

Research Article



How to avoid DAD?

Abstract

DAD is an acronym for Dementia Alzheimer Disease which has damaged 5.5million families in 2017 in the US alone. Most patients of the DAD are aging World-War II (WWII) Baby-Boomers (BB). Although Dementia is not a disease itself, it draws our attentions as it can lead to Alzheimer's which is not a normal part of growing old. Epidemiologically speaking, the greatest risk factor for the disease is increasing age; after age 65, the risk of Alzheimer's doubles every five years, and after age 85, the risk reaches nearly 50 percent. We have detailed the Bio-Medical Wellness (BMW) of causes of DAD. Furthermore, we provided WWII BB with the common sense advice for leading a healthy lifestyle are: (1) Regular Exercise (daily hour), (2) Social Engagement (Be Happy), (3) Healthy Diet (you are what you eat), (4) Mental Stimulation (use it, or loss it), (5) Quality Sleep (circa 8 hours), and (6) Stress Management (not by Alcohol). Thus, we reviewed Alzheimer disease. Unfortunately, the vicious cycle between the causes and the effects of Alzheimer Disorder becomes difficult to be disentangled. It is caused by Amyloid plaques in the synapses gaps among neurons in our brains. Alzheimer's disease is marked by the presence of Amyloid beta (A β) denoted as the Protein Precursor Peptides (PPP) consisting of 36–43 amino acids. The PPP is derived from the Amyloid Precursor Protein (APP), which is "cut or cleaved by beta secretase and gamma secretase" to yield A β . Furthermore, the A β molecules can aggregate to form flexible soluble pathogenic Oligomers (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4598734/>). The Oligomers are toxic to nerve cells with multiple toxin receptor candidates under investigation. It is now believed that certain "misfolded Oligomers" (MO) act as initiation "seeds" that are harmful and can induce other A β molecules to take the MO seed form, leading to a chain reaction akin to a Prion infection. The misfolded A β can induce tau protein to form MO seeds resulting in a vicious open loop cycle. This might be the reason why once mild dementia occurs it accelerates quickly to Alzheimer's.

These interventions might come a bit late or lightly to millions of families, nevertheless, some will benefit. However, for these interventions to have utility, not just in common sense level, we need to thoroughly understand the BMW basis. For readership convenience, to Mental Stimulation we provided "To read further Appendixes) Appendix A DNA Discovery; B: Eat Right; C: Exercise Regularly. This paper suggests noninvasive interventions to delay the onset of dementia reducing the chance for Alzheimer's disease for all cohort groups.

Keywords: glymphatic system, dementia alzheimer disorders, atrocities glial cells to ship energy byproducts to blood stream during sleep

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Abbreviations: DAD, dementia alzheimer's disease; PPP, protein precursor peptides; APP, amyloid precursor protein; MO, misfolded oligomers

Introduction

Why sleep is vital for mental health?

Epidemiologically speaking, the Dementia is not a disease, but it can be a precursor leading to Alzheimer's disease (AD). People with Dementia may have short-term memory problem, e.g. keeping track of a purse, keys, or wallet, paying bills, planning and preparing meals, remembering appointments or traveling out of the neighborhood. Vascular dementia, which occurs after a stroke, is the second most common dementia type. But there are many other conditions that can cause symptoms of dementia, including some that are reversible, such as thyroid problems and vitamin deficiencies. On the other hand, AD typically progresses slowly in mild (early-stage), moderate (middle-stage), and severe (late-stage). On average, a person with Alzheimer's disease lives four to eight years after diagnosis, but can live as long

as 20years, depending on other factors. The greatest risk factor for the AD is increasing age. After age 65, the risk of Alzheimer's doubles every five years. After age 85, the risk reaches nearly 50percent. So far, 5.5million DAD have cost the United States (US) \$259 Billion per annum in 2017. The Alzheimer is the sixth leading cause of death in the US, more than the combined breast cancers and prostate cancers. The rate is not slowing down either. Consequently, the US public health social security system might be facing the severe tests in decades to come. The number of DAD will be tripled to 16 millions, 3 decades later and the cost at \$1.1 Trillion circa 2050. We observed that this DAD calamity might be originally due to an Endangering Cohort Group (ECG) called World War II (WWII) Baby Boomers (BB), who were born as the result of the end of WWII. The so-called WWII BB was about 77 millions in the US alone, which suddenly increased the population resulting in the competition in education, job, and prosperity opportunities. They grew old now and become matured seniors about 50% at 38millions, and already retired about 50% at 19millions. One third of retirees at 5.5million have already developed DAD. In this paper, we talk about how to help the other

two third of Aging WWII BB retirees about 12 millions to live healthy lives avoiding DAD.

There are reasons behind the specific WWII BB having a high probability becoming DAD. The BB comprise nearly 40% of the American population. The No.#1 reason was the severe competition for the similar resources during their growing up, matured and retired lifetime. For example, they have acquired the habit: "working hard, playing hard, sleeping less, as well as lacking the Biomedical Wellness (BMW) knowledge about the importance of sleep at the night.¹ We can trace back, the growth in the population has created a secondary spur to the economy. More people have created more consumer demand, triggering an increase in manufacturing and production. This upward spiral created a long-lasting economic boom that raised the standard of living throughout the country and the developed world. Average income rose during these decades, which then further increased demand. They are competing against one another for the educations, the jobs. As a result, they learned to be "working hard, playing hard," and "sleeping less" throughout their lives. The first of the baby boom generation became eligible to retire in 2012. Today, with approximately one-third of them already at or over traditional retirement age, the BB will be the first generation to truly blaze the trail through the landscape of retirement in the 21st century. And in many ways, the way they spend their post-work years will be different from their parents' the lost generation of WWI ("génération perdue," by Gertrude Stein and "The Sun Also Rises," Ernest Hemingway). As a result, as they are getting old, retired, but did not have time to take care of themselves while they were young, busy & consuming a lot of fast food; and mostly likely are suffering from Dementia Alzheimer Disorder (DAD) from a mild degree to the seriousness. They might not have the experience and be able to take the advantage of modern brain physiology. Thus, we reviewed and summarized in the simplest possible but correct terms. Of the estimated 5.5million Americans living with Alzheimer's dementia in 2017, an estimated 5.3million are age 65 and older and approximately 200,000 individuals are under age 65 and have younger-onset Alzheimer's. One in 10 people age 65 and older (10percent) has Alzheimer's dementia.(cf. <https://www.alz.org/facts/>) in order to recommend (Appendix B) a temperament-matched Quick fixing Remedy(QR), e.g. daily 30min Reading, Walking, Tai Chi and/or Yoga on your own; and weekly Social classes learning Tai Chi and/or Yoga at local Community Centers.

We began with the common sense of a healthy brain. The brain behaves as if the central borough Manhattan Island confined within the rest of 5 boroughs of New York City as their body and limbs. Almost all big city, e.g. Chicago, the garbage collection comes at the night to avoid the daytime traffic jam. In order to be flicked up & dumped back into the big truck container, the smaller household container about the size of a dead neuron (in mm size) is carried with a specific Glue ears, called the Glial cells about one tenth of those plastic trash containers. Thus, if the garbage men on strike, everyone in the city will be suffered. Analogously, when there is not enough nighttime rest, brain remains at the night to produce more energy byproduct trash, it will block the garbage collection, and the trash will pile up over time and block the neuronal pathway of the associative memory recall at the Hippocampus memory, and the patients become DAD (Figure 1).²

Maiken Nedergaard and Steven A. Goldman are working over 5years to figure out how brain clears out energy byproducts at Univ. Rochester School of Medicine and Univ. of Copenhagen. The protein

fragments known as beta-Amyloid peptides, which are present in Alzheimer's disease, are examples of the cellular detritus cleared through the drainage system, mostly during sleep. In the healthy brain, the Glymphatic system clears proteins associated with Alzheimer's, Parkinson's and other neurological diseases. To survive, the brain must have some way of flushing out debris. It is inconceivable that an organ so finely tuned to producing thoughts and actions would lack an efficient waste disposal system. The remarkably high percentage of beta-Amyloid removed challenged the widely held idea that brain cells break down all their own wastes internally (through degradation processes called ubiquitination and autophagy); now we know that the brain removes a good deal of unwanted proteins whole, sweeping them out for later degradation. In our research, we found an undiscovered system for clearing proteins and other wastes from the brain-and learned that this system is most active during sleep. The need to remove potentially toxic wastes from the brain may, in fact, help explain the mystery of why we sleep and hence retreat from wakefulness for a third of our lives. This fluid enters tiny channels that extend from the cavity into cells called Astrocytes, whose end feet from the periarterial space by encircling blood vessels. The Cerebrospinal fluid (CSF) then moves out of the Astrocytes and travels by convective flow through brain tissue. Pharmaceutical regulates the Glymphatic system by increasing the rate of CSF flow during sleep could literally flush Amyloid out of the brain. The expansion and contraction of the interstitial space during sleep were important to both brain function and protein-waste clearance. The system serves the whole brain at 3 lb weight; but uses 20% body energy. It can produce the debris that must be removed at the night without daytime traffic jam, just like every City garbage trucks out trash at the night when less traffic jams. Our working hypothesis is that a less waste products to block the small Astrocytes glial cell to drain the debris, like "ants can slowly chip away a large load of trash & carry to a drainage place without road blocks."³⁻¹¹ The Glymphatic system has less wastes debris for easy trafficking and pre-empt limited brain volume to block regenerated neurons (Figure 2). Of course (Figure 3), Nothing beats Good Genes Homo Sapiens has about 50% in the Genome; another 50%, in the Phenome or the Epigenetic (Outer-genetic). Human species have 23 pairs of Chromosomes(C) (Mnemonics: holding your two hands together, that are divided into Peace Sign: 2+3, 23 pairs). Conveniently, we set 23 into 4 groups in rows. In summary, Figure 4 shows the G#1 & G# 4 group have 5C; G#2 has 7C; G#3 has 6C. Note that Huntington's disease is discovered in 1983: G#1C No. 4; Hereditary Breast Ovarian Cancer (HBOC) syndrome G#3C No. 17; Down's syndrome dementia Alzheimer disease Chromosome G#4C No. 21.

Epigenetic phenotype lifestyle

John Hopfield demonstrated optical diffraction to interference scattering to reveal the transcript RNA checking out along DNA gene the codec back & forth. A smaller error rate is unachievable with a one-step mechanism. . Since DNA (Deoxyribonucleic acid) has base pairs, i.e. A-T (adenine - thymine) and G-C (guanine - cytosine) with the hydrogen bonds. DNA with high GC-content than AT-content is more stable than DNA with low GC -content. Kinetic proofreading allows enzymes to discriminate between two possible reaction pathways leading to correct or incorrect products with accuracy higher than what one would predict based on the difference in the activation energy between these two pathways. Life style may not modify necessarily the 1-D gene expression but the 3-D epigenetic read-expression of those critical genes associated with physiologic

and pathologic processes, including embryonic development, aging, and carcinogenesis. Glucose hydrolysis at tenth Fructose sweetness cannot digest but converted to fat and meanwhile, the transport impedes meridian/lymph tubeless circulations while the circulation through sluggish blood vessels capillary beds where the arteries meets the veins. The back-chaining proofreading can reduce error rate substantially below Maxwell-Boltzmann probability Eq (1), 1 in 10,000 Thermodynamic free energy of Gibbs is not enough to keep coding stable, thus the dynamic of error correction back-chaining of the transcript RNA codec is important element.

$$\exp\left(-\frac{\Delta G_{C-D}}{RT}\right) \leq \exp\left(-\frac{\Delta G_{A-T}}{RT}\right) \quad (1)$$

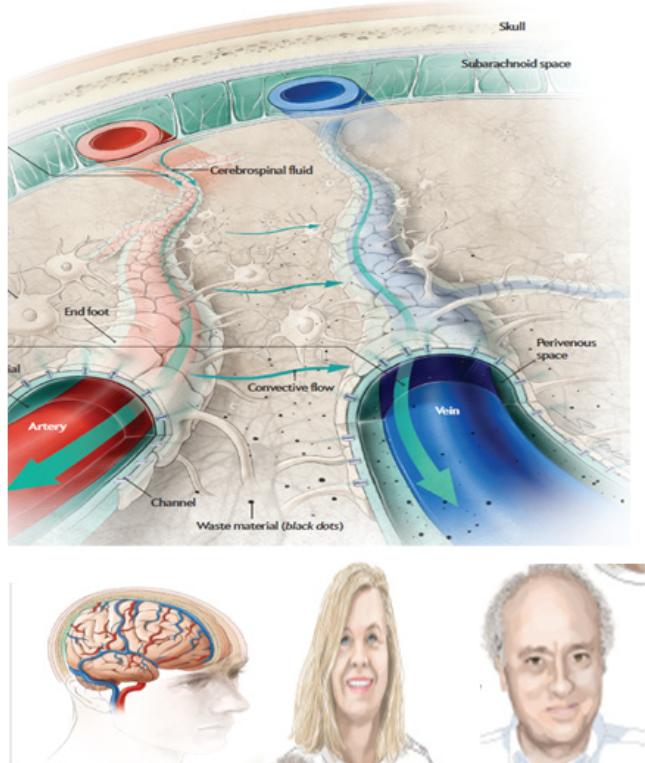


Figure 1 Brain Drain Glymphatic System (March 2016, Sci. Am. 45).¹

where isobaric Gibbs free energy of C-D moving along the reaction pathway containing less probability of correct recognition sites versus other more stable G-T sites. John Hopfield studies using laser scattering to probe the interference spectrum of transcript RNA dynamics was direct evidence of such nature error correction mechanism (cf. NAS decade science book series:1900-2000) Life style (Phenome: food & exercise) can influence epigenetic mediating DNA Methylation (express or not) and Histone spooling (winding tightly or loosely) for easy gene expression or not. Occasional hunger can reduce specifically Insulin-like Growth Factor-1 (IGF-1), Target of Rapamycin (TOR) Protein Kinase A (PKA) factor and revitalize immune stem cells. In contrary to popular belief, the hydrogen bonds do not stabilize the DNA significantly, and stabilization is mainly due to 3-D stacking interactions (epigenetic Phenome codes run the genetic genome machine). Appendix A to read further about genome (Figure 5).

Health brain biological neural networks natural selection

Healthy brain thinking and memory may be modeled as Biological Neural Networks (BNN) serving Massively Parallel and Distributed commutation, computing, and learning at synaptic weight junction between j -th and i -th neurons that Donald Hebb introduced a learning model $[W_{j,i}]$ 5 decades ago, defined mathematically, since McCullough-Pitts and Von Neumann introduced the concept of neurons as binary logic element,

$$0 \leq \bar{a} = \sigma(\bar{X}) \equiv \frac{1}{1 + \exp(-\bar{X})} \leq 1;$$

$$\frac{d\sigma(X)}{dx} = a(1-a) - 1 \leq \bar{a} = \tan(i\bar{X}) = \frac{e^{\bar{X}} - e^{-\bar{X}}}{e^{\bar{X}} + e^{-\bar{X}}} = \frac{\sinh(\bar{X})}{\cosh(\bar{X})} = \tanh(\bar{X}) \leq 1;$$

$$\frac{dtanh(x)}{dx} = 1 - \tanh(x)^2 \quad (2)$$

Biological Neural Networks (ANN) Computing are those Activation Column Vector \bar{a} of thousands neurons $\bar{a}^T = (a_1, a_2, \dots)$ after squash binary sigmoid logic function, or bi-polar hyperbolic tangent logic function within the multiple layer deep learning, with the backward error propagation requires gradient descent derivatives: Massively Parallel Distributed Processing; superscript $1 \in (1, 2, \dots) = R^1$ denotes 1-th layers (Figure 6). The 1K by 1K million pixels image spanned in the linear vector space of million orthogonal axes where the collective values of all neuron's activations $\bar{a}^{[l]}$ of the next l-th layer in the infinite dimensional Hilbert Space. The slope weight matrix $[W^{[l]}]$ and intercepts $\bar{e}^{[l]}$ will be adjusted based on the million inputs $\bar{X}^{[l-1]}$ of early layer. The threshold logic at the output will be Figure 5(a) bipolar sigmoid, and (b) within layers will be bi-polar hyperbolic tangent

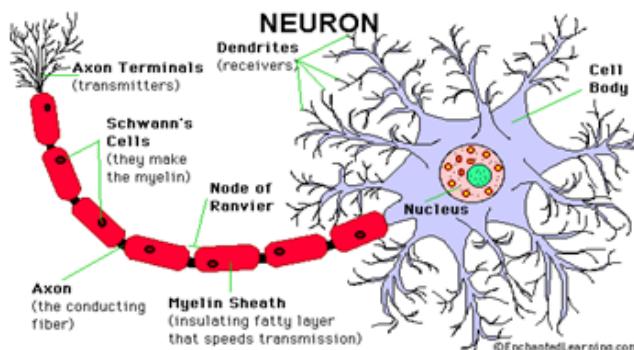
$$\bar{a}^{[l]} = \sigma\left(\left[W^{[l]}\right]\bar{X}^{[l-1]} - \bar{\theta}^{[l]}\right), \quad (3)$$

Frank Rosenblatt developed ANN, as Marvin Minsky coined the name of Artificial Intelligence. Stanford Bernie Widrow, Harvard Paul Werbos, UCSD David Rumelhart, Carnegie-Mellon James McClelland, U. Torrente Geoffrey Hinton, UCSD Terence Sejnowski, have pioneered the Deep Learning multiple layers Models, Backward Error Propagation computational (backprop) model. The Output Performance could efficiently be the supervised learning at Least Mean Square (LMS) error cost function of the desired outputs versus the actual outputs. The Performance model could be more flexible by the relaxation process as unsupervised learning at Minimum Herman Helmholtz Free Energy: Brain Neural Networks (BNN) evolves from the Charles Darwinian fittest survival viewpoint he breakthrough came when he noted Lyell's suggestion that fossils found in rocks that the Galapagos Islands each supported its own variety of finch bird, a theory of evolution occurring by the process of Natural Selection or Natural Intelligence at the isothermal equilibrium thermodynamics due to Nedergaard M¹ for a constant temperature brain (Homosapiens

37 °C ; Chicken 37 °C) operated at a minimum isothermal Helmholtz free energy when the input power of pairs transient random disturbance of \hat{a} – brainwaves may be represented by the degree of uniformity called the entropy S, as indicated by the random pixel histogram are relaxed to do the common sense work for the survival.

Thermal equilibrium brain

$$\min. H = E - T_o S \quad T_o = 37 \text{ } ^\circ\text{C} \quad (4)$$



whil $T_o = 37 \text{ } ^\circ\text{C}$ is for the optimum elasticity of Hemoglobin of a red blood cell, the chicken need the extra heat hatching the eggs. The power of pairs \bar{X}_{pair} sensory provides us the vector inputs for rapid fusion, Figure 2 taking no time to run away from a distant crouching tiger,

Power of pairs input

$$\bar{X}_{pair} = [A] \bar{S} \quad (5)$$

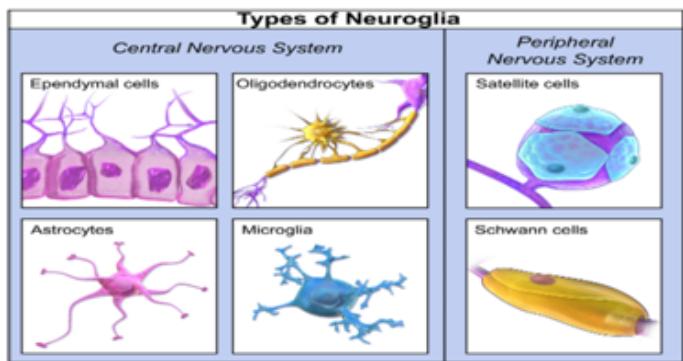


Figure 2 6 kinds of Active Glial Cells: Some Glial Cells (Schwann cells) are surrounding the Axon neuron known as "Myelin Sheath" insulating fatty layer that speeds transmission (keeping the output repulsive positive ion vesicles align up in the axon pipe, like ducks cross the road, so that one pushes in, the other pushes out in pseudo-real time). House-Keeping Servant Cells have 4 kinds. They are electrically insulated Glial Cells to keep those positive ions line-up within communication Axon channel: Astrocytes, Oligodendrocytes, Ependymal Cells, Microglia, in Central Nervous System, 2 kinds Satellite cells and Schwann cells in Peripheral Nerve System. Albert Einstein has 10 billion neurons; but 100 billion Glial cells that are charge neutral and missed in the first cut conducting measurement. During 8 hour good night sleep, the brain produces much less physiological by-products and the brain wave calms down to the delta waves (5~10Hz). There are about 100 billion Glial cells (Astrocytes: Latin: star-shape) that can haul energy byproduct other physiology trash produced by billions neurons and also dead neurons about 10 times in the size through the lymph blood capillary system toward the liver for purification & recycling. One cannot help but question an general design question why brain has to piggy back the liver by going through the trouble of a long distance passage through the neck and spinal cord to the liver. Why do we not doing the similar thing like liver directly at the end of brain stem? Of course, we understand the rest of body also produce energy by-product about 80% that requires the liver to purify the blood

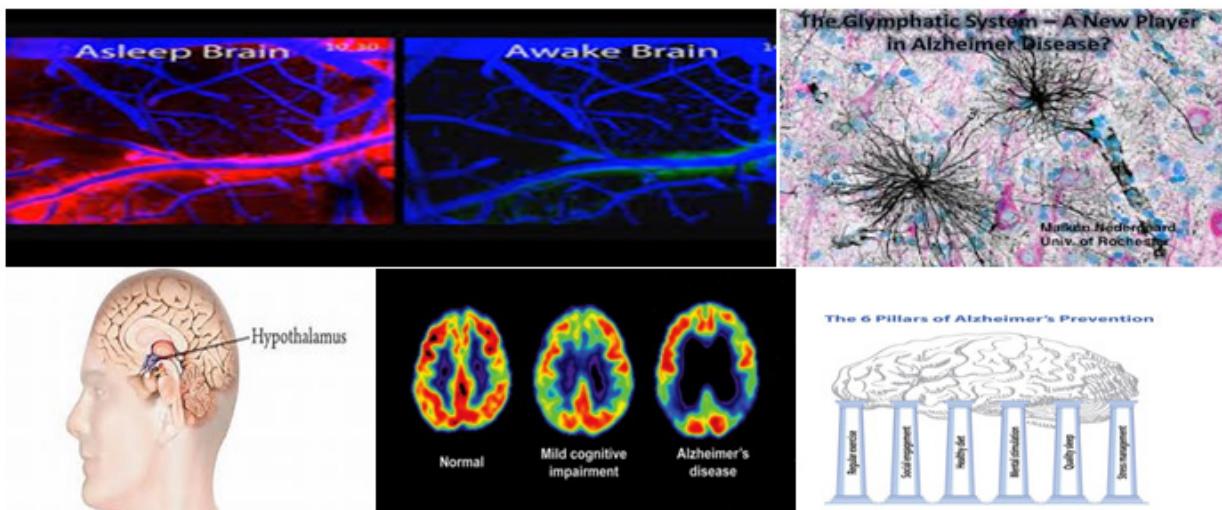


Figure 3 Human Glymphatic System: During awake brain, Hypothalamus, & underneath Pituitary gland controlled & regulated hormone clock. According to the study, the brain used about 20% of the whole body energy. Likewise, it produce 20% energy by-product that seems to take a good eight hours sleep to clean out from the Brain-Blood Barrier (BBB) Glymphatic System. Brain Drain Glymphatic System work when you sleep; Of course, there are "Six pillars in healthy life style" to support our healthy brains. They are "quality sleep," "regular exercise" to grow neuronal plasticity at the cortex and cerebellum near the central brain or stem spinal cord by Regular Exercise, Social Engagement, Healthy Diet, Mental Stimulation, Quality Sleep, Stress Management; to prevent Alzheimer (Wikipedia)

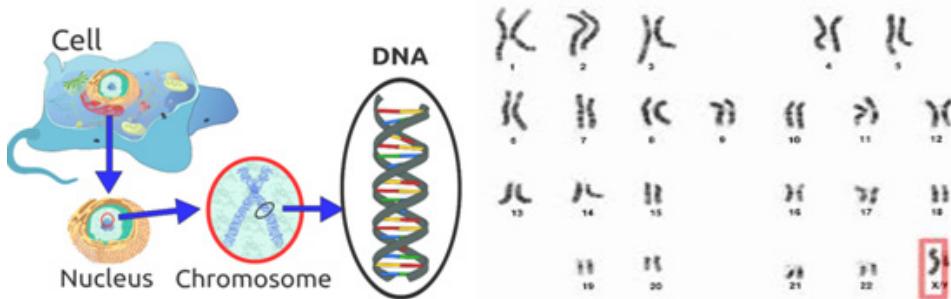


Figure 4 Genome (a) Nucleus Chromosome, DNA; (b) Homo Sapiens 32 pairs of 64 Chromosome un-winded in a total 3 meters long or the total statistics led to Human Genome Program. Realizing the significance to biostatistics of BB mental diseases in 1988, the National Research Council recommended a national concerted program to map the whole human genome in 10 to 15 years. Given the gene is not enough, it is often the transcript from the gene might suffer errors.

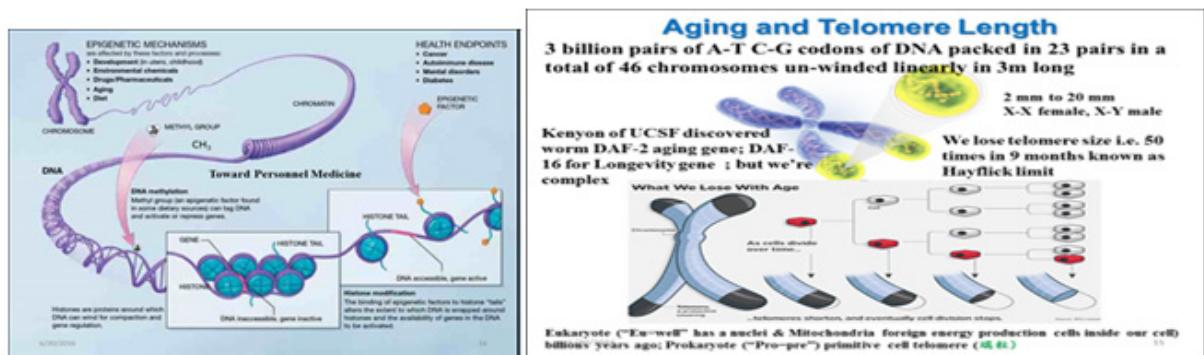


Figure 5 Human Epigenetic Program officially respectively started after Human Genome Program in 1990 in the US, by Department of Energy (DOE) and the National Institutes of Health (NIH) publishing a plan for the first five years of the anticipated 15 year project; in 1995. Completed in April 2003, the HGP gave us the ability, for the first time, to read nature's complete genetic blueprint for building a human being. European Union's led by France, British German, etc. The HGP was one of the great feats of exploration in history - an inward voyage of discovery rather than an outward exploration of the planet or the cosmos; an international research effort to sequence and map all of the genes - together known as the genome - of members of our species, Homo sapiens

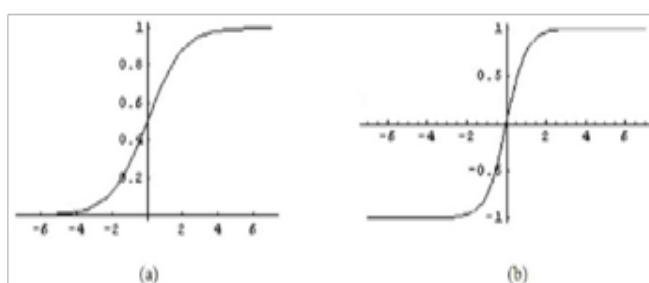


Figure 6 Nonlinear threshold logics of Activation firing rates (a) for the output classifier, (b) hidden layers hyperbola tangent

We have reviewed how to appreciate the BNN with Glial Cells other than Neurons. In the following paragraphs, we have derived mathematically the model of glial cells (Figure 7). Although there is only one unified definition of Glial Cells: as the Minimum free energy slope over the dendrite tree summation, which have 6 different dendrite tree summations lead to 6 different glial cells. For example, the star shape Dendrite Summation defines the Astrocytes Glial Cells. Albert Einstein has 10 billion neurons just like we do, but he has 100B Glial cells, e.g. Astrocytes, that is important for house cleaning servant function to minimize DAD, which might have made him different from some of us. These house-keeping smaller glial cells surrounded the each neuron output called Axon that can keep positive ions vesicle which are repulsion to one another in line, as one ion is pushed in from one end of the Axon, so that those conducting positive charge ion vesicles have no way escape but line up by those insulating Glial

cells in their repulsive chain in about 100Hz, 100 ions per second, no matter how long or short the axon is. The longest axon is about 1 meter longer from the neck to the toe for the instantaneously issue the order from HVS to run away from the tiger. The insulated fatty acids, Myelin sheath, are known to be Glial cells, among those 6 types of Glial Cells; (d) Einstein's Brain has been kept after his pass away.

The *Glial Cells* (glue force) is derived by us for the first time when the internal energy E is expanded as the Taylor series of the internal representation \bar{S}_i related by synaptic gap with vesicle transmission proportional to the weight matrix $[W_{i,j}]$ to the Power of the Pairs $\bar{S}_i = [W_{i,j}] \bar{X}_{pair}$ of which the slope turns out to be biological *Glial cells* \bar{g}_j

$$\bar{g}_j = -\frac{\partial H}{\partial \bar{D}_j}, \quad (6)$$

where the j -th Dendrite tree sum \bar{D}_j of all i -th neurons whose firing rates in proportional to the internal degree of firing rate S_i called the Entropy uniformity:

$$\bar{D}_j = \sum_i [W_{i,j}] \bar{S}_i$$

From which we have verified Donald O. Hebb learning rule who has formulated six decades ago in the brain neurophysiology. Given a time increment $\varsigma = |\Delta t|$ the learning plasticity adjustment is

proportional to the pre-synaptic firing rate \bar{s}_i and the post synaptic glue force \bar{g}_j

$$\Delta[W_{i,j}] = \frac{\partial[W_{i,j}]}{\partial t} \mathbf{c} = -\frac{\partial \mathbf{H}}{\partial [W_{i,j}]} \mathbf{c} = -\frac{\partial \mathbf{H}}{\partial \mathbf{D}_j} \cdot \left(\frac{\partial \mathbf{D}_j}{\partial [W_{i,j}]} \right) \mathbf{c} \equiv \bar{g}_j \bar{s}_i \mathbf{c}$$

(Bilinear Hebb Rule) (7)

This Hebb Learning Rule may be extended by chain rule for multiple layer “Backprop gradient descent learning causality algorithm”:

$$[W_{i,j}] = [W_{i,j}]^{\text{old}} + \bar{g}_j \bar{s}_i \quad (8)$$

We can conceptually borrow from Albert Einstein the space-time equivalent special relativity to trade the individual time experience with the spatially distributed causality experiences gathered by Asynchronously Massively Parallel Distributed (AMPD) Computing Robots.



Figure 7 A constant temperature brain as heat reservoir can take the Power of the Pair sensor inputs to generate local excitements, e.g. a distant crouching tiger, then the relaxation of thermal excitation to the reservoir temperature following the irreversible thermodynamics learning without a teacher. While those are agreed, it must be the signal; disagreed, the noises. The thermal noise energy $T_0 S$ is necessary to allow the fluctuations of human brain waves at delta, theta, alpha, beta (5Hz < D, T, A, B < 30Hz; Chaos) generating “free wills”, which collectively might be called the Consciousness, Compassion, Commonsense Intelligence (CCCI). This is the bases of life quality of Unsupervised Learning Natural Intelligence (NI) when it is approached from the Darwinian Natural Evolution “the fittest, the survival” viewpoint

Theorem asynchronous AI robot team and their causality convergence proof

If & only if there exists a global optimization scalar cost function H known as Helmholtz Free Energy at isothermal equilibrium to each robot member, then each follows asynchronously its own clock time in Newton-like “gradient descent learning” at its own time frame “ \dot{a}_j t= \dot{a}_j ”; $\dot{a}_j \geq 1$ causality with respect to the global clock time “t”

$$\frac{d[W_{i,j}]}{dt_j} = -\frac{\partial \mathbf{H}}{\partial [W_{i,j}]} ; \quad (9)$$

Prof: The overall system is always convergent the causality guaranteed by a quadratic **Lyapunov** force function independent of the temporal pace $\dot{a}_j \geq 0$:

$$\frac{d\mathbf{H}}{dt} = \sum_j \frac{\partial \mathbf{H}}{\partial [W_{i,j}]} \dot{a}_j \frac{d[W_{i,j}]}{dt_j} = -\sum_j \dot{a}_j \left| \frac{\partial \mathbf{H}}{\partial [W_{i,j}]} \right|^2 \leq 0 \quad \dot{a}_j \geq 1 \text{ causality}$$

Q.E.D.

We shall illustrate a smaller size feature processing after the back of our head Cortex 17 area V1-V4 layers of feature extraction, these feature feed to underneath the control Hypothalamus Pituitary Gland Center there are two walnut/kidney shape Hippocampus for the Associative Memory storage as the image Post-processing.

Hippocampus associative feature memory: write outer product and read by matrix inner product

From thousand by thousand face images pixels we extract the three Grand Mother (GM) feature neurons representing the eye size, nose size, and mouth size in a transpose of a row vector (Figure 8).

$$\begin{aligned} GM \text{ features} &= [eye, nose, mouth]^T \\ [AM] &= \begin{bmatrix} (1) \\ 0 \\ 0 \end{bmatrix} (1 \ 0 \ 0) aunt + \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} (0 \ 1 \ 0) uncle = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{bmatrix} \\ [AM] & \begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix} smile uncle = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} = remain \ big \ nose \ uncle \end{aligned}$$

The brain disorder may be computationally represented the population density waves in the following Figure 9 of Epileptic seizure.

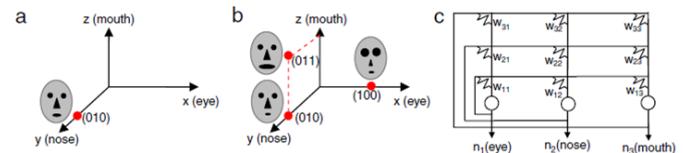


Figure 8 Associative Memory: Either Fault Tolerance with one bit error out of three bits about 33% or the generalization to within 45 degree angle of orthogonal feature storage. Both are two sides of the same coin of Natural Intelligence

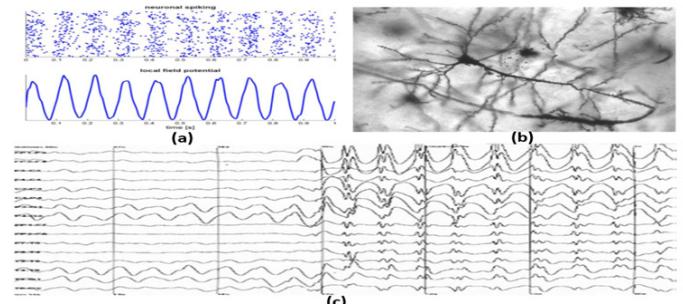


Figure 9 Epileptic Seizure: There is no travelling Electromagnetic wave in the BNN, rather neuronal population of firing rates observed 5 decade ago by D.O. Hebb: “linked together, firing together”(LTFT) that is why the dots density appears to be modulated from on 100Hz to off less than 50Hz.

Healthy diet

Relaxing Mind, Body & Eating Greens can improve holistic health. You are what you eat! To be healthy is not just reducing the calorie of foods, regular & moderate exercise such as walking, but also increase the nutrient density per calorie intake. The major calorie sources are hydrocarbon 4Cal/gm, Protein 4Cal/gm, Fat 7Cal/gm. The key to be truly healthy is to understand what the nutrient of food is. For example, Organic Garden Plants are high nutrient per calorie, e.g. one pond of Swiss Chard, Kale, and Spinach. Food is better variety than chemical purified compound. For senior osteoporosis concern, the Vitamin D is a nutrient with zero calorie. However, one form of chemical Vitamin D could not be represented by natural variety

mixture of Vitamins D, e.g. D₃ in the Calcium group that may all be needed to grow the bone. For example, Chinese Bok Choy has the highest Calcium content among all, e.g. it is 4times of Milk and without other harmful side effect (Insulin Growth Factor IGF-1) that milk has, much more than sea foods having harmful pollutants mercury and other metals. Over few millions years, the selective evolution has symbiotic effect to randomly choose the garden sun & water plants but those were good to health of the farmers, who can live longer and taught offspring to plant more of them. We don't get health from a bottle, but from eat the holistic veggie. This might account for why Buddhist Monks on Vegetable diet remains strong going up and down the mountain. The danger of nutrient scientist is to take scientific reductionist viewpoint, try to isolate the essential component, and missed the synergistic orchestration is the value. This is perhaps similar to Occidental holistic herbal medicine viewpoint. One pond of Cooked vegetable includes Broccoli, stream bean, eggplants, etc. However, such a symbiotic selective evolution is not happening to the animal & diary food products, because the business third party involved for an instant profit motive.

We had to cut loose entirely from the Modern American Diet (MAD) habit. The madness is because the US are in the unprecedented opportunity (in a rich & agriculture produce country, in the highway convenience of food transportation, and the household kitchen tools & refrigeration, as well as the public education in K-12 schools and TV media in everywhere available place for the scientific and medical knowledge education) but we don't eat to live but live to eat. The madness remained, because the US large Conglomerate business in meat and dairy food wish to harvest near-sight quick profits. (cf. Crusade of Dr. Campbell & Dr. Essetylen, in a movie made in 2011, named as "Forks and Knives," Monica Beach, and also pointed out the conspiracy of these large business invested on interns of medical schools, supermarket chains, television station to brain washed American consumers). The Society still in love with Fast Food Chain peddled low nutrient high calorie food in the meats, eggs, meat, milk, cheese, and wheat bread with oil processed donuts, pizzas with cheese & meats, as well as rice, and fish flavored either by Chesapeake Bay powder fill with sea salt, or by Chinese soy sauce, MSG, etc.

Rosette Stone of Health Recipe: We purchased directly from the cold room, a box of about ten bags of one pound bag of Power Green vegetables (brand name of mix of clean washed organic Swiss Chad, Kale, Spinach). When the Power Green was liquefied in a cup of clean water without any sea salt, and blended with halves of 5 fruits group (banana, apple, pear, orange, kiwi, grapes, etc.), the taste became more agreeable. Furthermore, if we add crushed ice, it became even more palatable like fruit smoothie. Some peoples are borne with sensitive super-taster ability; as such the natural tendency is taking salty non-Vegan diet. Then, you might have more challenge to break off your old eating habit. Dr. Fuhrman regimen 10pounds less weight was reduced, and dropping both the systolic and di-systolic pressures steadily dropped from a chronic hypertension range to a normal person of my young age days.

Dr. Joel Fuhrman (JF) took 1lb green leafs, planted farmer at garden growth in an organic fashion, e.g, Swiss Chad, Kale, Spinach, etc. JF suggested liquefying them with blender; mix together with halves of 5 fruits (Banana sweet, Pear sweet, Orange sweet, Apple tar, Kiwi tar, in whole or in halves) to made 2 large cups 16 Oz, 4 small cups 8Oz, of veggie-fruit smoothie to drink up during the day. One can enjoy in the rest of day the other halves of fruits, and 4 raw & unsalted nuts, as well as 1lb of cooked vegetable (Stream Beans, Broccoli, Mushroom, Onion, etc. to releasing different kinds of nutrients). The JF's Vegan

manure "eat to live," characterized by a high nutrient density per calorie intake. Basically, Dr. Fuhrman recommends a high "nutrient density per calorie intakes as the healthy eating guideline:

$$\text{Health} = \text{Nutrient}/\text{Calorie}, \text{ nutrient density} \quad (12)$$

Deeper Understanding helps: Daily garden green leaf intakes help lose the weight because of the total one pound of power green about 100 calorie per days, and cooked 1 pound of vegetable, as well as some nuts, and fruits complete the diet. (Plants) Fats are essential (JF book, p.220): the low chain Omega-3 fatty acids, which can form a long chain called Docosa-Hexaenoic Acid (DHA) that can avoid blood clogging together get rid of plaque fat without the pain of hungry. Note that Omega-3 is not bad vegetable oil and animal products having the Omega-6 fat implicated the diabetes, heart disease, and inflammatory illness. One can repair body damage as well as increase immune-resistance to avoid 4 major attacks of Home Alone Seniors (has) (Diabetic Type II, Heart Attack, Stroke, Some forms of cancers). We believe the correct answer is in the lifestyle mediating the epigenetic that repair the body through lifestyle Phenome and keep good genome.

Selective Evolution Viewpoint: How could it be? From the co-evolution between our ancestor human and planted red sweet fruits, our previous selective evolution might be working. In conclusion: it seems that Dr Fuhrman "Eat to Live" with a lot of Green Leaf may be consistent with Herbal Medicine Chinese philosophy. Dr. Fuhrman is not alone in the US: More Records of Clinical & Scientific Studies were ignored by the public, due to strong Special Interests Lobbyists Group to attempt brain-washing the public by \$B TV advertisement Champaign including influence the official FDA position. This is exposed in a factual motivation movie known as Forks over Knives by Monica Beach Production, 2011. Some information is given as follows: Macro-nutrient in nutrient density and micro-nutrient molecular Genetics:

There is an excellent companion movie, called Forks over Knives by Monica Beach Production, 2011 that described Dr. Essellyn clinical studies of 18 to dozen patients and Dr. Campbell scientific epidemiology studies about Finland project and China Project. The former studies WWII German took away the live stock food intake for Soldiers, and left Finland no more animal protein. Dr Campbell found a strong correlation with much less disease. Similarly, the 1st Gen immigrant children at Hawaii and compared with earlier Hawaii immigrants are leaner and healthier. Lab mice studies with tumors reveal that a close correlation in 3 week cycle of those mice having tumors into two groups: one group was feeding with 20% milk & byproducts, compared with the other group fed with 5% milk & byproducts. Dr. Campbell discovered for the tumor growth large or small respectively; On the one hand, the Monica Beach production movie "Forks over Knives" says why we must Eat to Live not vice versa live to eat. On the other hands, Dr Joel Fuhrman's book "Eat to Live," tells us "how." In summary of Eat Right: Uninitiated readers should view the Movie "Forks over Knife" first, before read Dr. Joel Fuhrman book: Eat to Live. (e.g. cross reference of China project by Dr. Campbell, etc.)

Why & how plant green has high density nutrient per calorie and reducing bad body substances and repair us?

Selective evolutions between the farmers who plant the green and consume it How? Plants have various Chlorophyll C₅₅H₇₂O₅N₄Mg for photosynthesis (Figure 10). Newly discovered (Min Chen, U.

Sydney circa 2010) Chlorophyll- f (for infrared, 0.706 microns) in Cyanobacteria and other oxygenic microorganisms different to other 4 types a, b, c and d. An isomor of Chorophyll d is Chorophyll f that can convert the near-infrared 0.706 to energy as an-oxygenic photosynthesis condition. Magnesium mineral of plant leafs is different from any other minerals (mercury, alumina, lead, etc. pison to us). It is a good mineral for generating antioxidant, such as glutathione (that was rich in our co-evolution partner Mitochondria that has own Genes. As opposed to human 23 pairs of chromosome, Mitochondrial DNA contains 37genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in Oxidative Phosphorylation. Oxidative Phosphorylation is a process that uses oxygen and simple sugars to create Adenosine Triphosphate (ATP), the cell's main energy source. The remaining genes provide instructions for making molecules called Transfer RNA (tRNA) and ribosomal RNA (rRNA), which are chemical cousins of DNA. These types of RNA help assemble protein building blocks (amino acids) into functioning proteins.). This antioxidants defends against dementia Alzheimer & Parkinson caused by inflammation and free radicals that can trigger immune response signaling microglia for the cell self-destruction. Dr. Blaylock Wellness Report: After his own parents died of Parkinson disease, he investigated what's bad practices causing dementia. One shall avoid Excitoxin stimulating Microglia to signal the brain cell self-destruction. We shall avoid: (1) Processed food with MSG; (2) No annual flu shot with mercury; (3) No toothpaste with tooth whitening fluent metal having alumina; (3) No high calorie diet with low nutrient, e.g. jelly beam (President Reagan, sugar and fat); (4) No Omega-6 oil, Soybean Oil, Flaxy oil, Corn oil; etc. (5) No sugar substitute such Aspartame in loosing mind (good substitute might be Stevia) Dr. Blaylock wellness report furthermore suggested good practices: Taking vitamin daily supplement such as Vitamin D, Modern Cod liver oil Omega-3s, Curcumim, etc. Vitamine D, Dr. Blaylock recommends some holistic doctors who may administrate IV drips of glutathione and chelatin for antioxidant brain self-defense.

No animal, fish, diary milk, egg, wheat & rice & oat meal, cookie, fast food for the reasons of low nutrient per calorie density, and some have harmful food additives, as well as no positive repair body damage effect. Such a counter-American food cultures, that was cancer, heart attack, stroke, and obesity causing diet, was quite difficult for me to undertake in the beginning.

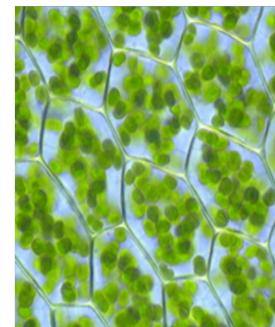


Figure 10 Photochemical Photo-synthesis: Green Chlorophyll $C_{55}H_{72}O_5N_4Mg$ (Sci. Am. 2010 Aug.19, Ferris Jabr) The Chlorophyll of plants have Carbone, Nitrogen & Magnesium minerals products, but are healthy, symbiotic to help our bodies, than man-made products seem to be; plants have other components that have rich Calcium, (e.g. bok choy has the highest calcium among all vegetables, 775 calcium in 100 calorie, 7 times higher than milk, fish and egg; a whole orange has 60mg calcium, not the juice, JF p.110) and other minerals that keep elephant, horse strong in borne. There is a plenty of Phytochemicals in human-planted green leafs that can prevent and repair damaged cell, at two major aspects from the Genome viewpoint

The Chlorophyll of plants have Carbone, Nitrogen & Magnesium minerals products, but are healthy, symbiotic to help our bodies, than man-made products seem to be; plants have other components that have rich Calcium, and other minerals that keep elephant, horse strong in borne. There is a plenty of Phytochemicals in human-planted green leafs that can prevent and repair damaged cell, at two major aspects from the Genome viewpoint (Figure 11) (Figure 12).



Figure 11 Longest Life Animal on the Earth: Galápagos (Darwin's island) giant tortoise lives up to 190 years; Arctic Clam at 400 years. The bodies of Galápagos tortoise and Arctic clam have telomerase keeping longevity Astrocytes Cells are part of Central Nerves System (CNS) with 4 kinds of Glial cells as the house-keeping servant cells. They get their name because they are "star-shaped". They are the most abundant Glial cells in the brain that are closely associated with neuronal synapses. They regulate the transmission of electrical impulses within the brain. ... Metabolic support: They provide neurons with nutrients such as lactate. [Image courtesy of EnCor Biotechnology Inc.; An Astrocytic cell from rat brain grown in tissue culture and stained with antibodies to GFAP (red) and vimentin (green). Both proteins are present in large amounts in the intermediate filaments of this cell, so the cell appears yellow. Visualization of individual DNA molecules in solution by light microscopy: DAPI[4,6-Diamidino-2-phenylindole] staining method developed to visualize individual DNA molecules in solution under a fluorescent microscope connected to a highly sensitive video camera. The blue material shows DNA visualized with DAPI stain, and reveals the nuclei of the Astrocyte and other cells]; Cause of Dementia Amyloid beta peptide (beta-APP) A partially folded structure of Amyloid beta(I-40) in an aqueous environment (pdb 2lfm). A recent study suggested that APP and its Amyloid potential is of ancient origins, dating as far back as early deuterostomes. The normal function of A β is not well understood. Though some animal studies have shown that the absence of A β does not lead to any obvious loss of physiological function, several potential activities have been discovered for A β , including activation of kinase enzymes, protection against oxidative stress, regulation of cholesterol transport, functioning as a transcription factor, and anti-microbial activity (potentially associated with A β 's pro-inflammatory activity)

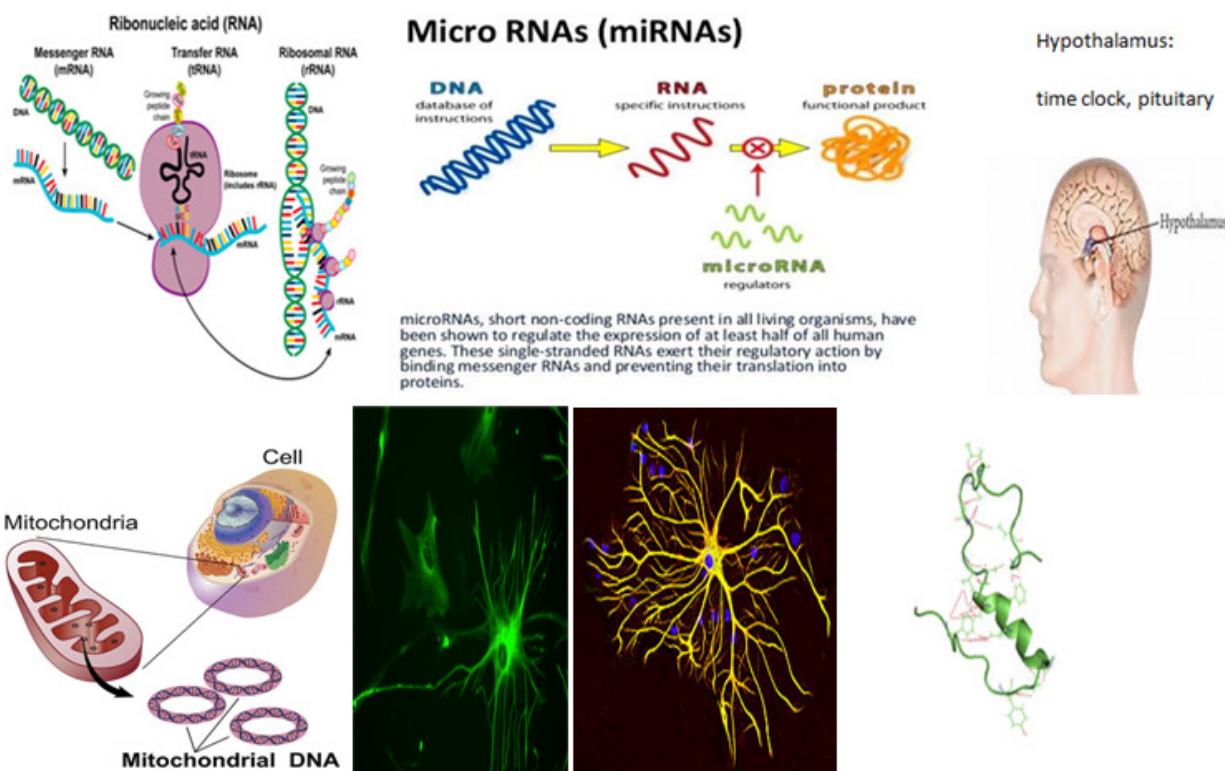


Figure 12 Mitochondria cells: within our cell as co-evolution partner in power generation. Mitochondria convert ATP-ADP energy to support multi-cellular organism. The Weakest link of brain neurophysiology is the Astrocytes Glial Cells are part of Central Nerves System (CNS) with 4 kinds of Glial cells as the house-keeping servant cells. They get their name because they are “star-shaped”. They are the most abundant Glial cells in the brain that are closely associated with neuronal synapses. They regulate the transmission of electrical impulses within the brain. Metabolic support: They provide neurons with nutrients such as lactate. [Image courtesy of EnCor Biotechnology Inc. An Astrocytic cell from rat brain grown in tissue culture and stained with antibodies to GFAP (red) and vimentin (green). Both proteins are present in large amounts in the intermediate filaments of this cell, so the cell appears yellow. Visualization of individual DNA molecules in solution by light microscopy: DAPI [4,6-Diamidino-2-phenylindole] staining method developed to visualize individual DNA molecules in solution under a fluorescent microscope connected to a highly sensitive video camera. The blue material shows DNA visualized with DAPI stain, and reveals the nuclei of the Astrocyte and other cells]; Cause of Dementia Amyloid beta peptide (beta-APP) A partially folded structure of Amyloid beta(I-40) in an aqueous environment (pdb 2lfm). A recent study suggested that APP and its Amyloid potential is of ancient origins, dating as far back as early deuterostomes. The normal function of A β is not well understood. Though some animal studies have shown that the absence of A β does not lead to any obvious loss of physiological function, several potential activities have been discovered for A β , including activation of kinases enzymes, protection against oxidative stress, regulation of cholesterol transport, functioning as a transcription factor, and anti-microbial activity (potentially associated with A β 's pro-inflammatory activity).

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Conflict of interest

Author declares that there is no conflict of interest.

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Appendix A to read further: genome DNA discovery

It often said it's all in the gene. What is the gene? The "Deoxyribo-Nucleic Acid (DNA)" is the double helix carrier of genetic information, as discovered by Rosalind Franklin by 2-D X-ray pictures of DNA crystals; but unfortunately she died of ovarian cancers Wilkins imprudently showed it to Watson. This image, along with the

knowledge that Linus Pauling had proposed an incorrect structure of DNA (backbone outside rather inside) Maurice Wilkins, Francis Crick, and James Watson were awarded the 1962 Nobel Prize for Physiology or Medicine, "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material for the 3-D structure of double helix structure of DNA as a double-helix, two spirals held together by complementary base pairs C(cytosine)-G(guanine), A(adenine)-T(thymine) (Figure 13).

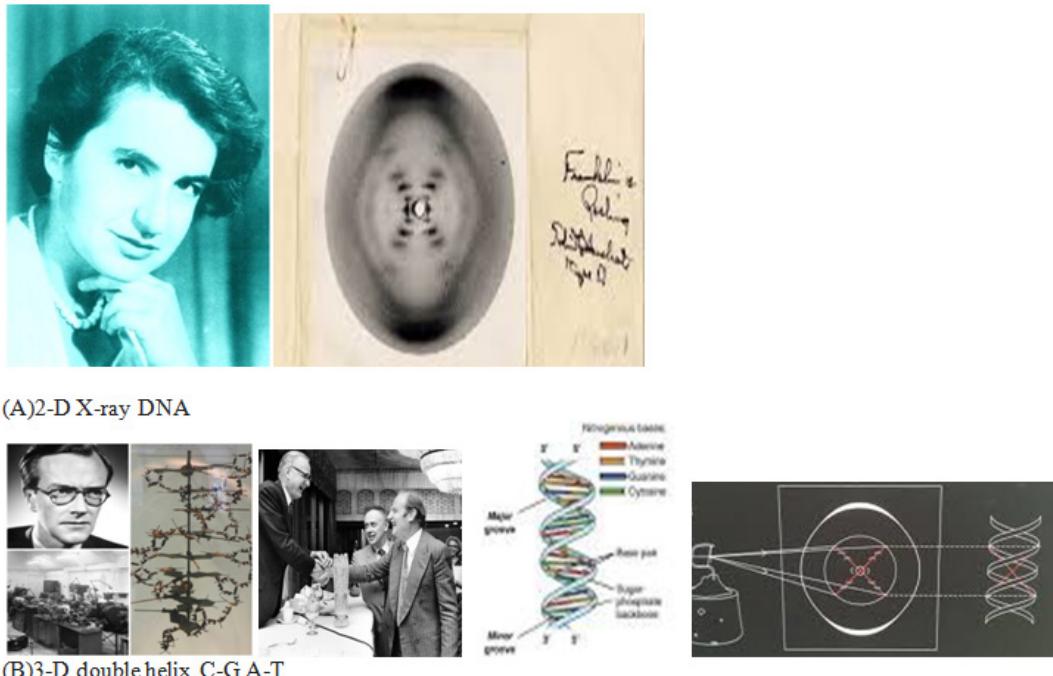


Figure 13 A1 (A) 2-D X-ray Pictures by Rosalind Franklin, King's College of London four years after Franklin's death at age 37 from ovarian cancer, versus (B) 3-D DNA model C(cytosine)-G(guanine), A(adenine)-T(thymine) by Maurice Wilkins, James Watson and Francis Crick received a Nobel Prize in 1962 for the double-helix model of DNA.

The human genome contains approximately 3 billion of these base pairs, which reside in the 23 pairs of chromosomes within the nucleus of all our cells. Each chromosome contains hundreds to thousands of genes, which carry the instructions for making proteins. Each of the estimated 30,000 genes in the human genome makes an average of three proteins. Then, realizing the 3-D folding of the outside genetic program based on "Methylation (CH₃ marker) & Histone" wrapping spool into Chromosome. The gene for the Amyloid Precursor Protein is located on chromosome 21, among 23 pairs of chromosomes. Accordingly people with Down syndrome have a very high incidence of Alzheimer's disease. Glial Cells, like Neuron Cells, Share the same cellular biology: genetics (1-D chain C-D A-G pairs) & epigenetics (3-D Methylation Histone). Cursory Review of cellular Genetic and Epigenetic wrapping compact into Chromosome, as well as the neatly 50 Hayflick turns knot before it's loosen up and getting old with mutation. Male has X-shape with Y shape chromosomes; female has both Y shape chromosomes. The ends of Chromosome are made of single strand Telomere. Besides the Genome by 3meter long DNA genes winded into 23 pairs of Chromosomes; the Phoneme controls and commands the winding and un-winding of Chromosomes, mediated by epi-genetic by CH₃-Mythelation in order to tag a specific DNA piece to be located outside when winds 3 meter long, DNA around the spools known as the Histone with Histone tails to further decide the aggregates of Histones.

Genetic DNA are made of 3 billion pairs of A-T C-G codons of DNA packed in 23 pairs in a total of 46 chromosomes un-winded linearly in 3m long. Chromosome ends are monomer called Telomere having into 50 turns of Hayflick limit. Losing the turns maintained by Telomerase is a sign of aging. Incidentally, the genetic evolution is like Genetic Re-Engineering. Since the primates, apes, huminids and neanderthal all have 24 pairs chromosomes, of which their #2 & #3 chromosomes were fused together by spliced into a single long one #2, to become that of human, genetically known as Homosapien. likewise, Dolphin has one less pairs than human. Note that a less # of chromosomes is not necessary better. Perhaps, the same GRE going on at Dolphin survival selection level in the Oceans. For the purpose of cell mitosis (differentiation), the reproduction system must read the DNA codes, first the epigenetic issues command & control how to un-wind DNA to reveal for de-code by copy molder, known as transcript RNA that rides on the unzipped DNA into a single strain RNAs, and the copy molder have built in error correction back-chaining coding.

Epigenetic mechanisms encompass a number of molecular marks, such as Histone modifications, DNA Methylation, and micro-RNA that can affects aging and offspring. The Phenome viewpoint is the Epigenetic manipulating what's should be inside and what's outside by tagging DNA with, e.g. CH₃-Mythelation for winding on the film spool, known as Histone. Moreover, Histones have tails that decides

how all Histones should be packed from future easy access for the decode reading. These are molecular markers revealing “the fittest to survive” from molecular genetics viewpoint. Nothing beats good Genes, except good Epigenetic” While the gene may determine about 25%, the rest is the lifestyle affecting the epigenetic. Worms have localized DAF-2 aging gene; or DAF-16 for longevity gene; Homosapiens have distributed genes and epigenetic in complex. Macroscopic Selective Evolution: Green vegetable might not have the intelligent mind to design themselves the ability to repair farmers’ bodies; but those who happened to do so will have more healthy farmers to plant them more. In other words, this is a positive feedback cycle, if the farmer planted green leafs growing health under the sun that can also repair their body to live longer, those farmers can teach their children to continuously plant more such greens. Such a cause and effect happened in tenth thousands trials over five thousand years of recorded human history. Today we enjoy the consequence of such a selective evolution, as if it were an “intelligent design” from the onset. This was a lesson that Darwin had been taught us. “I think; therefore I am.” - Rene Descartes.

Appendix B: to read further: dad disease diagnoses overview and drug availability (skip for home alone seniors)

DAD diagnosis for different diseases

The “Amyloid hypothesis” for DAD that the plaque are responsible for the pathology of Alzheimer’s disease, is accepted by the majority of researchers but are by no means conclusively established. An alternative hypothesis is that Amyloid Oligomers rather than plaques are responsible for the disease. Mice that are genetically engineered to express Oligomers but not plaques develop the disease. Furthermore, mice that are in addition engineered to convert Oligomers into plaques, are no more impaired than the Oligomer only mice. Intracellular deposits of tau protein are also seen in the disease, and may also be implicated, as has aggregation of alpha synuclein. Glymphatic system clears metabolic waste from the mammalian brain, and in particular beta Amyloids. The rate of removal is significantly increased during sleep. However, the significance of the lymphatic system in A β clearance in Alzheimer’s disease is unknown. A β is the main component of Amyloid plaques (extracellular deposits found in the brains of patients with Alzheimer’s disease). Similar plaques appear in some variants of Lewy body dementia and in inclusion body Myositis (a muscle disease), while A β can also form the aggregates that coat cerebral blood vessels in cerebral Amyloid angiopathy. The plaques are composed of a tangle of regularly ordered fibrillar aggregates called Amyloid fibers, a protein fold shared by other peptides such as the prions associated with Protein Misfolding diseases. Recent research suggests that soluble Oligomeric forms of the peptide may be causative agents in the development of Alzheimer’s disease. It is generally believed that A β Oligomers are the most toxic. The ion channel hypothesis postulates that Oligomers of soluble, non-fibrillar A β form membrane ion channels allowing the unregulated calcium influx into neurons that underlies disrupted calcium ion homeostasis and apoptosis seen in Alzheimer’s disease. Computational studies have demonstrated that also A β peptides embedded into the membrane as monomers with predominant helical configuration, can Oligomerize and eventually form channels whose stability and conformation are sensitively correlated to the concomitant presence and arrangement of cholesterol. A number of genetic, cell biology,

biochemical and animal studies support the concept that A β plays a central role in the development of Alzheimer’s disease pathology. Brain A β is elevated in patients with sporadic Alzheimer’s disease. A β is the main constituent of brain Parenchymal and Vascular Amyloid; it contributes to cerebrovascular lesions and is neurotoxic. It is unresolved how A β accumulates in the central nervous system and subsequently initiates the disease of cells. Some researchers have found that the A β Oligomers induce some of the symptoms of Alzheimer’s Disease by competing with insulin for binding sites on the insulin receptor, thus impairing glucose metabolism in the brain. Significant efforts have been focused on the mechanisms responsible for A β production, including the Proteolytic Enzymes gamma- and β -secretases which generate A β from its precursor protein, APP (Amyloid Precursor Protein). A β circulates in plasma, Cerebro-Spinal Fluid (CSF) and brain Inter-Stitial Fluid (ISF) mainly as soluble A β 40. Senile plaques contain both A β 40 and A β 42, while vascular Amyloid is predominantly the shorter A β 40. Several sequences of A β were found in both lesions. Generation of A β in the central nervous system may take place in the neuronal axonal membranes after APP-mediated axonal transport of β -secretase and presenilin-1.

Increases in either total A β levels or the relative concentration of both A β 40 and A β 42 (where the former is more concentrated in cerebro-vascular plaques and the latter in neuritis plaques) have been implicated in the pathogenesis of both familial and sporadic Alzheimer’s disease. Due to its more hydrophobic nature, the A β 42 is the most Amyloidal form of the peptide. However the central sequence KLVFFAE is known to form Amyloid on its own, and probably forms the core of the fibril. One study further correlated A β 42 levels in the brain not only with onset of Alzheimer’s, but also reduced cerebrospinal fluid pressure, suggesting that a build-up or inability to clear A β 42 fragments may play a role into the pathology.

Down syndrome

Adults with Down syndrome had accumulation of Amyloid in association with evidence of Alzheimer’s disease, including declines in cognitive functioning, memory, fine motor movements, executive functioning, and visuospatial skills.

Formation

A β is formed after sequential cleavage of the Amyloid Precursor Protein (APP), a transmembrane glycoprotein of undetermined function. APP can be cleaved by the proteolytic enzymes α -, β - and γ -secretase; A β protein is generated by successive action of the β and γ secretases. The γ secretase, which produces the C-terminal end of the A β peptide, cleaves within the transmembrane region of APP and can generate a number of isoforms of 30-51 amino acid residues in length. The most common isoforms are A β 40 and A β 42; the longer form is typically produced by cleavage that occurs in the endoplasmic reticulum, while the shorter form is produced by cleavage in the trans-Golgi network. The A β 40 form is the more common of the two, but A β 42 is the more fibrillogenic and is thus associated with disease states. Mutations in APP associated with early-onset Alzheimer’s have been noted to increase the relative production of A β 42, and thus one suggested avenue of Alzheimer’s therapy involves modulating the activity of β and γ secretases to produce mainly A β 40. One major issue with this therapeutic approach are the consequences of interfering with enzymes like β and γ secretases, which have other functional roles besides within the Amyloidogenic pathway. Exemplary of this are the results which clinical trials that approach the Amyloid beta

problem using γ secretase inhibitors have faced, including severe cognitive dysfunction and an elevated incidence of skin cancers. A β is also destroyed by several Amyloid-degrading enzymes including neprilysin. Genetics Autosomal-dominant mutations in APP cause hereditary early-onset Alzheimer's disease (a.k.a. familial AD). This form of AD accounts for no more than 10% of all cases, and the vast majority of AD is not accompanied by such mutations. However, familial Alzheimer disease is likely to result from altered proteolytic processing.

Intervention strategies

Researchers in Alzheimer's disease have identified several strategies as possible interventions against Amyloid: β -Secretase inhibitors. These work to block the first cleavage of APP inside of the cell, at the endoplasmic reticulum. γ -secretase inhibitors (e. g. semagacestat). These work to block the second cleavage of APP in the cell membrane and would then stop the subsequent formation of A β and its toxic fragments. Selective A β 42 lowering agents (e. g. tarenflurib). These modulate γ -secretase to reduce A β 42 production in favor of other (shorter) A β versions. β - and γ -secretase are responsible for the generation of A β from the release of the intracellular domain of APP, meaning that compounds that can partially inhibit the activity of either β - and γ -secretase are highly sought after. In order to initiate partial inhibition of β - and γ -secretase, a compound is needed that can block the large active site of aspartyl proteases while still being capable of bypassing the blood-brain barrier. To date, human testing has been avoided due to concern that it might interfere with signaling via Notch proteins and other cell surface receptors.

Immunotherapy

This stimulates the host immune system to recognize and attack A β , or provide antibodies that either prevent plaque deposition or enhance clearance of plaques or A β Oligomers. Oligomerization is a chemical process that converts individual molecules into a chain consisting of a finite number of molecules. Prevention of Oligomerization of A β has been exemplified by active or passive A β immunization. In this process antibodies to A β are used to decrease cerebral plaque levels. This is accomplished by promoting microglial clearance and/or redistributing the peptide from the brain to systemic circulation. One such beta-Amyloid vaccine that is currently in clinical trials is CAD106. A β 42 immunization resulted in the clearance of Amyloid plaques in patients with Alzheimer's disease but did not prevent progressive neuro-degeneration. While these results appear promising, large-scale literature reviews have raised questions as to immunotherapy's overall efficacy. One such study assessing ten anti-A β 42 antibodies showed minimal cognitive protection and results within each trial, as symptoms were too far progressed by the time of application to be useful. Further development is still required for application to presymptomatic patients to assess their effectiveness early into disease progression. Anti- aggregation agents such as apomorphine, or carbenoxolone. The latter has commonly been used as a treatment for peptic ulcers, but also displays neuroprotective properties, shown to improve cognitive functions such as verbal fluency and memory consolidation. By binding with high affinity to A β 42 fragments, primarily via hydrogen bonding, carbenoxolone captures the peptides before they can aggregate together, rendering them inert, as well as destabilizes those aggregates already formed, helping to clear them. This is a common mechanism of action of anti-aggregation agents at large. Studies comparing synthetic to

recombinant A β 42 in assays measuring rate of fibrillation, fibril homogeneity, and cellular toxicity showed that recombinant A β 42 had a faster fibrillation rate and greater toxicity than synthetic amyloid beta 1-42 peptide. Modulating cholesterol homeostasis has yielded results that show that chronic use of cholesterol-lowering drugs, such as the statins, is associated with a lower incidence of AD. In APP genetically modified mice, cholesterol-lowering drugs have been shown to reduce overall pathology. While the mechanism is poorly understood it appears that cholesterol-lowering drugs have a direct effect on APP processing.

Dual polarization interferometer (DPI)

DPI is an optical technique which can measure early stages of aggregation by measuring the molecular size and densities as the fibrils elongate. These aggregate processes can also be studied on lipid bilayer constructs blood samples. New research has shown promise in testing whole blood samples for Amyloid beta levels on the basis of electrical impedance. Interdigitated microelectrodes prepared with Amyloid beta antibody measure differentiated impedance of flow in samples before and after antibody reactions to Amyloid beta, comparing with normalization to account for regular variance between electrodes. When applied to control mice versus transgenic Amyloid precursor protein/presenilin 1 mice (APP/PS1), strains could be differentiated via their differing Amyloid beta levels.

Post mortem or in tissue biopsies

Amyloid beta can be measured semi-quantitatively with immunostaining, which also allows one to determine location. Amyloid beta may be primarily vascular, as in cerebral Amyloid angiopathy, or in senile plaques in white matter. One sensitive method is ELISA which is an immunoassay which utilizes a pair of antibodies that recognize Amyloid beta. Atomic force microscopy, which can visualize nano-scale molecular surfaces, can be used to determine the aggregation state of Amyloid beta in vitro.

Cognitive enhancer drug status

More than 80 medications are currently being investigated for use in the treatment of Alzheimer's disease. Patients, families, and clinicians are eagerly awaiting the availability of agents that will more effectively control the symptoms of this most common of dementias. While clinicians await the arrival of new treatments, they currently have access to two classes of medications approved by the Food and Drug Administration (FDA) for the treatment of Alzheimer's disease. These widely used medications have sparked controversy between those who consider them valuable treatment tools and those who regard them as hazardous and costly. The FDA approved "cognitive enhancers" fall into two classes.

Cholinesterase inhibitors

Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne) are inhibitors of the enzyme acetylcholinesterase. They work by diminishing the brain's normal breakdown of the neurotransmitter called acetylcholine, an important player in the transformation of thought and experience into retrievable memories, unless we have seen the chaos that results from its disruption. Donepezil is also available in a new and relatively higher dose pill, and rivastigmine is the only one yet available in a skin patch delivery system, suitable for use by patients more amenable to a patch than a pill, or unable to tolerate the gastrointestinal side effects of this class

of drugs. These medications share disruption of sleep, enhanced risk for bleeding, and slowing of the heart rate to the point of potential danger from fainting or disrupted heart rhythm.

Memantine

The other class of cognitive enhancers approved for Alzheimer's treatment contains one lonely member, memantine (Namenda). Memantine's unique mechanism of action involves enhancement of the brain's sensitivity to an important excitatory amino acid neurotransmitter, glutamate. Glutamate plays a key role in uniting the brain cells that must collaborate to form a specific memory. Glutamate also plays a more sinister role in the brain, contributing to the neuron-destroying process called apoptosis (programmed cell death). Memantine's side effects are often minimal, though occasionally it can enhance or initiate confusion, agitation, constipation, or headache. The effectiveness of these medications appears to be modest but significant for a large number of patients who can tolerate their side effects. At their best, the cognitive enhancers slow down for six months or more the encroachment of Alzheimer's disease on multiple areas of functioning and to reduce the burden of care giving by perhaps an hour a day. Memantine is an Alzheimer's drug which has received widespread approval. It is a non-competitive N-methyl-D-aspartate (NMDA) channel blocker. By binding to the NMDA receptor with a higher affinity than Mg^{2+} ions, meantime is able to inhibit the prolonged influx of Ca^{2+} ions, particularly from extra synaptic receptors, which forms the basis of neuronal excitotoxicity. It is an option for the management of patients with moderate to severe Alzheimer's Disease (modest effect). The study showed that 20mg/day improved cognition, functional ability and behavioral symptoms in patient population. Measuring Amyloid beta Micrograph showing Amyloid beta (brown) in senile plaques of the cerebral cortex (upper left of image) and cerebral blood vessels (right of image) with immune-staining. Imaging compounds, notably Pittsburgh compound B, (6-OH-BTA-1, a thioflavin), can selectively bind to Amyloid beta in vitro and in vivo. This technique, combined with PET imaging, is used to image areas of plaque deposits in Alzheimer's patients.

Appendix C to read further regular exercise

Remarks on Yoga Exercise for those who could not sleep enough

Counting one breaths is a natural way not think anything thing seriously to trans into deep sleep. Those professional, e.g. Medical Interns, Professionals Nurses, shall consider Complimentary

Alternative Methodology (CAM) besides walk and food. For examples, recommend you got to take (i) Indian Yoga for whole body stretch warm up in 30 minutes until the child post sleep. Yoga is Sanskrit: transcend suffering by breathing by nose "Vjjayi". It begins with "Ashtanga Vinyasa" (Sun Salutation A & B (with Chair, Warrior posts) just to push up (Prank), lean forward with high head (Updog) bending upward the spinal cord and backward hip high (down dog lambda shape) in 5 times, Then, it begins with standing position of Triangle, Slant Triangle, Big Toe. It can generate a hiss exhale sound whenever they have time to do. Yoga restrictively controlled breathing uses only those above diaphragm lung capacity where is associated with Vegas nerves. It finish with Child Pose sleep position. further divided in two concerted rings, top and bottom ring, known as "Bandha" keeping the strong abdomen muscle to protect the spinal cord, only the top $\frac{3}{4}$ lung capacity is used to slowly breath-in and breath-out at equal smooth path 'Prana "Chi-life force" that is directly associated with autonomic Vegas (Greek: Wandering) nerves along the spinal cord in order to efficiently secrete the Dopamine, the so-called "exercise high hormone" in about tenth breathes. Besides Marshal Art aspect, Chinese Tai Chi Quan (TCQ) keeps the upright pose and thus only keeps one Banda, the Central of Gravity at the "Red-Field," in 100% natural inhale and exhale. It has an aspect of walking meditation calming down the brain wave nerve in minutes (e.g. brainwaves toward Theta waves, 10~15Hz). Abdomen Breathing Control (ABC) without vibration by balancing the inhale with the exhale doing TJQ at Den Tien can build a strong cord muscles (4+2) preventing falls and learned marshal art techniques for self-defense, and biomedical wellness. TJQ is a walking meditation that can calm down sub-consciousious 30 Hz Beta brainwave to 15Hz soothing Alpha wave. "3 times TJQ keeps alpha brainwaves relaxing & doctors away.

Authors Biography



Dr. Harold HwaLing Szu has been a champion of Unsupervised Deep Learning Computational brain-style Natural Intelligence for 3 decades. He received the INNS D. Gabor Award in 1997 “for outstanding contribution to neural network applications in information sciences. He pioneered the implementations of fast simulated annealing search. He received the Eduardo R. Caianiello Award in 1999 from the Italy Academy for “elucidating and implementing a chaotic neural net as a dynamic realization for fuzzy logic membership function. Dr. Szu is a foreign academician of Russian Academy of Nonlinear Sciences for his interdisciplinary Physicist-Physiology to Learning (#135, Jan 15, 1999, St. Petersburg). He is a Fellow of American Institute Medicine & Bio Engineering 2004 for passive spectrogram diagnoses of cancers; Fellow of IEEE (#1075, 1997) for bi-sensor fusion; Fellow of Optical Society America (1995) for adaptive wavelet; Fellow of International Optical Engineering (SPIE since 1994) for neural nets; Fellow of INNS (2010) for a founding secretary and treasurer and former president of INNS. Dr Szu has graduated from the Rockefeller University 1971, as thesis student of G. E. Uhlenbeck. He became a visiting member of Institute of Advanced Studies Princeton NJ, as well as a civil servant at NRL, NSWC, ONR, and then a senior scientist at Army Night Vision Electronic Sensory Directorate, Ft. Belvoir VA over 40 years. To pay back the community, he served as research professor at AMU, GWU, and CUA, in Wash DC. Besides 640 publications, over dozen US patents, numerous books & journals (cf. [researchgate.net/ profile/Harold_Szu2](https://www.researchgate.net/profile/Harold_Szu2)). Dr. Szu taught thesis students “lesson in creativity: editorial” (for individual with 4C principles and for a group by 10 rules) following a Royal Dutch tradition from Boltzmann, Ehrenfest, & Uhlenbeck (Appl. Opt. 54 Aug. 10, 2015). He has guided over 17 PhD thesis students.



Dr. Moon was born in Taegu, Korea, in 1959. He received the B.S. degree in Control and Instrumentation Engineering from Seoul National University, Seoul, South Korea in 1982, and the M.S. and Ph.D. degrees in the Department of Electrical Engineering and Computer Science at the George Washington University, Washington D.C., USA in 1990 and 1992, respectively. From 1982 to 1988, he worked as a Member of Technical Staff for Electronics and Telecommunication Research Institute (ETRI), Korea, during which he worked as a visiting engineer at VLSI Technology Inc., San Jose, USA for two years. He has been working actively in CMOS integrated circuit design, both digital and analog, focusing high-speed/low-power system implementation. With this high-performance capabilities, he is working on various sensors (mostly from conventional CMOS process) and embedded sensing module equipped with MEMS sensors (hybrid or 3D type) to measure bio signals on human, or for chemical, bio-engineering applications. He chaired International Ubiquitous-Health Symposium, 2008, Chuncheon, Korea, sponsored by Department of Education, Korea, and published several research papers in health care area, developing and proposing ubiquitous sensors and utilization system for elders who are staying out of daily care services. He has been also involving and consulting many industrial companies, both in Korea and US, as a primary investigator and a consultant, focusing mostly in sensor and actuator area. He served as full professor, a Director of Electronics and Informatics Research Center, and later Dean of School of Engineering, Hallym University. He also served years as a Technical Consultant in National Frontier Research Project for Ultra-High Speed Digital System & Applications, at Ministry of Science and Technology, Korea.