Changing Your Own Genetic Destiny

The Genetics and Epigenetics of Neuroplasticity and Neuronal Functioning

Alec Parent | April 7th 2015

From Fairly Local to All-Around

Altering the sum of your parts

The constantly changing brain has remained an object of fascination ever since the discovery and proposition of neuroplasticity. The awe has remained not only among scientists, but the general public as well. This neural fluctuation is why children are sent to school young, while their minds are still fragile and malleable, why learning a new language was long thought to be impossible once adulthood is reached. It is why addictions are easily created and why old habits die hard. Thanks to the constantly increasing knowledge of the matter, it is also why terrifying developed neurological diseases such as Alzheimer's are inching ever closer to being cured. At its core, neuroplasticity is often defined as the capacity of the nervous system to develop new neuronal connections. It is the inherent ability of the brain to change itself, and it can be manipulated and exploited by nearly anyone.[5]

The idea that the brain is a plastic organ was first suggested by Dr. Paul Bach-y-Rita, who identified as both a basic scientist and a rehabilitation physician, an uncommon combination, but the perfect expertise for what he was proposing. In 1969, Bach-y-Rita had an article published in *Nature* which described his exploits in making blind subjects see by sending electrical impulses to their backs, bypassing the visual nervous system entirely. These subjects learned to see and recognize common objects such as a telephone and make out depictions of a framed picture. These subjects had compensated for the loss of one of their senses by enhancing the capability of the others; in this case, touch was amplified at the cost of sight.[5] Bach-y-Rita's ideas seemed crazy and implausible at the time, and ended up being rejected by not only the skeptical public, but the scientific community as well. Only a few decades later, neuroplasticity will become the dominant view of the brain, entirely overriding the previous mechanistic view of localizationism.[5] The brain no longer had certain functions mapped to certain areas, it had become a network of co-operating functions.[1]

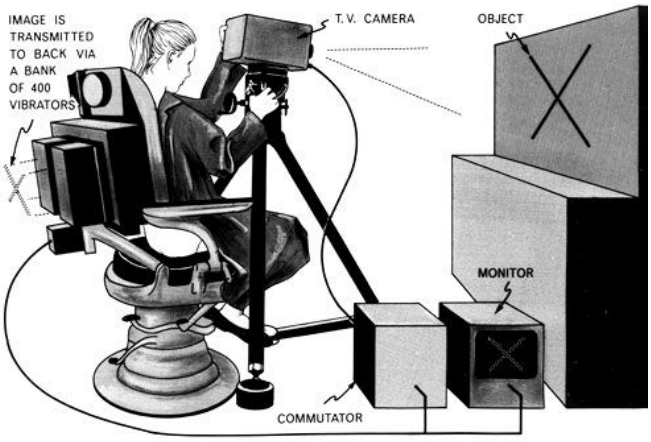

Figure I: Dr. Bach-y-Rita's original machine. This machine would send electrical impulses to the nerve impulses on the back of blind subjects, in a manner that would create an image in their mind using touch instead of sight.

Thus, a new field of study was born. It has provided insight into overcoming genetic diseases affecting countless individuals worldwide, whether they be born with the impairment or it has introduced itself later on in life. Mental and physical exercises are designed to enhance weaker neurological functions and build a better brain. Machines are built to stimulate inactivated functions.

This is all made possible on the sole condition that the disorder is understood.

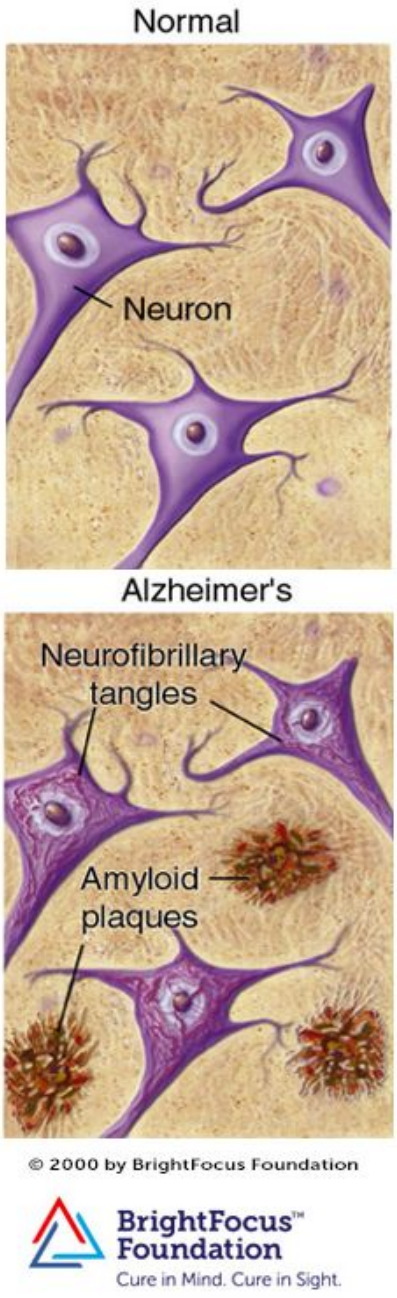

Figure II: Neuron degeneration in a brain affected with Alzheimer's disease. Image courtesy of BrightFocus Foundation

Escaping Your Fate

Outrunning DNA

Alzheimer's disease (AD) has been, for a long time, one of the most severe neuronal disorders. Caused by a startling accumulation of amyloid-β proteins outside neurons and an abnormal form of tau proteins inside neurons, it is mainly characterized by extreme cognitive decline in aging.[2] For a complete visual, refer to figure II.

The amyloid-β protein is part of a much larger precursor protein appropriately named the amyloid-β precursor protein (AβPP).[11] This protein is processed by three proteases, named α, β, and γ secretases (secretases are enzymes that "snip" pieces off a long protein, rendering that long protein useless, lethal, life-saving, or anything in between). In a healthy genome, the α secretase first splits AβPP in the middle of the amyloid-β domain, followed by the β and γ secretases each contain one half of the full amyloid-β protein. If the α secretase is not the first to cleave AβPP, the full amyloid-β protein is formed and begins to aggregate into clumps on the brain, forming one of the phenotypes associated with AD. For a complete visual, refer to figure III.

However, as more discoveries surrounding the heritability of many known diseases are being made, we learn that the environment can have an impact on the development of such neurological impairments. These changes can be brought upon by the introduction of pesticides in prenatal and postnatal development, but epigenetic changes can take place in various developmental stages through the introduction of environmental agents such as mercury and lead, and can disrupt the epigenetic program, increasing the production of amyloid-β at maturity.[9]

Gjoneska et al. carried experiments in both mouse and human

specimens across diverse cell types and tissues.[6] The results of their experiments showed enhanced expression of the CD14 receptor gene (the gene responsible for the interaction and detection of bacterial lipopolysaccharides)[16] in concordance with amyloid-β deposition.

But that was a neurodegenerative disease that is, for the most part, inherited. The story changes once diseases caused by epigenetic changes begin to manifest themselves.

Midnight Resurrections

Learning to live again

Figure III: (Left) The cleaving of a healthy amyloid-β protein, resulting in a halved protein that can be degraded by the nervous system. (Right) The cleaving of an unhealthy amyloid-β protein, resulting in longer indigestible protein oligomers that aggregate into clumps on the brain, causing Alzheimer's. Image courtesy of Discovery Medicine.

Three quarters of strokes worldwide can be accounted for by brain infarctions and impairments, increasing age only worsens an individual's susceptibility to a sudden stroke, to the point where it has now become the third leading cause of death in the United States, and a main cause of disability among adults worldwide.[8] Spontaneous motor recovery has been documented to a certain degree, but full recovery is only made possible through rehabilitation;[5] neuronal plasticity allows individuals whose lives were thought to be forever changed to regain a certain degree of functionality.

Understanding the role of the brain-derived neurotrophic factor (BDNF) protein is the key to acquiring information of post stroke rehabilitation strategies.[10] BDNF exercises its effects on neuroplasticity by strengthening and lengthening the long-term potentiation between two neurons, the strength of the connection between the two. Evidence shows[3] that aerobic exercise increases cerebral BDNF concentrations, facilitating recovery. This exercise leads to a sum of events that ultimately increases the expression of BDNF in the central nervous system.[10] For a brief summary of the effects of BDNF due to exercise, refer to figure IV.

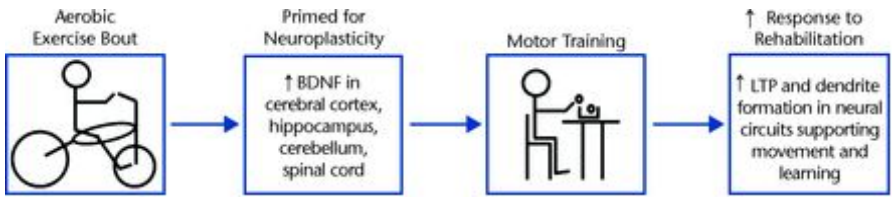

Figure IV: Appropriate action and consequence when exercising to improve neuroplasticity. Intense aerobic exercise followed by intense motor training or vice versa can bring about increased retention of motor skills. Original image courtesy of Physical Therapy.

Despite the epigenetic changes that can be brought about by the increase of recovery proteins, certain genetic mutations can completely nullify one's efforts for recovery. A notable example of such an unfortunate case is the *val66met* mutation.

The *val66met* mutation is a polymorphism located on the 66th nucleotide of the BDNF precursor peptide (proBDNF). This mutation is due to a single nucleotide polymorphism (SNP) which changes a valine amino acid into a methionine amino acid (a GUG codon into an AUG codon).[10] This mutation also brings about more visually obvious phenotypic traits, aside from the reduction in activity-induced BDNF

secretion: *val66met* carriers display a reduced volume of the prefrontal cortex, which brings about reduced cognitive function and in turn impairs performance on memory dependent tasks.[10]

What's important to take away from these *"facts"* is that the aerobic and neural activity undergone by stroke victims is not an action that can induce and bring about neuroplasticity. Rather, it creates a neuronal environment that supports plasticity. This is evidence that can not only be seen in victims of unfortunate brain traumas, evidence also suggests[15] that bouts and bursts of intense physical exercise immediately before or after specialized motor training will yield significantly better retention of motor skills. This ability turns neuroplasticity into a choice, not an inherited feature.

Microscopic Reversal

Turning DNA into a choice

While the mentioned examples may portray the idea that the plasticity of the brain is only of interest when dealing with the unfortunately ill, the case is very much the opposite. Gene expression is what moderates and interrelates social activities; social behaviours from caregiving to stress reactivity, cognitive socialization such as trust and envy, instinctive reactions that were long thought to be solely a part of a person's nature such as love and positive nurture.[14] All of these are regulated by epigenetic microscopic behaviour, and can be switched off at any moment by the changing environment and, by consequence, the changing brain.

The oxytocin hormone is commonly associated with acting on peripheral organs, found within the body in organ systems such as the reproductive system, but it is also commonly linked to highly specialized neurological processes, such as trust or envy, as was noted in the previous paragraph.[14] However, the true effect of oxytocin at different levels was not known for a long time, and remains largely a mystery, as the action of the hormone is wholly dependent on the expression of the oxytocin receptor gene (*OXTR*). A new potential mechanism driving the differing susceptibility may be epigenetic variation and factors that change genetic expression without changing structure. The gene is located at the chromosomal locus 3p25.3, for information regarding its structure, refer to figure V.

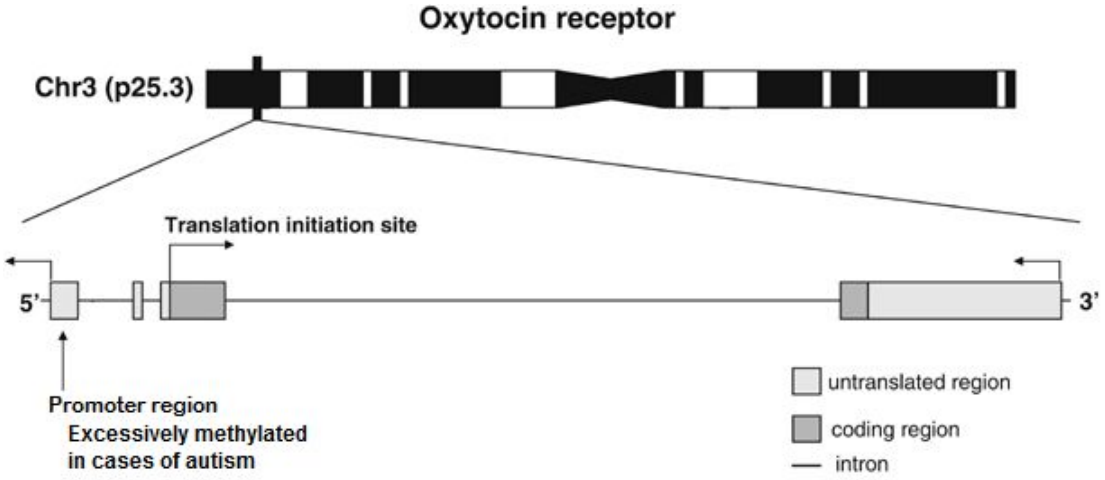

Figure V: The oxytocin receptor gene, located on the short arm of chromosome 3, is seen. Excessive methylation of the promoter region of the gene will inhibit its expression and is associated with certain autistic phenotypes. Original image courtesy of Nature (modified).

Autism, a genetic disability which is highly associated with cognitive disturbances and impairment of childhood development, is known to be highly heritable.[7] While the impairment cannot be associated to a single genetic defect, Gregory et. al have narrowed one cause to the hypermethylation of the OXTR promoter region in the cells comprising the temporal cortex. This excessive methylation prevents the expression of oxytocin in these individuals, thereby preventing the expression of some or all phenotypes associated with their presence (trust and envy, among others).

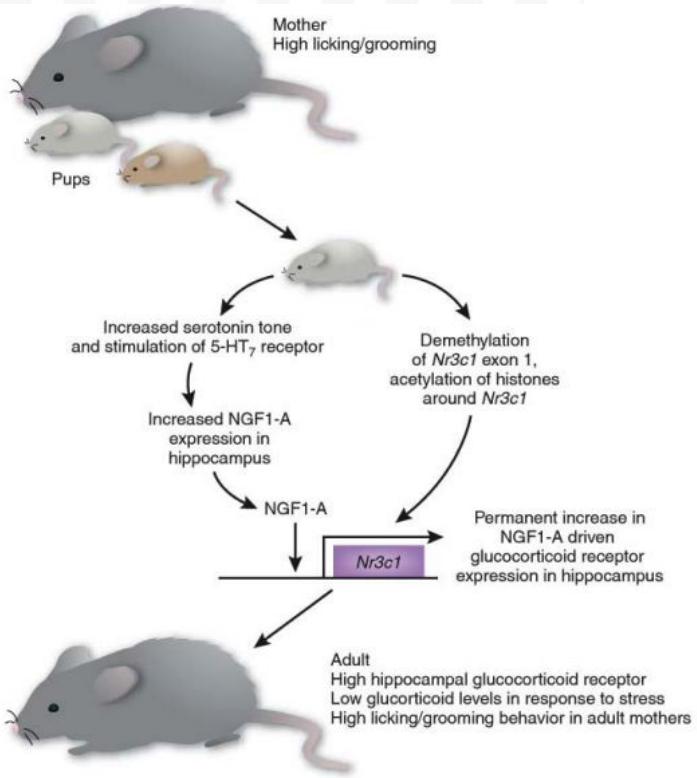

Figure VI: The process and outcome of nurturing offspring. On the left, an anxious pup is raised due to failure to demethylate the GR gene. On the right, a nurturing pup is raised due to increased serotonin release and demethylation of NR3C1 and acetylation of associated histone proteins. Original image courtesy of S. Darwish.

A second example of emerging neuroplastic properties can be seen in the glucocorticoid receptor (GR) gene. This example doesn't require as much explanation, as it can easily be conveyed using a single example: lick your rats.

A high nurturing mother will, in the end, activate the expression of the GR gene (NR3C1), thereby preventing methylation of the gene, shutting down stress responses. Low nurturing mothers will

fail to demethylate the gene and thus raise anxious offspring.[4] For complete information regarding the genetic nurturing cycle, refer to figure VI.

Despite these advances and ideas that have been paving the road for years now, there is still a significant amount of advancement left to be made.

Blurry Visions

A future with infinite possibilities

Patients suffering from psychiatric and neurological disorders is nothing new, but recent therapeutic progress has been slow.[12] New methods are needed to deploy new and effective treatments for both old and new diseases, this new field of research and development is known as neuropsychopharmacology (literally the study of neurons, the mind, and drugs). This field of study, centred with the European College of Neuropsychopharmacology (ECNP), aims to improve our understanding of the brain and better manage mental disorders.[12] Despite the field being already 60 years old, the moment remains opportune to research and survey the brain using their techniques, as there is still much left to learn.

Despite this seeming crawl forward, it has still been possible to pinpoint genes associated with hundreds upon hundreds of neurodegenerative disorders, from schizophrenia to bipolarism to attention deficit disorder, and related these to the epigenome.[13] The blood and brain of every individual has been marked with gene methylation, histone acetylation, microRNA and small interfering RNA expression, so these disorders can be understood and cured with the help of drug development. The turning point for considering environmental factors that may epigenetically impact the brain is now.

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