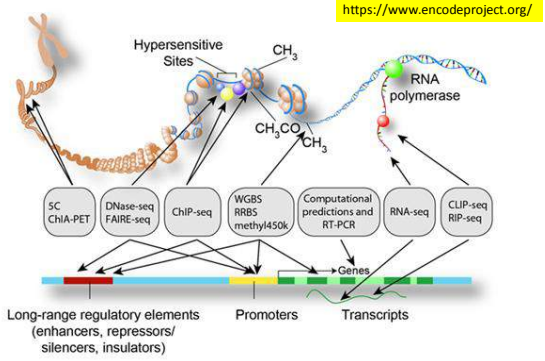
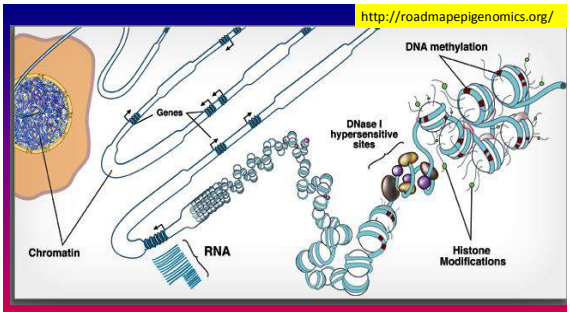
https://www.encodeproject.org/



ENCODE: Encyclopedia of DNA Elements

http://roadmapepigenomics.org/



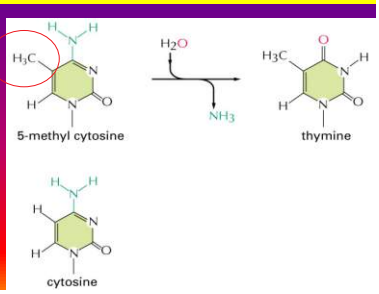
DNA methylation

→ **Covalent modification of the DNA** is also important for gene silencing human cells.

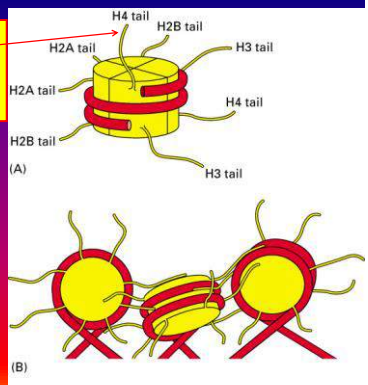
→ **Most genes have GC rich areas of DNA in their promoter regions,** referred to as **CpG islands.**
→ **Methylation of the C residues within the CpG islands leads to gene silencing**

2

(highly *unstable* base)



The Histone tails are a critical determinant of chromatin structure



1

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

Histone Tails are subject to a variety of covalent modifications

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

E.g. generally,
Histone Acetylation is associated with transcriptionally active genes
Deacetylation is associated with inactive genes (= gene silencing)

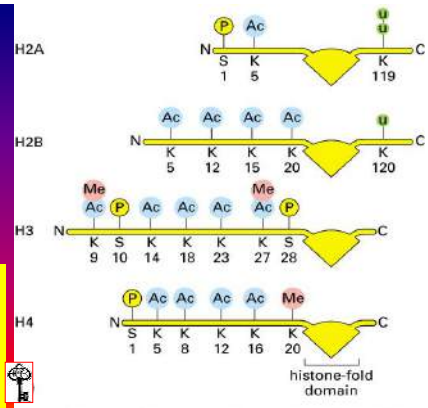
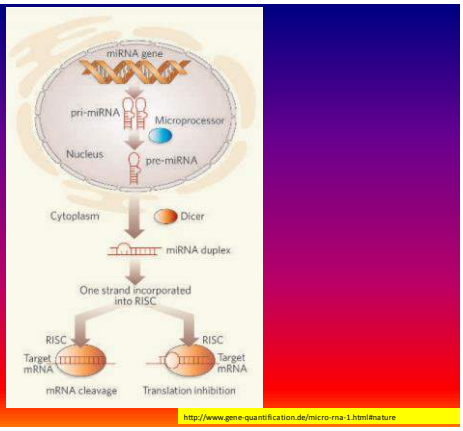


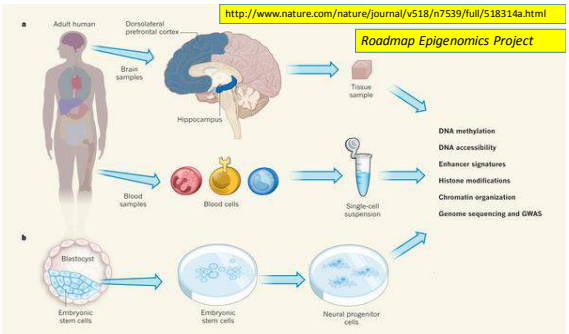
Figure 4–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

3



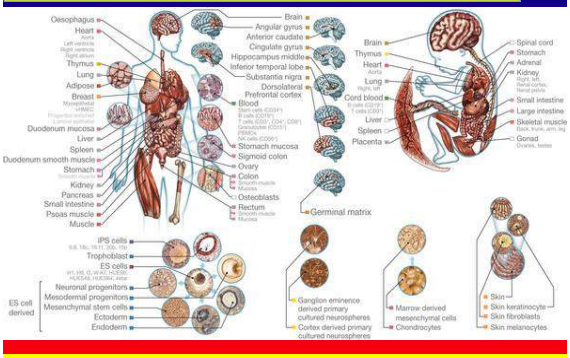
http://www.nature.com/nature/journal/v518/n7539/full/518314a.html

Roadmap Epigenomics Project



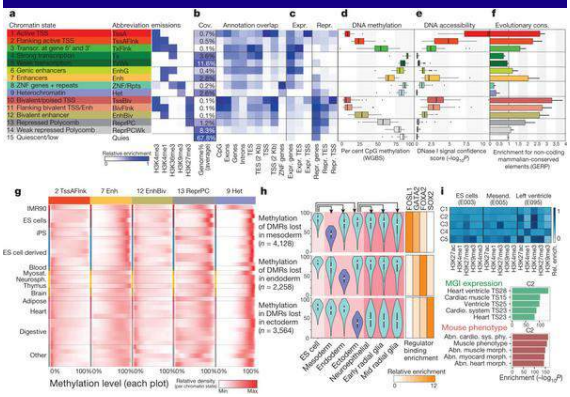
The Roadmap Epigenomics Project has produced **reference epigenomes that provide information on key functional elements controlling gene expression in 127 human tissues and cell types.**. *Embryonic stem (ES) cells*, which are taken from the embryo at the blastocyst stage(b) and can give rise to almost every cell type in the body, were used to analyse, for example, the **differentiation** of stem cells into different neuronal lineages

Tissues and cell types profiled in the Roadmap Epigenomics Consortium



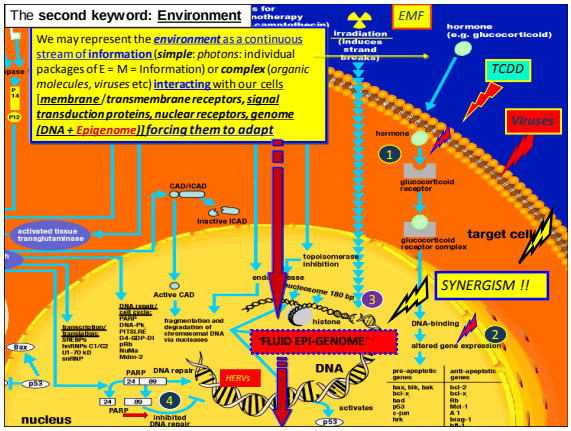
Primary tissues and cell types representative of all major lineages in the human body were profiled, including multiple brain, heart, muscle, gastrointestinal tract, adipose, skin and reproductive samples, as well as immune lineages, ES cells and iPS cells, and differentiated lineages derived from ES cells

Chromatin states and DNA methylation dynamics.



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***



ELSEVIER

Pathophysiology 16 (2009) 71–78

PATHOPHYSIOLOGY

www.elsevier.com/locate/pathophys

Electromagnetic fields stress living cells

Martin Blank [a,*], Reba Goodman [b]

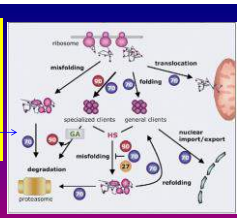
[a] Department of Physiology, Columbia University, New York, NY, USA
[b] Department of Pathology, Columbia University, New York, NY, USA

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**..)



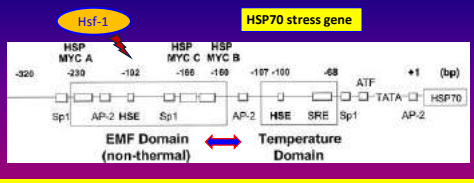
Induction of the stress response involves activation of DNA, and **despite the large difference in energy between ELF and RF, the same cellular pathways respond** in both frequency ranges.

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..

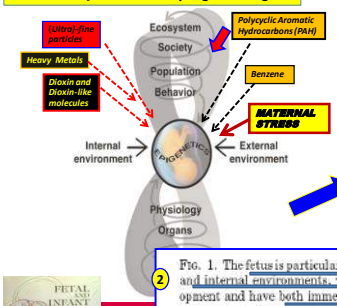


Synthesis of this stress protein is initiated in a **region of the promoter** where a transcription factor known as **Heat Shock Factor 1 (HSF-1) binds to a Heat Shock Element (HSE).**
The **EMF sensitive region on HSP70 promoter** is **upstream from the thermal domain of the promoter and is not sensitive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



… 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..

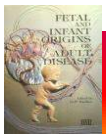
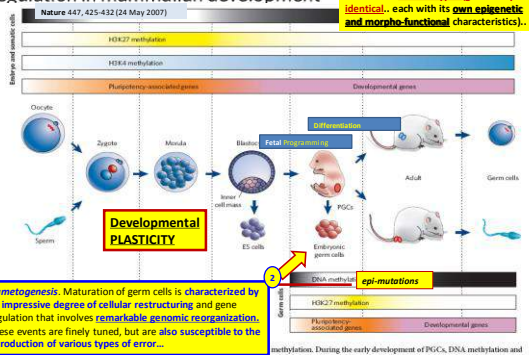


FIG. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular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

***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

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.

CHEMICAL FALL OUT

The gift our mothers never wanted to give us

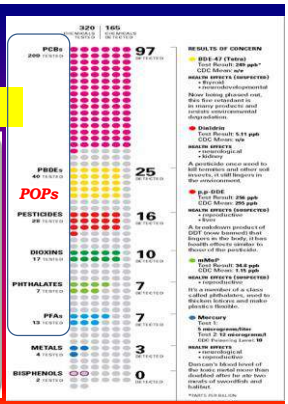
1. ENDOCRINE DISRUPTORS dioxin-like moleculles
2. HEAVY METALS
3. ULTRAFINE PARTICLES

.. 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,

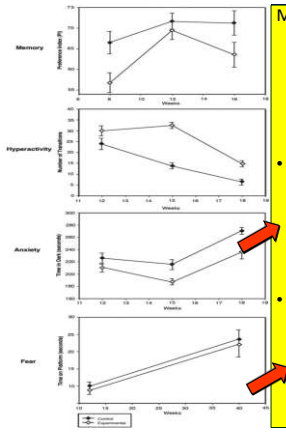


SCIENTIFIC REPORTS
www.nature.com
SCIENTIFIC REPORTS | 2 : 312 | DOI: 10.1038/srep00312

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.***

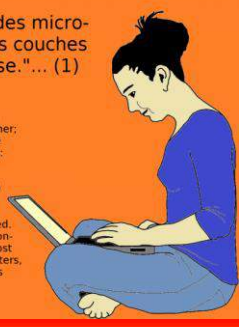
Among women **exposed to microwaves**
47% had **miscarriages before the 7th week of pregnancy**

"Parmi les femmes exposées à des micro-ondes, 47,7% ont eu des fausses couches avant la 7e semaine de grossesse."... (1)

Professor John R Goldsmith, International / Advisor Consultant for R.F. Communication, Epidemiology and Communications Sciences Advisor to the World Health Organisation, Military and University Advisor, Researcher; wrote concerning the low level exposure of microwave irradiation (below thermal level) incident upon women:

"Of the microwave-exposed women, 47.7% had miscarriages prior to the 7th week of pregnancy...."(1)

The level of irradiation incident upon the women was stated, as from, five microwatts per centimetre squared. This level of irradiation may seem meaningless to a non-scientist; however, when I say that it is below what most schoolgirls will receive in a classroom of wi-fi transmitters, from the age of approximately five years upwards, this level becomes more meaningful.



https://grossessequebec.wordpress.com/

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**. **T**his 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**

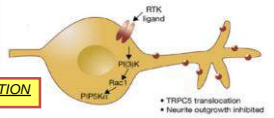
stem cells are the most relevant cellular model for validating safe mobile communication signals."

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*



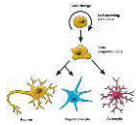
Ma Q, Deng P, Zhu G, Liu C, Zhang L, Zhou Z, Luo X, Li M, Zhong M, Yu Z, Chen C, Zhang Y ***Extremely low-frequency electromagnetic fields affect transcript levels of Neuronal differentiation-related genes in embryonic neural stem cells***. PLoS One 2014 Mar 3;9(3):e90041. doi: 10.1371/journal.pone.0090041.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

Disturbing the *CONNECTOME INSTRUCTION*

y 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.**

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.**



Mutation Research 704 (2010) 115–122

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

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Community address: www.elsevier.com/locate/mutres

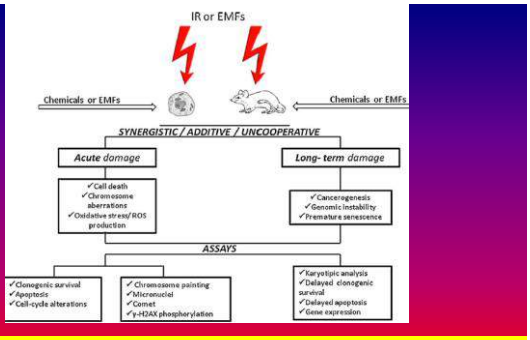
Review

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

Lorenzo Manti *, Annalisa D'Arco

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

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



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

Nerve Cell Damage in Mammalian Brain after Exposure to Microwaves from GSM Mobile Phones

Leif G. Salford,[1] Arne E. Brun,[2] Jacob L. Eberhardt,[3] Lars Malmgren,[4] and Bertil R. R. Persson[3]

[1]Department of Neurosurgery, [2]Department of Neuropathology, [3]Department of Medical Radiation Physics, and [4]Department of Applied Electronics, Lund University, The Rausing Laboratory and Lund University Hospital, Lund, Sweden

The possible risks of radio-frequency electromagnetic fields for the human body is a growing concern for our society. We have previously shown that weak pulsed microwaves give rise to a significant leakage of albumin through the blood–brain barrier. In this study we investigated whether a pathologic leakage across the blood–brain barrier might be combined with damage to the neurons. Three groups each of eight rats were exposed for 2 hr to Global System for Mobile Communications (GSM) mobile phone electromagnetic fields of different strengths. We found highly significant ($p < 0.002$) evidence for neuronal damage in the cortex, hippocampus, and basal ganglia in the brains of exposed rats. *Key words:* blood–brain barrier, central nervous system, microwaves, mobile phones, neuronal damage, rats. *Environ Health Perspect* 111:881–883 (2003). doi:10.1289/ehp.6039 available via *http://dx.doi.org/* [Online 29 January 2003]

VOLUME 111 | NUMBER 7 | June 2003 • Environmental Health Perspectives

Three groups each of eight rats were exposed for 2 hr to Global System for Mobile Communications (GSM) mobile phone electromagnetic fields of different strengths.
We found highly significant (p< 0.002) evidence for neuronal damage in the cortex, hippocampus, and basal ganglia in the brains of exposed rats

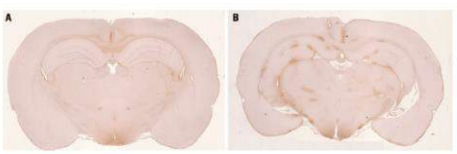


Figure 1. Cross-section of central parts of the brain of (*A*) an unexposed control rat and (*B*) an RF EMF-exposed rat, both stained for albumin, which appears brown. In (*A*), albumin is visible in the central inferior parts of the brain (the hypothalamus), which is a normal feature. In (*B*), albumin is visible in multiple small foci representing leakage from many vessels. Magnification, about ×3.

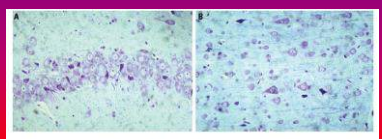


Figure 2. Photomicrograph of sections of brain from an RF EMF-exposed rat stained with cresyl violet. (*A*) Row of nerve cells in a section of the pyramidal cell band of the hippocampus; among the normal nerve cells (large cells) are interspersed black and shrunken nerve cells, so-called dark neurons. (*B*) The cortex, top left, of an RF EMF-exposed rat showing normal nerve cells (pale blue) intermingled with abnormal, black and shrunken "dark neurons" at all depths of the cortex, but least in the superficial upper layers. Magnification, ×160.

Int J Toxicol. 2015 Mar 5. pii: 1091581815574348. [Epub ahead of print]

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

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

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

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

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

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

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

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

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

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

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

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

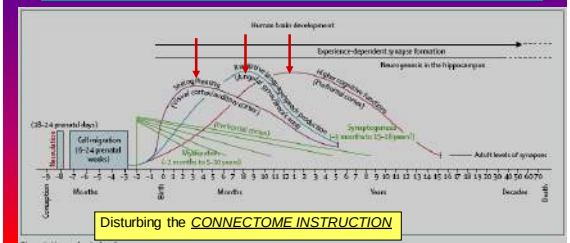
Blank M, Goodman R. ***Comment: a biological guide for electromagnetic safety: the stress response.*** Bioelectromagnetics. 2004;25(8):642–646

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

The ***Individual*** wiring

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

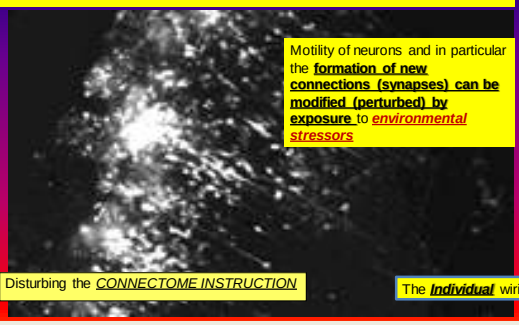
Formation of new synapses following stimulation..



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

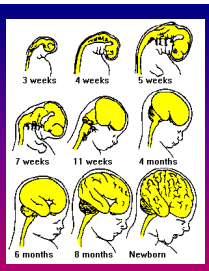


Motility of neurons and in particular the **formation of new connections (synapses) can be modified (perturbed) by exposure** to ***environmental stressors***

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*

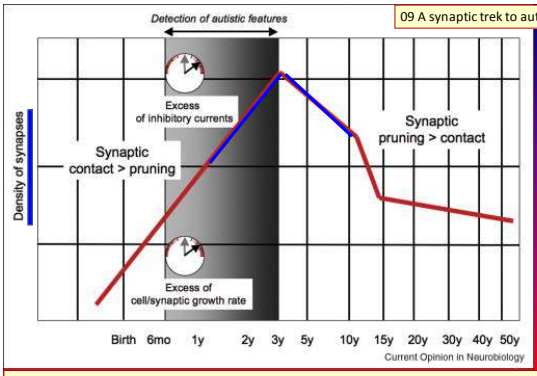
The brain grows at an amazing rate during development. At times during brain development, **250,000 neurons are added every minute!**
At birth, almost all the neurons that the brain will ever have are present.

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**

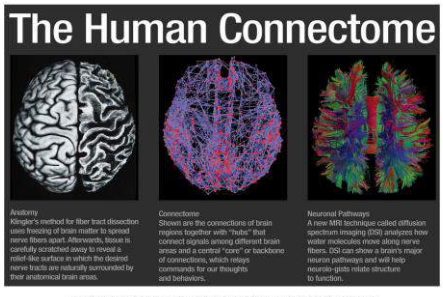
A **stegosaurus dinosaur weighed approximately 1,600 kg but had a brain that weighed only approximately 70 grams (0.07 kg).** Therefore, **the brain was only 0.004% of its total body** weight. In contrast, an adult human weighs approximately 70 kg and has a brain that weighs approximately 1.4 kg. Therefore,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

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.

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



http://www.humanconnectomeproject.org/

The **general, species-specific, structure of the human brain/cortex** is, indeed, a product of ***phylogeny***:

The ***ancestral*** wiring

in particular, the ***lateralization*** and the resulting ***dominance of an hemisphere over the other***

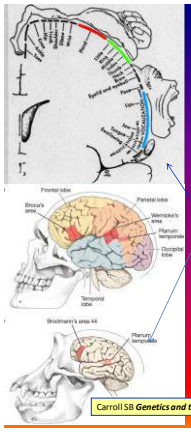
and the ***functional connections between the various regions and areas of the brain*** are **under genetic control (*body plans*), limiting** (*channelling*) **the transformative (evolutionary) potential of the information** coming from outside..

On the contrary

the **fine, individual and soft-wiring structure of the cortex, (i. e. the individual *connectome*), is the result of *ontogeny* and develops under epi-genetic control.**

The ***Individual*** wiring

http://www.humanconnectomeproject.org/



Le ***câblage*** ancestral

As with the **sensory cortex**, **Wilder Penfield** was responsible for **mapping the motor cortex… Chimps** also have a motor cortex, but the **area of cortex devoted to vocal control is restricted** relative to what you see in the human animal. **Their brains are just not built for the detailed vocalizations** you need to **in order to pronounce all the phonemes** that comprise linguistic verbal communication. Neurologists knew this, and **had the chimp trainers consulted a neurologist before starting, they would have saved themselves years of wasted effort**, and moved directly to the more realistic goal of seeing whether chimps could learn sign language

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

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

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

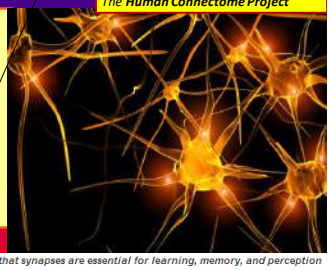
billion of dendritic tree structures are connecting with each other in response to information coming from the environment and **from the rest of the "network " under construction**

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

Autism

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

*The **Human Connectome Project***



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

As for the **causes of autism**

many hypotheses have been advanced:

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

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

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

I will try to show **why and in what sense this approach is not only simplistic, but also misleading**

as

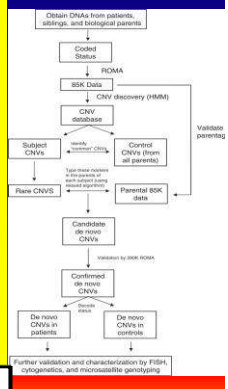
-the **increase of the cases is continuous and alarming,**

- **the traditional genetic risk factors** have **not so far been found**

-the most important mutations are ***de novo*** (which is to say, they are **not found in somatic cells of the parents .. but rather occur**

- in ***parents' gametes*** or
- ***during fetal development***

And that makes ***autism*** **a non-hereditary genomic disease**



Beaudet AL ***Autism: highly heritable but not Inherited*** Nature Medicine (2007) 13, 534 - 536

- The fact that these **problems usually occur after a latency period** (of **normal intellectual and motor development**) shows that
- **the brain basic structures** (cerebral neuronal differentiation and migration: definition of the **functional areas of the brain**), **are not changed**
- but, so to speak, **it is the *software (connectome)* - *synaptic*** connections .. **- *neuronal circuits* .. to be damaged**

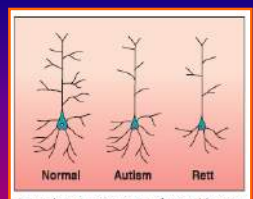


Fig. 2. Schematic representation of pyramidal neurons from control, autism, and Rett brains. In autism, the cell body is small and there is reduced dendritic branching. Similar changes occur in Rett, along with reduction in basilar dendritic branching. The reported changes are subtle and apply to a few neurons in selected brain regions in each disorder (50, 87).

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