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About Eumr

Mission Statement:

The Emory Undergraduate Medical Review is for Emory undergraduates interested in medical or health related careers to engage in scholarly discourse with their peers and medical professionals. EUMR publishes semesterly hard-copy and online copy journals in addition to smaller newsletters published throughout each semester. Each semesterly issue primarily features reviews on interesting and cutting-edge topics in the biomedical sciences, however medical opinion articles are also welcomed. All semesterly review pieces are reviewed by MDs/PhDs featured on our advisory board that are from institutions around the country. Newsletters feature more succinct and accessible pieces in recurring sections including ethics, biotechnology, Public Health, Nutrition, and more. EUMR also endeavors to put on educational events relevant to students interested in medical or health careers.

Our Advisor

Dr. Michael Crutcher, PhD

Emory

Dr. Michael Crutcher is one of the many distinguished faculty members part of Emory's Neuroscience and Behavioral Biology department. Having received his PhD in Physiology from Johns Hopkins University, he joined the Department of Neurology and of the Neuroscience Ph.D. program at Emory in 1991. His research is primarily focused on the neural mechanisms of visually guided reaching movements in monkeys.

Dr. Crutcher has taught many NBB courses over the years such as: freshman seminar courses (NBB 190) on Brain Enhancement, Curiosities of Neurology and Neuroscience, and Neuroethics as well as Perspectives in Neuroscience and Behavioral Biology (NBB 401 SWR), Biology of Movement Control (NBB 370), Neuroscience Research Methods (NBB 221), Functional Neuroanatomy (NBB 470), and Topics in Neuroscience and Behavioral Biology (NBB 270).

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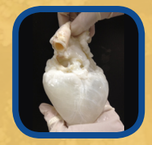






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Is Technology the Answer to an Increasing Superbug Problem?

Authored by: Ayushi Sharma
Edited by: Taylor Eisenstein **Reviewed by: Dr. Tom Woolf**

The first antibiotics were marketed in the 1940s, and since then, bacteria have consistently, and unpredictably, morphed and mutated to evade every new antibiotic developed. Due to trial and error of antibiotics in viral infections (Shlaes et al., 1997) and the application of antibiotics to animals in order to fatten livestock (Mathew et al., 2007), this resistance has been sped up.

Drug-resistant bacteria have been a steadily growing concern over the past decade. Standard antibiotics are proving to no longer work effectively, and although scientists and doctors are coming up with new drugs, there is a desperate need for a way to maximize these antibiotics. To close the gap between drug resistance and drug production, researchers at Duke University have invented an algorithm to predict the mutations that they may be faced with when bacteria start developing resistances to certain antibiotics (Reeve et al., 2015).

The software is used to locate genetic mutations that will most benefit methicillin-resistant Staphylococcus aureus (MRSA) in resisting drugs that are used to fight the superbug. When testing the experimental drugs with the bacteria, the software accurately predicted two of the genetic mutations that occurred in MRSA (Reeve et al., 2015).

This provides the healthcare industry with a prediction of what changes will occur in bacteria in response to the drugs, and what can be altered in the design of the antibiotic to avoid these genetic changes. This also gives researchers the chance to stop the production of drug therapies that will prove to be ineffective in the long run, saving ample time, money, and other resources.

In 1975 only 2% of bacteria were not treatable by routine antibiotics, and by 2015 that number has shot up to 55%. Previous approaches to predict the genetic mutations that bacteria will undergo in response to drugs proved to fall short. These methods relied on the use of genetic mutational libraries, derived from mutations that have already occurred in bacteria. This is ineffective because many bacteria mutate in ways that have not been seen before, and this is something physicians are unable to fight off readily because they have not had prior experience with it (Reeve et al., 2015).

This new protein design algorithm is called OSPREY (Open Source Protein Redesign for You). It identifies DNA sequence alterations that would produce certain proteins that could potentially prevent the drug from binding without disrupting

"In 1975 only 2% of bacteria were not treatable by routine antibiotics, and by 2015 that number has shot up to 55%."

normal function of the cell. OSPREY is a type of protein redesign approach called structure-cased computational protein redesign (SCPR). These types of programs flesh out a protein's 3-D structure and determine what mutations may occur on a native protein sequence that will have the designated effect on its biochemical characteristics, in this case, boosting the affinity a receptor has for an antibiotic-like protein. This algorithm provides in silico models of protein, similar to those found in real life. These models are unique in that they have better flexibility of protein structures in order to replicate conformational changes produced by mutations in a DNA sequence. SCPRs also model proteins and ligands together as low-energy structures to more accurately predict how well protein will bind. And finally, this universally-optimal design search guarantees that predictions are accurate with respect to the information that is being input (Reeve et al., 2015).

The software was tested on new experimental drugs (propargyl-linked antifolates). The basic function of these drugs is to prevent a bacterial enzyme called dihydrofolate reductase (DHFR) from catalyzing reactions, which helps create DNA and fuels other biological processes. These drugs proved to be effective according to the algorithm but have

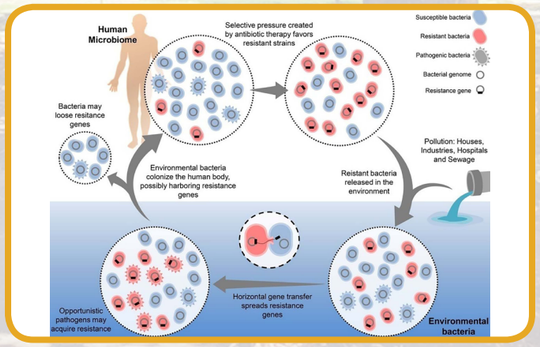

Figure 1. Antibiotic resistance mechanism. Pathogens can acquire resistance through the use of horizontal gene transfer and this helps spread genes that confer resistance.

not yet been tested on humans (Reeve et al., 2015).

The algorithm is very new, so there is no clear pattern yet as to whether the counterattack of bacteria that are used are previously viewed mutations, or novel ones altogether. Scientists are trying to pinpoint certain genes that play the largest role in aiding in antibiotic resistance. They have narrowed the results down to four single nucleotide polymorphisms (SNPs) that may potentially accelerate the antibiotic resistance process. None of these predictions were previously viewed in bacteria, but laboratory experiments proved these to be correct (Fuentes-Hernandez, 2015).

After these new, refined drugs were tested with MRSA, the bacteria that lived were analyzed to identify sequential changes. Over 50% of these bacteria carried the mutation that the software

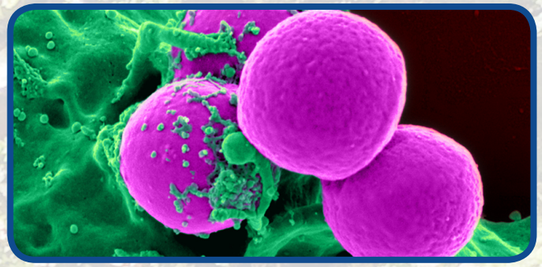

Figure 2. A common strain of methicillin-resistant Staphylococcus aureus, one of the many bacteria that OSPREY will be able to evaluate for future mutations to preempt antibiotic resistance.

predicted, which was coupled with greater antibiotic resistance. This small mutation produced a large effect – it decreased the efficacy of the antibiotic drug (propargyl-linked antifolates) 58-fold.

Currently, there are efforts to use this software to identify drug-resistant mutations to a variety of drugs that are made to battle bacteria like E. coli and Enterococcus. OSPREY would put the healthcare system one or more moves ahead of the superbugs that are rapidly and ever-changing.

"OSPREY would put the healthcare system one or more moves ahead of the superbugs that are rapidly and ever-changing."

One potential use for this algorithm in the future that is being explored involves tricking the bacteria. Researchers would create drugs that bacteria would purposefully try to evade by developing mutations that could actually make it highly susceptible to other antibiotic drugs (Imamovic and Sommer, 2013). Future applications for OSPREY include predicting mutational resistances in cancer, HIV/AIDS, and the flu (Sanga et al., 2006). Current barriers to this include difficulty in raising cells and strains in the laboratory, compared to growing bacterial cultures, which is relatively easy.

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Helping Haiti:

A Case for Neurosurgical Intervention

Authored by: Somnath Das
Edited by: Mansi Maini **Reviewed by: Dr. Jon Riley & Dr. Jordan Amadio**

Despite the rise in the quality of healthcare and its technologies, the application and distribution of adequate health remains sparse. Haiti in particular suffers from large inadequacies in healthcare, with catastrophes like the 2010 earthquake catalyzing negative healthcare outcomes such as massive outbreaks of infectious disease. As a country, Haiti has been in need of critical infrastructural interventions both before and after the earthquake in 2010. The current population is 9.5 million, with roughly 80% living below the poverty line. Comparatively speaking, Haiti ranked 158th out of 187 prior to the earthquake according to the United Nations Development Programme Human Development Index. As a result, healthcare is provided mostly via external sources, mainly Non-Governmental Organizations (NGOs).

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These factors led to a large centralization of healthcare in the capital city of Port-Au-Prince prior to the earthquake. This centralization, while adequate for the urban population, made healthcare difficult to deliver to rural populations. After the earthquake, the already weak infrastructure crumbled, meaning that healthcare became even more arduous for the country to ensure for its population. Therefore, it is critical that new healthcare systems seek to fix the current epidemiological problems in Haiti. From a policy standpoint, solutions should also seek to decentralize healthcare such that rural populations can receive care for both infectious and chronic disease.

In response to the folding healthcare infrastructure, Partners in Health (PIH) created Hôpital Universitaire de Mirebalais (HUM) in order to address tuberculosis outbreaks in the area. HUM is located near Port-Au-Prince, and sought to address the need in Haiti's rural areas for healthcare access. As time passed, the hospital began to address growing concerns in the area, and eventually targeted neurosurgical trauma. The reasons are very tangible: Haiti has only roughly .25 Neurosurgeons per 100,000 people. Data collected by Barthélemy et al. gave the problem an epidemiological backbone. Roughly 1 out of 7 patients admitted to the ER were those that had a neurological or neurosurgical disease. Common neurological conditions were cerebrovascular disease (31%) and neurotrauma (28%). The most pervasive neurosurgical condition was neurotrauma (87%). Additional data collected by the HNI team revealed just how fractured healthcare was in Haiti: one paper cited by the HNI noted that post-operative care was either classified as discharge or death.

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However, training of Neurosurgeons and ensuring of adequate care proved to be a challenging task for PIH in Haiti. A critical infrastructure problem that was prevalent specifically in Haiti was the fact that the few general surgeons that do serve the population have little training in specialized Neurosurgery. Thus, PIH partnered with the Emory School of Medicine to start the Haiti Neurosurgery Initiative (HNI) as part of a collaborative effort to bring more Neurosurgeons to Haiti.

Figure 1. HUM was founded by PIH in order to address various infectious disease outbreaks in Haiti. The Hospital has since expanded to address additional healthcare concerns in Haiti, such as neurosurgical care.

Over time, the HNI has had three goals during intervention. The primary goal is to respond to the high level of neurosurgical trauma in Haiti by providing a steady influx of trained professionals from partner healthcare systems. The HNI hopes to bridge the gap between various medical schools, such as Emory Medical School, and HUM in order to build a sustainable residency program that aims to address neurosurgical pathology in Haiti. The intervention would not only focus on treating the pathology, but would also aim to contribute towards a growing body of literature that seeks to discuss the need for neurosurgical aid in developing countries by collecting data from treated patients.

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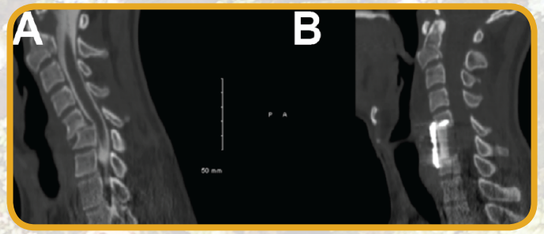

Figure 2. The model of care designed by the HNI focuses on providing both immediate and longitudinal relief to patients in Haiti. The above surgery was conducted by the HNI, and will receive post-operative care by HUM and HNI. Shown is a sagittal CT-myelogram of the patient before and after intervention.

The secondary goal of the HNI is to train current Haitian surgery residents in order to provide targeted neurosurgical support. While the quantity of medical professionals certainly can be addressed by increasing access to education and encouraging healthcare infrastructure investment, the quality of care will also have to be ensured as well. The initiative hopes that constant monitoring of surgical procedures and collaboration with surgeons in Haiti will ensure a continuous model of both intervention and training.

The final goal of the initiative is to provide sustainable training to community healthcare workers and Haitian citizens on the subject of neurosurgical trauma and how to properly address it. Often, the HNI team found grave mistakes in the referral pathways of when to both recognize and treat patients requiring neurosurgical trauma. Postoperative care also requires significant education, as healthcare workers must then continuously collaborate with physicians and patients in order to ensure safe recovery and discharge of patients.

Overall, the Initiative's aim is to provide what is referred to as a resident-based model of care to the Haitian population. This model is to be complemented by extensive data collection and training for Haitian surgeons in order to provide a sustainable model of neurosurgical care. HNI will allow for integration of both immediate and long-term relief aids in the decentralization of healthcare in Haiti, as the neurosurgical intervention is targeted specifically in areas outside of Port-au-Prince. The Initiative therefore effectively combines both immediate and longitudinal relief for the Haitian healthcare system.

Figure 3. The Initiative's original team went to Haiti back in February and successfully provided neurosurgical intervention and data collection. Pictured are Dr. Sukreet Raju, Annie McDonough, and Nicholas Boullis.

The Initiative has already conducted its pilot operation in February, successfully conducting 13 spinal surgeries. With that being said, the Initiative needs the engagement of the Emory community in order to accomplish its goals. A new student group called the HNI undergraduate committee (HNIuc) was started this September in order to fundraise for this organization. The group represents an ongoing collaboration between Emory undergraduates, graduate students, and the neurosurgery team. The Initiative's goals are to support the neurosurgery team and engage the Emory community in the issue of providing adequate neurosurgical care to Haiti. The team of physicians will be taking a trip to Haiti in late-November, and will therefore need all the help we can provide them such that their mission is successful. If you are interested in joining HNI's cause, please email haitineurosurgery@gmail.com and visit haitineurosurgery.org.

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Ghost Organs: Using Stem Cells to Create Patient Tailored Organs

Authored by: Vikrant Nallaparaju
Edited by: Mansi Maini **Reviewed by: Dr. Cun-Yu Wang**

Many researchers, in the field of artificial organ transplantation, face a major obstacle in the form of implanted cells. The issue arises from these foreign cells dying shortly after being grafted onto a failing organ. Further complications have arisen from the fact that the host's body often rejects the foreign cells of the new organ. Recent advancements at the Texas Heart Institute have paved the way towards resolving this major issue through a new device called the "ghost organ" heart. Essentially, the ghost organ is a protein shell of an organ that is unable to function on its own. When implanted with stem cells from the patient, the organ will ideally be able to function without complications. Scientists hope that this new procedure could potentially eliminate the need for wait times for organ transplants and give many people the chance to survive potentially fatal organ failures.

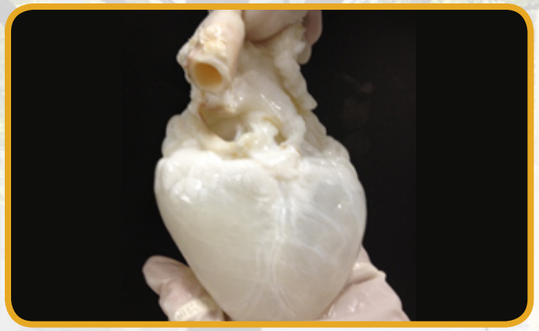

Figure 1. The bare matrix of the heart. (Texas Heart Institute 2015)

The central principle behind the ghost organ is aiming to adapt the transplant organ to fit the unique genetic makeup of a host. A patient's immune system is specifically designed to target any foreign cells within the body and destroy them immediately, thus fitting an organ to the host's genetic makeup is crucial. The immune system's defensive role can pose a problem during transplants since organs from donors possess foreign DNA that is rejected by the body. Ghost organs seek to circumvent this issue and allow the organ to mature from the stem cell layer which develops around the protein skin and thus serving as the ghost template.

The first step in the process is to take an unused organ from a deceased specimen and remove as much of the external tissue from the organ as possible. This is accomplished by heavily rinsing the organ in detergent until all that is left is a pale white protein tissue covering known as the extracellular matrix. The organs are then injected with hundreds of millions of native stem cells from the prospective patient. Through a method that is currently not fully understood by scientists, the stem cells are then able to detect the type of body cell that surround them and are able to develop into that type of cell, effectively forming a fresh heart around the remains of the donor template. "Cells sense their environment," says Dr. Angela Panoskaltsis-Mortari at the University of Minnesota in Minneapolis. "They don't just sense the factors. They sense the stiffness and the mechanical stress, which in turn pushes the cells down their proper developmental path" (Maher, 2013).

"Cells sense their environment...They don't just sense the factors. They sense the stiffness and the mechanical stress, which in turn pushes the cells down their proper developmental path."

While those steps summarize the broad strokes of the procedure, the biological mechanisms behind this procedure are a bit more detailed. There are numerous sub steps prior to the transplantation procedure. Even simply cleansing the fresh organ using the detergent can present a tricky situation. If not enough of the outer cells are removed, the organ will retain some of the donor's genetic information and will be rejected by the transplant patient. On the other hand, if too much is removed, vital protein and growth factors that regulate the reconstruction of the organ in the patient will be lost and the organ may fail to regrow.

After the organ is stripped to its extracellular matrix it must then be endothelialized; a process in which endothelial tissues are formed. This is accomplished by injecting the stem cells directly into the organ itself, usually through the aorta in the case of hearts. Perfusion, diffusion of oxygen into the organ, must then be continued for nearly a week to provide the stem cells with the oxygen they will need in order to grow and divide. Maintaining stable external conditions within the bioreactors in which the organs grow is essential for proper growth after stem cell introduction.The bioreactor must be able to simulate the actual beating of a functioning heart in order to provide the maturing cells the information they need to stimulate cardiac function once in the patient.

Cross sections of the developing organ are typically cut and embedded in paraffin, a wax-like substance, for functionality and strength testing. The strength is usually tested by tying a ring of the matrix around a post attached to Force Transducer at one end and another post fixed to a custom-made bath (Ott, 2008, 213). Microelectrodes are then used to generate waves that pass through the bath and into the matrix. Minimal reaction to the waves is necessary in order to ensure the organ can withstand the internal forces within the body of the transplant patient.

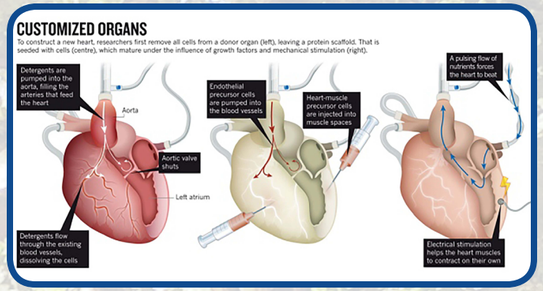

Figure 2. The introduction of stem cells into the matrix

Functionality is then assessed by simulating the actual contractions of the heart during cardiac activity. A pressure catheter is inserted into the left ventricle and electrodes are used again to send electrical waves through the heart to induce contractions. Heart movement is calculated using frames from video taken during the contraction process using the Fourier Theory (Ott, 2008). The Fourier Theory utilizes a series of sinusoids that vary in brightness as a proxy to measure frequencies as a function of time. These sinusoids can then be analyzed to determine the spatial frequency and magnitude of a sample, which are useful when determining the movement of a sample in response to a stimulus. As the intensity of the sinusoids change, scientists can see how the sample's movement changes in response to increasing magnitudes of stimulus.

Dr. Doris Taylor at the Texas Heart Institute has been at the forefront of this research since the early 2000's. While her team has yet to grow a human heart in this capacity, they have succeeded in developing fully functioning rat and pig hearts. The procedure can often face numerous complications during actual transplantation. For instance, the matrix must be completely impermeable and without any tears in the outer protein covering. If it has tears, blood clots can form, which can be fatal to the animal after the transplant. Another common complication is that the organ simply doesn't perform to its full capability. If the matrix has not fully developed, the organ can be ineffective and pose a greater threat to the patient, as the stem cells will not be able to grow properly around the framework."You can't have something pumping just 1 or 2 or 5% of the ejection fraction of the normal heart and expect to make a difference," says Dr. Stephen Badylak. "There is little room for error" (Maher, 2013).

"You can't have something pumping just 1 or 2 or 5% of the ejection fraction of the normal heart and expect to make a difference. There is little room for error."

These potential problems are obstacles researchers are facing in moving toward the final step of human transplantation. Even the very mechanism of preventing immune rejection can be dangerous to the patient. Anti-immune rejection drugs are often necessary to inhibit the body's release of antibodies during the period right after transplantation, but they can damage the kidneys and liver due to the heavy strain they place on the body. Despite setbacks, researchers are still optimistic about the future of the ghost organ in the field of regenerative medicine. Just six years ago, scientists were only able to grow new organs in petri dishes, but now the organ can grow within a prospective patient, saving time and reducing the chance of autoimmune rejection.

"There are some days that I go, 'Oh my god, what have I gotten into?' On the other hand, all it takes is a kid calling you, saying 'Can you help my mother?' and it makes it all worthwhile" - Dr. Doris Taylor said.

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Red Brains and Blue Brains

Authored by: Alec Shannon
Edited by: Yash Patel
Reviewed by: Dr. Cory Labrecque

As we eagerly approach the 58th United States presidential election in 2016, news stations across the nation will broadcast maps composed of predictable patterns of blue and red that illustrate the political leanings of each individual state at any particular moment in time. Based on our knowledge of previous elections, we expect the Electoral College map to feature some variation of the usual expanse of red that is roughly outlined by a coastline of blue. Aside from the notoriously capricious positions of a few swing states, we can reliably predict which states will cast their votes to which candidate based on centuries of evolving correlations between geography and political ideology. As science seeks to explain fundamental neurophysiological differences separating Democrats from Republicans, we continually come closer to translating the idea of an Electoral College map onto a map of the human brain, attributing certain regions with the colors blue and red based on an individual's political ideology.

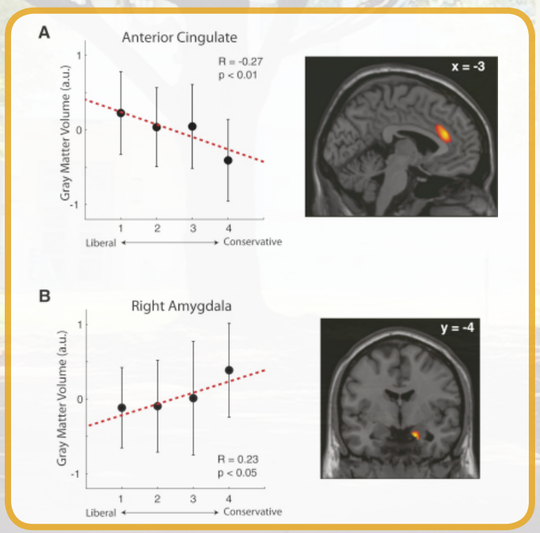

Figure 1. Comparative analysis of structural brain differences in the amygdala and anterior cingulate cortex (ACC) based on gray matter volumes. The graph shows a positive correlation between the grey matter volume of the right amygdala and the degree of political conservatism with which an individual aligns. There is a negative correlation, however, between degree of political conservatism and ACC size, suggesting differential activation of these brain regions based on political affiliation.

Before discussing the research that has reliably ascribed distinct neural processes to the conservative and liberal brain, it is critical to explore the various studies that have attempted to predict an individual's political ideology based on other variables besides cognitive function. The earliest research on this subject sought to correlate one's political identification with the political beliefs that his or her parents held: "Though expressed partisanship is not always meaningful among the very young…careful longitudinal study of Americans has shown that… among children who have a partisan preference, nearly all share it with their parents" (Achen, 2002). The findings in this study emphasize the efficacy of environmental factors on the formation of core values and beliefs that form political ideology. This paradigm, however, fails to explain a significant number of cases in which children later deviate from the expressed political position of family members.

Other research that seeks to explain the origin of an individual's political identity highlights key structural differences in brain regions of Democrats and Republicans, as shown in Figure 1: "The gray matter volumes of ACC [anterior cingulate cortex] and the right amygdala…distinguish individuals who reported themselves as conservative from those who reported themselves as very liberal with a high accuracy (71.6% ± 4.8% correct, p = 0.011)" (Kanai et al., 2011). Researchers that employ structural imaging techniques to predict political orientation caution that the complex cognitive processes involved in political ideation and reasoning are not limited to a few distinct brain regions, however. While these processes depend on the extensive interplay of several areas of the brain, it is valuable to study the brain regions that are essential to the development of fundamental "emotional and cognitive traits" (Kanai et al., 2011).

Recent studies involving functional brain imaging provide even stronger predictors of an individual's political orientation. After comparing the activation of certain brain structures during a task involving risk-taking, Democrats and Republicans revealed significantly different activity in both the right amygdala and the left posterior insula. Neural pathways implicated specifically in the evaluation of risk and conflict have been extensively studied and provide a powerful basis for comparison: "Behavioral research suggests that psychological differences between conservatives and liberals map onto the widely-studied self-regulatory process of conflict monitoring" (Amodio et al., 2007). Meta-analysis on these brain regions, namely the the "right amygdala, left insula, right entorhinal cortex, and anterior cingulate (ACC)" allow researchers to conduct detailed, comparative evaluations on the varying physiological responses of individuals who stated alignments with either the Democratic or Republican Party (Schreiber et al., 2013).

"After comparing the activation of certain brain structures during a task involving risk-taking, Democrats and Republicans revealed significantly different activity in both the right amygdala and the left posterior insula."

As depicted in Figure 2, the functional imaging results of self-reported Republicans during a risk-mediated activity correlate with increased activation of the right amygdala. Interestingly enough, the amygdala is highly implicated in the way we process fear and interpret "external cues" in order to form an assessment of our surroundings, suggesting that both emotionally guided apprehension and a strong measure of conscientiousness mediate a Republican's

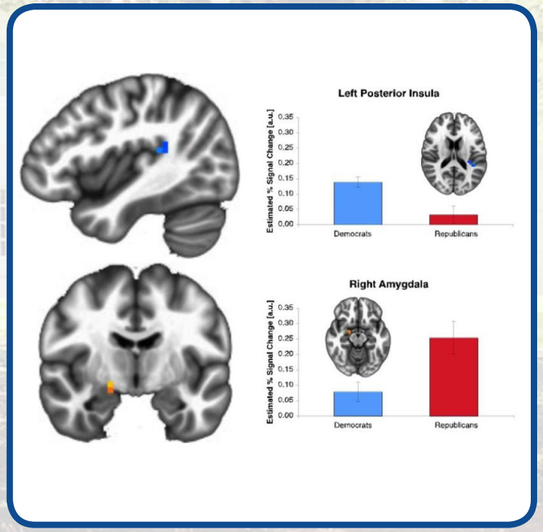

Figure 2. While performing an activity that involved executing risk-based decisions, Democrats show comparatively stronger left posterior insula activation than Republicans. Republicans, on the other hand, reveal stronger activation of the right amygdala compared to Democrats while completing the same task.

response to risk. Democrats, on the other hand, demonstrate a significantly increased activation of the insular cortex when completing the same task. When processing risk, the majority of individuals who identified as Democrats appear to engage cognitive processes that are traditionally involved in social cognition and insight, including empathy. Aside from social cognizance, the insular cortex functions to evaluate "internal bodily cues crucial for subjective feeling states and interoceptive awareness" (Schreiber et al., 2013). Due to the close proximity of the insular cortex to the temporal parietal junction, a brain area heavily implicated in empathic judgment, researchers claim this pattern of activation underlies a tendency to perceive and consider the inner state of others. The present research claims that individuals with an elevated level of consciousness project this inner awareness onto others during interactions.

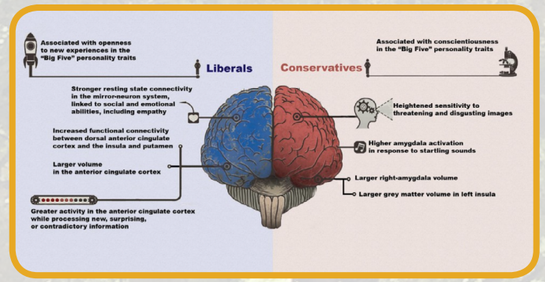

Figure 3. Generalized behavioral correlates associated with differential neural activation of certain brain regions, including the insula and amygdala.

In many ways, the disparities in functional imaging results offer convincing explanations for the emotionally driven values and convictions that are characteristic of political orientation. When we examine the political discourse on pivotal issues in this election such as gun control, Republicans defend their positions against increased regulation by highlighting the benefits of gun ownership as a measure of safety. This value, perhaps guided by the fear of vulnerability for not possessing a firearm, underlies a fundamental finding in this study that Republicans tend to activate neural pathways associated with fear in assessing risk. The argument that increased scrupulousness guides Republican policies can logically extend to other hallmark issues this election season as well, including defense spending and capital punishment.

"In many ways, the disparities in functional imaging results offer convincing explanations for the emotionally driven values and convictions that are characteristic of political orientation."

In the case of Democrats, with platforms rooted in attenuating income disparity and raising the minimum wage, greater activity near the insular cortex may not be a coincidence. Evident in many

social policies supported by liberals, a guiding measure of empathic consideration may render Democrats more inclined to be a champion for social justice and equal opportunities for success. Figure 3 expounds upon key functional differences in these two brain regions and relates these characteristics to generalizable attributes of Democrat and Republican behavior.

After examining this model of political prediction based on basic functional imaging studies, we often wonder about the biological mechanisms that cause these associations to occur. Does the sociopolitical environment in which we are raised influence how our brains are wired to interpret situations and form decisions later in life? Could it be that the association is more genetic and that the biology predetermines how we fall on the political spectrum?

Considering the strong connection between observed cognitive processes and expressed political ideology, the search for the direction of this correlation may be a futile endeavor. The research acknowledges that while a combination of these factors may predict which box one will select next November, the concept of neuroplasticity offers the most convincing explanation for the disparity in observed neural mechanisms between Democrats and Republicans. Beyond the standard epigenetic arguments for the origin of political ideology, the results of this study offer unequivocal evidence for the malleability of the brain in a number of critical neural processes. An individual's experiences as a partisan within a partisan environment undoubtedly determine the contrasting activation of certain neural pathways in a way that significantly modifies physiological activity in the brain. Understanding the differential activation of brain regions characteristic of those on opposing sides of the political spectrum offers a pivotal paradigm in the way we perceive the development of political ideology. In the future, we can extend this model of the basic mechanisms underlying cognitive function and ideology to research in broader socioeconomic and cultural applications.

"An individual's experiences as a partisan within a partisan environment undoubtedly determine the contrasting activation of certain neural pathways in a way that significantly modifies physiological activity in the brain."

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Revival of Herbal Medications: Common Remedies for the Elderly

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Edited by: Taylor Eisenstein

Alongside the popular western and/or modern medicine, a revival of herbal medicine is rising without further delay. There has been such an immense increase in interest and usage of herbal remedies and therapy that there is concrete data showing an approximate 400% increase in the use of herbal medicine by US citizens (Ernst, 1999). The increasing evidence of treatment success has guided a greater proportion of patients to utilize these resources as potential remedies. In order to understand the validity of these herbal medicines, several randomized clinical trials were performed to find what plant-based medicine could provide an efficient recovery for various ailments commonly found in the elderly. Such ailments include depression, Alzheimer's disease, Benign Prostate Hyperplasia, and Erectile Dysfunction.

"There has been such an immense increase in interest and usage of herbal remedies and therapy that there is concrete data showing an approximate 400% increase in the use of herbal medicine by US citizens."

Ailment	Western Medicine	Herbal Medicine
Depression	maprotiline, imipramine, bromazepam, amitriptyline, diazepam, and other antidepressants	*Hypericum perofratum*
Alzheimer's Disease	treatments that provide symptomatic relief	*Ginkgo biloba*
Benign Prostate Hyperplasia	minimally invasive surgical therapies (MIST), medications (desmopressin), therapies (watchful waiting, drug mono-therapy, and phytotherapy), ayurvedic treatments (Ushira, Khadir, and Punarvana)	*Serenoa repens*
Erectile Dysfunction	psychosexual therapy, lifestyle/dietary modifications, acupuncture, surgery	Yohimbine

Figure 1. Table comparing the medications offered by Western and Herbal Medicine.

Depression is an ailment not only among the elderly, but now common among younger generations as well. Abilify, Celexa, and Wellbutrin are just a few among the long list of drugs prescribed to treat depression, however, each is accompanied by its own set of side effects and conditions. On the other side of the spectrum, the plant tested in clinical trials for depression is called Hypericum perofratum. This plant consists of around 400 species, which are commonly used in Europe, Asia, North Africa, and North America.

"Most medicines also tend to have some level and extent of side effects, but it was concluded that those of Hypericum perofratum were much less dire than those of the synthetic antidepressants."

In 23 studies, the effects of Hypericum perofratum was compared to those of common antidepressants including maprotiline, imipramine, bromazepam, amitriptyline, and diazepam; using the Hamilton Depression Rating Scale to measure the level of depression (Ernst, 1999). 1757 patients diagnosed with mild to moderate depression were pooled together in these trials presenting statistically significant data that this herb is just as, if not more effective in resolving depression. Most medicines also tend to have some level and extent of side effects, but it was concluded that those of Hypericum perofratum were much less dire than those of the synthetic antidepressants (Ernst, 1999). Biologically, hyperforin (the phytochemical product of this herb) inhibits the reuptake of certain neurotransmitters, such as serotonin, adrenaline, and GABA in the brain (Muszynska, Lojewski et al., 2015). This inhibition alters the chemical balance in the brain cells that allow for better transmission of signals, and thereby promote the maintenance of positive mood or affect of a person.

The next disease of interest to scientists studying plant medicine is Alzheimer's disease (AD), a neurodegenerative disease common among the elderly. Current therapy trials for AD include testing on anti-inflammatories, statins, hormonal therapies, and chelators, all of which have been unsuccessful or failed to show significant evidence of improvement. The treatments that are giving some benefits are not yet universal either (Waite, 2015). So what is being done to treat AD? As of now, "currently available treatments provide symptomatic relief" (Waite, 2015) and the current mindset is one of caution when reporting a cure for AD. There is a great need for further screening and trials to be able to pinpoint a cause and a solution for AD, and one of these trials is set to study the leaves of the ginkgo tree (Ginkgo biloba).

Ginkgo trees are commonly found and used in Asian countries. This plant was used on 424 patients with Alzheimer's in four randomized double-blind

clinical trials. The results show data in favor of the efficacy of the herbal plant, proving that this plant has a significant effect in treating Alzheimer's. The Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-cog) was used to measure the effects of placebo and plant and it was concluded that a three percent difference in the scale was present (Ernst, 1999). In continuation of this data, further studies have been done in understanding the relationship between mitochondria and Alzheimer's. The understanding is that "mitochondrial dysfunction plays a critical role in AD and can be considered as an important target for the treatment of clinical symptoms of AD" (Kumar et al., 2015). With this relationship in mind, further evidence to the biological functions of Ginkgo biloba can be unearthed in the very near future, potentially providing more concrete methods of its usage to treat Alzheimer's disease.

Figure 3. Hypericum perofratum, used as a possible treatment option for depression

Another common ailment of the elderly is benign prostatic hyperplasia (BPH), which is a disease that typically occurs in men at the age of 40 or above, resulting in an enlargement of the prostate, bothersome lower urinary tract symptoms (LUTS),

Figure 4. Ginkgo biloba is used to treat Alzheimer's disease.

and bladder outlet obstruction (BOO) (Shrivastava & Gupta, 2012). For the past half century, the most common treatment was an ablative surgery; now, however, various new treatments have been introduced over the decade. Multiple new minimally invasive surgical therapies (MIST), medications (desmopressin), and therapies (watchful waiting, drug mono-therapy, and phytotherapy) have greatly reduced the risk of complications that would be present in a grand surgical procedure. Additionally, there are treatments in Ayurveda, a Hindu system of medicine involving diet, herbal treatment, and yoga, available for BPH including Ushira, Khadir, and Punarvana (Shrivastava & Gupta, 2012).

Following along the spectrum of medicine, Serenoa repens is the herbal plant that has been suggested to provide an improvement for this condition. The fruits of these plants are dried to make the extracts, and were "first used in the eighteenth century for testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation" (Ernst, 1999). In the study, 2939 men were composed in 18 randomized clinical trials for a duration of nine weeks. In conclusion, "erectile dysfunction was more frequent with finasteride (4.9%) than with S. repens (1.1%)" (Ernst, 1999) proving that the herbal medication exhibits an improvement in urological symptoms of BPH.

Figure 5. Serenoa repens is used to treat Benign Prostate Hyperplasia.

"The fruits of these plants are dried to make the extracts, and were "first used in the eighteenth century for testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation."

Similar to BPH, there is an increasing number of elder men with erectile dysfunction (ED). This condition not only consists of physiological effects, but it is also affiliated with emotional and social

ramifications. In addition, this condition also poses further threats to cardiovascular disease and other serious health conditions. Treatments for ED include "psychosexual therapy, lifestyle modifications" (Pastuszak, 2014), oral therapies, and acupuncture and complementary medicine. Furthermore, there are surgical options available such as penile prosthesis and penile revascularization surgery. Alternatively, "Yohimbine is an alkaloid derived from the bark of the central African yohimbine tree" which "produces a rise in sympathetic drive by increasing norepinephrine release and the firing rate of cells located in noradrenergic nuclei of the CNS" (Ernst, 1999). In the clinical trials, there were seven randomized, double-blind trials included in a meta-analysis, presenting an odds ratio of 6.7. This demonstrates that patients receiving the yohimbine are "6.7 times more likely to benefit than those treated with the placebo" (Ernst, 1999). As far as adverse effects of yohimbine are observed, it appears that the placebo group reported of experiencing them half as much as the experimental group (5-16 % in comparison to 10-30%), which does not provide enough evidence to say that the yohimbine's effects are truly drastic.

Figure 6. Yohimbe bark is used to treat Erectile Dysfunction.

The culmination of these trials presents a positive and encouraging mindset to the advancement of herbal medicinal practices. It is certainly necessary to further the research and experimentations to answer speculations and understand the fundamental, chemical reactions that these herbs create in the body. There is a great potential for the revival of herbal medicine to succeed in finding cures for many diseases and illnesses present in modern day society and to those to come in the future. Acknowledging this natural aspect of healthcare and being able to integrate this knowledge into everyday life is a vital key to fabricating both natural and synthetic medicine and practices.

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A Lost Childhood:
Early Onset Schizophrenia

Authored by: Allison Derovanesian
Edited by: Mansi Maini **Reviewed by: Dr. Waqar Azeem**

Characterized by any combination of disorganized thoughts, hallucinations, and delusions of grandeur, schizophrenia is a mental health disorder that effectively causes individuals to lose touch with reality. Typical onset of the disorder occurs around ages 18-25, however if someone is diagnosed with psychosis before the age of 13, they are identified as having Early-Onset Schizophrenia (EOS) (Dvir & Frazier, 2011). While this phenomenon is quite rare – less than 1 in 10,000 children - the disorder poses a particularly detrimental threat to children that are still developing (Remschmidt, 2005). While there is no cure for EOS, treatment options can alleviate some symptoms. Because the disorder specifically affects children, it poses additional problems beyond those originally associated with schizophrenia, and there is also a desperate need for further research on EOS.

Children with early onset schizophrenia are in a particularly precarious situation for two reasons. First, the disorder itself is quite malicious in nature. Altering perceptions of reality through hallucinations or delusions, and causing severe cognitive and behavioral disruptions, schizophrenia is a neurological disorder that is not curable and is best managed by alleviating symptoms. Unfortunately, complete dissolution of symptoms is quite rare, if not unheard of, and the disorder itself will typically need treatment throughout the duration of a person's life. Living with schizophrenia is therefore quite an undertaking for anyone and understandably places an increased burden on children diagnosed with the disorder.

"Altering perceptions of reality through hallucinations or delusions, and causing severe cognitive and behavioral disruptions, schizophrenia is a neurological disorder that is not curable and is best managed by alleviating symptoms."

What is of particular concern for those inflicted by EOS is the fact that children have not fully developed by the time that EOS becomes apparent. This menacing problem cannot only halt normal development but can actually negatively alter their behavior, personality, and cognition so that they may later be unable to function as normal members of society. Any individual diagnosed with schizophrenia needs to start treatments as soon as possible, and there is an even greater emphasis on early intervention in children diagnosed with EOS. Remschmidt (2001) explains that in spite of long-term prognosis being worse whenever symptoms become apparent early, early treatment of EOS can only help to improve the outcome. He further explains that from a psychosocial perspective of development, when EOS goes untreated, social functioning and mastery of social tasks will deteriorate, which can lead to a child's inability to properly interact with other members in their environment (184).

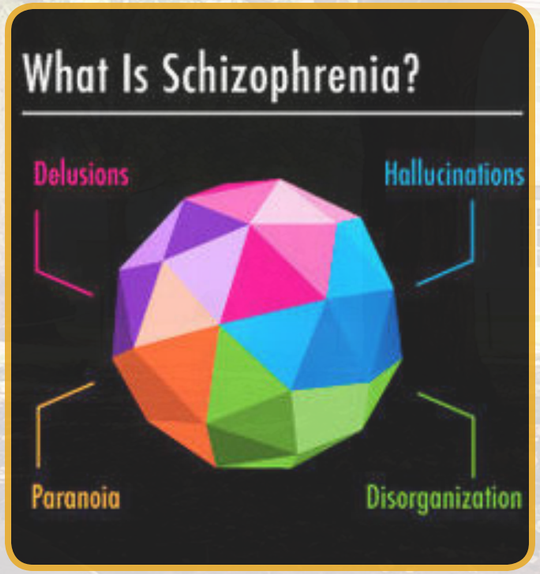

Figure 1: Schizophrenia is a mental disorder characterized by a disconnect with reality. Common symptoms severely disrupt one's life and can include delusions such as believing that the FBI is watching them, hallucinations, paranoia, and disorganized thoughts.

The longer that early onset schizophrenia goes untreated, the more devastating the outcome for the child. Side effects of EOS, if it is left to run its course, include severe cognitive deficits and social isolation (Cantor, 1988, 132-134). Several studies have shown that if not properly attended to, the

Figure 2. Though anyone with schizophrenia faces a steep uphill battle, children diagnosed with the disorder often lead drastically different lives than their peers. Social isolation from their friends and classmates is common for a child with EOS and this can negatively impact their personality and self-esteem as they grow older.

cognitive abilities of those with schizophrenia can resemble that of individuals with down syndrome, whom characteristically have a lower than average IQ score (Dvir & Frazier, 2011). Social isolation from peers can result because of the abnormal behaviors displayed by children with schizophrenia such as talking to inanimate objects they believe to be alive, aggressive tendencies, and delusions that their peers are out to hurt them. Childhood schizophrenia can go untreated because of parent's refusal of therapy or attempts to inappropriately thrust the child into mainstream society (most notably mainstream schooling), or from schizophrenic symptoms somehow going unnoticed (Cantor, 1988, 132-134). If EOS is not quickly addressed after the initial onset of symptoms, the disorder can pose a debilitating threat to children as they grow older, regardless of the reasons for lack of treatment.

"The longer that early onset schizophrenia goes untreated, the more devastating the outcome for the child."

Medical professionals will often prescribe antipsychotic agents (APAs) to children with early onset schizophrenia in conjunction with psychoanalytic treatment or other methods of treatment. Some professionals suggest that pharmacological therapy should only be used as supplemental therapy and not a first line of defense (Goldfarb, Mintz, & Stroock, 1969, 142-143). Drugs used to treat any individual with some form of psychosis can also cause serious side effects, and this feature should be of particular concern when APAs are prescribed to still-developing children. While the drug should be tailored to the severity of the child's condition as well as their weight and metabolism, it should always be started at a low dose and then further titrated as the child needs it. Also, there is not much substantive clinical research available specifically for drug therapy in children with EOS. For that reason, much of the current knowledge of effective drug therapies in this population is based on adults with schizophrenia, as well as trial and error studies.

Psychosis disorders such as schizophrenia encompass symptoms that are either positive or negative. These terms do not describe good and bad symptoms as one might intuitively expect but instead describe either the unusual presence or lacking of feelings and behavior that a child with EOS may be experiencing. Positive symptoms describe an extreme distortion of normal functions while negative symptoms describe a loss of normal functions (Porter, 2011, 1560). Therefore positive symptoms from the perspective of schizophrenia would be the hallucinations and delusions that give an individual an altered sense of reality, while negative symptoms would include emotional indifference or inability to speak.

The initial group of drugs developed to combat psychotic symptoms in individuals was first generation antipsychotic agents (APA), which have also commonly been called major tranquilizers or typical neuroleptics (Guzman, 2011). These drugs work specifically by blocking dopamine receptors in the brain, which is relevant to schizophrenia because it has long been thought that the disorder is linked to excess amounts of dopamine in the brain. However, with the blocking of this receptor, the first generation APAs are characterized by high extrapyramidal symptoms. When too much dopamine is antagonized, various severe side effects like Parkinsonism, tardive dyskinesia, and neuroleptic malignant syndrome can develop (NCBI, 1992). Parkinsonism and tardive dyskinesia can cause quite severe, uncontrollable muscle movements while the neuroleptic malignant syndrome can be fatal. Furthermore, first generation antipsychotic agents help in alleviating positive symptoms, but do little in the way of affecting the negative symptoms.

Once it was recognized that the side effects of the

first generation APAs may outweigh the marginal benefits of the drug, efforts were made to better refine the drugs available to treat psychosis. Second generation APAs are more selective in blocking dopamine receptors (Porter, 2011, 1562-1565). As a result, this class of drugs has been observed to not have as severe extrapyramidal symptoms as first generation APAs, but does introduce a new group of side effects: metabolic imbalances. Increased weight gain is the most notable side effect of these second generation drugs which is another serious problem to have early on in one's life. These refined drugs can help alleviate both positive and negative symptoms of schizophrenia, but not completely eradicate them. The relationship between the two classes of drugs is interesting: while 40% of adolescents with schizophrenia will not respond to first generation antipsychotic drugs, up to 60% of them reported improved symptoms under Clozapine which is the first second generation APA to be approved by the Food and Drug Administration for use in children (Remschmidt, 2001, 192 and Guzman, 2011).

Children diagnosed with early onset schizophrenia face a daunting challenge early in their lives that the vast majority of their peers do not have to deal with. The child's personal, cognitive, and behavioral growth is halted and steered in the wrong direction as a result of the disorder's tendency to distort perceptions of reality. There is a dire need in the scientific community for increased research and investigation into how treatment options can be better tailored to the unique needs of children dealing with schizophrenia. Improved course of treatment for children with early onset schizophrenia can help to give them back the childhood which they lost to the disorder, and which they so desperately deserve to regain.

"There is a dire need in the scientific community for increased research and investigation into how treatment options can be better tailored to the unique needs of children dealing with schizophrenia."

Images:

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A Non-Pharmacological Approach for Treating Alzheimer's

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Edited by: Yash Patel

Alzheimer's disease (AD) is a degenerative dementia characterized by a progressive decline in cognitive function due to the development of senile plaques and neurofibrillary tangles. They are associated with neuronal destruction, particularly in cholinergic neurons. Since no drugs have been proven to completely protect neurons, agents that inhibit the degradation of acetylcholine within the synapse of neurons are the main type of pharmacological treatments available to those inflicted by AD. The drugs that have been widely studied include Selegline, Vitamin E, acetylcholinesterase inhibitors, and estrogen. The use of these drugs remains controversial because of their strong side effects. None of them can cure the disease and they only delay the time before a patient is recommended for possible palliative care. All of the drugs can potentially improve some aspects of the symptoms but not all. Thus, most Alzheimer's patients complement their prescriptions with non-pharmacological treatments, or use alternate therapies altogether. Many of these non-pharmacological approaches have been developed in the past two decades and include cognitive training, sensory stimulation, music therapy, and motor stimulation. Among them, music therapy has become increasingly popular.

"Many of these non-pharmacological approaches have been developed in the past two decades and include cognitive training, sensory stimulation, music therapy, and motor stimulation. Among them, music therapy has become increasingly popular."

Music therapy first interested scientists post World War II when musicians traveled around the world and played music for traumatized soldiers. As a matter of fact, music therapy can be traced all the way back to the thirteenth century when Arab hospitals would provide special music rooms for the benefit of the patients (Antrim, 2006). Currently, music therapy is widely used in the context of dementia. Music has supporting evidence suggesting that it is beneficial even when taken out of the context of Alzheimer's disease. It has been documented that music has a clear, positive effect on vital parameters: from blood pressure to heart rate (Fukui et al., 2012). Studies from a decade ago on music therapy mainly focused on its efficacy. Clinical studies were able to show a causal relationship between music intervention and cognition improvement. Music therapy is known to be a very delicate process. Even small adjustments may result in ineffective treatment (Simmons-Stern, 2012), which is why early studies sometimes did not observe a statistical significance in the groups treated with music intervention.

Nowadays, well established music therapy includes active music therapy (AMT), music-based interventions (MBI), individualized listening to music (ILM), caregiver singing (CS), and background music (BM) (Raglio. 2014). In AMT, patients with dementia create music with guidance from a trained musical therapist. Sound and music are used in specific tasks to facilitate non-verbal learning, and interactions with the therapists facilitate communication, expression, and control of emotions. AMT research studies are largely randomized, controlled clinical trials, thus their results provide strong evidence for the efficacy of AMT. Among the several music therapy techniques mentioned, interactive music intervention, which is highlighted in AMT, is the most effective (Sakamoto et al., 2013). The interaction between the therapist and the patient can help restore residual cognitive and emotional functions (Li et al., 2015).

Recent studies are shifting focus to analyzing the neuroscientific basis of music therapy so as to understand the concepts underlying this form of therapy. Several theories have been proposed to explain the efficacy of music therapy from a biological basis. Correlations between changing levels of steroid hormones and music have been found and encouraged further research on steroids and music. As early as 1984, Dr. Hassler experimented on the relationship between testosterone and music ability (Hassler et al., 1984). In 2001, Dr. Fukui confirmed this relationship and even expressed in his article that music may have originally evolved because of its enhancement on steroid hormones. Now numerous investigations have confirmed that musical ability can be related to enhanced levels of testosterone. Parallel studies on steroid hormones and Alzheimer's led by Dr. Yaffe (2002) suggest that cognition improves with the rise of testosterone levels in elderly males. Testosterone has shown to lower the secretion of β-amyloid peptides that facilitates the progression of Alzheimer's (Gouras et al., 2000). In fact, prescription of testosterone was even suggested as a possible pharmacological treatment for Alzheimer's, but was eventually denied

because of its drawbacks (Hammond et al., 2001). However, this correlation nevertheless provides a strong evidence for the relationship between music and Alzheimer's treatment.

"Recent studies are shifting focus to analyzing the neuroscientific basis of music therapy so as to understand the concepts underlying this form of therapy."

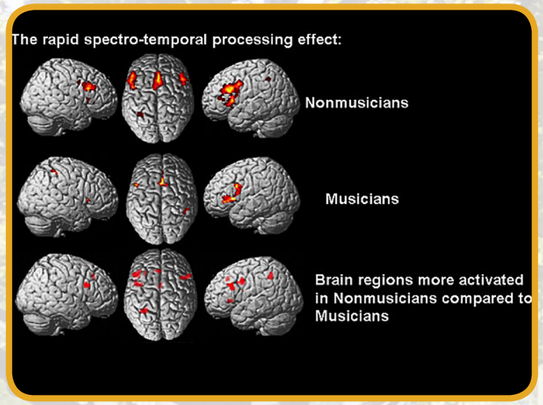

Figure 1: musicians use larger areas of the brain for information processing. Trei, L. (2005).

Available literature also suggests that music aids motor learning. According to previous studies on musicians, both long and short periods of music learning lead to stronger plasticity in motor areas of the brain. Scientists have used imaging techniques to picture the active areas of the brain when exposed to sounds. FMRI data show large areas of activity in the supplementary motor area (SMA) when Alzheimer's patients are exposed to music (Slobada, 2005). According to Schlaug (2009), activations in those areas eventually lead to a small degree of brain recovery.

Researchers have also questioned whether type of music is a relevant variable in music therapy for AD patients. Dr. Arroyo-Anlló (2013) and his group discovered that in patients with severe Alzheimer's, listening to familiar music enhances self-consciousness far better than listening to unfamiliar music (El Haj et al., 2012). Furthermore, familiar music can be considered an enhancer of general cognitive state, which means its application extends beyond Alzheimer's (Thompson et al., 2005). More in-depth study on music as a cognitive enhancer reveals that unfamiliar songs depend on episodic memory more than familiar songs do. Because AD patients have enhanced cortical and hippocampal atrophy compared to healthy individuals, impairments in episodic memory are expected. On the other hand, processing of familiar music involves a complex network of neurons that recruits information from all areas of the brain (Zatorre et al., 2007). Some of the more important areas involved in the processing of familiar music include the medial prefrontal cortex which is affected more slowly in Alzheimer' s disease than other brain areas (Ferreri et al., 2013). Areas affected more quickly include the posterior parietal and temporal lobes. The activation in this area helps create a more robust self-consciousness.

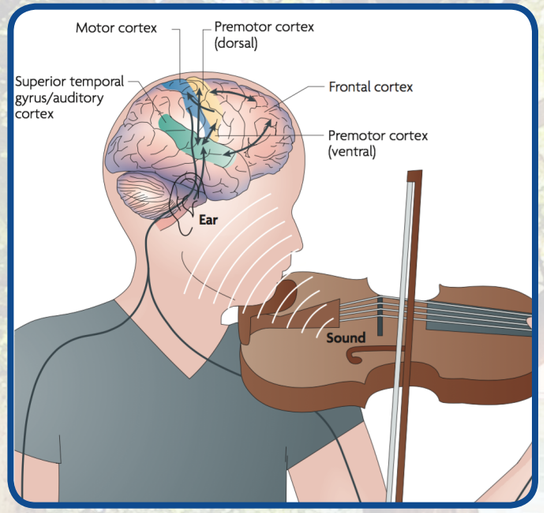

Figure 2: The auditory-motor interactions in music perception and production. Zatorre, Chen, & Penhune (2007).

Current research on music therapy still has many mysteries to solve. For example, Dr. Simmons-Stern (2012) and his colleagues found out that music encoding only enhances general information memory, but not specific content memory. A possible explanation for their recent results is that people access general content memory based on familiarity while specific content memory requires utilizing rather unfamiliar information.Processing unfamiliar information requires more brain areas that are impaired by Alzheimer's, while familiarity reduces the demand for cognitive functions.

Despite the fact that many questions about AD remain unanswered, the future of treating Alzheimer's disease is very promising. With the additional advancements in biochemistry and bioengineering, the pharmacological approach is rapidly evolving. At the same time, other seemingly unorthodox approaches, most notably music therapy, are also likely to make crucial differences for those suffering from Alzheimer's disease. What scientists already found on the relationship between music and brain function improvement suggests that music can indeed strengthen well-functioning brain areas and recover some impaired brain areas to a large extent compared to other methods or drugs. Many findings even apply to diseases other than Alzheimer's disease, including diseases due to brain impairments. To summarize, future investigation on music therapy will shine light upon many of perplexing problems regarding the brain.

"What scientists already found on the relationship between music and brain function improvement suggests that music can indeed strengthen well-functioning brain areas and recover some impaired brain areas to a large extent compared to other methods or drugs."

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The Oxytocin (OT) Paradox:
OT's Nuanced Role on Human Social Approach

Authored by: Sharon Hsieh
Edited by: Alec Shannon **Reviewed by: Dr. Astrid Prinz**

The neuropeptide oxytocin has garnered substantial attention over the last decade due to its therapeutic potential of mitigating social anxiety and enhancing interpersonal trust. Commonly touted as the "love hormone," oxytocin is a neurohypophysial hormone that is secreted from the posterior pituitary into the systemic circulation in response to a wide array of stimuli, including parturition, lactation, and suckling. In particular, the characteristic mechanisms of oxytocin are stimulation of uterine smooth muscle contraction as part of the process of childbirth and the ejection of milk during lactation (Gimpl, Fahrenholz, & Gene, 2001). Oxytocin also plays a significant role in other reproduction-related functions, such as ovarian steroidogenesis and the regulation of the estrous cycle length (Gimpl & Fahrenholz, 2001). In light of its large range of physiological and behavioral functions, oxytocin has also been identified in other tissues, such as the kidney, heart, thymus, and pancreas.

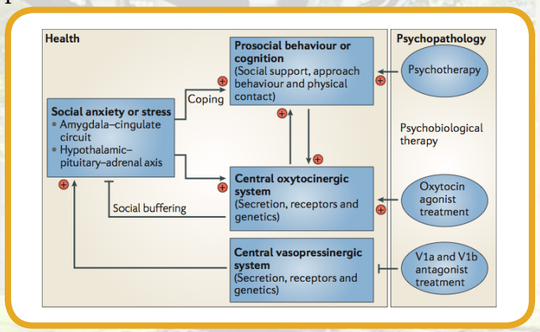

Figure 1. An Interactionist model of the effects of oxytocin on social approach behaviors in human neurophysiology.

Contemporary scientific literature has elucidated the anxiolytic effect of oxytocin. One study demonstrated that healthy male subjects who received a single dose of oxytocin in preparation for the Trier Social Stress Test (an assessment that investigates the psychobiological stress responses in a laboratory setting) manifested the lowest cortisol level. In contrast, subjects who received the placebo exhibited the highest cortisol level (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). Therefore, the subjects receiving oxytocin demonstrated reduced levels of social anxiety and higher levels of composure. On the same token, one particular study indicated that exogenous oxytocin augmented constructive communication pathways between men and women during a couple conflict. Their plasma cortisol levels were significantly diminished as a consequence (Meyer-Lindenberg et al., 2011). The results indicate oxytocin's capability of acting as a social buffer against stress responses. Compounded to the oxytocin-modulated cognitive and behavioral effects, the discovery that neuropeptide oxytocin can be non-invasively transported to the brain in the form of a nasal spray implicates its clinical relevance as a potential therapeutic intervention for psychiatric impairments. Autism Spectrum Disorders (ASD) is an archetypal impairment of social cognitive skills. Studies have shown that intranasal oxytocin helps individuals with ASD develop emotional recognition through extending the patients' gazing time in a computer-simulated game (Meyer-Lindenberg et al., 2011).

Yet, in spite of these apparently promising findings, Carsten De Dreu--professor of Psychology and Behavioral Economics at the University of Amsterdam--conducted a study on two hundred and eighty healthy male participants in order to explore the association between in-group affiliative behaviors and out-group spiteful demeanors, which are triggered by the self-administration of exogenous oxytocin. In all experiments, the determination of out-groups was founded upon the deliberation of international relations. Specifically, due to the heightened ethnic tension between the Dutch and Muslim communities, the two out-groups were the Arabs and the Germans. The research presented astonishing results: human subjects who received intranasal oxytocin projected prejudice and animosity towards the out-group members. Most notably, although oxytocin is conducive to the development of trust and compassion, its effects are limited to individuals belonging to a certain in-group (De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011). Thus, it can be perceived that the administration of oxytocin establishes intergroup bias and therefore ethnocentric and aversive emotions towards people who are excluded from their belonged groups. These paradoxical findings raise an important question: Does oxytocin really live up to the hype of being the universal elixir of social bonding?

Humans forge complex social bonds and intricate social interactions. The discrepant effects of oxytocin can be reconciled from a social behavioral perspective. The orbitofrontal cortex is essential to promoting behavior in response to reward processing (Moorman & Aston-jones, 2014). This

"..the administration of oxytocin establishes intergroup bias and therefore ethnocentric and aversive emotions towards people who are excluded from their belonged groups."

cognitive mechanism physiologically mediates when and how to release oxytocin in a context-sensitive fashion with respect to the interpretation of social information. Therefore, more layers have been added to the concept of altruism as observed in human social behavior. For instance, the anxiolytic effects of oxytocin may significantly decrease one's flight response when faced with a menace. Consequently, people who received exogenous oxytocin are less likely to shun away from threat and more inclined to engage in aggressive behaviors. Additionally, humans are tribal by instinct; the propensity to form bonds with members of the "in-group" and to express aversion towards those in the "out-group" is characteristic of human nature. Thus, in an effort to activate reward mechanisms involved in establishing partner recognition, humans may adopt preemptive strikes towards out-group members as a first-line response of social defense.

"Additionally, humans are tribal by instinct; the propensity to form bonds with members of the "in-group" and to express aversion towards those in the "out-group" is characteristic of human nature."

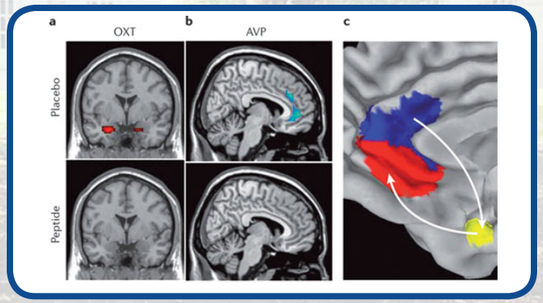

Figure 2. Intranasal OT influences the amygdala–cingulate circuit (right panel). Acute intranasal oxytocin administration exerts modulatory effects in healthy male subjects during the processing of unpleasant scenes. Under the placebo condition, the fear-inducing visual stimulus is activated (shown in red) in the amygdala. The amygdala-cingulate circuit is diagrammed on the right as the color yellow denotes the amygdala while the red exhibits areas of the cingulate that showed positive functional connectivity and the blue color exhibits areas of the cingulate that showed negative functional connectivity.

The idea of oxytocin-mediated responses as a function of the environment creates a unique paradox within the scientific community as we search for more definitive boundaries between the "in-groups" and "out-groups" that we observe in nature. The interpretation of "in-groups" and "out-groups" is very fluid, as people can classify the dichotomy based on ethnicity, culture, religion, sexuality, etc. The notion that oxytocin invariably facilitates in-group social bonding has dominated scientific literature up-to-date. However, characterizing oxytocin as the universal "love drug" or as "social glue" may be deceiving. The effect of oxytocin on promoting human prosocial behavior is discriminating and selective. Nevertheless, some of the nuanced effects of oxytocin remain ambiguous; more research is needed to address whether or not intergroup competition will dissipate when there is a higher-order, prevailing social group.

Images:

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What's Eating You, Europe? Dietary Vitamin B9 Deficiencies

Authored by: Zachary Charif
Edited by: Yash Patel **Reviewed by: Dr. Ben Langmead**

For a few decades, the epidemiology community has been aware that folic acid, a B vitamin, is responsible for the proper neural tube growth of unborn fetuses. This B vitamin is necessary for many processes, and in the early stages of pregnancy, folates to promote the growth of the neural tube and fluids. Lack of sufficient prenatal neural tube growth leads to a variety of disorders, predominantly spinal bifida and anencephaly. These disorders are related to insufficient spinal fluid production in the early stages of pregnancy (Obeid, et al., 2015). When the spinal column does not exert enough force towards the developing brain, the column may collapse and pull down the skull with it, causing major disruptions in neurological development at other stages in pregnancy. These disruptions are often crippling to many life functions. As a result, infants born with these neural tube disorders often are stillborn; survivors typically have similarly dark prognoses.

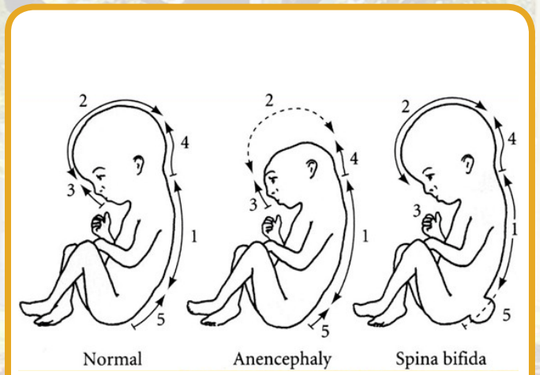

Figure 1. Diagram comparisons between a normal newborn's physiology and physiologies of newborns with anencephaly and spina bifida. (Institute for Computation Biomedicine, Weill Cornell Medical College, 2014)

Without proper prevention, these disorders are not uncommon, affecting about 1 per 1000 births in southern areas of China (Berry, et al., 1999), and somewhat similar numbers elsewhere, including America (Bol, Collins, & Kirby, 2006). Note that these statistics represent numbers before mandatory folic acid supplement programs were implemented in these countries; numbers have greatly improved since then. Admittedly, none of these studies were intervention studies, as withholding necessary dietary supplements from pregnant women is dubiously unethical, but these studies effectively demonstrate the prevalence of neural tube disorders (NTDs) without some supplementation program. Currently, the United States mandate folic acid fortification in cereals and other processed grain products, and China provides compulsory folic acid pills after marriage registrations (Berry, et al., 1999). Accordingly, incidences of these disorders have dropped in these countries.

At the Center for Disease Control in Atlanta, next to Emory University, a recent examination of European birth data has demonstrated a serious lack of improvement of NTD prevalence rates in the last two decades. This has been correlated to a lack of mandatory folic acid fortification programs in the European continent, where female blood levels average at only 50% of folate levels recommended by the World Health Organization (Obeid, et al., 2015). Without programs to provide more folic acid to the general population, Europeans simply lack folates. This may be surprising to hear for some, as European

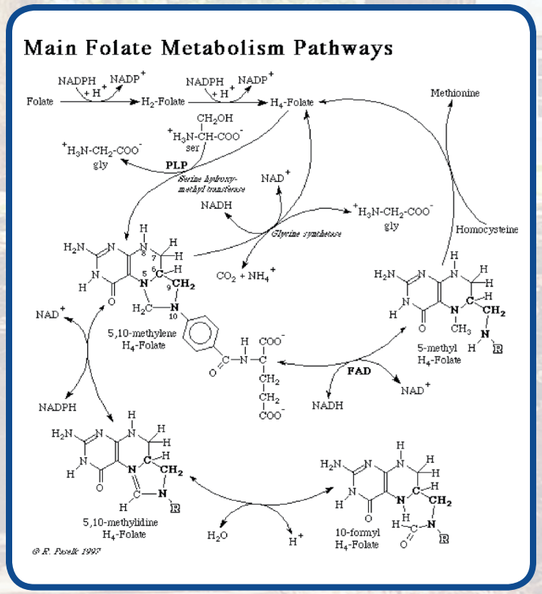

Figure 2. Diagram demonstrating one of many complicated mechanisms involved in utilizing folates in the body.

diets are often portrayed as well balanced. But the processes involved in the metabolism of folic acid explain this fundamental European malnutrition.

The B9 vitamin represents one of a few cases where the synthetic form, called folic acid, is more biologically available than the natural form, called folates. Folates are found naturally in green vegetables and are somewhat unstable polymers that are hard to digest. Digesting folate polymers is an inefficient process involving breaking down long chains to make individual folate monoglutamate molecules, which are bioavailable. Furthermore, folates are easily corrupted by heat, and thus cooking vegetables can destroy up to 40% of stored folates. As such, it is common for people to overestimate how much nutrition their diet is actually providing them. Congenital problems with folate absorption are also not unheard of. In contrast, folic acid is directly absorbed into the bloodstream and converted by the liver into usable forms by relatively simple steps. As such, folic acid is absorbed two-fold better than folates, despite its unnatural origin (Milman, 2012). As a result, despite dietary modifications, folate deficiencies are common without folic acid supplements.

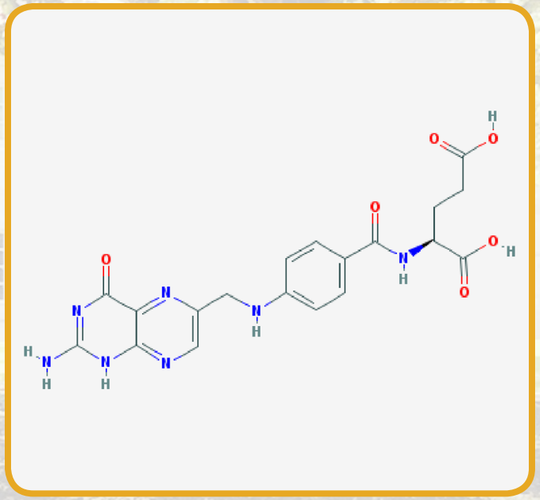

Figure 3. The folic acid molecule requires a couple of reduction steps to become usable as the B9 vitamin.

As such, the European problem is quite understandable; humans process natural folates inefficiently, so the lack of mandatory folic acid supplement programs contributes to the persistent folate deficiency in the European population. And as mentioned before, there is a strong correlation between folate deficiency in pregnant women and NTDs development in prenatal fetuses.

The costs of failing to create mandatory supplementary folic acid programs are incredible. The most visible result is that incidences of NTDs in Europe has not changed in the last few decades. Statistics vary, but the Obeid study estimate rates at 8.16 per 10,000 births, while another suggest 9.17 per 10,000 births. In comparison, modern folic acid supplement programs have been suggested to have halved NTD rates in non-European countries (Bol, Collins, & Kirby, 2006). The Obeid study also analyzed the economic side to NTD prevalence in particularly the European economic powerhouse of Germany. The estimates suggest that the halving of NTD rates correlated to folic acid supplementation could have prevented 293 spina bifida cases in Germany in 2009. This is a non-trivial number of cases. While the numbers are small, each infant born with spina bifida represents a heavy cost to the German state. The estimated medical cost for saving the live births, assuming the same 50% reduction in cases, was €32.9 million in 2009 (Obeid, et al., 2015). This does not include the lifetime costs of raising these typically mentally impaired children, which represents both an immeasurably heavy financial and social burden for European families. And finally, this does not begin to describe the damaging effects of all NTDs in general throughout Europe, which also includes anencephaly and other disorders.

These statistics aren't here just to say that Europe is somehow ignorant of these terrible facts. European governments indeed recommend folic acid supplement pills to the general population for potentially pregnant women (Oakley, Erickson, James, Mulinare, & Cordero, 1994). The problem is that these programs are entirely voluntary. Unlike the Chinese supplement pill program, the European program lacks both a timeframe and enforcement on these plans. The problem with preventing NTDs is that neural tube development occurs during the first few weeks of pregnancy, often a time when the woman may not be sure if she is pregnant. As such, it is often hard to gauge when it is necessary to start taking folic acid. To counteract this problem, the Chinese folic acid pill supplement program begins at certification of marriage though, which typically precedes the time when firstborns are conceived (Berry, et al., 1999). This program solves the issue by ordering a mandatory timeframe to begin taking folic acid supplements. Clearly, there is a problem of compliance without a mandatory program in place. As such, Europe does recognize a need for folic acid in the diet, but lacks any enforced policies to change the problem.

But what is the true European problem that prevents decisive action? This is where speculation and popular opinion by pundits tends to overrun the reach of the facts. Some opinions are floating between epidemiologists and social scientists in the world. A few suggest that the European phobia of unnatural products causes backlash against even European studies and institutions that recommend

folic acid supplement initiatives. Some believe that government fears of potential side effects of folic acid prevents European action on the matter. However, it would seem the matter is more complicated than these popular portrayals of a diverse continent would suggest. This idea is also only an opinion, but the facts suggest that the problem isn't as simple as fear of drugs. Firstly, Europe is many times more lenient in legalizing pharmaceutical products than America, even though America has long implemented a folic acid fortification program in processed grains. The European Medical Agency typically releases drugs after four years of trials, while many drugs wait nearly a decade to pass the FDA's iron laws in America. It is admittedly true that Europe perhaps is shaken by past mistakes made by the Agency, but the problem really should not be fears of drugs in general or particularly these imagined side effects, which seem to be provably nonexistent (Obeid, et al., 2015). And the quick enactment of these folic acid supplement programs in other countries indicate the problem is neither cost nor implementation. Rather, perhaps the problem is related to the size and diversity of a continent that may not be willing to change everyone's lives to save a few. Perhaps individual countries are ready, but somehow unsure about being the first country to try the supplement program. Perhaps other issues are currently shunting out conversation over the matter. Perhaps it's a matter of not enough people caring in Europe to incentivize politicians to act against NTDs. Again, these are strictly opinions, but the European NTD problem is very real and costly, and Europe can't afford to wait on these kinds of issues any further.

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Don't Judge a Monkey by Its Brain Size

Reviewed by: Dr. Aaron Stutz

Authored by: Rohan Yarlagadda

Edited by: Alec Shannon

Which came first, the chicken or the egg? As interesting a conundrum as that is, a more compelling one is found in this paradigm: which came first in primates, bigger brains or more complex ones? Scientists and anthropologists said that modern human brains are three times the size of those of our ancestors. As a result of the brain's expansion, there was a large number of untethered areas of the brain which could now be used to carry out various functions. Solving this conundrum requires us to trace evolutionary roots to determine where complexity and size began to differ. This would lucidify the relationship, if any, between the brain size and its complexity, and it would allow us to understand whether the relationship between brain size and brain complexity changed or remained constant over time. Furthermore, it would clarify whether or not there would be any evidence to support either argument. This would not only solve this universal question, but would also allow us to better understand how evolution played a role in influencing brain complexity and function.

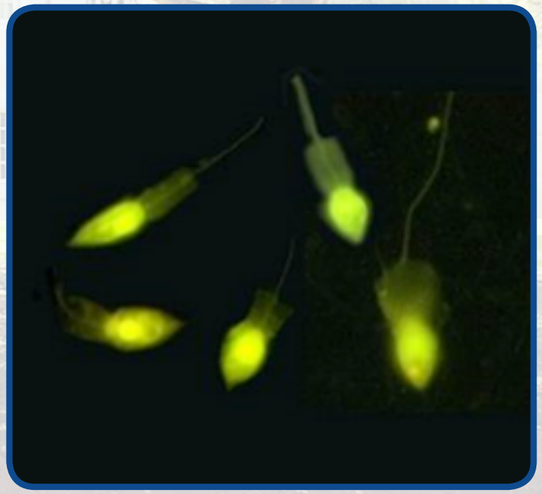

Figure 1: Choanoflagellates, in which first signs of electrical and chemical signal transmission occured.

The very first signs of electrical and chemical signal transmission occurred in single-celled organisms known as choanoflagellates (Robson, D., 2011)(Figure 1). Over time, cells began to specialize, directing their purpose towards the transmission and detection of various chemicals. There were times when the transmissions were required to travel faster to reach their target organ – and that is when gaps started to appear in biology and synaptic transmission began. Thus, the nervous system was formed. The nervous system began to vary between organisms, and soon these variations brought about its evolution in numerous organisms. The nervous system had grown to carry out a number of tasks, and from generation to generation, it gradually became more complex. Eventually, the first brain was born as specialized neurons began to group together (Robson, D., 2011).

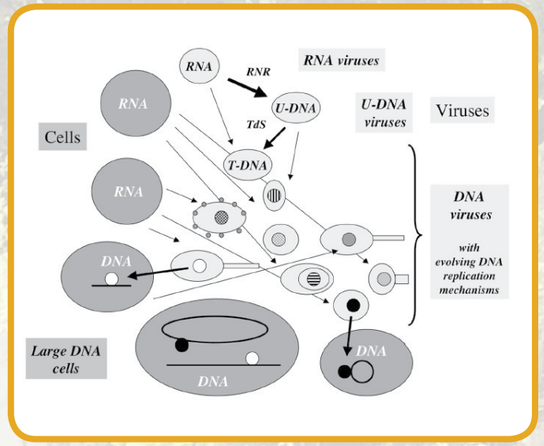

Figure 2: A map showing the evolution of replication mechanisms and cells and subsequent changes in DNA

Five hundred million years ago, the entire genome became replicated, not once, but twice. It is believed that this replication was initiated by the replication of DNA that first occurred in viruses (Forterre, P et al., 2004) (Figure 2).This replication of the genome allowed for a greater number of genes to be present which could grow, develop and specialize differently. Consequently, this allowed for new functions to be made possible. As the brain began to grow in size, the number of genes proliferated and began to develop in unique ways. This growth in turn resulted in a brain that could carry out a number of various functions. Although there is a significant amount of uncertainty surrounding this, the very first brain, or brain-like structure, is believed to be found in a creature that resembled a worm, known as the urbilaterian (Bailly, X, 2013). The urbilaterian is the ancestor of not only the worm, but also several other organisms including

vertebrates, mollusks and insects (Sprecher, S., 2009). Early brains were comparatively simplistic, being mere collections of ganglia bundled together. Similar brain structures can be found today in certain animals including worms, insects and snails.

As time progressed, the size of the brain in animals became larger and the intelligence of the respective creatures began to increase. Within the scientific community, the correlation between intelligence and larger brain size emerged from the observation that increased brain volume preceded growth in intelligence (Skottke, K., 2005). This growth in intelligence is measured through the examination of the brain sections, with larger brain sections with a large number of neurons implying greater specialization, function, and intelligence. An example of this is that brains with a larger cerebral cortex are better able to deal with the challenges of expanded workload than those with a smaller cerebral cortex (Skottke, K., 2005) . It is also important to consider natural selection in these cases (Skottke, K., 2005)- those organisms with larger brains were generally able to perform a greater number of functions, which in turn encouraged natural selection's favorability of them. In other words, those organisms with larger brains could carry out a greater number of tasks that enhanced their chances of survival, and in turn the continuation through reproduction. The number of organisms with the smaller and less able brains would therefore reduce in number, until the majority, if not

Figure 3: Reconstructed Victoriapithecus skull using 3D imaging, led to discovery of larger olfactory bulb.

all, of the organisms carry the genes for larger brains. For a long time, it was believed that an increase in brain volume would accommodate a greater number of neurons that could specialize and develop more complex functionality. Anthropologists argued that the increased diversity in brain function would lead to an overall increase in the complexity of the brain. In a nutshell, the increase in the brain size led to an increase in the complexity of the brain. Or did it?

"In a nutshell, the increase in the brain size led to an increase in the complexity of the brain. Or did it?"

Discovered in 1997 on Maboko Island in Lake Victoria, the fossilized skull of an Old World Monkey named Victoriapithecus (Benefit, B.R., 1997) has since been vital to the study of brain evolution in primates. Researchers from Duke University and the Max Planck Institute for Evolutionary Anthropology conducted research on the 15 million year old skull when they came across a startling discovery: although the skull was approximately half the size of a modern monkey's brain, there were a significantly greater number of folds, suggesting greater complexity (Gonzales, L, 2015). This discovery prompted researchers to conduct further investigations into this matter, which revealed that the olfactory bulb was three times larger than expected. This discovery prompted researchers to conclude that Victoriapithecus had a far superior sense of smell than modern-day monkeys. Studies on modern-day higher primates reveal that their brains, while remarkably larger than those of the Old World Monkeys, feature a significantly smaller olfactory bulb. Lauren Gonzales of Duke University hypothesized that the olfactory bulb reduced in size as the vision of the primates began to grow and improve significantly. "But instead of a tradeoff between smell and sight," Gonzales says, "Victoriapithecus might have retained both capabilities." (Gonzales, L, 2015).

"Studies on modern-day higher primates reveal that they have brains, which are remarkably larger than those of the Old World Monkeys, with a significantly smaller olfactory bulb."

This is not the only possible evidence for the idea of independent development of brain size and complexity. Another possible case that could be evidence is the 18,000-year-old skull, which belongs to a human ancestor, that was found in 2003 on the Indonesian island of Flores (Wayman, E., 2012). This skull belonged to a species of humans known as Homo floresiensis. It is currently not fully known whether or not this specific human ancestor had used stone tools for hunting and feeding, and although certain evidence suggests the possibility that this human ancestor may also have used fire. What was significant about this particular skull was the size of its brain: it was incredibly small. The inverse nature of the brain size and the intelligence of the Homo floresiensis caught the attention of many researchers due to its counterintuitive nature: a smaller brain should imply a less complex one, and thus its owner should carry out more simplistics tasks. If this was proven to be true, this would be consistent with the Graciel australopithecines and Homo habilis, which were using tools and hunting large animals over two million years ago in Africa. This would be further proof that the organization of the internal brain is of far greater significance than is its size.

Figure 4: The skull of a human ancestor, Homo floresiensis, under research.

As researchers continue to explore the relationship between brain size and complexity, more is unravelled about the evolution of the brain. This recent discovery between the independent development of the brain's size and growth only goes on to show that the brain remains a mystery. Scientists, with only minimal evidence, previously believed that the brain could only get increasingly complex as its size increased. However, the research conducted on the brain of the Victoriapithecus reveals something entirely different: an answer that goes against what a number of anthropologists believed. It introduced the idea that the brain's size and its complexity could develop independently, an idea that few anthropologists previously entertained. This of course raises many more questions: does the increasing complexity of the brain cause it to grow in size, to accommodate the growing complexity? What prompts this increased growth in complexity? Is there a limit to the increase in the brain's complexity? Does the size of the brain even matter? For now, we can only safely conclude that the brain remains a simple complexity. We know so much about it, and yet, there is still so much left to learn.

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