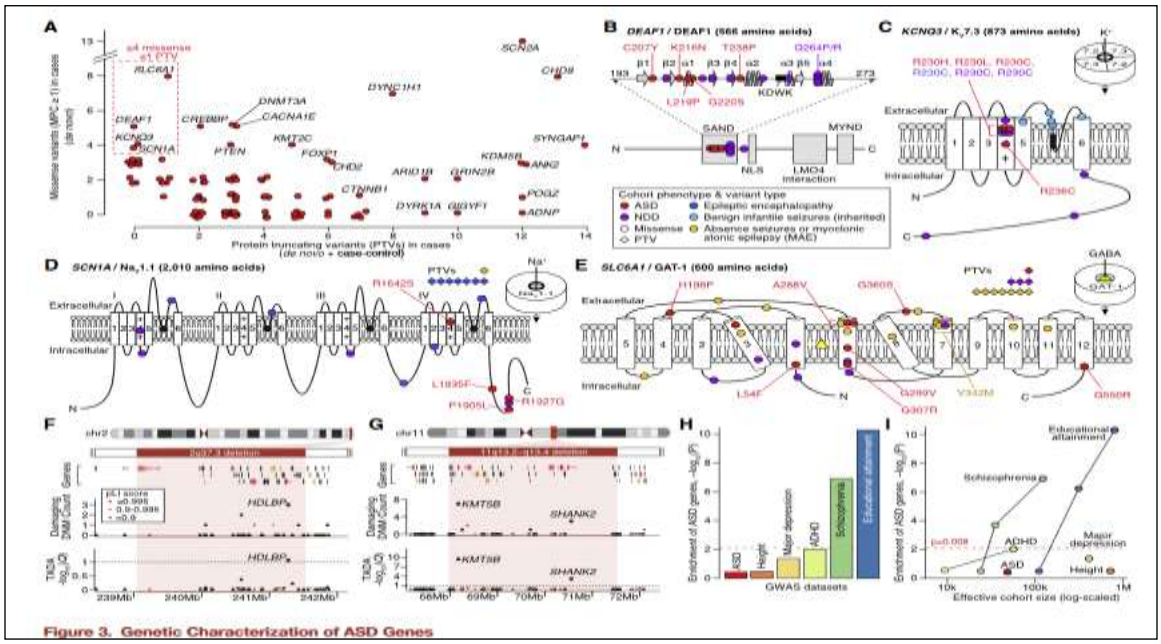
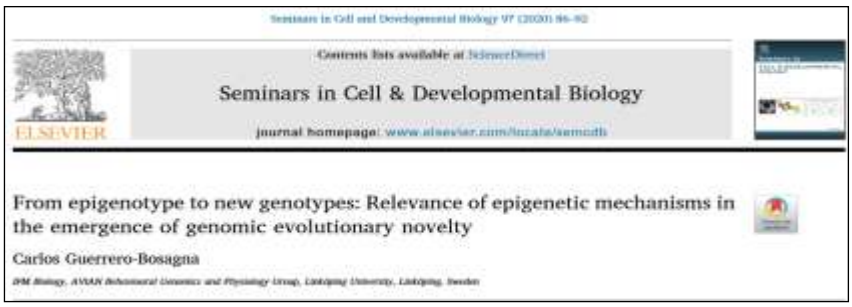


Figure 3. Genetic Characterization of ASD Genes


Seminars in Cell & Developmental Biology
journal homepage: www.elsevier.com/locate/semcdb

From epigenotype to new genotypes: Relevance of epigenetic mechanisms in the emergence of genomic evolutionary novelty

Carlos Guerrero-Bosagna

Epigenetic changes and the emergence of SNPs and CNVs

Epigenetic changes are known to be influenced by environmental exposures.

Epigenetic changes are reported to influence the emergence of single nucleotide polymorphisms and copy number variations.

This dual ability of epigenetic changes could mean **that germ line epigenetically influenced mutations could have an important role in the emergence of genomic evolutionary novelties**.

I **cambiamenti epigenetici sono noti per essere influenzati dalle esposizioni ambientali**.

È noto che i **cambiamenti epigenetici influenzano l'emergenza di polimorfismi a singolo nucleotide e le variazioni del numero di copie**.

Questa duplice capacità delle alterazioni epigenetiche potrebbe significare **che le mutazioni della linea germinale influenzate epigeneticamente potrebbero avere un ruolo importante nell'emergere di novità genomiche evolutive**.

Le conoscenze emergenti sulla relazione tra cambiamenti epigenetici e mutazioni aiuteranno a comprendere **un ruolo sottovalutato dell'ambiente nella speciazione e nella divergenza genomica: quella dell'influencer dei cambiamenti genomici**

Transposable elements can be seen as a natural genetic engineering system capable of acting not just on one location at a time but **on the genome as a whole** ..This dynamic view of the genome has been illustrated most impressively by *Shapiro* who stated that **the genome is composed of modular units arranged in a "Lego-like" manner that can be altered under circumstances**

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT

Gene 345 (2005) 91–100

GENE
SECTION
EVOLUTIONARY GENOMICS

www.elsevier.com/locate/gene

Review

A 21st century view of evolution: genome system architecture, repetitive DNA, and natural genetic engineering

James A. Shapiro

Department of Biochemistry and Molecular Biology, University of Chicago, 920 E. 58th Street, Chicago, IL 60637, United States

The last 50 years of molecular genetics have produced an abundance of new discoveries and data that make it useful to revisit some basic concepts and assumptions in our thinking about genomes and evolution. Chief among these observations are the complex modularity of genome organization, the biological ubiquity of mobile and repetitive DNA sequences, and the fundamental importance of DNA rearrangements in the evolution of sequenced genomes. This review will take a broad overview of these developments and suggest some new ways of thinking about genomes as sophisticated informatic storage systems and about evolution as a systems engineering process.

1 2 3 4 5

ELSEVIER

Current Opinion in Genetics & Development

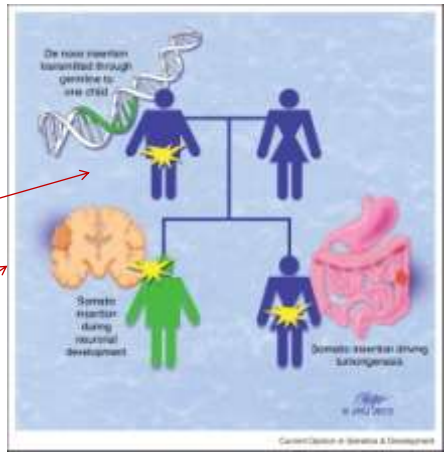
Volume 23, Issue 3, June 2013, Pages 264–270

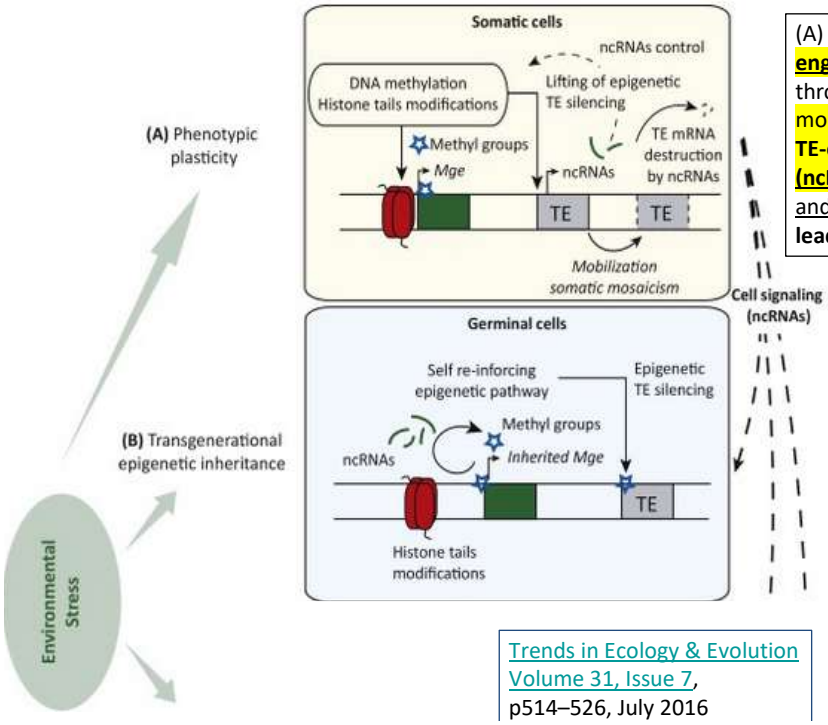
Functional impact of the human mobilome

Timothy D Babata [1,2], Kathleen H Burns [1,2,3,4,5]

Three families of human retrotransposons remain active today: **LINE1, *Alu*, and SVA** elements. Since 1988, *de novo* insertions at previously recognized disease loci have been shown to generate highly penetrant alleles in Mendelian disorders. Only recently has the extent of **germline-transmitted retrotransposon insertion polymorphism (RIP)** in human populations been fully realized. Also exciting are recent studies of **somatic retrotransposition in human tissues** and reports of **tumor-specific insertions**

(Stochastic *versus* Active/Reactive or even Pro-evolutive)





(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**.

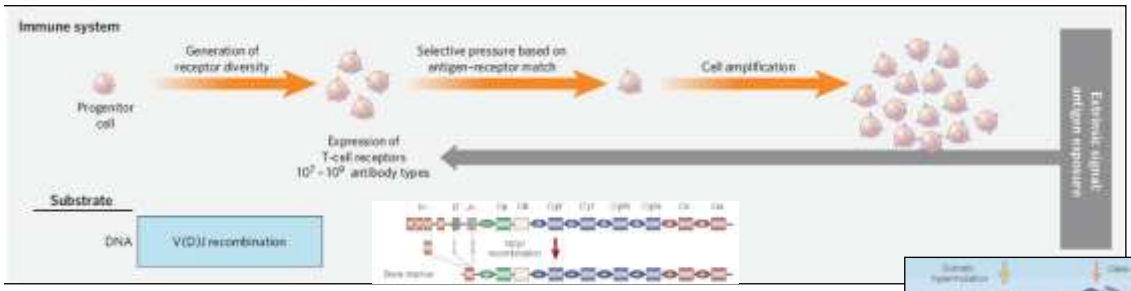
Stress perceived in somatic cells can also induce the **production of circulating ncRNAs that may modify the epigenome of remote germline cells** [dashed arrow from (A) to (B)].

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

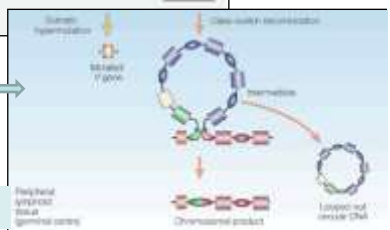
NATURE|Vol 441|29 June 2006|doi:10.1038/nature04959 INSIGHT REVIEW

Generation of neuronal variability and complexity

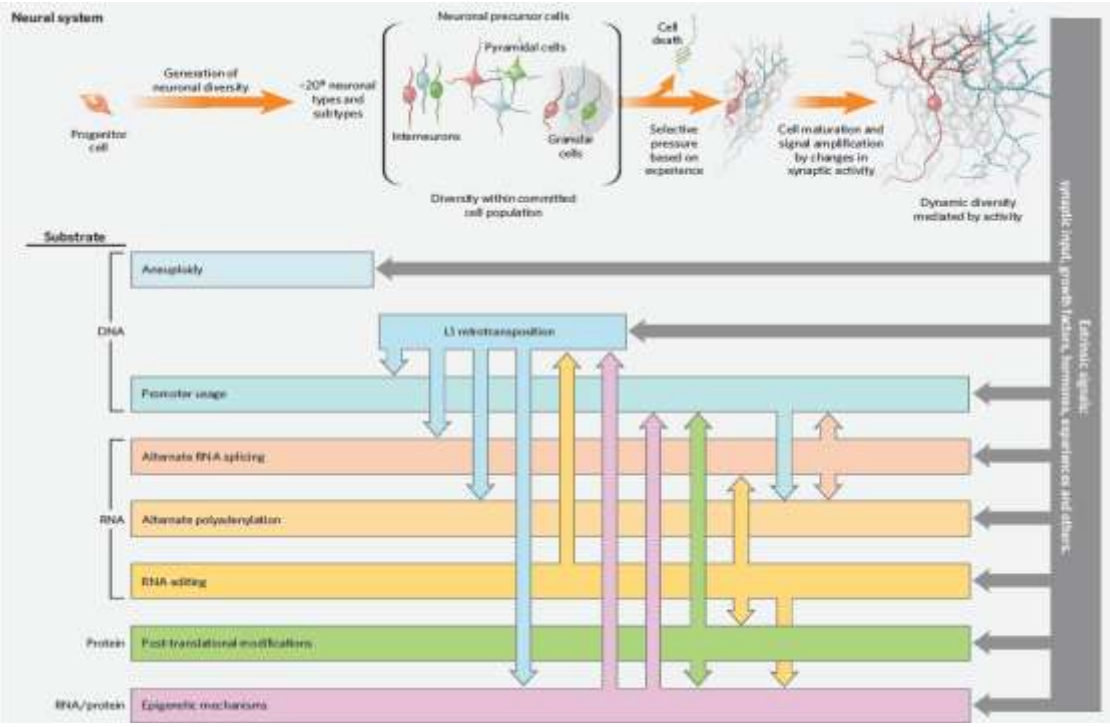
Alysson R. Muotri[1] & Fred H. Gage[1]



+ Somatic Hypermutation !



Kinoshita K., Honjo T. *Linking class-switch recombination with somatic hypermutation*
Nature Reviews Molecular Cell Biology (2001) 2, 493–503



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.

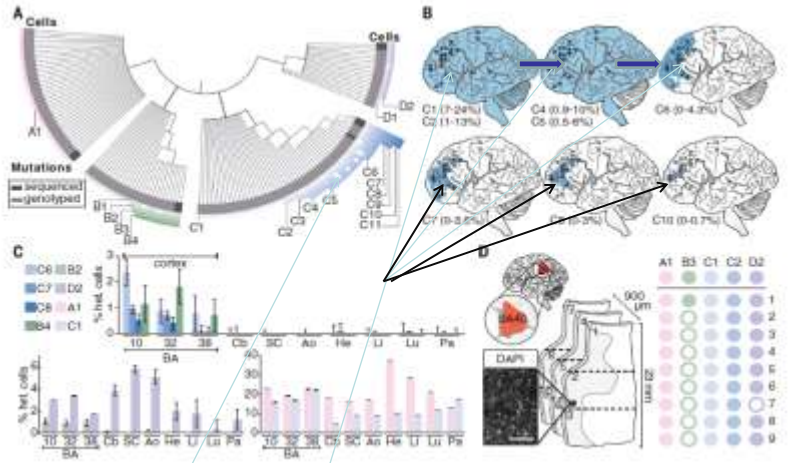


Fig. 3. Somatic mutations are shared between multiple neurons and demonstrate lineage relationships. (**A**) Lineage map of 136 human cortical neurons from brain B derived from 39 clonal somatic mutations, including SNVs, long interspersed nuclear element (LINE) insertions, and a TG dinucleotide expansion. 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. S3. (**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 BA46 (red, upper left) were dissected into three axial regions each (1 to 9). Right: Genotyping results for dissected sections. Solid circles denote presence of mutation in indicated sample; open circles, denote absence. Mutations with high allele fractions are present in all or virtually all regions, whereas only the least prevalent somatic variant (present in <0.5% of cells) is present in one region but not most regions.

Leading Edge
Previews

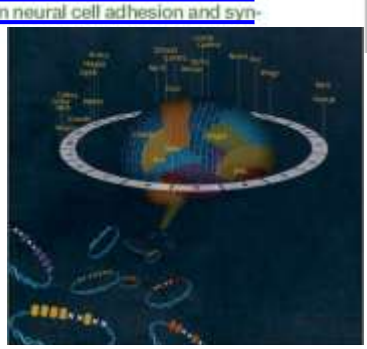
Cell 164, February 11, 2016 ª2016 Elsevier Inc. 593

Cell

A Mechanism for Somatic Brain Mosaicism

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

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



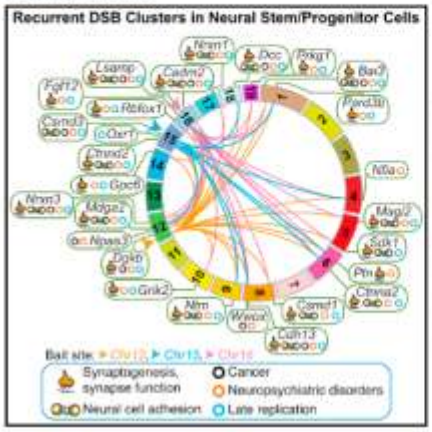
Many of the identified genes are **expressed in NSPCs located in the brain regions responsible for higher functions such as short-term learning,** and mutations in these genes in humans are associated with (and maybe predispose to) **psychiatric and neurological disorders manifested in mind functions—autism,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

Article

Cell

Long Neural Genes Harbor Recurrent DNA Break Clusters in Neural Stem/Progenitor Cells

Graphical Abstract



Authors

Pei-Chi Wei, Amelia N. Chang, Jennifer Kao, Zhou Du, Robin M. Meyers, Frederick W. Alt, Bjoern Schwer

Correspondence

alt@enders.tch.harvard.edu (F.W.A.), bjoern.schwer@childrens.harvard.edu (B.S.)

In Brief

Neural stem and progenitor cells undergo massive genomic alterations in a very restricted set of genes involved in synapse function and neural cell adhesion, processes that are likely to govern the special behavior of brain cells. Many of these genes have also been implicated in mental disorders.

Highlights

1) **27 Recurrent DSB clusters (RDCs)** are identified **in neural stem/progenitor cells**

2) All RDCs are within genes, most of which are long, transcribed, and late replicating

3) Most RDC genes are **involved in synapse function and/or neural cell adhesion**

4) A nucleotide-resolution view of **replication stress-associated fragile sites** is provided

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)

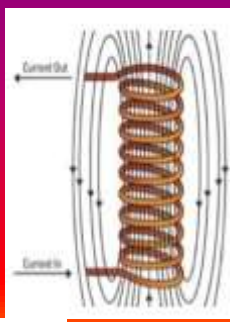
Many EMF frequencies in the environment can and do cause DNA changes.

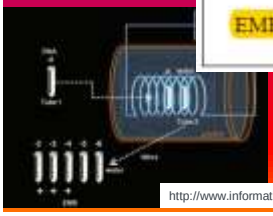
The EMF-activated cellular stress response is an effective protective mechanism for cells exposed to a wide range of EMF frequencies.

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)



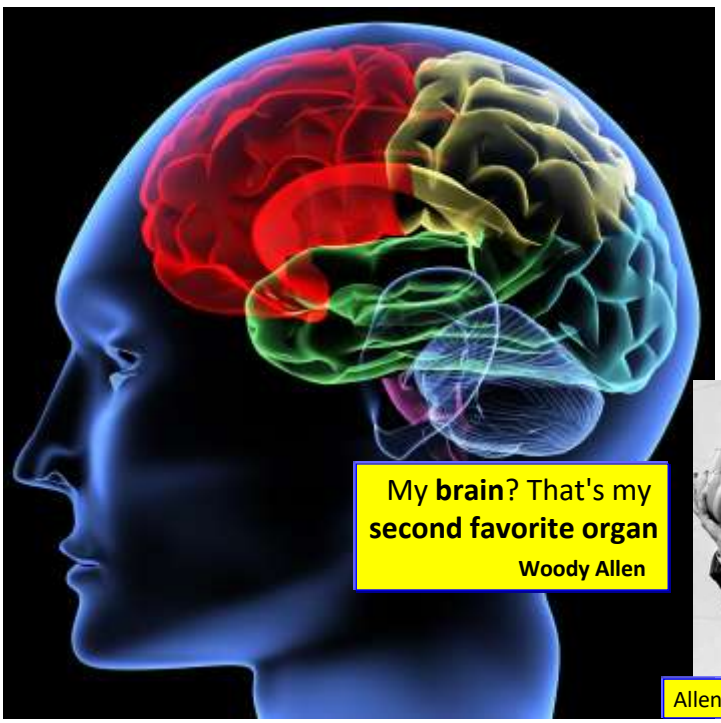


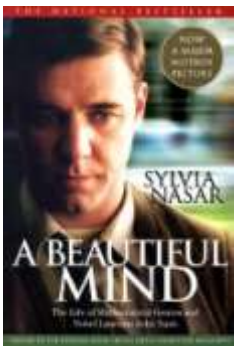
http://www.informationenergymedicine-academy.com/wp-content/uploads/coil-to-generate-7-Hz-carrier-wave-300x228.jpg 300w" sizes="(max-width: 500px) 100vw, 500px" /

Capitolo 3. **Disturbi del neurosviluppo: dalla genetica all'epigenetica**, di Ernesto Burgio, Daniela Lucangeli e Maria Antonietta De Gennaro

1. I disturbi dello spettro autistico nell'ambito dei disturbi del neurosviluppo
2. Dati epidemiologici: aumento reale o semplice incremento di diagnosi?
3. Verso un nuovo paradigma: dalla genetica lineare alla genomica sistemica (epigenetica, metagenomica, ologenomica)
4. *Nurture* e *Nature*
5. Filogenesi e ontogenesi: genetica ed epigenetica
6. I fattori di rischio
7. Il cervello nell'adolescente
8. Epigenetica *vs* genetica

In sintesi
Domande per l'autoverifica
Bibliografia





Allen Stewart Königsberg

Developmental changes in large-scale network connectivity in autism

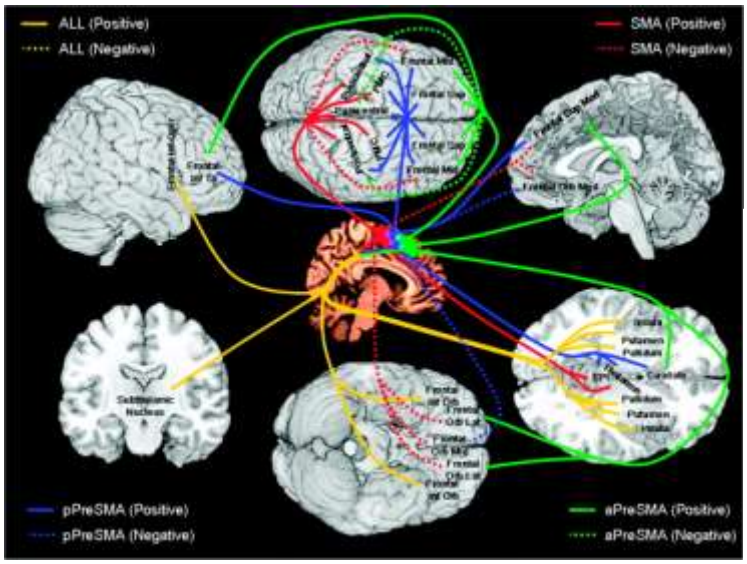
Nomi JS, Uddin LQ. ***Developmental changes in large-scale network connectivity in autism*.** Neuroimage Clin. 2015 Mar 6;7:732-41.

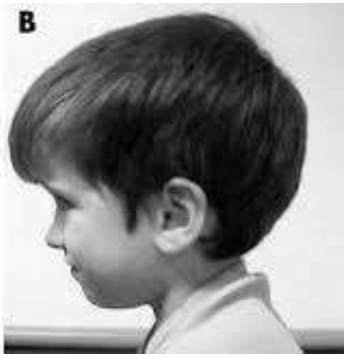
A recent theory attempting to reconcile conflicting results in the literature proposes that **hyper-connectivity of brain networks may be more characteristic of young children with ASD**, while **hypo-connectivity may be more prevalent in adolescent and adults** with the disorder when compared to typical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

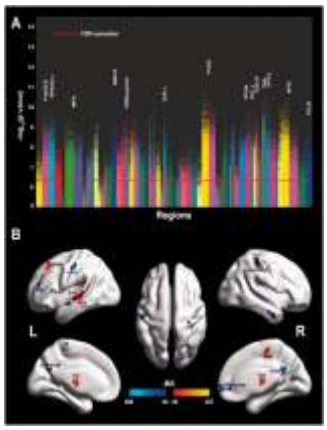
Cheng W, Rolls ET, Gu H, Zhang J, Feng J

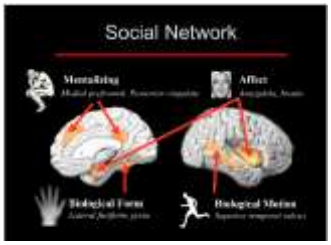
Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. Brain. 2015 May;138(Pt 5):1382-93.

..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

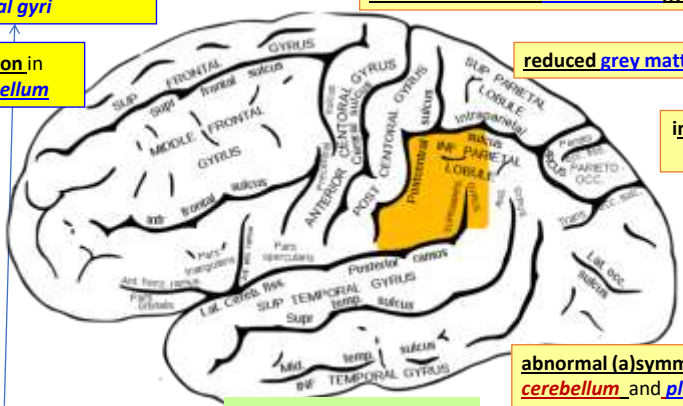
under-activations in the **left hemisphere fusiform** and ***supramarginal gyri***

decreased cerebral white matter gyrifications

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

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***

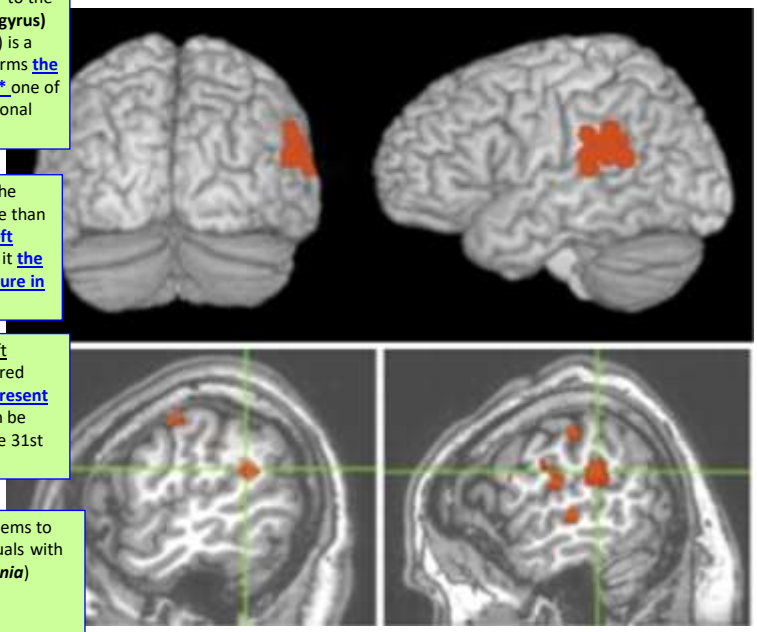
Elnakib A, Soliman A, Nitzken M, Casanova MF, Gimel'farb G, El-Baz A. ***Magnetic resonance imaging findings for dyslexia: a review.*** J Biomed Nanotechnol. **2014** Oct;10(10):2778-805.

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.



SCIENTIFIC REPORTS

OPEN

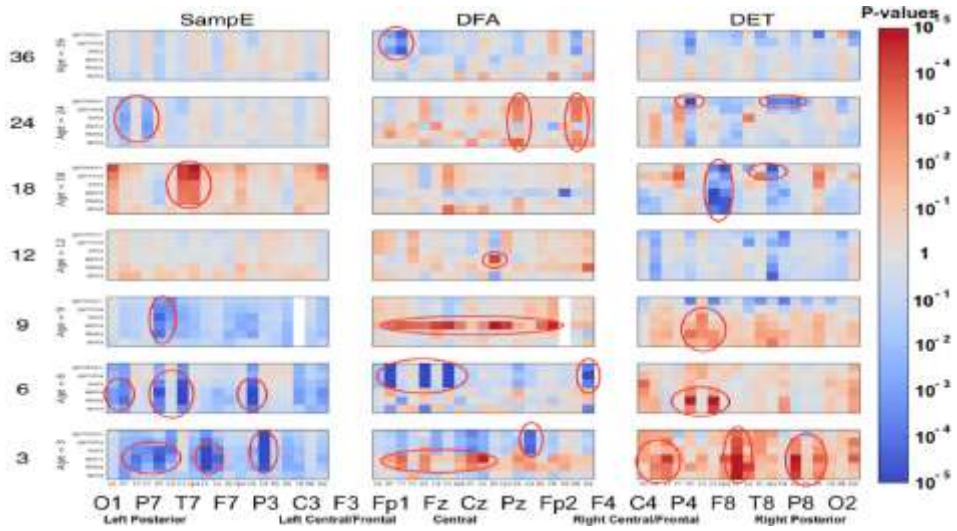
EEG Analytics for Early Detection of Autism Spectrum Disorder: A data-driven approach

Received: 15 August 2017
Accepted: 28 March 2018
Published online: 01 May 2018

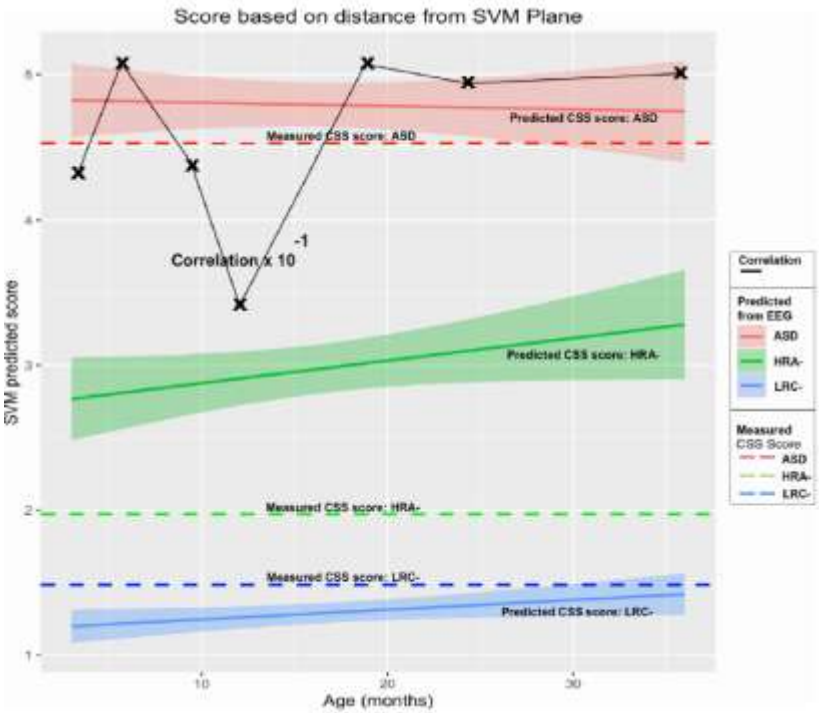
William J. Bosl[1,2,3], Helen Tager-Flusberg[4] & Charles A. Nelson[1,2,5]

Autism spectrum disorder (ASD) is a complex and heterogeneous disorder, diagnosed on the basis of behavioral symptoms during the second year of life or later. Finding scalable biomarkers for early detection is challenging because of the variability in presentation of the disorder and the need for simple measurements that could be implemented routinely during well-baby checkups. EEG is a relatively easy-to-use, low cost brain measurement tool that is being increasingly explored as a potential clinical tool for monitoring atypical brain development. EEG measurements were collected from 99 infants with an older sibling diagnosed with ASD, and 89 low risk controls, beginning at 3 months of age and continuing until 36 months of age. Nonlinear features were computed from EEG signals and used as input to statistical learning methods. Prediction of the clinical diagnostic outcome of ASD or not ASD was highly accurate when using EEG measurements from as early as 3 months of age. Specificity, sensitivity and PPV were high, exceeding 95% at some ages. Prediction of ADOS calibrated severity scores for all infants in the study using only EEG data taken as early as 3 months of age was strongly correlated with the actual measured scores. This suggests that useful digital biomarkers might be extracted from EEG measurements.

L'autismo è difficile da diagnosticare, soprattutto all'inizio della vita. Un nuovo studio su *Scientific Reports* mostra che **EEG** (oltretutto poco costosi) **predicono accuratamente o escludono il disturbo dello spettro autistico (ASD) in neonati di appena 3 mesi**.



Gli **algoritmi computazionali hanno analizzato sei diverse componenti (frequenze) dell'EEG (high gamma, gamma, beta, alpha, theta, delta) usando una varietà di misure di complessità del segnale**.
Queste misure **possono riflettere le differenze nel modo in cui il cervello è cablato e in che modo elabora e integra le informazioni**



I risultati sono stati sorprendenti.. **l'accuratezza predittiva a 9 mesi è stata quasi del 100%,** inoltre si è potuto **prevedere la gravità dell'ASD,** come indicato dal punteggio di gravità calibrato ADOS..

Le **differenze precoci di complessità del segnale**, mostrano **molteplici aspetti dell'attività cerebrale**, e corrispondano all'idea che **l'autismo sia un disturbo che inizia durante lo sviluppo precoce del cervello,** ma può assumere **diverse traiettorie**.

The "MS-ROM/IFAST" Model, a Novel Parallel Nonlinear EEG Analysis Technique, Distinguishes ASD Subjects From Children Affected With Other Neuropsychiatric Disorders With High Degree of Accuracy

Clinical EEG and Neuroscience 1–13
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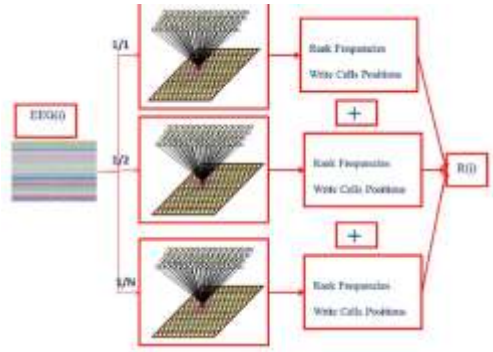


Enzo Grossi[1], Massimo Buscema[2,3], Francesca Della Torre[2], and Ronald J. Swatzyna[4]

Abstract

Background and Objective. In a previous study, we showed a new EEG processing methodology called Multi-Scale Ranked Organizing Map/Implicit Function As Squashing Time (MS-ROM/IFAST) performing an almost perfect distinction between computerized EEG of Italian children with autism spectrum disorder (ASD) and typically developing children. In this study, we assessed this system in distinguishing ASD subjects from children affected with other neuropsychiatric disorders (NPD). *Methods.* At a psychiatric practice in Texas, 20 children diagnosed with ASD and 20 children diagnosed with NPD were entered into the study. Continuous segments of artifact-free EEG data lasting 10 minutes were entered in MS-ROM/IFAST. From the new variables created by MS-ROM/IFAST, only 12 has been selected according to a correlation criterion. The selected features represent the input on which supervised machine learning systems (MLS) acted as blind classifiers. *Results.* The overall predictive capability in distinguishing ASD from other NPD cases ranged from 93% to 97.5%. The results were confirmed in further experiments in which Italian and US data have been combined. In this analysis, the best MLS reached 95.0% global accuracy in 1 out of 3 classes distinction (ASD, NPD, controls). This study demonstrates the value of EEG processing with advanced MLS in the differential diagnosis between ASD and NPD cases. The results were not affected by age, ethnicity and technicalities of EEG acquisition, confirming the existence of a specific EEG signature in ASD cases. To further support these findings, it was decided to test the behavior of already trained neural networks on 10 Italian very young ASD children (25–37 months). In this test, 9 out of 10 cases have been correctly recognized as ASD subjects in the best case. *Conclusions.* These results confirm the possibility of an early automatic autism detection based on standard EEG.

How Music shapes our Brain

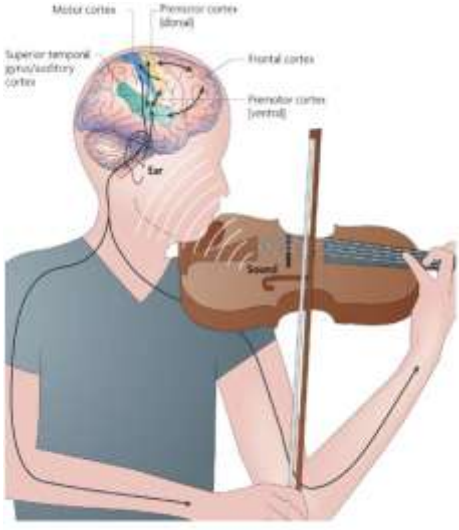
Un caso estremamente interessante è quello del **cervello del musicista** che presenta una **struttura alquanto particolare, almeno nei casi in cui lo studio della musica ha avuto inizio nelle primissime fasi della vita..**

"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

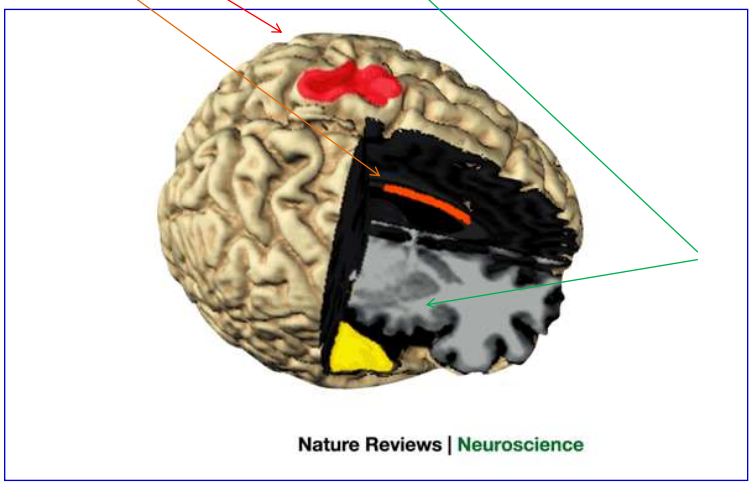
We generally assume that learning a musical instrument can be beneficial for kids, but it's actually useful in more ways than we might expect.

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**.



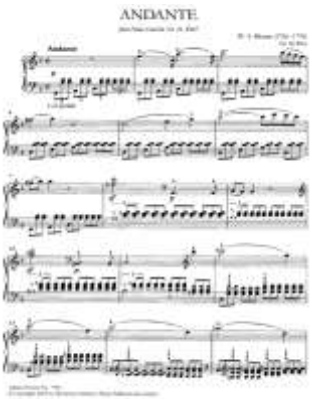
08 PLOS ONE ***Practicing a Musical Instrument in Childhood is Associated with Enhanced Verbal Ability and Nonverbal Reasoning***

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!