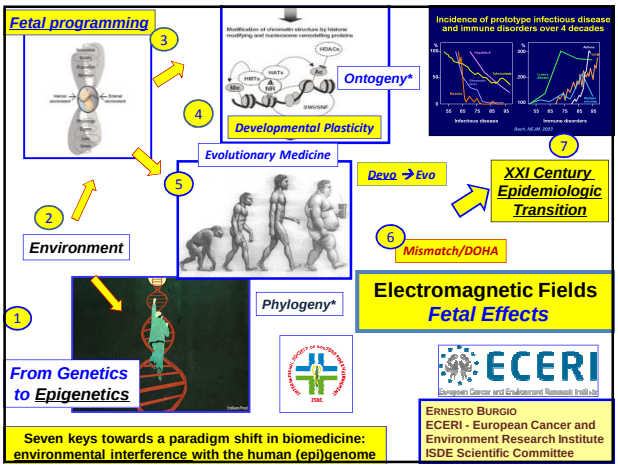


We are currently facing a ***paradigm shift*** in biomedicine

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

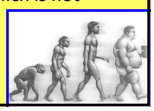
In the last ten years and especially since the appearance of **the first molecular epigenetic studies** we have begun to understand that the construction of the phenotype is the **result of the interaction** between the **information** coming from the **environment** and the **information** deeply inscribed inside the DNA

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

⇩

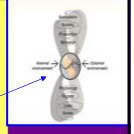
Therefore it can be argued that there is **no stable change in our phenotype (both physiological and pathological)** which is not

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



Other **key concepts** (obviously interdependent) are:
- ***developmental plasticity***
- ***fetal programming***

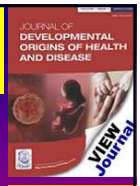
allow ing us to understand how **the fetus epigenetically program (for life) all its cells in a *predictive* and *adaptive* way** responding to **information** coming from the environment (through the ***mother bias***)

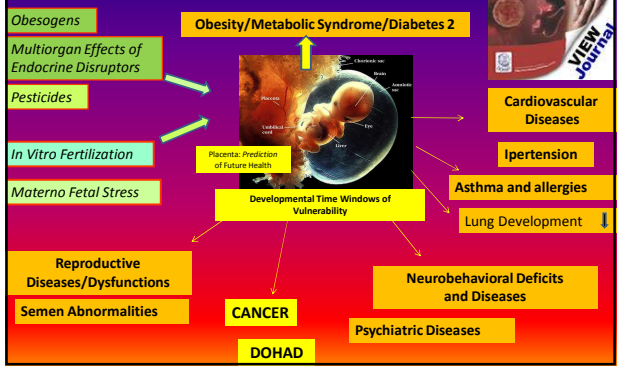


It is important to note that in this period
incorrect information **(*pollutants, endocrine disruptors* ..)** and /or
discrepancies between the **information** that the baby receives before and after birth **(*mismatch*)**
may create **epigenetically bad programmed cells** (including **gametes**), thus causing **chronic diseases in adulthood** or **even in subsequent generations**

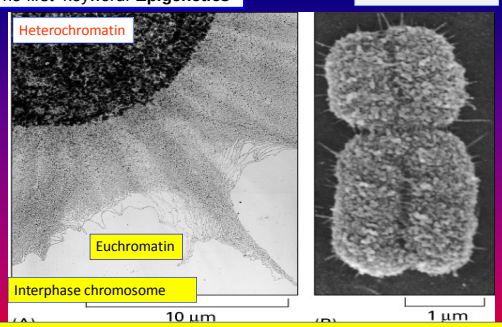
This theory (***DOHaD Developmental Origins of Health and Disease***) could help us to **explain the current epidemiological transition** ..

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





The first keyword: **Epigenetics**



Our proposal is **not to consider epigenetics just as a (minor) part of genetics** (*the marks of DNA, the histone modifications, the interference of microRNAs* modulating in various ways the transcription and translation of the message contained in the DNA), but to recognize in the study of **epigenetics** the most appropriate and powerful tool to build up **a new systemic and molecular model of genome,** finally understood as a **dynamic and fluid network which can interact inside itself and with the outside**

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

Epigenetic Regulation, a mechanism that allows the genome to integrate
– intrinsic **with**
– environmental **signals**

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

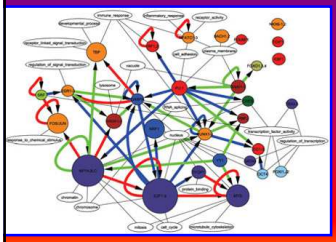
Science AAAS — ScienceInsider
Breaking news and analysis from the world of science policy

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

....Genes Know How to Network...BUT...

Strohman R. , April 2001 ***Beyond genetic determinism***

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

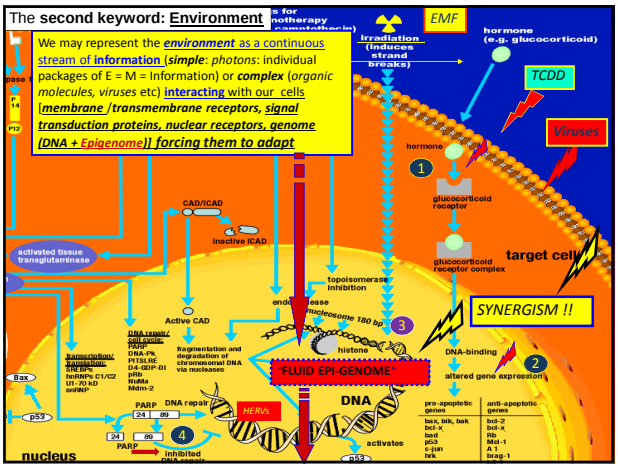


IN FACT Genes need to be told to switch "off" and "on":

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

The **second keyword: Environment**

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



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Electromagnetic fields stress living cells

Martin Blank[a,*], Reba Goodman[b]
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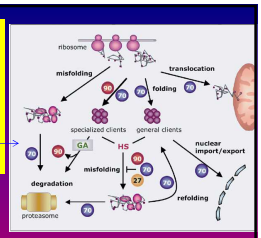
Received 30 January 2009; accepted 30 January 2009

Abstract

Electromagnetic fields (EMF), in both ELF (extremely low frequency) and radio frequency (RF) ranges, activate the cellular stress response, a protective mechanism that induces the expression of stress response genes, e.g., HSP70, and increased levels of stress proteins, e.g., hsp70. The 20 different stress protein families are evolutionarily conserved and act as 'chaperones' in the cell when they 'help' repair and refold damaged proteins and transport them across cell membranes. Induction of the stress response involves activation of DNA, and despite the large difference in energy between ELF and RF, the same cellular pathways respond in both frequency ranges. Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF, and studies with model biochemical systems suggest that EMF could interact directly with electrons in DNA. While low energy EMF interacts with DNA to induce the stress response, increasing EMF energy in the RF range can lead to breaks in DNA strands. It is clear that in order to protect living cells, EMF safety limits must be changed from the current thermal standard, based on energy, to one based on biological responses that occur long before the threshold for thermal changes.

Electromagnetic fields (EMF), in both ELF (extremely low frequency) and radio frequency (RF) ranges, activate the cellular stress response, a protective mechanism
that induces the expression of stress response genes, e.g., **HSP70**, and increased levels of stress proteins **hsp70**...
(The 20 different stress protein families are **evolutionarily conserved** and act as '***chaperones***' in the cell when they **'help' repair and refold damaged proteins** and **transport them across cell membranes**..)



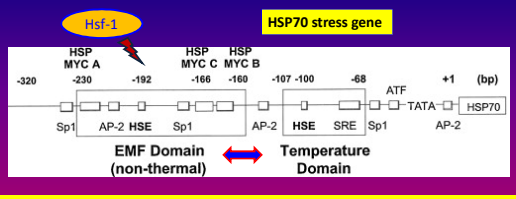
Induction of the stress response involves activation of DNA, and **despite the large difference in energy between ELF and RF, the same cellular pathways respond** in both frequency ranges.

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

While **low energy EMF interacts with DNA** to induce the **stress response**, **increasing EMF energy in the RF range can lead to breaks in DNA strands**.

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

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

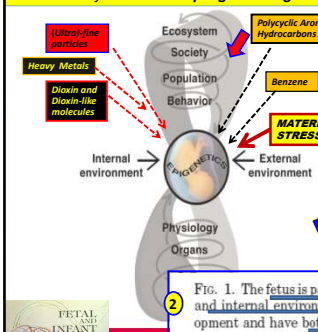


Synthesis of this stress protein is initiated in a **region of the promoter** where a transcription factor known as **Heat Shock Factor 1 (HSF-1) binds to a Heat Shock Element (HSE).**
The **EMF sensitive region on HSP70 promoter** is **upstream from the thermal domain of the promoter and is not sensitive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

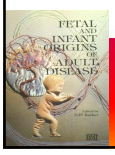
The **third** key word is ***fetal programming ...***



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

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

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

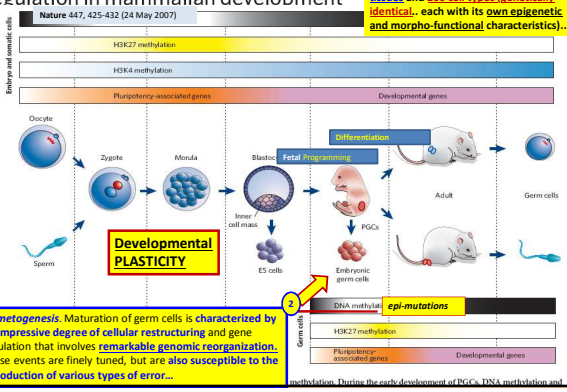


3

Cellular Differentiation*: an *epigentic process

Stability and flexibility of epigenetic gene regulation in mammalian development

Differentiation occurs numerous times **during the development of a multicellular organism** as the organism changes **from a single zygote to a complex system** of **tissues** and **200 cell types (genetically identical).. each with its own epigenetic and morpho-functional characteristics)..**



Gametogenesis. Maturation of germ cells is **characterized by an impressive degree of cellular restructuring** and gene regulation that involves **remarkable genomic reorganization.** These events are finely tuned, but are **also susceptible to the introduction of various types of error..**

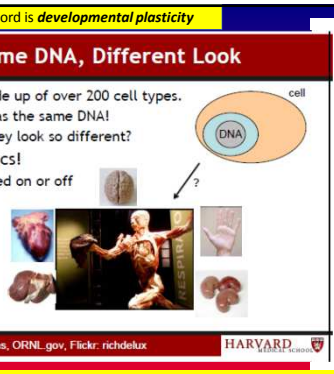
The **fourth** keyword is ***developmental plasticity***

Same DNA, Different Look

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

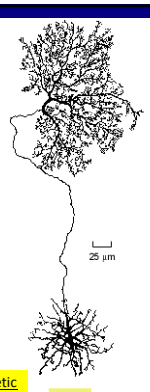
Epigenetics!

- Genes turned on or off



Wikimedia Commons, ORNL.gov, Flickr: richdelux

HARVARD MEDICAL SCHOOL



In contrast to what it is often asserted, **DNA** does not contain the genetic program of the individual, but simply an enormous amount of **potential information.. *Developmental plasticity*** refers to the many possible phenotypes (*polyphenisms*) that may result from a single genome.

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

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

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

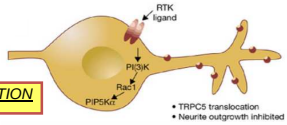
stem cells are the most relevant cellular model for validating safe mobile communication signals."

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

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

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

Disturbing the *CONNECTOME INSTRUCTION*

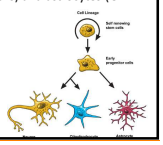


Ma Q, Deng P, Zhu G, Liu C, Zhang L, Zhou Z, Luo X, Li M, Zhong M, Yu Z, Chen C, Zhang Y ***Extremely low-frequency electromagnetic fields affect transcript levels of Neuronal differentiation-related genes in embryonic neural stem cells***. PLoS One 2014 Mar 3;9(3):e90041. doi: 10.1371/journal.pone.0090041. eCollection 2014.

Previous studies have reported that extremely low-frequency electromagnetic fields (ELF-EMF) can affect the processes of brain development, but the underlying mechanism is largely unknown. **The proliferation and differentiation of embryonic neural stem cells (eNSCs) is essential for brain development during the gestation period**. To date, there is no report about the effects of ELF-EMF on eNSCs. In this paper, we studied the effects of ELF-EMF on the proliferation and differentiation of eNSCs. Primary cultured eNSCs were treated with 50 Hz ELF EMF; various magnetic intensities and exposure times were applied. **Our data showed that there was no si** cell viability (CCK-8 assay), DNA synthesis (Edu incorporation), average diameter of neurospheres, cell cycle distribution (flow cytometry) and transcript levels of cell cycle related genes (P53, P21 and GADD45 detected by real-time PCR). **When eNSCs were induced to differentiation, real-time PCR results showed a down regulation of Sox2 and up-regulation of Math1, Math3, Ngn1 and Tuj1 mRNA levels after 50 Hz ELF EMF exposure (2 mT for 3 days),** but the percentages of neurons (Tuj1 positive cells) and astrocytes (GFAP positive cells) were not altered when detected by immunofluorescence assay. Although cell proliferation and the percentages of neurons and astrocytes differentiated from eNSCs were not affected by 50 Hz ELF-EMF, **the expression of genes regulating neuronal differentiation was altered.**

Disturbing the *CONNECTOME INSTRUCTION*

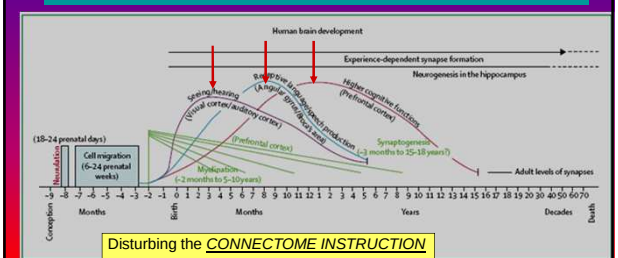
In conclusion, **our results support that 50 Hz ELF-EMF induce molecular changes during eNSCs differentiation, which might be compensated by post-transcriptional mechanisms to support cellular homeostasis.**



The ***Individual*** wiring

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

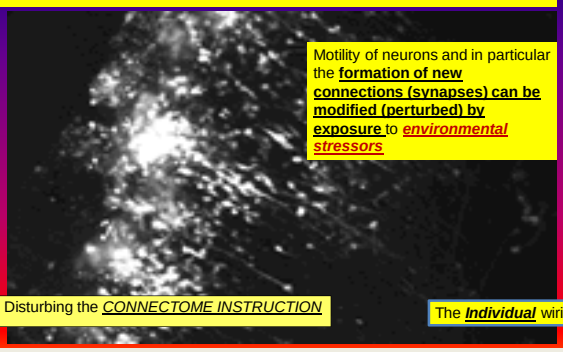
Formation of new synapses following stimulation..



Disturbing the *CONNECTOME INSTRUCTION*

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

Brain plasticity and modulation of its structure and its functions

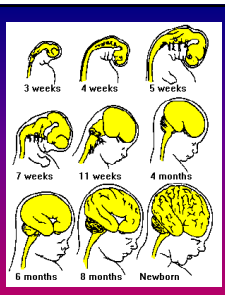


Motility of neurons and in particular the **formation of new connections (synapses) can be modified (perturbed) by exposure** to ***environmental stressors***

Disturbing the *CONNECTOME INSTRUCTION*

The ***Individual*** wiring

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



Disturbing the *CONNECTOME INSTRUCTION*

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**

CHEMICAL FALL OUT

The gift our mothers never wanted to give us

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

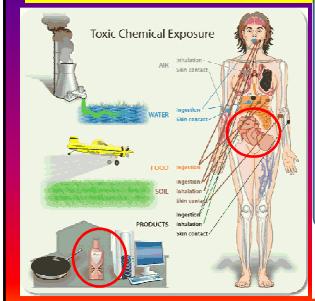
BodyBurden
The Pollution in Newborns
A benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood

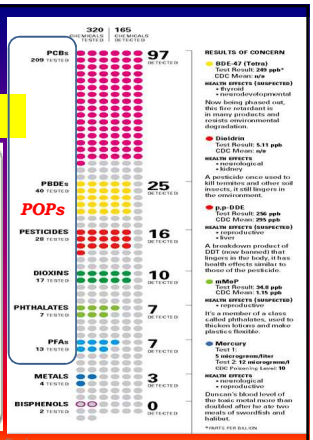
.. at present many studies in various parts of the world are evaluating the ***chemical body burden*** .. especially in women, children, embryos / fetuses, **providing dramatic results**.

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

Monitoring Body-Burdens

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





SCIENTIFIC REPORTS

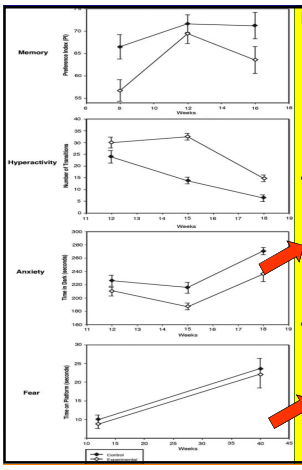
www.nature.com

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

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

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

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



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

- **We further demonstrated *impairment of glutamatergic synaptic transmission* onto pyramidal cells *in the prefrontal cortex* associated with these behavioral changes**
- **suggesting *a mechanism by which in-utero cellular telephone radiation exposure*** may lead to the ***increased prevalence of neurobehavioral disorders.***