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A Shared Mechanism in the Functioning of the Normal Brain and its Dysfunction in the Diseases of the Brain and Mind

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Abstract

During the evolutionary transition from a single cell organism, existing in an anaerobic environment to a multi-cellular metazoan, which had to cope with an oxygenated environment, new genes and phenotypes had to emerge. Among those genes, new structures and functions that were associated with this transition were (a) stem cells, that had the ability to divide symmetrically and asymmetrically; (b) low oxygen micro-environment stem cell niches; (c) epigenetic mechanisms to regulate, differentially, sets of genes in the total genome; (d) and cell-type connexin genes and gap junctions to regulate, homeostatically, cell proliferation, differentiation, apoptosis; and senescence. Furthermore, with the formation of neurons and brain functions, consciousness appeared. More than any other organ, the brain contained unique regions that controlled either conscious or unconscious functions. With the appearance of *Homo sapiens*, who became "conscious" of its "consciousness", the philosophical and scientific question is: "How could this unique organ develop and maintain all these very different functions?" and "What happens when the underlying mechanism(s) are disrupted?". Given the unique appearance of adult organ-specific and function-specific brain stem cells, differential expression of the connexin genes and gap junction functions in the brain, and genetic (mutational) or epigenetic alteration of the genes, that affect either stem cell quality or quantity or the function of gap junctional intercellular communication, a hypothesis has been offered that might link the very different brain and mind functions and diseases.

Keywords: *Stem Cells; Cell-Cell Communication; Epigenetics; Gap Junctional Intercellular Communication; Inflammation in the Brain; Microbiome and Brain Axis*

"Placed in this context, the variables affecting epigenetic inheritance can be properly assessed as a key mechanistic principle of evolution that significantly alters our understanding of homeostasis, pleiotropy, and heterochrony, and the purposes of sexual reproduction…. Consideration within this frame reduces biology to cellular information sharing through cell-cell communication to resolve ambiguities of every scope and scale" [1].

Introduction: The link between the normal functions of the brain and the diseases of the brain and mind

Over the ages, philosophers and more recently, scientists of every discipline, from physics to neuroscience, have tried to understand how the brain of the *Homo sapiens* made the transition from being conscious of the exterior world to being conscious of one's consciousness. Human consciousness of one's consciousness ultimately led to the beginnings of the understanding of the normal functions of the brain and now to the many very different clinical manifestations of the diseases of the brain and mind. That transition led *Homo sapiens* to have abstract thinking and symbol-making of external objects, language formation, tool making and consequently, value or moral

decision-making. In effect, the creation of "culture" occurred at that point. The interface of biological evolution with cultural evolution, while always creating new conditions for the brain to adapt, more recently, has created a major cause of concern because of the influence of the brain on so many factors affecting human health [2].

Guided by the wisdom afforded by the quote of Theodosius Dobzhansky: "Nothing makes sense except in the light of evolution" [3], this short "Commentary", tries to bridge the normal functions of the human brain and the many diseases associated with both the brain and mind. While being fully conscious of the tens of thousands of writings and musings by philosophers, theologians and anthropologists over hundreds of years, and more recently, by scientists of every discipline, a hypothesis will be offered to provide a biological basis, that will not only bridge the gap between normal functions of the brain/mind and the diseases of the brain and mind, but help to bridge the gap between the biology of the human body and to the "biology of human nature" [4]. Clearly, our scientific understanding of the brain/mind issue is a philosophical issue, and one where many believe science will never understand that gap. On the other hand, Rene Dubos believed that, because the brain and its consciousness that created culture and the humanities, including his ecstasy, logic, experiences of happiness and despair, religions and ethical doctrines, philosophy, linguistics, literature, the arts, it leads to "…the preoccupations, which constitute his humaneness, and are inseparable from the physiological needs and urges which biological experiences has inscribed in his flesh and bones" [5]. While this objective is way beyond the goal of this "Commentary", the task here is based on the assumption that the normal functions of the brain/mind are the result of a shared fundamental mechanism by many of the diseases of the brain/mind [6].

Taking this Dobzhansky's quote as a guiding principle, it now seems that the appearance of life in the single cell organisms was the result of obtaining energy by the conversion of glucose to obtain ATP, via the process of glycolysis in an oxygen-deficient environment, conditioned by the limited range of temperature, radiation, diurnal light, gravity, etc. These single cell organisms had to adjust after the oxygenation of the earth, in order to find another way to survive and reproduce by new sets of genes and phenotypes. One of the adaptive features was the ability to "communicate" with each other via extra-cellular signals (primitive "hormones", cytokines, growth regulators), that could trigger Intra-cellular signals to affect the physiology and behavior of that single cell organism. This has been referred to as "quorum sensing" [7].

The new appearance of multi-cellular organisms occurred when, among other events, collagen-type molecules could be synthesized [8], which allowed cells to adhere to each other. These new societies of adherent cells, in turn, created other situations to force new genes to allow these cells to survive and reproduce. The reason for this new situation to select for new genes is because a 3-dimensional ball of cells had to have growth control and means to assure that cells on the inside of the 3-dimensional organism had access to nutrients and oxygen, which the cells on the exterior had. The new genes and phenotypes that eventually appeared included (a) stem cells; (b) stem cell niches to provide low oxygen microenvironment;(c) epigenetic mechanisms to regulate, differentially, sets of genes from the total genome; (d) ability to divide symmetrically or asymmetrically for maintaining self -reproduction, versus differentiation; (e) the ability to remove, selectively, cells by apoptosis or autophagy; and (f) senescence.

During that evolutionary transition from uni-cellularity to multi-cellularity, there was not a discarding of all the early genes, but a new "re-purposing" of these genes. In other words, the function of a particular gene in a single cell organism, that has no neurons or brain, was re-purposed when that gene was saved during the appearance of multicellular metazoan. While many genes appeared during this early transition of the multi-cellular metazoan, it turns out the connexin genes, that coded for a protein channels on the membranes of these cells, allowed for the direct exchange of ions and small molecular weight regulatory molecules between contiguous cells [9] appeared in the early metazoan [10]. The new form of communication or gap junctional -intercellular communication (GJIC) helped to integrate the other two forms of communication, such that modulation of one form would modulate the other two forms. The introduction of the gap junction allowed for a cell (a stem cell cell) to divide either symmetrically for self- replication or asymmetrically for self -replication of one daughter but unique differentiation of the other daughter cell. In this manner, an ancient gene that served one function in a unicellular

organism could have been integrated into the total genome of a multicellular organism and specifically expressed out of the total genome in a specific differentiated cell, such as a neuron. After the connexin family of genes and epigenetic regulation of that gene's expression from the total genome in a cell that became a differentiated neuron, now found its new function [11].

It was shown early that "contact inhibition" [12], differentiation [13] and later apoptosis [14] of multi-cellular metazoans was correlated with functional gap junctional inter-cellular communication in normal cells, and the absence or dysfunction of the gap junctions was correlated with cancer cells [15]. Later, it has been shown that various endogenous chemicals (hormones, growth factors, cytokines [16-18], as well as many different exogenous agents (dietary factors; pollutants, pesticides, medications, etc. [19]) could modulate gap junction function. Inherited mutated connexin genes have been associated with various unique human diseases [20]. Cancer cells, with no gap junction function, have been associated with either no expressed connexin genes or with expressed connexins genes, but where the protein has been rendered dysfunctional by some viral gene (e.g. SV40 [21]). Normal cells with expressed oncogenes, such as Hras, SV40 or Neu [22], also, can convert a normal cell to a cancer cell with dysfunction GJIC. On the other hand, cancer cells with dysfunctional GJIC can be restored to a "normal" phenotype by genetically engineering it with a "tumor suppressor" gene [23]. Along those lines, some non- gap junctional intercellular communication cells can have either its gap junction gene expressed with drugs, such as SAHA [24], or cancer cells, that have expressed connexin genes but have their protein non-functional, be restored by other agents that make the viral or oncogene dysfunctional [25].

The fundamental role of this integrated cell communication network in normal brain /mind function

During the development from a single fertilized egg to the embryo, fetus, neonate, adolescent, mature and senile human being contain approximately two hundred trillion cells [26], the differential expression of the connexin genes must take place in a delicate sequential manner. All organs of the human being have both adult-specific stem cells that differentiate into several differentiated cells within that organ. Evidence seems to show that stem cells express the Oct4 gene and do not have either expressed connexin genes or functional gap junctions [27-29]. The adult stem cells give that organ specific physiological functions, such as hepatocytes in liver for detoxication; renal medullary tubular cells of the kidney for filtering; gut epithelial and immune cells for both nutrient extraction and ability to deal with microbiome toxins; keratinocytes for barrier function; rod cells for visual light detection; beta cells in the pancreas for insulin production; and glial, astrocytes, oligodendrocytes, neuron and microglia cells in the brain for the multiple discrete functions of different regions of the brain.

Of course, many organs seem to have multiple functions; however, few other organs have as many functions as does the brain, with specific regions associated with either unconscious but vital physiological functions, whereas others with more abstract mind-like conscious functions (Figure 1).

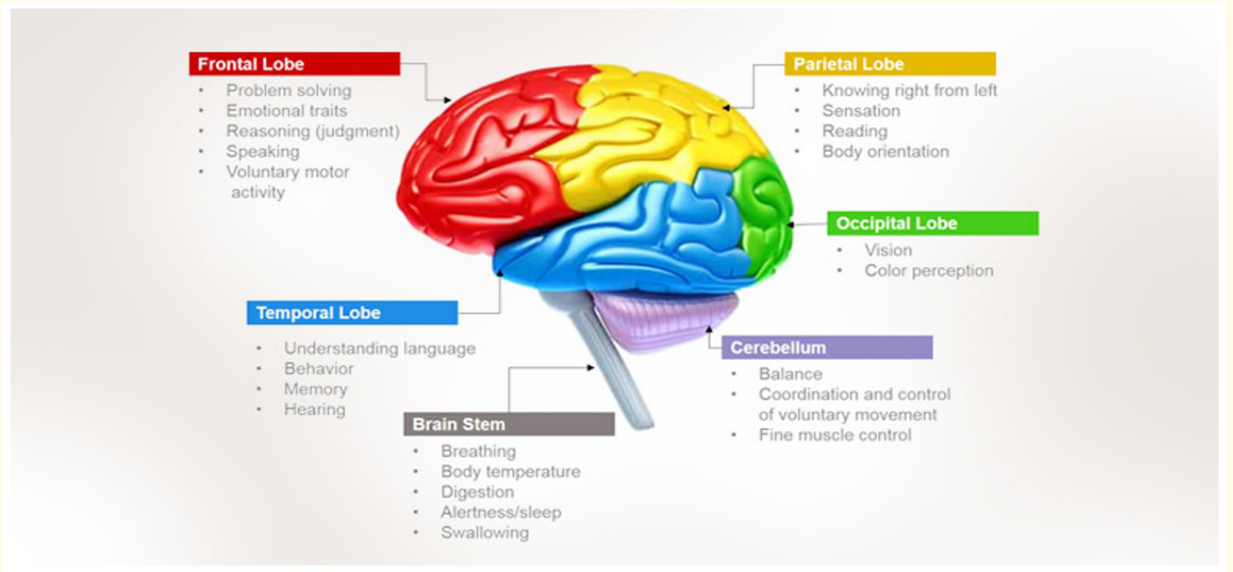

Figure 1: *Diagram illustrating the many discreet unconscious physiological functions of regions of the brain and the many discreet conscious functions of unique regions of the brain. Copyright © 2016-2018 www.humanbrainfacts.org.*

Underlying these functions affecting the unconscious physiological functions, which do affect the conscious mind-like functions, are the few brain stem cells, the glial, astroglia, microglia, astrocytes, and different kinds of neurons. While the current idea that the main communication of the neuronal function is via chemical neural transmission between the neurons, neurons not only communicate with other neurons via gap junctions, but also, they are dependent on glia -neuronal gap junctional communication [30]. Gap junctions appear to play a fundamental role in exocrine and endocrine secretion of organs, including the brain [31].

Clearly, as with the development in other organs, gap junctional intercellular communication is well documented in the brain [32]. In addition, the microglial, which serves as an immune modulator of inflammation, helps to integrate the extra-, intra- and gap junctional inter-cellular communication network [33].

With both endogenous chemicals, such as serotonin [34], melatonin hormone [35]; oxytocin impacts emotional, cognitive, and social behaviors [36] and any cytokine secreted from microglial, that might affect brain inflammation [37], or exogenous chemicals, such as caffeine [38], alcohol [39], marijuana [40] affecting gap junction in brain cells [41], can affect both physiological brain and mind functions. Interference with this ability of the gap junctions to be expressed or function could lead to death of the embryo, as is seen with knock out connexin 26 and connexin Cx43 mice [42]. Furthermore, modulation of gap junction function by a sedative drug, such as thalidomide [43] or valproate acid [44] can lead to birth defects. Alcohol, which can inhibit GJIC during fetal development, can also lead to "fetal alcohol syndrome". Too much alcohol in the alcoholic can lead to dysfunction of the brain and mind of the adult. One needs only to search the literature to see that GJIC has been associated with all kinds of diseases, including hypertension [45], cancer [46], hearing dysfunction [47], diabetes [48] and sleep disorders associated with Oleamide [49], seem to be mediated by gap junctions. Again, the expression level of connexins in glial cells and in particular, astrocytes, normally is very high [50], however, in the depression state, dramatic changes in the expression is observed. The function of connexin43 in astrocytes has been noted when anti-depressive drugs are used [51]. Modafinil, a drug used to treat sleep disorders, narcolepsy, cataplexy, increases glial gap junctions [52] and cortical astrocytes [53].

To illustrate the "good news/bad news" aspect of agents that could affect the role of cell-cell communication in different regions of the brain, is the recent evidence of the role of the chemicals in marijuana. Smoking marijuana or taking extracts has shown physiological effects, such as alleviation of nausea; stopping convulsions; alleviation of eye pressure and the decreasing of muscle spasms [54]. At this time, the mechanistic basis for these marijuana-linked physiological effects are not known, several chemicals in marijuana, such as tetrahydrocannabinol (THC), which modulates the immune systems, might give insight by which it works to affect many organ systems, including the brain. Many of the organs have intrinsic immune cells (liver, brain, skin, gut, etc.) that also respond to immune secreted factors from other organs. Therefore, many physiological effects seen after exposure to marijuana might be due to these intrinsic immune responses.

Comparing the short -term physiological responses to cigarette smoking, such as perceived pleasurable effects and unperceived addiction, the long-term consequences can lead to lung dysfunctions. To make the comparison even more convincing, it has been well documented that cigarette smoke chemicals can modulate gap junctional intercellular communication [55].

Even more interestingly, marijuana has been correlated with slowing mental declines in many HIV patients [56]. The cannabinols have been documented as potential inhibitors of gap junctional intercellular communication [40] and that there exists gap junction coupled cell networks which can be targets of inflammation [51]. A hypothesis could be generated that states any disrupted cognitive function that is associated with modulated gap junction function might be modulated anti-inflammatory agents. Therefore, marijuana compounds seem to be acting as anti-inflammatory agents, by blocking the effects of inflammatory inhibitors of gap junctional intercellular communication [57]. This speculation implies that this fundamental biological process that regulates homeostasis in all organs, including the brain, might be the target for further experimentation [51].

Given that inflammation is associated with many chronic diseases, by preventing inflammation by a natural chemical, such as THC, if given in the right protocol, rather than smoking a "joint", could be an effective preventive/therapeutic strategy to affect multiple brain dysfunctions. Natural anti-inflammatory chemicals found in fruits and vegetables, many of which are known to modulate gap junctional intercellular communication, some mixture might be found that might be effective in treating several brain dysfunctions. Care must always be practiced since these chemicals, under different circumstances, can be converted from an anti-inflammatory agent to a pro-inflammatory agent. Indeed, these chemicals could have very different effects at different stages of development and in different genders.

Given the current complex link between the microbiome on both the normal physiology [58], cancer [59] and neurodegeneration [60], via chronic inflammation due to various cytokines, again a suggestion of organ-specific stem cell number modulation, and changes in gap junction function might be inferred.

In general, the mechanism by which these chemicals work to modulate gap junctional intercellular communication in the brain is via epigenetic mechanisms, not by mutagenic or cytotoxic mechanisms. However, another mechanism that has to be considered, especially during development, is that mechanism, which can predispose the fetus and neonate to diseases later in life, could be the modulation of adult brain stem cell numbers. In other words, by either increasing or decreasing adult brain stem cells in various regions of the brain during early development could alter either or both physiological or mind/behavioral functions attributed to specific brain regions. While there has been no evidence to date to test this hypothesis, the Downs syndrome might be a human example. This syndrome, the result of a chromosomal mutation whereby an extra set of normal genes on the 21 chromosome seems to cause, by epigenetic mechanisms, abnormal regulation of genes during development. As a result, many chronic abnormal development features and diseases are associated, with variable severity, the classic birth defects, predisposition to diabetes, leukemia, cardiovascular diseases [61], premature aging, Alzheimer's [62] and autism-like spectrum disorders [63]. In non-Downs individuals, these multi-factorial diseases can be the result of multiple mechanisms during a multi-stage process. Yet in the Downs syndrome, these syndromic features seem to be the complex result of epigenetic mechanisms that can affect many organ systems, including the brain.

In summary, although many genes and phenotypes evolved in the emergence of the brain of the *Homo sapiens*, the thesis, presented in this short "Commentary", proposed that two fundamental biological structures and function must be kept in mind, in order to understand both the normal functions and diseases of the brain and mind, namely, the appearance of stem cells and gap junctional intercellular communication. Both genetic and environmental factors can affect both the quality and quantity of adult stem cells, especially during development, and the functioning of the gap junction in the homeostatic regulation of genes via epigenetic mechanisms to control cell proliferation, differentiation, apoptosis and senescence in all organs, including the brain. Untimely disruption of both the stem cells and gap junctional intercellular communication does lead to normal brain function and multi-kinds of diseases of the brain and conscious mind.

Finally, while Rene Dubos [5] and Joseph R Royce [64] tried to address, as hundreds of others have, how does one bridge the "gap" between the sciences and the humanities, or between the "facts versus values" or the "is" and "ought" issue? Biological evolution led to the *Homo sapiens* brain, which involved genetic and epigenetic alterations in the DNA of cells, enabling the brain to create an ever -changing culture. This has and is forcing ethical choices to be made. If there continues to be a view that the conscious brain has no underpinning biological influences on our moral decision- making activity, there will be a global train wreck. This does not imply the science can determine values from fact, i.e. the "Naturalistic Fallacy" or "Scientism". However, as Dr. Van R. Potter has stated, "One can't ignore or arrogantly defy facts when making value decisions". That was his basic philosophy encompassed by "Global Bioethics" [65].

Therefore, the aim of future brain/mind studies will have to study how various biological mechanisms influence the so-called "free will" or conscious decisions, and therefore are influenced by these conscious decisions. One must understand those biological mechanisms, via evolution, led to the creation of stem cells and an integrated cell- cell communication network that shaped the brain and its

many physiological "body" functions, in addition to the emergent mind or conscious functions. To ignore one's creative thought, feeling of sadness, fear, joy or ethical value decision, as having biological underpinnings in one's experiences, that locked in information, epigenetically, from one's social and cultural interactions, is to perpetuate our current failed view of human nature. The concept of Free Will, which assumes the false assumption that those external experiences were not involved in any choice made, is that barrier to an adaptive "global quorum sensing" [66].

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