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## **The Three Neurogenetic Phases of Human Consciousness**

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### **ABSTRACT**

This paper is an organization and conceptualization of a genetic account of human consciousness and to establish an initial list of the neurogenetic correlates of consciousness (NgCC). This will be accomplished by establishing networks of genes that are involved in the multiple facets of the process of human consciousness. The methodology utilized in this work is the evaluation of a small number of genes that have been researched experimentally in order to understand their role in brain development and function. The results demonstrate that most neurogenetic genes can be categorized into three phases: the emergence of neuron-based consciousness, the continuum of neuron-based consciousness, and the neurodegeneration of consciousness. This work also revealed that some genes have a function in more than one of the neurogenetic phases. As of now a starting point has been established in terms of identifying some NgCC but there is room for expansion as there are likely to be hundreds of more genes that have yet to be identified or the function pertaining to human consciousness has not yet been fully understood.

### **Introduction**

A framework of consciousness based on the neural correlates of consciousness (NCC) was proposed by Francis Crick and Christof Koch in 2003.<sup>1</sup> Within this framework brain systems are active in tandem with the conscious experience. Some of the NCC were discussed at the *Towards a Science of Consciousness 2012 conference*. Here is a quick summary of some of the NCC currently being investigated:

- Areas affected by anesthesia e.g. the frontal cortex integration to the posterior parietal cortex.
- Decreases in brain connectivity and cerebral integration seen in PET scans and fMRI studies in patients in vegetative states (unresponsive wakefulness syndrome) and minimally conscious states.
- Frontoparietal connections that provide a global workspace. Two examples of these connections are: 1) lateral prefrontal and parietal cortices that function to provide external sensory awareness and 2) precuneal and mesiofrontal midline activity functions to provide an internal awareness.

- Critically emergent properties of collective widespread connectivity of consciousness found in the thalamo-cortical regions.

For more detail on the *Towards a Science of Consciousness 2012 conference* a conference report is available.<sup>2</sup>

The neurogenetic correlates of consciousness (NgCC) is a newer field of consciousness studies that focuses on the study of genes and gene products (e.g. transcription factors) that are involved in (and have an effect on) the conscious experience, or what I have termed *the continuum of neuron-based consciousness*. Another way of saying this is that the NgCC are actively underlying the NCC during all points of the conscious experience. In addition to the continuum of neuron-based consciousness, NgCC are also found in the initial construction of the brain and nervous system, as well as in the later in life processes of neurodegeneration. These neurogenetic phases will be discussed section by section in this article.

We must keep in mind that the genetic quality underlying the NCC works on a very different scale than the neurons themselves. The neurons work at amazing speeds and utilize quantum properties, for example the movement of electrons across the synapse or along the length of an axon. Another example of quantum properties utilized by neurons is the quantum mechanical electron tunneling effects that take place within the synaptic cleft, which was described by Evan Harris Walker.<sup>3</sup>

The proper functioning of the neurons underlies many of the modalities that integrate the conscious experience of the human brain. This can be seen at the level of interactions between the brain and the environment. For example, the optic nerve needs to function properly in order to see what is there, the amygdala needs to function in order to rate the appropriate response to what is seen, and the hippocampus needs to function properly in order to remember what was seen. However, beneath the proper functioning of any of the neurons is the proper functioning of the genome. There is also a network of RNA and protein species that are constantly interacting with each other and the genome. Thus, as the neurons function on their scale of performance during a conscious experience the DNA, RNA, and proteins are functioning below that on a different scale.

Similar to the neurons the DNA scale also utilizes quantum properties, but they are poorly understood at this point, for example the quantum nature of hydrogen bonding forces between the nucleotides, DNA methylation determination, and chromatin signals. This network of nucleotides and proteins interacting at this particular scale of complexity has been referred to as *DNA consciousness*, which is a degree of consciousness that is different from the degree of human consciousness.<sup>4</sup> Not only is DNA consciousness a degree of consciousness in its own right, but this degree of consciousness possesses the ability to give rise to higher degrees of consciousness e.g. cellular consciousness and human consciousness. When the degree of DNA consciousness gives rise to human consciousness I propose that it occurs in three neurogenetic phases, which will be the topic of this paper. Before I discuss the three neurogenetic phases I will first need to explain how they were developed. Consequently it is necessary to explain three other concepts that precede the three neurogenetic phases of human consciousness.

### **Where did the concept of the three neurogenetic phases of human consciousness emerge?**

The three phases of the neurogenetics of consciousness were first presented, collectively, at the *U.S. Psychiatric and Mental Health Congress Conference* November 2011, in Las Vegas, Nevada- “The Neurogenetics of Consciousness”.<sup>5</sup> However, I did also briefly mention the neurogenetics of consciousness at an earlier presentation at the *Towards a Science of Consciousness Conference* at Stockholm, Sweden, May 2011- “DNA Consciousness”.<sup>6</sup> At that time the three phases were:

- Neurogenesis- the focus was primarily on Hox and Pax genes that are involved in body patterning and the early emergence of the brain regions.
- Genetic mutations that affect degrees of human consciousness and are associated with psychiatric disorders.
- Genes involved in neurodegeneration- the focus was primarily on genes involved in Alzheimer disease (AD) as a primary example of a neurodegenerative process that affects modalities of human consciousness.

Additionally, the neurogenetics of consciousness as a newer topic was discussed in detail in the chapter “DNA Consciousness: From Theory to Science” which is forthcoming in Ingrid Fredriksson’s *Aspects of Consciousness II*.<sup>7</sup> Some of the contents of that chapter will be highlighted in this article as well during the discussion of the current description of these three neurogenetic phases.

The main points regarding the neurogenetics of human consciousness and the direct relationship that it maintains with DNA consciousness was discussed further at a presentation at the *Towards a Science of Consciousness Conference* at Tucson, Arizona April 2012- “Neurogenetics and DNA Consciousness”.<sup>8</sup> Next, more conclusive work was done on the third neurogenetic phase and these results were presented at the *International Journal of Arts and Sciences Harvard Conference* at Boston, Massachusetts May 2012- “Alzheimer’s Disease and DNA Consciousness”. Finally, the three neurogenetic phases of human consciousness were presented at the *Vigier VIII- British Computer Society Joint Meeting Conference* at London, England August 2012- “The Neurogenetic Correlates of Consciousness”. The proceedings from the Vigier conference are an initial outline of the three neurogenetic phases of human consciousness.<sup>9</sup> Also in this particular work the importance of neuron plasticity to the second neurogenetic phase was recognized.

In conclusion, the investigation of the three neurogenetic phases of human consciousness and their emergence as a topic span research done during the course of five conference presentations and the completion of a book chapter. As a result of obtaining new information and revising the three neurogenetic phases of consciousness the titles were modified:

- Phase One: The emergence of neuron-based consciousness
- Phase Two: The continuum of neuron-based consciousness
- Phase Three: Neurodegeneration

*Making a connection: From genes to consciousness*

As mentioned previously, the NCC has been established as a minimal set of neuronal events that give rise to a specific aspect of a conscious percept. So how then are genes also involved in a minimal set of neuronal events that gives rise to a specific aspect of a conscious percept? I propose that the NgCC lie beneath and should be considered a substructure to any of the NCC. This theme will be addressed rigorously in the discussion of all three neurogenetic phases. However, before I discuss the three phases of the neurogenetics of human consciousness I must briefly provide a general definition of three other concepts: the interaction-based model of consciousness, the concept of interaction-complexity-consciousness (ICC), and the theory of DNA consciousness.

**The Interaction-based Model of Consciousness, ICC, and DNA Consciousness**

When approaching the three neurogenetic phases of consciousness a completely different approach in thinking is required. This thinking requires a slightly different way of defining what consciousness *is*. Therefore, I will very briefly define these three concepts in order to establish a general understanding so that we can move on to the main goal of this article which is discussing the three neurogenetic phases of consciousness. The interaction-based model of consciousness, the ICC, and DNA consciousness have all been discussed in other works listed in the references, specifically the article *The DNA molecule is autopoietic, dynamic, evolving, and a form of consciousness* if the reader requires more detail.<sup>4</sup>

The interaction-based model of consciousness defines consciousness as *the interaction of things (be it an organism, DNA molecule, or atom) with other things, the external environment, different forms of energy, and forces*. This concept is built upon the foundation that consciousness *is* interaction. This allows everything in the universe to have a *degree* of consciousness; from quarks to molecules to cells to brains- as they all interact in various degrees. This definition maintains that without interactions consciousness is glaciated.

An interesting phenomenon occurs when following the recurring salient thematic element of the interaction-based model of consciousness and that is as things interact they become more complex. So complexity appears to be bridging the gap and serving as an operator (mathematically) between interactions and degrees of consciousness i.e. how those degrees of consciousness are affected. For example, if we take a handful of quarks there is a certain type of interaction taking place on a certain level of complexity which gives rise to a degree of consciousness- some may consider this *quantum* or *primordial* consciousness. However, as these quarks continue to interact and form subatomic particles and those subatomic particles begin to form small molecules e.g. hydrogen and helium, there is now interactions on a different level. As a result we have a different scale of complexity and a higher degree of consciousness- some may consider this *atomistic* consciousness. At this point we can visualize the relationship of interactions and the ensuing concept of interaction-complexity-consciousness (ICC).

The concept of the ICC states that as things interact they become more complex and as complexity increases there is an associated increase in the resulting degree of consciousness. Thus all matter and energy in the universe is seen to have a degree of consciousness that ascends in a complexity-dependent fashion via interactions. In this way the ICC is an extension of the

interaction-based model of consciousness, with the notion of complexity being the bridge or operator connecting interactions and consciousness. Please keep in mind that the ICC is not a rating system of consciousness, nor is it an attempt to establish a teleology placing humankind at the top. It is recognition of how everything in the universe possesses a degree of consciousness.

Now that we have a general understanding of the interaction-based model of consciousness and the ICC allow me to discuss another illustration. I have made a demonstration involving quarks, subatomic particles, and atoms interacting and giving rise to complexity-dependent degrees of consciousness. Thus the next step would be to discuss the molecular degree of consciousness. At this level molecules emerge and something *special* takes place- the assembly of nucleotides. This begins with RNA (ribonucleic acid) species and shortly thereafter DNA (deoxyribonucleic acid). This is a special degree of consciousness known as *DNA consciousness*. The interactions between RNA and DNA allow an explosion in complexity and a subsequent explosion in various degrees of consciousness. Although I maintain that RNA in all likelihood appeared first it was not able to launch an explosion of consciousness anywhere close to the robustness of the explosion catalyzed by the emergence of DNA. This is why I give priority to DNA in the theory or phrase *DNA consciousness* while still recognizing the importance of RNA.

The theory of DNA consciousness maintains that DNA has a degree of consciousness (which is supported by the ICC) and that it possesses the ability to give rise to other degrees of consciousness. For example, DNA consciousness provides the platform for *cellular consciousness* to emerge (also called polyzoism). Cells continue to evolve and form tissues and multicellular organisms due to the development of new genes. Eventually cells will develop new genes that allow the transformation of simple neurons to emerge. An example of one of these types of genes is the synapsins genes.

There are three mammalian synapsins genes (I, II, and III), although orthologs (versions of genes found in more than one species traced to a common ancestor) are found in the invertebrates and lower vertebrates. Synapsins genes code for synapsins proteins. It is well established that synapsins modulate neurotransmitters at the pre-synaptic terminal of the neuron. Specifically, synapsins III has been demonstrated to negatively regulate the release of dopamine whereas serotonin appears to be unaffected.<sup>10</sup> These genes also have been shown to play a critical role in neuronal development.<sup>11</sup> More recently, synapsins have also been shown to not only be involved in dopamine release but in the fine-tuning of neuronal plasticity.<sup>12</sup> Therefore it can be seen how a novel gene family that is being expressed can contribute to a neuron becoming a neuron. Of course keep in mind that many other genes are responsible for the differentiation of a neuron.

There are many genes that are known that produce transcriptional proteins and neurotrophic factors that are critical for the development of neurons. The vast majority of these genes are not expressed in other cell types, thus a distinction is made from cellular consciousness and *neuron-based consciousness*. The genomic expression of certain genes allows a neuron to be a neuron; as seen in our example with the synapsins. This is not a merely random act! There is a degree of consciousness at work, which I have proposed to be DNA consciousness.

At this point in the ICC we have the arrival of neurons and the emergence of nascent degrees of neuron-based consciousness. This is seen in many of the higher invertebrates that have large nerves that allow them to interact with the environment in a completely new way. As time goes

on these organisms become more complex and newer genes emerge e.g. the Hox genes that allow body segmentation to take place, which is seen very profoundly in the vertebrates. Also unique to the vertebrate nervous system is the production of myelin, which is produced by *myelin-related genes* that have not been found at this point in time in the invertebrates. Myelin is important as it allows the faster conduction of nerves.

In collaboration with the Hox gene family, the Pax gene family allows the centralization of the nervous system and cephalization- the appearance of a head and brain. The emergence of primordial brains allows more unique interactions and higher degrees of consciousness to emerge. Eventually, during the course of natural selection, the primate brain will emerge and subsequently human consciousness evolves.

This brings us to our discussion on the three neurogenetic phases of human consciousness. My proposal, in a basic sense, is that when DNA consciousness gives rise to human consciousness this process takes place in what I have termed three neurogenetic phases. I will discuss each phase separately and provide many specific NgCC as examples to justify this proposal.

### **The Three Neurogenetic Phases of Human Consciousness**

I have given a brief description of the interaction-based model of consciousness and how it transmogrifies into the concept of ICC. Additionally, I have explained how the degree of DNA consciousness emerges within the trajectory of the ICC and how DNA possesses the ability to give rise to higher degrees of consciousness by developing new genes. I also highlighted the importance of the evolution of new genes and how certain genes allow higher degrees of consciousness to emerge.

This brings us face to face with an attempt to understand a genetic account of human consciousness. In this undertaking I have divided this phenomenon into three phases. I have selected a handful of genes to use as examples to illustrate each of the three phases of my hypothesis, with the understanding that hundreds of genes may be at work in each of these phases, perhaps thousands of genes!

It is also important to note that some of the genes mentioned in this work have been studied in animal models. However, we must keep in mind that many of these genes are highly conserved throughout the animal kingdom and thus a reasonable extrapolation can be made in terms of function for the purpose of explaining this hypothesis. In addition, as of now performing pure neurogenetic experiments on humans is not realistic or ethical.

#### **Phase One: The Emergence of Neuron-based Consciousness**

The DNA molecule gives rise to cellular degree of consciousness. It does this with a simple but yet complicated system of genes being turned on and off by master genes higher in the developmental hierarchy. This is accomplished by gene-gene interactions through a network of RNA species, nuclear transcription factors, and epigenetic proteins. As cells evolved new genes appeared via mutations, after which some genes were favored by natural selection and remained in the genome. Novel genes would allow neurons to emerge. Earlier, synapsins were

mentioned as an example and I will point out that there are many more but this is not the focus of this article.

The fact that DNA is primarily responsible for the emergence of neurons is significant as these neurons are the primary machinery by which human consciousness functions. Once neurons begin to form and mature they differentiate and compartmentalize into brain regions. Very small changes on the level of the nucleotide can have observable effects at the macroscale level of human consciousness.

The process of forming the brain and the central nervous system requires regulation by master genes higher in the developmental hierarchy. These genes control the transcription of other genes downstream, which when activated will style undifferentiated progenitor cells into cells with a specific function. In this case, different types of neurons and ultimately specific brain regions. I will now discuss some genes that execute these functions.

### The Pax3 gene

The Pax3 gene codes for Pax3 protein, which is a developmental transcriptional factor that is expressed during early embryogenesis.<sup>13</sup> It is required for neural tube development and closure, which is proposed to be regulated by stimulating the ubiquitination and degradation of p53.<sup>14</sup> Ubiquitin is a protein that causes inactivation of other proteins. Therefore, Pax3 inactivates p53 by regulated stimulation of ubiquitin.

The p53 is produced by the TP53 gene and controls the rate of cell division. This is accomplished by the involvement of p53 in the G1-phase of the cell cycle, which allows a delay between the cell phases. This delay affords time for defects in the DNA molecule to be detected and repaired by the *DNA damage response pathway* before the cell enters into G0-phase. In the G0-phase *cell cycle mitosis suppressor proteins* activate *tissue-specific proteins* to be synthesized, which is interesting because this is the phase of the cell cycle where the DNA molecule expresses what the physical characteristics of the cell will be. Thus, Pax3 demonstrates some control over the cell cycle during neural tube development and closure by its influence over p53.

*Trans*-activation is the process of stimulating a gene or a set of genes. Pax3 operates as a transcriptional regulator that regulates the developmental process in early neurogenesis. It accomplishes this by utilizing sequence-specific DNA binding domains that direct *trans*-activation. Through this mechanism Pax3 acts as a *master gene* and has been shown to directly and indirectly regulate the expression of many genes as downstream targets. For example, Pax3 regulates *Hairy and enhancer of split homolog-1* (Hes1) and *Neurogenin-2* (Neurog2) expression by acetylation (which is the addition of a  $-\text{COCH}_3$  group).<sup>15</sup> This is important to neurogenesis as Hes1 is important for neural stem cell maintenance and Neurog2 plays a role in the specification of neuronal subtypes and neurogenesis of both sensory neurons and neural crest cells.

Another example that demonstrates how Pax3 controls the expression of another gene's influence on the development of brain regions is seen in Meis2 gene regulation. The Meis2 gene codes for Meis2 protein that has been shown to be pivotal in the development of the tectum.<sup>16</sup> The tectum is the dorsal portion of the mesencephalon (midbrain) and is composed of two

divisions: the *inferior colliculi* that serves an auditory function and the *superior colliculi* that serves a visual function. It has recently been discovered that tectal Meis2 expression levels are modulated by Pax3 (and Pax7).<sup>17</sup>

It can be visualized with the Pax3 gene example that this gene dynamically effects the formation and closure of the neural tube, which is the nascent version of our brain and central nervous system. In addition, by functioning as a master gene high in the developmental hierarchy this gene, in essence, orchestrates the formation of neuron subtypes and brain regions that will ultimately be used by the human brain to experience consciousness.

### Pax2 and Pax8 genes

Early in development, the Pax 2 gene produces Pax2 protein, which is active in neural crest cells that give rise to neurons and glial cells of the sensory, sympathetic, and parasympathetic system. It has been demonstrated in many studies that Pax2 and Pax8 genes are responsible for the overall ear morphogenesis and the continuous neurosensory development. Specifically, Pax2 is required for the proper formation of the organ of Corti development,<sup>18</sup> which lies within the cochlea of the inner ear. It has been observed that Pax8 plays a key role in orchestrating the dynamic changes in the early gene expression and initial ear morphogenesis.<sup>19</sup>

The two genes Pax2 and Pax8 are responsible for the development of the ear. The ear is important as it allows the perception of sound from the external environment, which is interaction at a more complex level. It also allows modalities of communication and increases in the degrees of consciousness. In addition, Pax2 is involved in the activation of neuron subtypes that are differentiated from the neural crest cells.

### Pax6

The Pax6 gene codes for Pax6 protein, which is a developmental transcription factor. This gene and its orthologs are well known master regulators of eye development and are highly conserved throughout the animal kingdom.<sup>20</sup> Pax6 initiates control over eye development as it mediates the ectoderm above the optic vesicles to form the lens of the eye.<sup>21</sup> During development Pax6 controls transcriptional expression of genes that code for transcription factors that are responsible for lens formation e.g. *musculoponeurtic fibrosarcoma* (L-maf), *SRY-box containing gene* (Sox-1), *prospero homeobox* (Prox-1), and *lens structural proteins* ( $\alpha$ -,  $\beta$ -, and  $\gamma$ -crystallins). Mutations to the Pax6 gene have been shown to result in ocular dysgenesis and aniridia (the absence of an iris).<sup>22</sup>

It has also been shown that Pax6 promotes the neurogenic fates (neuronal lineage development and migration patterns) of neural progenitor cells, specifically the glial progenitor cells of the forebrain.<sup>23</sup> The size and cell number of every brain region is controlled by the organization and behavior of the neural progenitor cells during embryonic development. One group of important cells is the basal progenitor cells found in the subventricular zone and they give rise to the majority of the thalamus and the six-layered mammalian neocortex. Recent studies on brain morphogenesis demonstrate that the proper thalamocortical development is dependent on Pax6 and neurogenins (Neurog1 and Neurog2).<sup>24</sup> Keep in mind that Neurog2 expression is also influenced by Pax3 during specifications of neuronal subtypes. In addition to the corticogenesis



of the forebrain and the development of the thalamus, Pax6 has been revealed to participate in the regulation of neurogenesis of the Neuron-Glia 2 progenitor cells in the hippocampus.<sup>25</sup>

At this juncture it can be seen that Pax6 is involved in development of the eyes, thalamus, some of the thalamo-cortical connections, neocortex, and hippocampus. All of these brain regions are vital machinery for human consciousness. In the same way that the ears are important for the perception of sound, the eyes perceive light, the thalamus is important as it serves as a relay station that integrates cortical structures throughout the brain, and the hippocampus is important as it is required for the long-term potentiation of memory. But how does Pax6 do all of this?

In addition to Pax6 control over genes associated with lens formation, Neurog1, and Neurog2, Pax6 also accomplishes control over the development of other brain regions on the cellular and molecular level with its role in regulating the orientation and mode of cell division during early neurogenesis. One of the mechanisms of control is achieved by the regulation of adhesion and apical anchoring of apical progenitors, and the transcriptional regulation of the *sperm-associated antigen 5 gene* (Spag5) expression.<sup>26</sup> Spag5 gene codes for the microtubule-associated protein Spag5, which is vital to cell division by its direct association with the spindle machinery and the regulation of kinetochore microtubule dynamics both of which are vital to cell division and migration.

As we have seen with Pax3 gene, the Pax6 gene also acts as a master gene by regulating the expression of other genes- L-maf, Sox-1, Prox-1, Neurog1, Neurog2, and spag5. I also demonstrated the importance of these genes in the differentiation of neural progenitor cells and in the development of regions of the brain and nervous system that will eventually be crucial to modalities of human consciousness.

#### Hox genes: Hoxd4 and Hoxb4

Hox genes are pivotal key determinants of anteroposterior (AP) patterning of all embryos throughout the animal kingdom and are a highly conserved gene family. During AP patterning of the developing hindbrain, which collectively becomes the cerebellum, pons, and medulla, the genetic expression borders of many of the transcription factors are aligned at interfaces between neural segments. These interfaces are referred to as rhombomeres, of which there are seven segmented lineage-restricted units. The rhombomeres give rise to some of the ganglia of the cranial nerves (CN) e.g. the *geniculate ganglion* (CN VII) and the *petrosal ganglion* (CN IX). Also keep in mind that the hindbrain plays critical roles in regulating sleep-wakefulness, motor coordination, proprioception, and internal sensation.

The expression of certain Hox genes are involved in the early formation of cranial nerves and the maintenance of the rhombomere borders. For example, Hoxb4 and Hoxd4 genes act as neural enhancers that enforce the border of the anterior brain and rhombomeres 6 and 7 in the hind brain. This has been proposed to function on a feedback circuit that aligns the segmental expression borders. The feedback circuit involves Hoxb4, Hoxd4, and *retinoic acid receptor  $\beta$ -gene*.<sup>27</sup> It has also been suggested that anterior and posterior embryonic compartments are distinguished by distinct chromatin states that undergo histone modification at the Hoxd4 locus.<sup>28</sup>

So here we have a very good example of a few genes- Hoxb4 and Hoxd4 that can have a profound effect on the large scale development of the brain and central nervous system; in this case the rhombomere borders, and some portions of the cranial nerves. Another point of interest is the Pax6 gene that was discussed previously has been shown to exert control over Hoxd4 gene expression.<sup>29</sup>

#### Hox genes: Otx1 and Otx2 genes

Otx1 and Otx2 gene (vertebrate homologues of the *orthodenticle* gene) code for the proteins Otx1 and Otx2, respectively. Both have been demonstrated to be required for the proper formation of the thalamus, specifically the intervening boundary region known as the *zona limitans intrathalamica* in early neuroembryological development.<sup>30</sup> The thalamic complex serves as a central relay center for all the information-generating sensory systems. Therefore, its role in consciousness is of vital importance, which was previously pointed out in the Pax6 section when thalamo-cortical connections were mentioned.

Otx1 and Otx2 proteins have been shown to be expressed in the human fetal brain during weeks 7 to 14.<sup>31</sup> Otx1 was located predominantly in the proliferative zones of the neocortex and hippocampus whereas Otx2 was expressed in the diencephalon, mesencephalon, choroid plexus, basal telencephalon, and hippocampal anlage. In other studies Otx1 was shown to be critical in the proper development of the overall cerebral cortex. For example, mutant Otx1-null mice where shown to have developed a cortex 10% smaller than their wild-type litter mates.<sup>32</sup>

During development the neural tube regionalizes in an AP and dorsoventral (DV) direction. It is well established that the regional identity, control of growth rate, survival of neuronal precursors, and the specification of neuronal fate is controlled along the DV axis by *sonic hedgehog gene* (Shh) and along the AP direction by the *fibroblast growth factor-8 gene* (Fgf8). Otx1 and Otx2 exert dose-dependent antagonism on Fgf8 and Shh expression during the patterning of the midbrain.<sup>33</sup> Otx2 specifically is essential for the identity, extent, and fate of neuronal progenitor domains of the ventral midbrain region, which is the tegmentum.

Even though only four Hox genes were discussed it can be seen that they play a significant role in establishing the early machinery for human consciousness. At this juncture we have examples where Hox genes demonstrate pivotal roles in the maintenance of rhombomere borders, formation of divisions of some of the cranial nerves, the development of numerous brain regions, and some influence on the total size of the cerebral cortex.

#### Summing up phase one

As a starting point we have 8 genes (4 Pax genes and 4 Hox genes) that illustrate the first neurogenetic phase- the emergence of the brain and the birth of human consciousness. There are perhaps hundreds of more genes and thousands of more interactions that are involved in this process that were not mentioned e.g. the Emx2 gene and the TUBB3 gene, just to name a few. Note that not just one gene is responsible for brain development or the formation of a specific brain region. Rather it is the interactions of multiple genes that must cooperate in a coordinated fashion. Examples of this are seen with the genes that give rise to the thalamus and midbrain. These genetic examples also demonstrate how DNA gives rise to human consciousness. This

coordinated effort implicates that a degree of consciousness is at work as this process also requires the action of master genes that command and communicate with other genes. Consequently, this collectively justifies that the first neurogenetic phase is not a random act that evolved surreptitiously. There is a degree of consciousness behind this- DNA consciousness.

### **Phase Two: The Continuum of Neuron-based Consciousness**

Before I discuss some of the neurogenetic correlates of human consciousness involved in the second phase I first want to clarify what I mean by the *continuum of neuron-based consciousness*. I will begin by briefly discussing a current model that relies on neuron-neuron connections to explain the process of human consciousness.

In the article *Biology of Consciousness* by *Gerald Edelman et al.* (as well as many other works by Edelman), a strong case was made to support that consciousness (at least in vertebrates) is a dynamic, integrated, and multimodal mental process which is entailed by physical events in the forebrain.<sup>34</sup> Consciousness, in this proposal, is primarily supported by the infrastructure of cortical-cortical, cortical-thalamic, and thalamo-cortical neuron connections. These connections provide a structural basis, in a neurological sense, for the dynamic reentry of signals between regions of the brain. Specifically between different parts of the cortex and between the cortex and the thalamus, all of which are reciprocal. The neural activity between the thalamus and the cortex (reciprocally) constitutes what is referred to as the *dynamic core hypothesis*.

This proposal gives a great deal of understanding, at least conceptually, as to what the brain does during the process of human consciousness. According to this proposal the dynamic core provides a sequence of integrated discriminations which produces unitary conscious scenes that establish the phenomenal experience of consciousness. This ongoing process is what I collectively refer to as the continuum of neuron-based consciousness. I make this distinction because if human consciousness is to be viewed as a process that functions on neuron activity producing a continuous stream of stimuli-generated scenes then the phrase *continuum of neuron-based consciousness* seems appropriate.

What is the main difference between the dynamic core hypothesis and the continuum of neuron-based consciousness? The distinction is that the continuum of neuron-based consciousness follows the format established in the concept of the ICC, which allows some partition from the other degrees of consciousness e.g. cellular or atomistic. Secondly, I do not maintain that only neurons and the brain are responsible for human consciousness. My proposal maintains that there are neurogenetic correlates involved in the continuum of neuron-based consciousness.

In this section I am attempting to get beneath the neurological machinery in an attempt to understand what happens in a neurogenetic sense during the continuum of neuron-based consciousness. The DNA in the genome of the neurons continues to function during the ongoing process of human consciousness throughout the lifespan. If there are abnormalities in the functioning of DNA e.g. mutations, deletions, or single nucleotide polymorphisms (SNP) then disturbances or decreases in the degree of human consciousness can be observed clinically. Once again, small changes on the level of the nucleotide can have observable effects at the macroscale level of human consciousness. In the first part of this section I use psychiatric disorders to illustrate this point.

An additional quality that is important to the continuum of neuron-based consciousness is the process of neuron plasticity. In the second part of this section I will discuss some genes that are involved in this process. Keep in mind some of the genes that I will discuss in this section are also involved in neurodevelopment and therefore can be placed in the first or second neurogenetic phase depending on when they are being expressed.

#### PTCHD1 locus disruptions- association with Autism

Autism is characterized by impairments in communication and socialization; specifically reciprocal interaction, and the presence of restrictive and repetitive behaviors. In terms of consciousness there is impairment in interaction and the autistic person appears to be more introverted. This signifies a difference in degree of human consciousness- not good or bad but merely an observable divergence in degree.

The PTCHD1 gene is located on the X-chromosome and it produces the *patch-related transmembrane protein 1* (PTCHD1). PTCHD1 and other transmembrane signaling proteins (neuroexins and neuroligins) function to strengthen the synapses of the neurons. Disruptions in regions of this gene have been strongly associated with autism spectrum disorders and intellectual disability.<sup>35</sup>

A more recent study on a family with two boys with a PTCHD1 gene abnormality demonstrated intellectual disability with and without autism in each of these boys.<sup>36</sup> Therefore other genes besides PTCHD1 are likely to be involved in autism and other variations of this disorder. At this point much is being discovered about the neurogenetics of autism. More candidate genes are likely to emerge, but for the purpose of illustrating NgCC in the second neurogenetic phase PTCHD1 serves as a good example as it does demonstrate an association with Autism.

#### Schizophrenia-associated genes

Schizophrenia (SZ) is characterized by profound emotional and cognitive disturbances. These symptoms are also associated with defects in cortical activity and hallucinations. In terms of consciousness SZ represents a disorder of thought and volition in where there are alterations in the degree of human consciousness.

Several gene abnormalities have been associated with SZ etiology. Hypothetically this has suggested that epistatic interactions between multiple susceptibility genes converge into a network resulting in SZ pathology. This will eventually function to illustrate that the coordinated orchestration of genes and genetic products are required in order for the continuum of neuron-based consciousness to provide the infrastructure of human consciousness. I will now discuss a few examples of genes that are involved in SZ.

#### PDE4B gene

The PDE4B gene belongs to a family of genes (PDE4A-D) and produces phosphodiesterase 4B protein. PDE4B has been characterized as being able to hydrolyze cAMP and to turn off cAMP signaling cascades. These cAMP are very important for intercellular communication. PDE4B also plays an important role in synaptic plasticity that is involved in learning and memory. PDE4B polymorphisms (a variation in a gene too common to have recently occurred by a new

mutation) have been strongly associated with SZ, which was demonstrated in a recent cohort study involving 428 cases.<sup>37</sup> However, many diagnosed schizophrenics do not carry the PDE4B polymorphism. Therefore PDE4B polymorphism is only associated with a portion of SZ patients.

### DISC1 gene

*Disrupted in Schizophrenia 1* (DISC1) gene produces DISC1 protein. This protein interacts with multiple proteins at different locations and developmental periods. DISC1 has effects on neuronal development and neuron signaling. It is also part of the microtubule organizing center (the centrosome) and is involved in the cytoskeletal process in neuronal migration.<sup>38</sup> DISC1 activity in the centrosome is similar to the function rendered by Spag5 gene that is controlled by the Pax6 master gene mentioned in the first neurogenetic phase.

DISC1 and PDE4B proteins interact to form the DISC1-PDE4B complex. The abnormal functioning of this complex has been implicated in many of the molecular mechanisms underlying SZ and other mental illnesses.<sup>39</sup> This illustrates not only the individual contributions that DISC1 and PDE4B make to SZ, but also the importance of their interactions in the proper formation of the DISC1-PDE4B complex. A genetic abnormality in either the DISC1 or PDE4B gene results in the improper functioning of the DISC1-PDE4B complex which has a strong association with SZ.

### ZNF804a transcription factor

ZNF804a is a transcription factor that regulates the expression of four SZ-associated genes- PRSS16, COMT, PDE4B, and DRD2. Consequently, it has been proposed that ZNF804a expression is a possible candidate mechanism that confirms SZ risk.<sup>40</sup> This is significant because it demonstrates that one gene can produce a transcription factor that in turn can have downstream effects on multiple genes which results in an alteration in the degree of human consciousness seen in SZ. This alteration in consciousness can be observed and quantified clinically.

In the first part of this section the use of an autism-associated gene (PTCHD1 locus disruptions) and several SZ-associated genes demonstrate the importance of genetic interactions that underlay the continuum of neuron-based consciousness. This is seen with PDE4B and its interactions with DISC1. It is also seen with ZNF804a and its control over the expression of PDE4B (and the other three genes listed). Interactions such as these are important to human consciousness, which relies on the proper functioning of the genetic biology underlying the neuron.

### Neuron plasticity

Earlier in this article I briefly discussed a family of genes called synapsins, which are involved in neuron plasticity and contribute to making a neuron a neuron. During the discussion of PDE4B it was mentioned that one of its many functions was the involvement in neuron plasticity. Neuron plasticity is defined as the ability of the neuron to reorganize and form new connections throughout life. Human consciousness requires that the neurons in the brain change and form new connections in response to new information or stimuli. Consequently, the process of neuron plasticity is crucial to the continuum of neuron-based consciousness. In addition, neuron

plasticity would also be required in the dynamic core model mentioned at the beginning of this section, which would imply that these genes are important to that model as well.

The proper genetic expression of certain genes is vital to neuron plasticity. Hence they are equally important to human consciousness. Next I will discuss three specific genes that are involved in neuron plasticity and discuss their importance to the second neurogenetic phase.

#### Brain-derived Neurotrophic Factor (BDNF) gene

BDNF gene is located on chromosome 11 and produces BDNF which is called a neurotrophic factor because it was discovered in the early 1980's that it promoted the survival of a subpopulation of neurons.<sup>41</sup> A multitude of stimuli e.g. light, osmotic stimulation, and electrical stimulation have been shown to increase BDNF expression (measured by mRNA production) in several brain regions- the visual cortex, hypothalamus, and hippocampus, respectively. The BDNF gene is involved in the maturation of the prefrontal cortex and the hippocampus, as well as being involved in learning and memory.<sup>42</sup> A genetic defect (polymorphism of val66met) in the BDNF gene has been shown to impair memory and hippocampal function by decreasing the modulation of hippocampal plasticity.<sup>43</sup> Therefore, neuron plasticity in the hippocampus is an important process underlying memory and can be adversely affected by mutations in the BDNF gene.

A different study also supports that BDNF is a potent modulator of plasticity in the synapse of the neuron.<sup>44</sup> In this study the important association of another brain structure, the amygdala, in addition to the hippocampus is highlighted. The hippocampal-amygdala circuitry is modulated by BDNF-induced changes in synaptic plasticity in response to emotional memory. Other roles of neuron plasticity and connectivity in the amygdala will be discussed in the section on the  $\Delta$ FosB transcription factor.

#### Fibroblast Growth Factor-2 (FGF-2) gene

FGF-2 gene produces FGF-2 which is known to promote the proliferation of neuroprogenitor cells and also has been demonstrated to be generated in the hippocampus after brain injury.<sup>45</sup> FGF-2 has established key functions in neurogenesis, promotion of axonal growth, neuron differentiation during development, and in the maintenance of neuron plasticity during adulthood.<sup>46</sup> In addition, FGF-2 has been shown to have important roles in synapse plasticity associated with learning and memory.

BDNF and FGF-2 have very similar functions as far as their involvement in neuron plasticity during memory and learning. Interestingly, both of these factors have been shown to have an association in depression. BDNF demonstrates reduced expression in the hippocampus and the prefrontal cortex in subjects with depression, which is further associated with the induction of dendritic atrophy in these regions.<sup>47</sup> FGF-2 expression is also reduced in depression which was seen by decreased FGF-2 mRNA levels in the frontal cortex and regions of the hippocampus.<sup>48</sup>

Both genes BDNF and FGF-2 are underactive in the frontal cortex and hippocampus in depression. Depressive disorders are significant to the understanding of human consciousness as they represent deficits in emotional processing, bias toward negative stimuli, and decreased motivation. These clinical symptoms are reflections of the underlying morphological changes in the brain that are the end result of decreased neuron plasticity. Therefore underactive BDNF and

FGF-2 genes result in decreases in neuron plasticity, consequent neuron atrophy, and decreases in connectivity in the frontal cortex and hippocampus. The dysfunction of neurons in these brain regions are correlated with associated objective symptoms e.g. decrease in memory (hippocampus) and decrease in concentration (frontal cortex) in depressed patients. All of this represents a decrease in the degree of human consciousness that is connected to genes that are involved in neuron plasticity. Keep in mind that many other factors are proposed to be involved in depression e.g. low serotonin in the brain.

#### $\Delta$ FosB transcription factor

$\Delta$ FosB is a transcription factor produced by the FosB gene. This transcription factor has been shown to affect the expression of four other genes. It induces (as a *trans*-activator) the GluR gene, the Cdk5 gene, and the NF $\kappa$ B gene; whereas it represses the dynorphin gene expression.<sup>49</sup> This is important as these four genes have the following functions:

- GluR- decreases the glutamatergic response to AMPA-GluR
- Cdk5- decreases the regulation of dopamine and glutamate
- NF $\kappa$ B- decreases the dendritic spines produced on the medium spiny neurons
- Dynorphin- decreases the inhibition of dopamine release

Interestingly, many drugs of abuse increase the production of  $\Delta$ FosB in the brain.  $\Delta$ FosB then demonstrates a sustained expression and continues to have a prolonged effect on the four genes listed above. These four genes in turn have negative biological effects on neurons in the brain. These effects consist mainly of decreases in neuron plasticity that results in gross brain loss and decreased connectivity that can be seen on imaging studies. An example of this was demonstrated in the *Prescription Opioid Addiction Treatment Study* (POATS), in where imaging studies on patients who underwent long-term prescription opioid use demonstrated bilateral loss of the amygdala and a decrease in connectivity in three of the amygdala white matter tracts- the *stria terminalis*, *ventral amygdalofugal*, and *uncinate fasciculus*.<sup>50</sup> These white matter tracts connect the amygdala to the brainstem, nucleus accumbens, and prefrontal cortex respectively.

These  $\Delta$ FosB drug-induced changes in the brain produce a behavioral phenotype that promotes addictive behavior. In the case of the amygdala, this region of the brain is involved in pain perception and rating the emotional response to the environment. Decrease of gross mass in the amygdala and decreases in its connectivity to other brain regions can be correlated to specific clinical symptoms e.g. hyperalgesia and hyperkatifeia.<sup>51</sup>

Hyperalgesia is defined as a clinical symptom in where there is an increased sensitivity to pain that is not proportionate to the injury; and in the case of opioid-induced hyperalgesia the opioids actually cause the patient to experience more pain due to the long-term use of opioids. In hyperkatifeia opioid use causes the patient to experience a hypersensitivity to negative emotional states as well as increased intensity of emotional distress. As mentioned above the use of opioids increases  $\Delta$ FosB expression which has downstream effects on the amygdala, which is one of the brain regions involved in pain perception and rating emotional response. So here we have an example where a drug has an effect on a gene which in turn has a negative effect the brain's perception of external events e.g. pain perception and emotional response to the external environment.

The amygdala has been mentioned a few times in this section and so has depression. Interestingly, a recent comprehensive review of imaging studies has demonstrated decreases in connectivity between the amygdala and the insular cortex in patients with major depressive disorder.<sup>52</sup> The amygdala-insular cortex connection is important in the formation of emotional memory.

A possible neurogenetic correlate has been associated with this connection between the amygdala and the insular cortex. A functional deletion variant of the ADRA2B gene, which encodes for  $\alpha$ 2b-adrenergic receptor, has been associated with an increase in functional connectivity between the amygdala and the insular cortex.<sup>53</sup> No current studies have confirmed any gene abnormalities with decreases in connectivity between these two brain regions. Of course at this point more research is needed in order to associate clinical symptoms and changes in the brain to the underlying neurogenetic correlates. However, it does highlight the importance of the connections of the amygdala to the other regions of the brain.

### Summing up phase two

To illustrate some of the NgCC in the second neurogenetic phase of human consciousness genetic factors involved in psychiatric disorders and neuron plasticity were utilized. It was demonstrated that genetic abnormalities in PTCHD1, PDE4B, DISC1, and ZNF804e can result in alterations in the degree of human consciousness, which was observed in the psychiatric disorders discussed in this section.

Genetic factors were shown to have an effect on neuron plasticity which affects neuron connectivity. The plasticity and connectivity of the neurons and the correct functioning of the underlying neurogenetic correlates are necessary for the proper functioning of the neuron-based continuum which is vital for the degree of human consciousness. It was demonstrated that  $\Delta$ FosB induction results in prolonged addictive behaviors and eventual brain loss in the amygdala, which has been correlated with clinical symptoms. This was also seen with the decreased expression of BDNF and FGF-2 in the frontal cortex and the hippocampus which were correlated with symptoms of depression.

It has been clearly demonstrated that genetic abnormalities have a direct relationship to degrees of human consciousness by their unswerving effect on the infrastructure i.e. the continuum of neuron-based consciousness. Malfunction of the genes result in the improper functioning of the neurons which ultimately produces objective clinical symptoms that can be utilized to represent an alteration in the degree of human consciousness. Finally, in the second neurogenetic phase I have provided evidence that the continuum of neuron-based consciousness involves both NCC and NgCC. This differs from many current models of human consciousness that gravitate solely on NCC. In my model the continuum of neuron-based consciousness, which is the crux of the second neurogenetic phase of human consciousness, the importance of NCC is recognized, but NgCC are acknowledged as being equally, if not more, important.

### **Phase Three: Neurodegeneration**

Neurodegeneration is an age-related process of deterioration of the brain and nervous system. This process has observable symptoms that are noted on the spectrum of human consciousness



e.g. decreases in awareness, abnormal thoughts, memory impairments, and difficulty concentrating. However, neurodegeneration can be accelerated in diseases like Alzheimer Disease (AD) which has a genetic component. I will use AD as a prime example for the third neurogenetic phase. Before I do this allow me to give a brief description of AD.

AD slowly erodes some of the modalities of consciousness. Memory loss is the primary symptom in AD and when this deteriorates the patient's sense of past, present, and future gradually becomes downgraded. The AD patient also begins to lose the ability to place names with faces (prosopagnosia) and the ability to identify objects (anomia). Cognitive functions are also affected, which makes processes like performing calculations difficult. The AD patient can also become disorientated and unable to associate ideas with events or words. In addition, behavioral abnormalities can occur in AD e.g. screaming and inappropriate mannerisms. Essentially, with all of these symptoms the person ceases to be the person that they once were. This is to say that their degree of consciousness has been reduced secondary to the AD pathology.

There are two main pathological features of AD. The first is the abnormal accumulation of beta-amyloid ( $A\beta$ ) that forms senile plaques and the second is the formation of neurofibrillary tangles (NFTs) that consist of hyperphosphorylated tau. I will not go into detail in regards to the pathophysiology of AD as this has been done in other publications.<sup>54</sup> However I will discuss  $A\beta$  accumulation as some of the gene mutations that I will discuss next in this section are correlated with AD due to  $A\beta$  accumulation.

It is now understood that  $A\beta$  begins to accumulate decades before signs and symptoms of AD are manifested. Consequently, a new model and a new view of AD have been established in where three clinical phases have been formulated according to the 2011 AD diagnostic guidelines. These guidelines have been reviewed in previous works.<sup>55</sup> The three phases are an asymptomatic preclinical phase, a symptomatic predementia phase, and dementia phase. I will now discuss five AD genes.

#### The Amyloid Precursor Protein (APP) gene

The APP gene produces the APP protein which is an integral membrane protein in the neuron that is concentrated in the synapse, regulates synapse formation, neural plasticity, and iron export. Proteolysis of APP is performed by another protein complex called  $\gamma$ -secretase. This process generates  $A\beta$  39-42. There is a large amount of evidence that indicates that some cases of AD are caused by mutations in the APP gene. In earlier studies it was found that a point mutation in the APP gene on chromosome 21<sup>56</sup> and double mutations in exon 16<sup>57</sup> were pathogenic mutations associated with AD. Currently there are many more mutations of the APP gene that are under investigation for this gene's correlation to AD.

#### The PSEN1 and PSEN2 genes

Presenilin-1 (PSEN1) and Presenilin-2 (PSEN2) genes produce the proteins PSEN1 and PSEN2 respectively. These two proteins, along with nicastrin and APH-1, form a protein complex known as  $\gamma$ -secretase. The  $\gamma$ -secretase cleaves the APP while it is still in the neuron membrane.

Therefore the normal functioning of  $\gamma$ -secretase is required in order for this process of cleavage to work.

Mutations in PSEN1 and PSEN2 have been strongly correlated with AD.<sup>58</sup> It is proposed that when there are mutations in the PSEN1 and/or PSEN2 genes that the  $\gamma$ -secretase complex formed is abnormal. Consequently, the ability of the  $\gamma$ -secretase complex to cleave the APP is impaired. This improper cleavage of APP is proposed to be another factor that contributes to abnormal A $\beta$  accumulation.

In the second neurogenetic phase we saw the importance of protein complex DISC1-PDE4B and its relationship to SZ. Here we see something similar with  $\gamma$ -secretase and its relationship to AD. In both protein complexes the proper genetic expression of all the proteins involved are important to the overall function of that complex. A genetic mutation in even one of the protein's genes can result in pathology that has a negative effect on human consciousness e.g. SZ and AD.

#### APOE- $\epsilon$ 4 phenotype

*Apolipoprotein- $\epsilon$ 4 gene variant* (APOE- $\epsilon$ 4) produces the APOE- $\epsilon$ 4 protein. This protein can influence brain structure and function by affecting synaptic generation and other restorative mechanisms involving cholesterol transport and metabolism. Carriers of the APOE- $\epsilon$ 4 allele show an increased risk for developing AD in a gene dose dependent manner.<sup>59</sup> The APOE- $\epsilon$ 4 allele is present in about 60% of AD patients and this allele's presence reduces the median age of onset to 68 as opposed to 84 in non-carriers.<sup>60</sup>

A recent study demonstrated that APOE- $\epsilon$ 4 directly damages the blood vessels of the blood brain barriers and this neurovascular damage decreases A $\beta$  clearance.<sup>61</sup> This is interesting as this vascular damage has a secondary effect on the neurons that in turn contribute to AD pathology.

#### TREM2 gene

The *triggering receptor expressed on myeloid cells-2* (TREM2) gene produces the TREM2 protein. TREM2 functions to regulate phagocytosis, suppress inflammatory reactivity, and repress cytokine production and secretion in the microglia cells in the brain. Two recent studies verified that a rare missense mutation that results in an abnormal TREM2 variant is associated with a significant increase in late-onset AD.<sup>62,63</sup>

At this juncture I have discussed five genes that are associated with AD. These gene mutations result in an abnormal protein product that has a negative effect on the neurons and the brain that ultimately result in the AD pathology. However, I would like to briefly discuss a gene therapy that may reverse the loss of memory seen in AD. This will further illustrate the connection between the neurogenetics in the third phase and human consciousness.

#### FGF-2 gene therapy

FGF-2 was discussed in the section on neuron plasticity. It was also discussed that FGF-2 (and BDNF) expression was decreased in depression. FGF-2 is an established neurogenic factor of

proliferation and differentiation for multipotent neural progenitors. In 2011, a study involving the injection of active FGF-2 gene into AD-mice resulted in improvement in memory.<sup>64</sup>

Even though this was only tested in transgenic mice the significance of the reversal of AD-associated memory loss should not be underrated. If we look at the mouse's degree of neuron-based consciousness and the fact that it's degree of consciousness was decreased secondary to AD pathology and then increased with FGF-2 gene therapy this would suggest that neuron-based consciousness can be manipulated or modified with gene therapy.

### Summing up phase three

The process of neuron degeneration results in decreases in the degree of human consciousness. Neuron degeneration has this effect on human consciousness as it erodes the global modalities associated with its proper functioning. In previous works I have discussed the connection between AD and DNA consciousness.<sup>65</sup> Here I have discussed five AD genes- APP, PSEN1, PSEN2, APOE- $\epsilon$ 4, and TREM2. These genes have all been associated with a significant increase in the risk of AD.

By using AD genes as an example, I have demonstrated that genes have a direct effect on decreasing modalities of human consciousness later in life. Some of these gene abnormalities result in A $\beta$  accumulation, but it takes decades of gradual accumulation before enough damage has been done to the neurons and brain before objective symptoms manifest. Other gene abnormalities which were demonstrated with the examples of APOE- $\epsilon$ 4 and TREM2, have adverse effects on other processes e.g. circulation and inflammation, respectively. However, these types of gene abnormalities have a long-term secondary effect on the neurons and the brain that contribute to AD.

Collectively this section verifies the third neurogenetic phase of human consciousness as it was demonstrated that genes can affect, in this case decrease, degrees of human consciousness. Genetic therapies e.g. the FGF-2 genetic therapy make it obvious that this process of neuron degeneration may be reversible. In addition, ongoing research with stem cells may yield similar results.

## Discussion

When looking at the first neurogenetic phase of human consciousness initially, embryonic development requires the production of undifferentiated cells and subsequently those cells must mature into cells with a specific function. The maturation of a cell with a differentiated phenotype requires stringent control of gene expression, which must be regulated in both space and time throughout this process. This requires the active regulation of developmental control genes which are also called master genes that influence the activity of other genes. This is accomplished by transcriptional regulation. It has been demonstrated in this article that neurogenetic developmental genes that act as master genes e.g. Pax3 and Pax6 exert their control by turning on and off other genes. Consequently, Pax3 and Pax6 both have critical roles in brain morphogenesis and give rise to the large scale structures that allow the human brain to interact with and interpret the environment.

Later, the developing neural tube is subdivided by regionalization events that are distinguished by the genetic expression of specific combinations of transcriptional regulators. The anterior ectoderm will regionalize into the forebrain, midbrain, and hindbrain. This ultimately gives rise to molecularly defined regions that will subsequently differentiate into anatomically and functionally specific regions of the human brain with a distinct AP and DV character.

When observing what is known at this point of neurogenetic development are we to accept that this is all a series of random acts committed by genes or is there a degree of consciousness at work here orchestrating the final outcome? If we look at just the small sample of genes that were provided as an example in the first neurogenetic phase and then add to this the total number of potential genes that are involved we simply cannot accept that is a serendipitous process that randomly fell together by trial and error. Hence we must change our way of viewing DNA. We must entertain the concept that there is a clandestine degree of consciousness at work here that has been undetectable up until 50 or 60 years ago.

In the second neurogenetic phase we saw the importance of gene-gene interactions and the control of genetic expression. Genetic abnormalities can produce psychiatric disorders like autism and SZ. These psychiatric disorders demonstrate a variance in the degree of human consciousness where reality is not only perceived in a different manner but effects on cognition are also evident. This phenomenon demonstrates how a very small change at the level of the nucleotide can manifest objective changes seen on the macroscopic scale of human consciousness.

While the brain functions the neurons change morphologically by making new connections to other neurons and losing connections to others. The phenomenon of neuron plasticity allows the neurons to provide an infrastructure for the continuum of human consciousness, which connects all of the individual series of stimuli into a collective whole. The under-expression of genes e.g. BDNF and FGF-2 inhibit the neurons ability to provide the continuum by decreasing neuron plasticity. This results in decreases in the degree of human consciousness that is seen in mood disorders like depression, which can have a profound effect on cognitive modalities and memory that are related to human consciousness. In depression the end results of neuron plasticity on the brain can be confirmed objectively on imaging studies.

In the second neurogenetic phase it was also seen that certain transcription factors that act as *trans*-activators can have an effect on multiple genes. This was demonstrated with ZNF804e transcription factor's effect on SZ-associated genes and  $\Delta$ FosB transcription factor's effect on genes associated with neuroplastic changes in the brain involved in addiction.

The results discussed in the second neurogenetic phase shows that NgCC underlay the correct functioning of the continuum of neuron-based consciousness. Abnormalities in the function of any NgCC can result in psychiatric disorders and/or decreases in neuron plasticity, which both have objective effects on human consciousness.

The third neurogenetic phase demonstrates the genetic influence on neurodegeneration. The significance of neuron degeneration is that it represents an erosion of human consciousness. AD was used as a primary example, but other genes have been associated with other forms of dementia as well. Mild cognitive impairment is considered the result of normal aging but

essentially there is a decrease in normal gene expression which is involved in the maintenance of neurons that are responsible for the resulting symptomatology. The expression of many genes is affected in an age-dependent fashion, but specific mutations have been associated with an increase in earlier onset and severity of impairment as seen in AD.

The end result of neuron degeneration demonstrates decreases in the degree of human consciousness which is seen objectively in diseases like AD. Essentially, in the third neurogenetic phase the degree of human consciousness is gradually decreased over time. However, with the promise of new genetic therapies the process of neuron degeneration may be able to be reversed. The concept of reversing neuron degeneration with gene therapy is interesting because it suggests that the third neurogenetic phase may not be a one-way street.

## **Conclusion**

The neurogenetics of consciousness is the study of the genetic processes in where the degree of DNA consciousness gives rise to the emergence of neuron-based degrees of consciousness. It is an initial identification and enumeration of the NgCC.

I have summarized that after the emergence of the machinery used for neuron-based consciousness that this genetic process then provides a continuum of human consciousness. Unfortunately, toward the end of life neurodegeneration takes place. This happens at an age-related pace, but some gene mutations are associated with an acceleration and earlier onset of this process. Every gene discussed in each of the three neurogenetic phases in this article represents, at least to some degree, a NgCC underlying the NCC.

This article provides evidence that genes have a tangible effect on human consciousness. This is demonstrated in three obvious neurogenetic phases. This should not be too hard to accept as for some time now we have readily accepted the role of genes in tangible attributes e.g. behavior and intelligence. As scientists learn more about the human genome and the downstream effects that can be observed on the phenotypic expression a more complete picture will begin to crystallize.

The small amount of evidence accumulated in this article justifies the second hypothesis that was purposed in the theory of DNA consciousness, which is that DNA gives rise to higher degrees of consciousness e.g. human consciousness. The first premise of the theory of DNA consciousness is that DNA possesses a degree of consciousness. This is justified in that the emergence and maintenance required during the development and continuum of human consciousness is not a random process that serendipitously evolved. It is an orchestrated process that requires a degree of consciousness even if this is a degree of consciousness that we cannot see.

At this point in time the difficulty of discovering a testable model is a significant problem for both proposals put forth by the theory of DNA consciousness. First, how to test whether or not DNA possesses what we would accept as a degree of consciousness? Second, is it ethical to run neurogenetic experiments on the human brain? Therefore, this author is left solely with the process of extrapolation in order to attempt to establish a core of this nascent model of human consciousness. Perhaps this will someday lead to more objective methods.

In the future, when genetic therapies become more reliable, enhancements on some of the modalities of human consciousness may be obtainable. The possibility of a selected genetic destination made available by human enhancements was proposed in previous works.<sup>66</sup> Some may consider this unrealistic or even science fiction. However, with new neurogenetic therapies underway, as seen with FGF-2 therapy in AD, it is not a far stretch to think of using this same type of therapy in a non-AD patient for the sake of enhancing degrees of human consciousness. In this way DNA consciousness could continue to give rise to higher degrees of consciousness beyond that of human consciousness.

As far as this article is concerned I have just scratched the surface in terms of the three neurogenetic phases of human consciousness and it is not close to being complete. It is the initiation of a much larger and long-term project. At this juncture this is the information that I have collected but in the future this skeleton will grow flesh.

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