LAByrinth

2022

The Science Journal of Manhattan High School for Girls

Artwork by Michali Rosenberg

LABYRINTH[2022]

The Science Journal of Manhattan High School for Girls

We are pleased to grant this year's

HARRY KAPLAN SCHOLARSHIP AWARD FOR EXCELLENCE IN SCIENCE WRITING

TENTH GRADE AWARDEE

Naama BenAmi

for her essay

Lou Gehrig Would Smile

NINTH GRADE AWARDEE

Devorah Pluchenik

for her essay

Can You Hear Me Now?

We gratefully acknowledge Dr. Tuckel and her family for their generous sponsorship.

LABYRINTH[2022]: Foreword

Brenda From, Editor

The ambition of every educator is to instill in her students an appreciation for independent inquiry and to imbue them with the tools to accomplish this task.

The ambition of every educator is to instill in her students an appreciation for independent inquiry and to imbue them with the tools to accomplish this task. This need is especially acute when it comes to the field of science. Our knowledge of science is expanding at an exponential rate, and we are charged with the responsibility of empowering our students with the skills necessary to critically evaluate, assimilate and communicate to the broader audience what is assuredly coming down the pike. Decisions that they make will impact the future course of progress for generations to come. For the science faculty at Manhattan High School, this goal, while most commendable and worthy, is insufficient. We want to go beyond and instill in our students a sense of wonder and marvel, to engage viscerally with the "wonder"ful and "marvel"ous. That is the purpose of this year-long project and judging by the finished product, I feel a sense of achievement.

The cover, painted by Michali Rosenberg in Ms. Serene Klapper's art class, was deliberately chosen to illustrate this point. Albert Einstein wrote of the lasting impression a compass made upon him at the age of four or five, "Something deeply hidden had to be behind things." With science offering more and more explanations of natural phenomena, it may appear to the simple minded that Hashem's role is shrinking. The rain is a perfect example. It was once thought that rain is brought by forces beyond our comprehension. In our hubris, we now think the entire hydrologic cycle is illuminated–until it is not. We retreat from the unreliable security of the laboratory and find succor and shelter in the dependable halls of our *batei medrash*. When we are inevitably confronted with the inexplicable we turn to the ineffable. Does that make filling the gaps the only role we can assign to Hashem? On the contrary, we should find Hashem in what we do know; not in the unsolved problems but in the ones that are solved. The challenge of modernity is to make room for wonder and marvel; to be deeply cognizant that we are in the presence of something extraordinary; to dig for the deeply hidden behind all things; to thank Hashem for the miracle of rain.[1]

אָמַר רַבִּי חָמָא בְּרַבִּי חֲנִינָא: גָּדוֹל יוֹם הַגְּשָׁמִים כְּיוֹם שֶׁנִּבְרְאוּ שָׁמַיִם וָאָרֶץ. (תענית ז, ב)

This issue of LAByrinth is the most ambitious to date and includes contributions from every grade at Manhattan High School. The smorgasbord of topics is diverse and there is something to tempt and satisfy every palate. If you have a hankering for artificial intelligence, atomic/nuclear structure, biotechnology, ecology, ethics, immunology, mind-computer interfaces, molecular biology, music, neuroscience, space, or time travel, you have come to the right place. Pull up a chair and get comfortable. Where there were overlaps and recurrent themes between the papers, I inserted crosslink alerts. One of the beauties and excitement of science is that the disciplines are not clearly demarcated and compartmentalized, but knitted together in a complex glorious tapestry of scholarship.

[1] Adapted from: Brown, J. *"Rain and the God of the Gaps."* Talmudology, 14/11/2021. https://www.talmudology.com/jeremybrownmdgmailcom/2021/11/12/taanit-2-rain-and-the-god-of-the-gaps

I was tasked with the agonizing job of choosing from a plethora of quality submissions to include for publication. Some of the criteria I applied were: Was it well written? Was it well researched? Was it clearly explained? Was it interesting? Did it challenge me and force me to revisit what I thought I already knew? Did it expand my repertoire of science knowledge? Did it quench the thirst for the deep joy of illumination that science provides? Did it display sensitivity to and sensibility of our heritage? Most of all, did it brim with passion for the topic with the ferocious intensity of a dog on a bone? And then there were my own personal idiosyncrasies–the indefinable *je ne sais quoi* quality of "When you see it, you know it." Admittedly, a tall order challenge to which twenty nine of our students admirably rose. I bear sole responsibility for the choices and any disappointment caused by omission.

A project of this dimension is the result of the collaboration of many, and each is due separate acknowledgment and appreciation. Firstly, my right hand partner in crime, Mrs. Sheila Minis. Hailing from the Weizmann, starting from the first day she joined our staff, she made herself an invaluable integral member of the faculty. It is no easy feat teaching biology to close to 60 freshmen students, hailing from different grade schools, with varying science backgrounds, and to unify them, herd them together and usher them towards advanced science study; yet she succeeded masterfully and with gracious aplomb. I know I can dependably lean on her, and her suggestions and sage advice are always on target. *Todah Rabbah* and *Kol HaKavod*.

I owe a debt of thanks to the lifeblood of our school, the dynamic duo whose inspiring vision gives form and function to our institution, Mrs. Tsivia Yanofsky, Menaheles and Mrs. Estee Friedman-Stefansky, Principal General Studies. Your stalwart leadership is worthy of emulation. Your commitment to excellence brings out the best in our students and allows the faculty to shine. Mrs. Friedman-Stefansky invested great effort into this publication to ensure its standard of excellence is second to none. Rabbi Prager, our *Moreh D'Asra*, meticulously reviewed all submissions to ensure that they displayed appropriate accuracy, sensitivity and sensibility to our *mesorah*. To Mrs. Dena Szpilzinger, our resident wizard in all things technology, your panache endowed a polished look of sophistication and style, the icing on the cake. To Zehava Sanders, our resident helpdesk, thank you for meticulous proofreading and ensuring that everything sparkles.

Lastly, and most importantly, thank you to all my students, who patiently bore with me through all my demands for clarification and suggestions for revision. You have surpassed my expectations and I am awed by your enthusiasm. I am enriched by learning alongside you and from you. I am humbled to call myself your teacher; more accurately, you are mine. Pirkei Avot 4:1 *"MiKol M'Lamdei Hiskalti."*

Acknowledgements

Mrs. Estee Friedman-Stefansky, Principal, General Studies

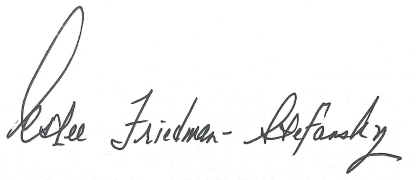
Dear readers,

On behalf of Mrs. Yanofsky, myself and our entire school community, this year's academic science journal is dedicated to Mrs. Brenda From, our esteemed Science Chair. This year, we have an unprecedented high registration in both the AP Biology and AP Chemistry elective courses, a testimony to Mrs. From's ability to share her scholarship with remarkable clarity.

Mrs. From continues to strengthen our appreciation for Hashem and His masterful world, and to fill our schoolhouse with excellent learning.

We are so proud of Naama Ben Ami and Devorah Pluchenik for presenting their wonderful science research in beautiful written form.

With warm wishes for a delightful summer,



Lou Gehrig Would Smile

Naama Ben Ami

Now, imagine a world where organs, such as brains, can be cultivated and grown in a petri dish like plants on a farm. No need to wait for an exact match organ donor for a life-saving transplant.

David (name changed to protect privacy) was diagnosed at the young age of 45 with amyotrophic lateral sclerosis (ALS), a neurodegenerative disease that attacks the brain and nervous system. ALS is more commonly known as Lou Gehrig's Disease. The diagnosis brought his passion for world travel to a screeching halt. Loss of movement occurred in stages. First came muscle weakness, which caused cramping and twitching. Months passed, and David started feeling physical pain in his unused muscles. Then the muscle started to become rigid, and the deformation of the joints became visible, causing difficulty in standing and walking. David lost his voluntary muscle movement, such as chewing, walking, talking, and even breathing. The last phase is accompanied by 90% of muscle paralysis. Sadly, this means that any needed nutrients must be received from a feeding tube and oxygen via requisite ventilator. Most patients will die at this stage (Lancastre). There is no cure and medical options are limited. David needs a miracle. *(See Eberstark in this publication)*

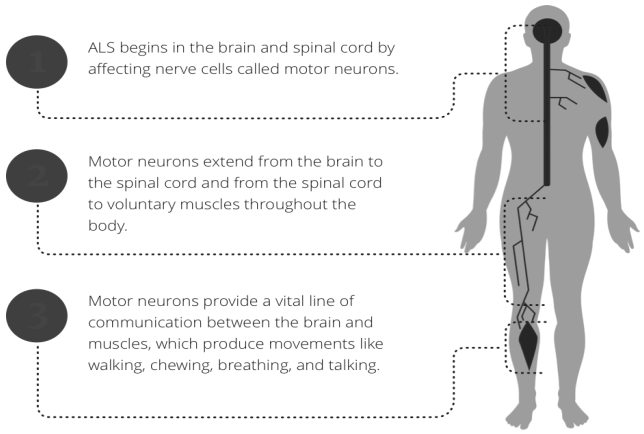


Figure 1: Effect of ALS on the nervous system.

Now, imagine a world where organs, such as brains, can be cultivated and grown in a petri dish like plants on a farm. No need to wait for an exact match organ donor for a life-saving transplant. It sounds incredible, but scientists have made major breakthroughs in the last decade to bring that closer to reality. These miraculous organs are called organoids. Organoids are currently being used primarily to study how cells communicate and interact together, to examine and study organ development, and to use them to test drugs. Organoids are an invaluable tool of medical research and experiments.

To understand how organoids are formed, one must first understand stem cells because organoids start out as cultures of stem cells. Stem cells are unspecialized cells that can renew themselves and/or differentiate into any specialized cell. There are three types of stem cells: Embryonic stem cells, adult stem cells, and induced pluripotent stem cells.

Embryonic stem cells are found in human embryos and are the source of all the embryo's future cells which will eventually develop into a fully formed infant. The remarkable thing about embryonic stem cells is that they can specialize into any type of cell of the body. Embryonic stem cells are used in medicine and therapeutics as replacements for diseased body cells. Embryonic stem cells grown in vitro (in culture) are injected, implanted, and transplanted into a patient to repair mutated diseased cells by manipulating the stem cell to develop into the specific type of cell needed (Zakrzewski).

Embryonic stem cells are incredible, but there is an ethical issue when utilizing these cells for research that limits their use. Harvesting these stem cells leads to the destruction of an embryo and a possible future human life. In 2001 US congress issued a ban on federal funding for embryonic stem cells research. President Bush later changed the ban by only allowing work within existing lines. The need for human embryonic cells is acute because they demonstrate most accurately how human cells behave. However, IVF (In Vitro Fertilization) clinics argue that these embryos would most likely be discarded anyway but using embryonic stem cells will significantly benefit mankind and give the destruction of these embryos a purpose. The Declaration of Helsinki, The Nuremberg Code, and The United Nations of Declaration say that the interest and concern of the subject must come first before science. In the case of embryos in stem cell research, the embryos would be destroyed without any benefit for research, an even more immoral alternative (Thomas).

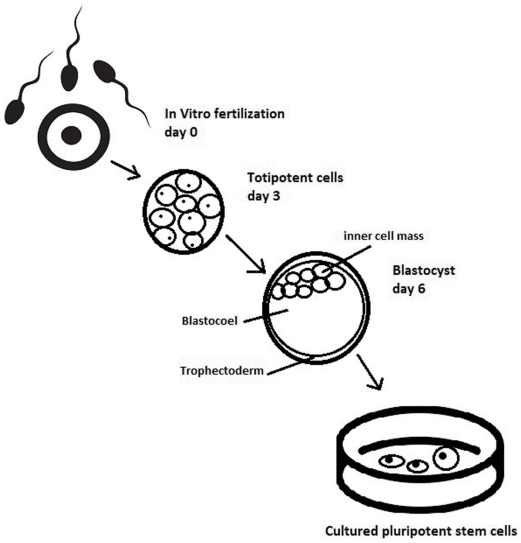


Figure 2: Culturing of stem cells in vitro. After three days from fertilization, the totipotent cells are formed. At day 6 the stem cells can be transmitted to a dish.

While embryonic stem cell research is seen as ethically compromised, adult stem cells do not raise these concerns. Adult stem cells provide the organ with new cells as it grows and develops and is a source for replacement of damaged cells. Most adult stem cells are found in the bone marrow and other specific organs. Unlike embryonic stem, adult stem cells are multipotent and can only change into tissue specific cells. For example, adult blood stem cells known as hematopoietic will only replace cells in the blood. Due to their ability to replace cells in the bloodstream, adult stem cells have been used in bone marrow transplants. Bone marrow transplants have successfully treated leukemia and other blood or bone cancers (Zakrzewski). Clearly, adult stem cells lack the versatility of embryonic stem cells; fortunately there is an alternative solution.

In a recent feat of cellular engineering, scientists have turned back the clock on adult stem cells, called induced pluripotent stem cells. Induced pluripotent cells are created when scientists take normal cells like blood or skin cells and manipulate and reprogram them into stem cells, giving the cell the ability to develop into any cell of the body like embryonic stem cells. When reprogramming induced pluripotent stem cells, scientists need to switch on the genes that tell the cell to be a stem cell, specifically in the early embryonic stage, and turn off the gene that tells the cell to specialize. The outcome is that scientists are taking adult cells and manipulating them to become embryonic stem cells. Induced pluripotent stem cells are the primary cells used in developing organoids. Induced pluripotent stem cells have a high risk of mutations due to their reprogramming and genetic

instability, increasing the possibility of leading to cancerous tumors. Scientists limit genetic damage by using younger tissue and identifying mutated cells (Zakrzewski).

Adult stem cells are usually extracted from the body and reprogrammed into their early development stage to develop into different cells, cultured and allowed to multiply so they could be used as replacement for damaged tissue. Historically however, they would not self-assemble into structures that functioned together like they do in organs within the body. Another problem with culturing stem cells is that they do not indefinitely survive and multiply in vitro. Apparently, it is a complicated and incompletely understood process. Scientists face the challenge of not knowing the proper nutrients and conditions the cell needs. Stem cells need proteins to reproduce, and the proteins are made from cultures of other cells. Serums and blood extract also provide the cells with nutrients. An early method of culturing stem cells was to place them over a base scaffold layer of mouse fibroblasts bathed in calf serum. Fibroblasts are support cells that secrete collagen proteins used to maintain a structural framework, and also to provide nutrients for other cells. Scientists worried that stem cells cultured with contaminants from animals couldn't be safely implanted in a human—fearing that the cells could carry viruses. This is one reason researchers prefer human embryonic stem cells because they are grown free of animal contaminants.

Cells grown in vitro are grown isolated from similar cells without the support network provided by all the other cells of the tissue (Alden). Scientists are finding that these cells won't thrive under laboratory conditions. Just like it takes a village to raise a child, stem cells need a lot of outside cellular support to encourage them to properly grow. Recently however, scientists have figured out the specific environmental requirements for these stem cells to follow their genetic instructions, communicate with one another and self- organize to develop into three-dimensional living tissue, which is organoids. Organoids can be formed into practically every type of living tissue: gut, stomach, kidney, liver, pancreas, mammary glands, brain, etc. (Hofer).

One specific organoid that has been useful in the medical field is the brain. Brain organoids, sometimes called mini-brains, allowed neurologists to study fatal neurological disorders like dementia, Parkinson's disease, and ALS. Scientists grow model organoids with a specific neurological disease by taking stem cells from a patient suffering from this disease and developing the organoids based on these particular stem cells (University of Cambridge).

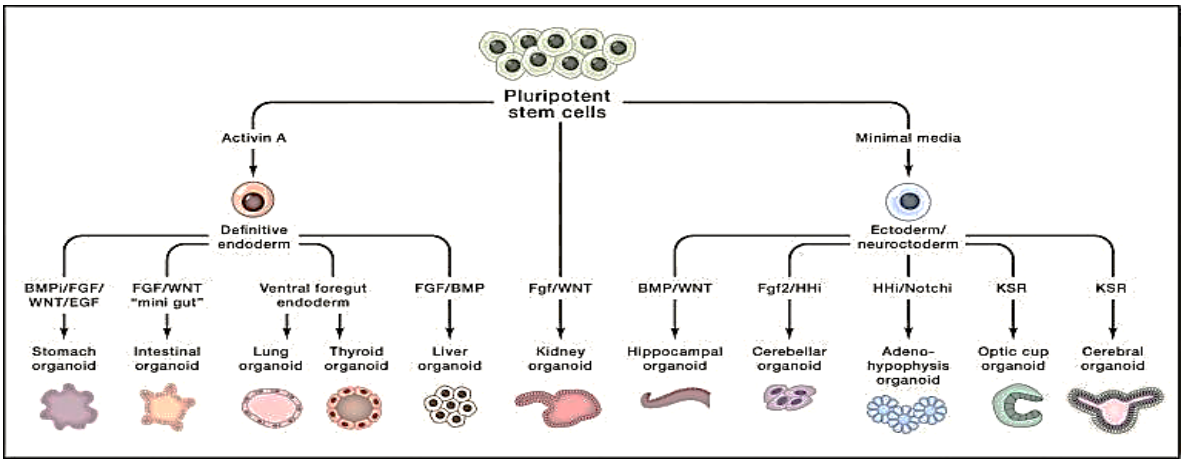


Figure 3: Different types of organoids that can be developed from stem cells.

Growing brain organoids with neurological disease isn't something groundbreaking; scientists were able to do it in the past. The significant part of the new method of organoid cultivation is how long they last. Cambridge reported that they grow organoids that can last up to 240-340 days. Neurological diseases like Dementia, Parkinson's, and ALS usually take time to progress; the long-lasting organoids allow the condition to completely take over the cells and give scientists time to see the effect of the disorder. Dr. Kornélia Szebényi used a technique to grow longer-lasting organoids by growing the stem cells in slice cultures rather than balls of cells. This method ensures that all cells are exposed to the proper nutrition to live longer. Even with this research, the organoids are still not surviving long enough for a complete pathology of these diseases (University of Cambridge).

Scientists have published research that could make it possible for growing long-term organoids in the early stages of ALS/FTD (a type of dementia). To accomplish this, scientists have created an organoid slice model stemming from induced pluripotent stem cells reaped from patients with ALS/FTD containing a mutation called the C9ORF72b (NCBI). By examining the pieces from the organoid slide model, scientists were able to see the outcome of the mutated part of the organoids' DNA when transcription occurs. Usually, DNA repair would fix this problem, but this function too was mutated. Scientists can now use the organoid slice model and test certain drugs to correct the mutation. Scientists also use the model to examine pre-symptomatic ALS/FTD mechanisms. The models allow scientists to study the cellular change in the organoid in the early stages of development. For example, stress on the cell, the damage that may have occurred to the DNA, the modification on how the DNA is transcribed into proteins, have all been demonstrated to negatively influence astroglia, (brain cells that control brain power and muscle movement). Researchers reported that changes in the cells occurred way earlier than expected; it can even arise from when a baby is born. This hypothesis is not hundred percent proven and more research is needed (Szebényi).

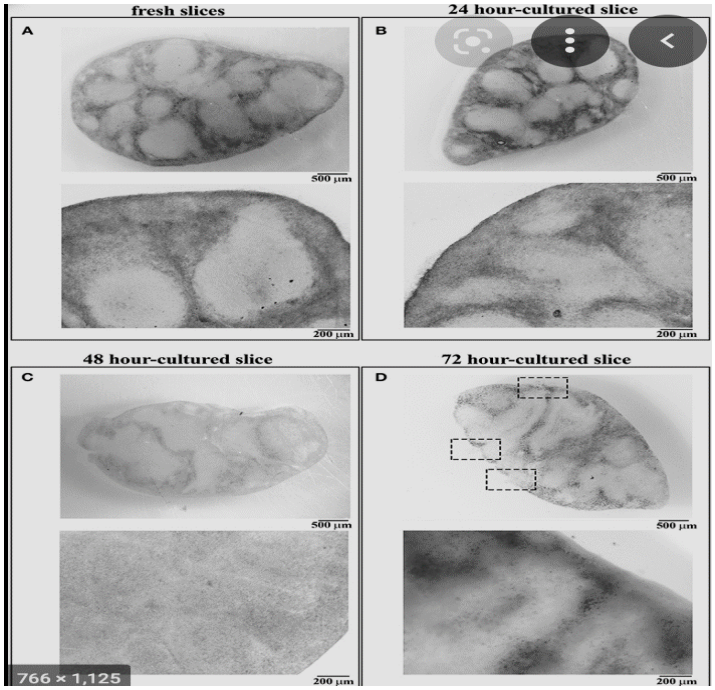


Figure 4: Images of sliced organoids. In box A, the sliced organ is freshly cut and has a pinkish reddish color. In box B, 24 hours passed, and the organoid is starting to lose its coloring. In box D, many hours pass, and the organoid slice completely turns brown, which is not usable for research. The chart indicates how the organ slices decay and how time-sensitive it is to be useful for research.

While organoids are extremely useful for research and understanding the disease, they can also be used to test drugs. The testing can determine which drugs prevent and slow down the progression of a disease. Organoids are more valuable than animal models because animal models don't show identical changes to human models and experimenting with human brains is impossible. Since organoids are derived from actual human brain tissue, they are the closest approximate to a real human brain for experimental testing (Sedivy-Haley). One experiment that scientists conducted was the testing of the drug GSK2606414. GSK2606414 alleviated many cellular problems in ALS/FTD cells like toxic proteins, cell stress, and loss of nerve cells. More suitable medications are currently being tested in clinical trials for neurological diseases where the nervous system stops working (Jiang).

The search for a cure is still in the preliminary stages. There are many important questions that remain unanswered. What is the cause of ALS? Is there a way to prevent it? Why does the disease primarily affect white males? The more scientists study ALS, the closer we come to the answers. Although the answers are still elusive, organoid research brings us one step closer to a cure. A cure for ALS/FTD is imperative because it is one of the most devastating neurological diseases out there. David is currently living on a ventilator and just celebrated his 65th birthday. David's whole life was turned upside down by this disease. He is not just another statistic; David is someone with whom I am personally familiar. I am an eyewitness to his heartbreaking descent into the depths of his imprisonment. David needs a miracle.

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Redheads: Teenage Mutant Superheroes

Mindy Bober

...there is one claim about redheads that does meet the test of scientific rigor. Red hair is the result of a mutation that confers superhero status.

Some say redheads are quick-tempered; others say redheads are wild. They always need to be doing something. They never compromise on anything. There are even those who say that redheads are clownish. It can be argued that all these traits are due to a certain inner fire that matches their outward appearance. In the interest of full disclosure, I must reveal that I am a redhead. All of these are anecdotal stereotypes that have not been subjected to scientific scrutiny, but there is one claim about redheads that does meet the test of scientific rigor. Red hair is the result of a mutation that confers superhero status.

The tale starts with DNA, the acronym for DeoxyRiboNucleic Acid. This molecule, found in all cells, serves as the carrier of genetic instructions for all living organisms. The molecular subunits of DNA are called nucleotides, and it is the sequence of these nucleotides that codes for all cellular processes. All cellular processes are carried out by proteins and other assorted biological molecules; the instructions for assembling amino acids together in proper sequence to make a functional protein are encoded by the sequence of nucleotides of the DNA. This is referred to as the Central Dogma of Molecular Biology (Hartl).

What would happen if the sequence of nucleotides was changed? A mutation is a change in the DNA sequence that leads to a change in the gene product. There are several types of mutations and the one of relevance here is called base substitution. This occurs when one nucleotide base is mistakenly replaced by a different one, causing a different amino acid to be inserted into the protein. These molecular changes in DNA have a significant effect on protein function. A mutation can be a gain of function mutation, in which the gene codes for a new improved protein, or a loss of function mutation, in which the gene can no longer create a functional gene product (Collins).

Red hair is a result of a mutation in the MC1R gene located on chromosome 16. The MC1R gene produces the melanocortin 1 receptor located on the surface of specialized melanin producing cells called melanocytes. The pigment melanin is the reason our eyes, hair, and skin vary in color from person to person. Eumelanin and pheomelanin are two types of melanin produced by melanocytes and the color of hair, eyes, and skin depends on how much of each type is produced. Greater amounts of eumelanin result in darker hair color and likewise greater amounts of pheomelanin result in red hair. Eumelanin is produced when the melanocortin 1 receptor is activated and triggers a series of chemical reactions within melanocytes. However, in the case of the red hair mutation, there's a loss-of-function

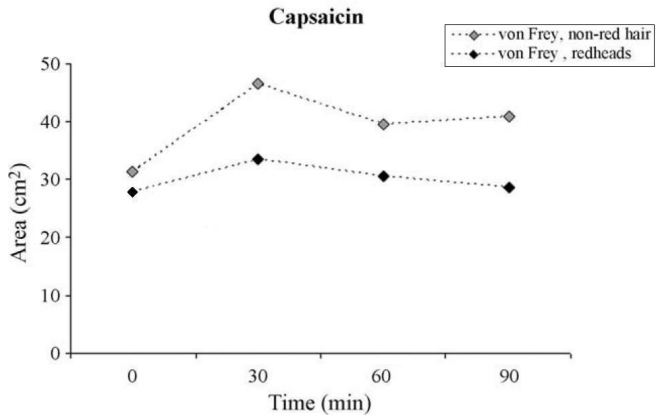

Figure 1

mutation in the MC1R gene. This mutation is the result of several base substitutions, and it creates a mutated receptor that is unable to initiate the series of reactions needed in order to produce eumelanin. Without being able to produce eumelanin, the melanocytes alternatively mostly produce pheomelanin, thereby resulting in red hair color.

The mutation in the MC1R gene causes red hair, but does it have any other effects? Think about all of the commonalities between redheads. For example, did you ever notice how redheads tend to be more resilient to pain? Try punching a redhead and you'll find that they won't even wince and yet when you punch a brunette or blonde with the same force, you will find them complaining about their bruised arm. Is the only result of the loss of function mutation in the MC1R gene red hair or can there also be a positive correlation between the mutation in he MC1R gene and the threshold for pain?

To find the answer, a study was conducted with forty females, twenty of whom had red hair and the other half of whom had either blonde or dark hair. Each individual's arm was marked and topical capsaicin cream derived from chili peppers that creates a burning sensation, was applied to the marked area for thirty minutes. After these thirty minutes, the cream was removed and the hyperalgesic area surrounding the application site was assessed. The hyperalgesic area, an area that overreacts to a stimulus that normally elicits pain, such as a needle, was evaluated by using a von Frey filament, a tool designed to determine pain thresholds by pressing a needle into the skin. The researchers observed the threshold for pain of each individual by how intensely they reacted to the stimulus as they moved the stimulus closer and closer to the application site. As displayed in Figure 1, redheads had a smaller area of hyperalgesia than those with alternate hair colors. A smaller hyperalgesic area indicated that those with red hair had a higher pain tolerance and therefore didn't overreact to the needle until it reached the sensitive area close to the application site. From the results of this study, researchers concluded that those with a mutated MC1R gene experienced lower levels of pain than those with a functional MC1R gene (Andresen).

It appears that redheads have a higher pain tolerance than others, but for WHICH kind of pain do they have a higher tolerance? WHY do they have a higher pain tolerance? And HOW is pain tolerance related to the red-hair gene? To investigate the reason behind redheads' unusually high pain tolerance, Fisher performed experiments on genetically clean mice (genetically identical inbred mice except for the difference in the MC1R gene). This allowed the experimenters to attribute the cause of the difference in pain tolerance solely to the MC1R mutation and no other. To eliminate the possibility of experimenter bias, only albino mice were used. These mice were engineered to be white by blocking the enzyme responsible for the production of melanin. One group of white mice had the MC1R mutation, while the other group had a normal MC1R gene, so even the experimenters could not distinguish between mice that were genetically red and mice that were genetically a different coat color because they all appeared identical white (Fisher).

The albino white mice were assessed in the areas of pressure and temperature. Similar to the capsaicin experiment, the mice were assessed for pressure through the von Frey filament process. At first the mice were first poked on their feet with a strand of hair and then slowly stronger and stronger filaments were used until the mice finally lifted their feet in response to the stimulus. The threshold for pressure was evaluated by observing the thickness of the stimulus needed to elicit a response from the mice. As can be seen in the graph on the left of Figure 2 below, those with a functional MC1R gene reacted to about three grams of pressure while those with a mutated MC1R gene only began to react to the stimulus when it reached over four grams. From this experiment

it was clarified that redheads have a higher pressure threshold. In this same study, it was found that the genetically red-haired mice had a higher threshold to thermal pain. They assessed their response to thermal pain by placing the mice on a hot plate to observe how many seconds it would take until they jumped from the heat. From the graph of Figure 2, it can be seen that it took the mice with the functional MC1R gene approximately twelve seconds until they perceived the heat while it took the mice with the mutated gene an additional four seconds to respond to the heat (Fisher).

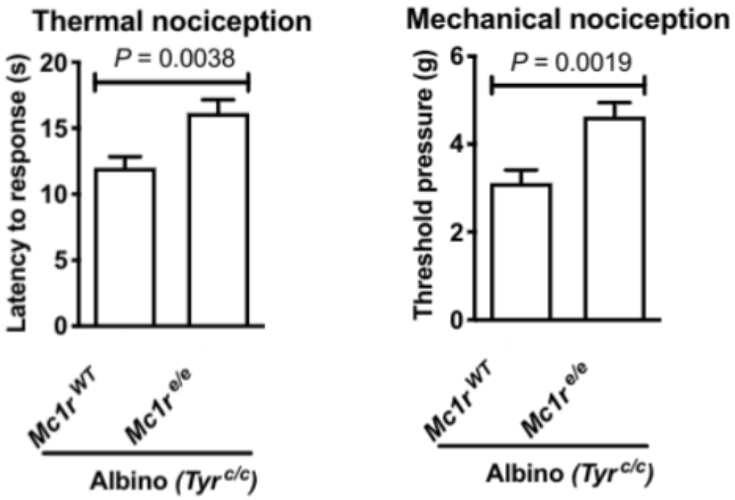

Figure 2

However, there are other studies which concluded that redheads are, in fact, extremely sensitive to both heat and cold (on the graph shown above the difference in heat pain didn't reach statistical significance (Liem). This discrepancy can't be explained and therefore the pressure response will be the sole consideration for the "pain" response for the rest of this paper.

To further understand WHY redheads have a higher pressure pain tolerance than others, scientists discovered that the pigment cells secreted POMC (propiomelanocortin), a polypeptide precursor to several hormones that enhance or block pain by binding to pain receptors, thereby exerting an influence on pain perception and pain sensitivity. Furthermore, they found that there was a statistical difference in POMC concentrations in different colored mice. In the graph of Figure 2, it can be seen that the red-haired mice with the mutated MC1R gene had a concentration of POMC that was less than half of the concentration within the black-haired mice. From this, we can conclude that a mutated MC1R gene results in a lower production of POMC, which can account for the difference in pain perception (Fisher).

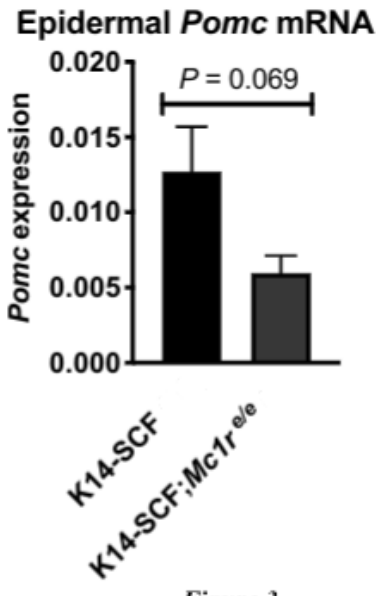

Figure 3

Surprisingly, other studies prove that redheads require more pain medication than others and a 19% greater anesthetic requirement, which seems to contradict their higher pain tolerance. However, a higher pain tolerance doesn't necessarily contradict the fact that redheads require higher doses of medication, since it is possible to be more resilient to pain and yet still need more medication to control the pain once the pain is eventually felt. Science still has not figured out exactly why they require higher doses of medication, but as of now, scientists think that it's related to their differently tuned nervous system pathways, which in some way or another result in altered sensitivity to pain medications (Liem).

All of these findings on the correlation between red hair and pain tolerance provide scientists with a better understanding of how pain can be modulated. This new understanding may provide a novel avenue of exploration to help researchers create new pain relief pharmaceuticals by controlling POMC production. These new pain medications will be created thanks to those angry, crazy, wild, clownish redheads, the superheroes of our story.

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Laughing Through Depression

Leah Borenstein

Imagine you are sitting in the dental chair...and the last thing you feel is some orange plastic nose put over your own. All of a sudden, you are transported to a different world.

Imagine you are sitting in the dental chair, with that bib to collect your spit, and the last thing you feel is some orange plastic nose put over your own. All of a sudden, you are transported to a different world. That is your experience with laughing gas. Scientists think that aside from calming anxiety in children waiting to get treated, this might also work to heal depression.

Depression is a common mental illness, affecting more than 18 million American adults every year *(Mental Health America)*. Depression is markedly different from just feeling moody or temporary sadness. Especially when it recurs with intensity, depression can actually become a serious health condition. It can cause a person to suffer in all areas of life, affecting day to day functioning. In the worst-case scenario, if left untreated, people with depression contemplate suicidal ideation and will even go all the way and commit suicide. It is estimated that almost sixty percent of people who commit suicide have a mood disorder (DCD).

There are effective treatments for depression. One common treatment is ECT (electroconvulsive therapy) which is a stimulation therapy that shocks the brain. The patient goes under general anesthesia and gets small doses of electric current which passes through the electrodes and can produce many seizures *(Mayo Clinic)*. Electrodes are the tips of the wires that administer the electric current to the brain. Scientists are uncertain how the seizures relieve neuropsychiatric symptoms. Another solution for treating depression is antidepressant pharmaceuticals. However, many people are treatment resistant, and they need a better option. There has been much effort recently toward developing new drug treatments for mood disorders. They specifically look for drugs that block NMDA (N-methyl-D-aspartate) receptors, which prevent the neurotransmitters from binding receptor molecules that are found on the surface of neurons. The medication ultimately blocks the NMDA(N-methyl-D-aspartate) receptors from activating reactions from the neurotransmitters.

NMDA receptor is an ion channel, found in the neurons of the brain in the hippocampus and cerebral cortex (which is part of the limbic system that regulates memory, emotion and motivation) (Dutta). The receptors are blocked by magnesium (Mg^{2+}) and require the binding of glutamate and glycine for the ion channel to open efficiently (Yu; Lau). By releasing lots of glutamate into the postsynaptic cell, the pathway to the NMDA channel opens up, causing the magnesium to leave the NMDA receptors and allowing calcium ions into the cell (Dubac). Once calcium (Ca^{2+}) gets into the neuron they trigger the neuron to release the neurotransmitters, which then go and bind to the receptors on the next cell, starting a cycle or chain reaction that needs to take place. It's important that Ca^{2+} gets into the neuron because it triggers the neuron to release the neurotransmitters that need to go to the next neuron. Without Ca^{2+}, no neurotransmitters are released.

NMDA receptors are involved in the pathophysiology of mental diseases like major depression. Ketamine, which blocks NMDA receptors, could act as an antidepressant, even in patients with treatment resistant depression (Adell). See Figure 1 below for an in-depth explanation of how ketamine works. Although this sounds great, ketamine has negative side effects, like high blood pressure *(WebMD)* and psychosis *(Healio)*.

Scientists think they might have found an alternative to help treat depression by means of laughing gas (Nagele) which binds only to non-NMDA receptors (Kalmoe).

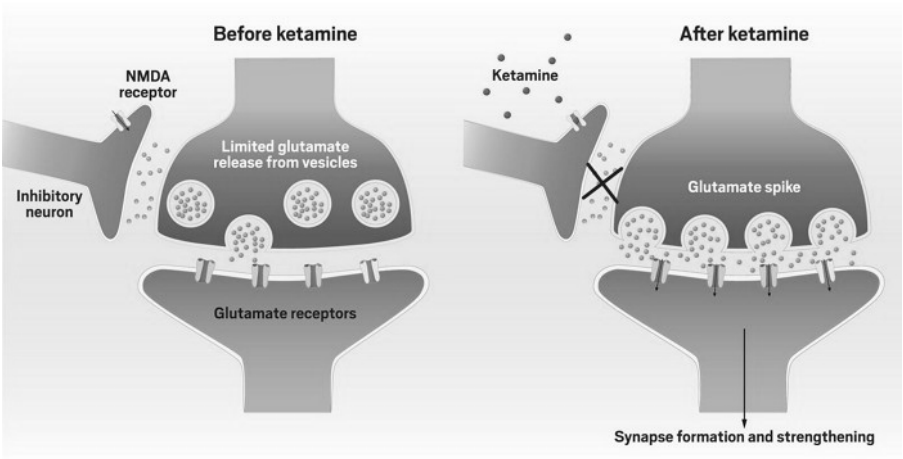
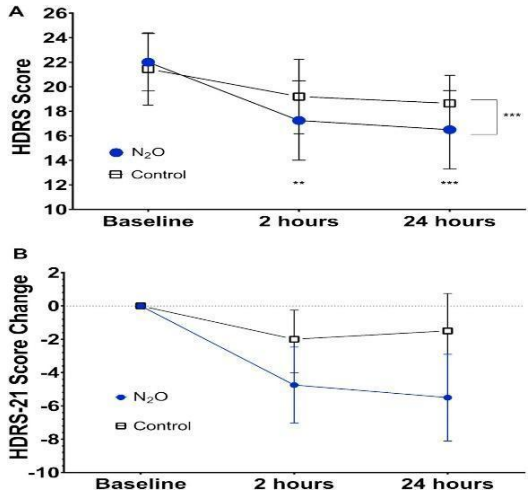


Figure 1 shows the interface between the two neurons, the synaptic cleft. The vesicles fuse with the end of the presynaptic terminal membrane and release the glutamate onto the glutamate receptors of the postsynaptic terminal. Glutamate is a general stimulant of neurons. The first diagram shows how the cells are working before ketamine. The green is the inhibitory neuron which oversees slowing messages down by slowing the release of glutamate. Depression is characterized by slow movement of messages through the nervous system. When the neurotransmitters (balls) are released, they bind to the NMDA receptors which are on the surface of the inhibitory neuron. This makes them less likely to send messages to release glutamate. That's why in the first model there's not a lot of glutamate being brought to the glutamate receptor on the postsynaptic terminal. Glutamate is a neurotransmitter which sends signals throughout the brain and helps regulate mood. Dysregulation of the glutamate plays a part in causing mood disorders. The next diagram we see the ketamine (purple balls), which block the NMDA receptors from slowing down the messages. Therefore, there's a glutamate spike because NMDA is prevented from doing its job. This makes the transmission of messages through the synapse stronger, relieving the depression symptoms. Credit: Yang H. Ku/C&EN and Chemical & Engineering News

Laughing gas, also known as nitrous oxide (N_2O), is known for its calming effect, and gives short mood boosts (Wilson). Laughing gas is a mild sedative that dentists give children at their office to reduce their anxiety. It's great for people who are anxious, have special needs, younger patients who must undergo a big procedure etc. The patient wears a mask that fits over the nose, and inhales the gas mixed with oxygen. It makes them feel tingly and lightheaded. Some people feel heaviness in their arms or legs. It's safe and wears off quickly. After the gas is turned off, the dentist will let pure oxygen be inhaled for a few minutes, so you don't feel dizzy or get headaches etc.

Experiments with the laughing gas were conducted to see if laughing gas could relieve depression symptoms. Twenty patients exhibiting symptoms of depression were administered 50% N_2O for an hour. Patients were measured before treatment, two hours after treatment, and twenty-four hours after treatment using the Hamilton Depression Rating Scale, where patients answered questions on their symptoms (Nagele).



This is a graph of data showing the results of the HDRS-21 depression test, patients used to rate their symptoms after being treated with nitrous oxide. The control (placebo) who had not been given the treatment, is the black line. The blue line shows the score the people got on the depression test, after being treated with the gas. Both groups started off with a score of twenty-two. As they moved from baseline point to two hours, until 24 hours, their score of depression symptoms went down. As it got closer to a week, the scores started to go back up a little, which showed this treatment wasn't a one-time thing. This is an ongoing process. But on their second treatment their scores are already lower, starting at two and reaching the negative numbers. When looking at both lines, the blue one definitely screams lower scores of depression ratings, which shows the N_2O is working (Nagele).

Credits: "Nitrous Oxide for Treatment-Resistant Major Depression: A Proof-of-Concept Trial." Biologicalpsychiatryjournal.com

The results confirmed that the gas worked, but unanswered questions remained. Would this treatment work with lower doses of N_2O, and how long would it last? When they tried the study again with 25% of the N_2O, it was nearly as effective with less side effects (Simon). The participants found their depression symptoms dropped for even two weeks after. They measured the relief on the Quick Inventory of Depressive Symptomatology Self Report scale, twenty- four hours after treatment. The QIDS-SR is a self-rating depression scale. Patients rate the number of different symptoms they are experiencing, like sleep disturbance, suicidal thoughts, decrease/increase appetite, and weight, sad mood etc. (Rush). While this does sound great, many people did have lots of side effects like nausea, vomiting and headaches. The good news is that this is an old drug. Scientists know about laughing gas already, it's not an unfamiliar substance. Therefore, they can hopefully figure out how to suit it for depression.

The American Academy of Pediatric Dentistry (AAPD) listed several factors people should consider before taking the drug. People who have a vitamin B12 deficiency should not take this drug. Laughing gas lowers the level of that vitamin (Pasha), so if you are already low and lose more, then that's not good since the vitamin helps in forming red blood cells and preventing dementia as well as other important functions (Mayo Clinic). People who have a history of addictions should not either use laughing gas since this drug makes people high, so it can be addictive (Aviary Recovery Center). Taking this drug is contraindicated for someone who has struggled with addiction. Laughing gas is listed as the fourth most common inhalant used nationally among teenagers (Nagele). If these people have depression and are unstable, by giving them something that makes them feel good, they might just get addicted, and it will end up doing more harm than good. Another concern is how healthy is it really to inhale N_2O all the time since the results don't seem to be lasting very long?

Although it still needs more research, laughing gas has proven effectiveness in helping depressive symptoms, and is a promising remedy for the future. To help address the issue of addiction, perhaps its chemical structure could be modified, so laughing gas will still have all the benefits, without the negatives. Let's see what the future holds. In the meantime, keep smiling.

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I Can See the Light

Anaelle Cohen

What do green algae and light have to do with new control over eyesight, neurons, and a deeper understanding of brain activity?

Forty-three million people globally suffer from blindness but a new technology promises that light and green algae may hold the potential to change that. What do green algae and light have to do with new control over eyesight, neurons, and a deeper understanding of brain activity?

Genetically engineered nerve cells. expressing light-sensing proteins taken from the algae, afford scientists the ability to use light to control neurons like marionettes and manipulate activities in the brain. This technology is known as optogenetics because of its use of a combination of light (opto) and genetics. The use of optogenetics allows new insight into how the nervous system operates, the malfunctions in the brain that cause neurological diseases, a novel understanding of how perception is created, and can even be used in vision restoration (6).

This new technology, developed by neuroscientist Karl Deisseroth, edits neurons in the brain by insertion of the gene for opsins, light-sensitive proteins taken from green algal cells. Normally, these neurons in the brain are stimulated by the optic nerve which originates in the retina of the eye. With this new technique, these cells can be stimulated directly by using light delivered through a fiber optic wire, bypassing the eye and the optic nerve.

The origins for this line of research began in a study done by neuroscientist, Ed Boyden, that showed great potential with this new technique. Boydon was studying a dish of cultured neurons that contained the light-sensing gene found in algae known as channelrhodopsin-2. When Boydon flashed a blue light on the neurons, they reacted with a burst of activity. Wild type cultured neurons show no such activity when flashed with blue light (6). Boyden also found that light-sensitive proteins create an electrical current that stops neuron activity when flashed with yellow light. Neurons stained with fluorescent dyes allow researchers to not only observe behaviors in single neurons, but also illuminate neural circuit activity when an animal is tasked with specific commands (2).

In the late seventeen-hundreds Italian physician, Luigi Galvani observed that the nervous system is largely influenced by electrical signals. In the early twentieth century, Swiss researcher Walter R. Hess utilized this observation to control the brain activity and behavior of cats and dogs by implanting wires in their brain. The results further indicated that emotions and behavior are controlled by electrical impulses in the brain. Further experimentation was done by Spanish physiologist, José Manuel Rodriguez Delgado, who used a self-invented device called a “stimoceiver”, an electrode operated by remote control. When he used it on epileptics and schizophrenics, he was successful in generating emotional and intellectual responses.

Brain research has been limited in the past because researchers have been circumscribed in their abilities to accurately test the brain. Deisseroth changed this reality by introducing optogenetics to the lexicon in the neuroscientist’s tool chest, with its ability to provide insight into what was previously a mysterious black box. Optogenetics introduced the ability to target specific cells from regions that contain hundreds of different cells. In addition, it allows researchers to stimulate the activities of cells at the speed that the brain works, and allows a

new level of precision in experiments previously never thought possible (2). The technique proved successful in vitro (neurons cultivated in a petri dish) but an essential question remained. Would this technique be able to be used in a live animal?

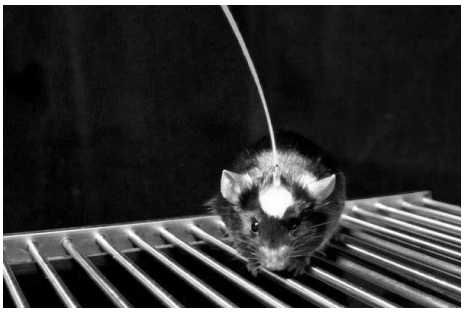


Figure I: A mouse is manipulated using optogenetic therapy. It was difficult to get the opsins in the mouse to target specific cells connected to brain activities such as sleeping, anxiety, and memory. Pieces of DNA were attached to the opsins and acted like a passcode to make sure that the opsins target only the necessary neurons. The researchers delivered light to deep regions of the brain using a fiber-optic wire attached to a laser diode, a device pumped with an electrical current (3). They began testing on cells in the hypothalamus, a region of the brain that controls sleep in mice. A blue light was shined into the brains of mice put to sleep in a dark room. The mice twitched and fell back to sleep, only indicating subtle responsiveness. Next, they tried simulating a mouse to run in circles using the blue glow delivered through the fiber-optic wire. When the light was on the mouse ran in circles but as soon as the light was shut off it stopped running and reverted to its calm state. This proved the motor cortex in an animal could be stimulated by light almost like a character in a video game controlled by the remote (2).

Mice with gene-edited neurons have had hallucinations of rooms they have never been in and have hallucinated imaginary lines. Deisseroth and his team monitored mice that were trained to lick water from a spout when they saw the orientation of lines. Next, the team created the perception of lines with lasers and using optogenetics stimulated the mice neurons to identify the sight and react by licking the water. In this way, scientists can create many other perceptions, and control more complex brain tasks (7). So far optogenetics has been used primarily in mice *(see Figure 1 above)*. Once its applications extend to more complex brains like those of primates, fascinating new understandings of the brain, particularly in the area of perception, are sure to follow.

The use of optogenetics has restored a blind mouse's sight and has even restored parts of a blind man's vision. *(See Figure 2)* This man has a degenerative eye disease who previously could only detect light but couldn't identify objects or motion. With the help of optogenetic therapy and special goggles, he was able to make out a book and a bottle of hand sanitizer (5).

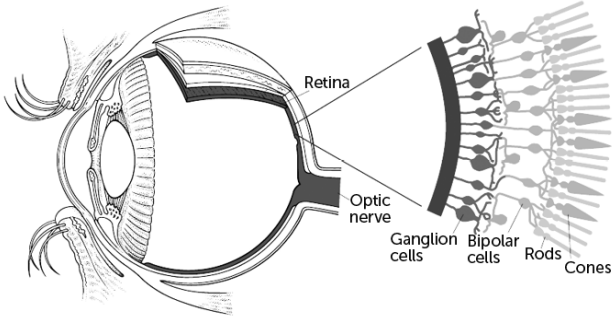
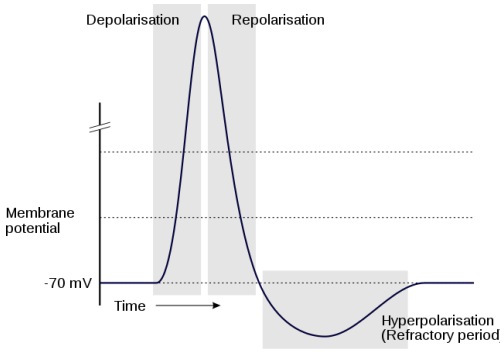


Figure 2: The retina depicted in the figure above is a multilayered tissue in the back of the eye. Photoreceptor cells are in the back of the retina then there is a layer of nerve cells that process the information taken in by the receptors and pass on the information to ganglion cells located in the third layer of the retina. The ganglion cells transport the signals to the visual centers in the brain. Degenerative eye diseases tend to kill photoreceptors leaving the nerve cells and ganglion cells to receive optogenetic therapy. The team used a particular virus known as the adeno-associated virus to deliver instructions on how to get light-sensing proteins into cells in the man's eye. Then this protein that responds to amber light is inserted into ganglion cells restoring vision. The goggles are required because ganglion cells react to changes in light so the goggles send continuous pulses of amber light to the eye. The therapy isn't perfected yet because it requires very specific ranges of light levels to work, and the goggles

are necessary to help the wearer process the visual information. Still, this experiment is a major breakthrough and holds much promise for future vision restoration and research (5).

Additionally, optogenetics can be used to slow and stop neuronal activity and allow researchers to study neural circuits in the brain. Inhibitory opsins are light-sensitive proteins that stop neuron activity. One of these opsins, NpHR, when activated by light, pumps negative chloride ions into the cell, thereby stopping neuronal activity through hyperpolarization. (Hyperpolarization is a process where protons are pumped out of the cell, across the cell membrane, giving the cell's interior a more ***negative*** charge. Hyperpolarization stops impulses (electrical signals with instructions to be carried out by effectors) because now a more powerful stimulus is required to generate an action potential. An action potential requires depolarization, a more ***positive*** cell membrane, but when the cell membrane undergoes hyperpolarization, action potentials are inhibited. These opsins are important because they create a negative hyperpolarized charge in the cell membrane slowing brain activity to allow researchers to gain a greater understanding of neural circuits in the brain (4).

Figure 3: This graph shows the changing membrane potential of an action potential. Depolarization is when positively charged sodium ions enter the cell membrane causing a more positive charge. This causes the neuron to fire an action potential because of the increased electrical activity in the cell. Repolarization is when the neuron restores the difference in charge inside and outside the cell after depolarization. Hyperpolarization happens when the membrane potential becomes more negative which inhibits action potentials stopping neuronal activity (4).



The evolving scientific field of optogenetics is revolutionizing the way researchers study the brain and holds so many promising possibilities for an enhanced understanding of the nervous system. Jeanne Paz of the Gladstone Institutes in San Francisco has used optogenetics to control nerve cells in the thalamus, an important center of nerve connections in the brain. When Paz shone light into the thalamus, it stopped the spread of a seizure across the brain.

Neuroscientist Talia Lerner of Northwestern University in Chicago utilized optogenetics to help study the connections between cells that produce and react to dopamine, a neurotransmitter responsible for movement and reward. These connections in neuron cells highlighted by optogenetics can give insight into what motivates an individual and how learning takes place. Optogenetics is being used to stimulate specific populations of neurons from a miscellaneous group. This allows researchers to study specific populations of neurons relating to a particular function of the brain (2). This can help researchers study how memories are stored, how perception is created and holds great potential to restore vision and deafness. Who knows what incredible discoveries optogenetics will lead to next?

Optogenetics seems particularly promising for curing neurological diseases such as Alzheimer's disease, epilepsy, and autism. Optogenetics proves to be especially promising for depression with neuron stimulation being utilized in therapy (1). Deisseroth has done trials on patients with depression using optogenetics to isolate relevant cells and study their connections *(see L. Borenstein, in this publication.)* Other potential treatments include using a stimoceiver, similar to the one utilized by Delgado, to transmit electrical impulses through

implanted electrodes in the brain, that flash light into the brain to stop anxiety and hallucinations. Further research is required to discover a less invasive way to study the brain that doesn't require inserting a fiber-optic cable into the brain. In addition, more research is required to allow optogenetics to simultaneously control many groups of neurons all across the brain (2).

Optogenetics is a clear illustration of the concept that Hashem creates the cure before the disease. The concept of רפואה לפני המכה is mentioned in the Talmud. "Hashem doesn't bring an affliction on *Bnei Yisrael* unless He created the cure first" (Megillah 13b). Before human beings or animals even existed, Hashem in his infinite wisdom had already created light, an essential instrument needed for curing human neurological diseases and restoring vision and hearing. On the first day of creation, Hashem created an instrument to help heal diseases that weren't discovered until years later. This shows the genius of Hashem in how he runs the world. Furthermore, who could have ever imagined that a gene from a simple green alga, that has no nervous system and uses pigments to collect light for photosynthesis, would be the solution to devastating neurological problems that plague humans. Optogenetics has begun to be used to help further understand the human brain and potentially cure neurological diseases and restore sight and hearing. Everything is thought-out and organized for the benefit of human beings and our tzelem Elokim. With further experimentation and research, the potential of what optogenetics can teach scientists about the brain is endless.

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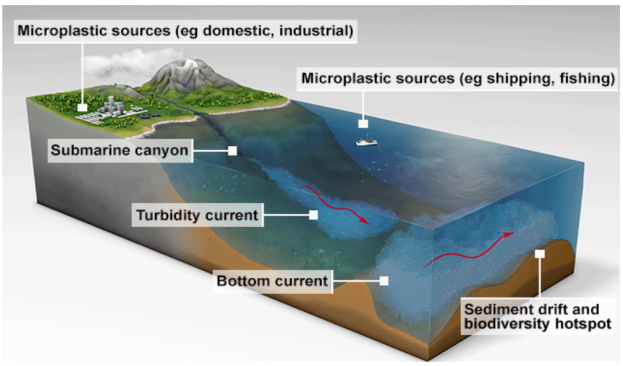
All That Glitters Is Not Gold

Shevy Dreifus

Who would have ever thought that something as seemingly innocuous as glitter can dramatically affect the environment, but that is what is so deceiving about glitter; you never can know how far it really spreads.

Your little sister's science project just exploded and spewed glitter all over your house. Your mother is beside herself. It spread into every nook and cranny. What to do with all that glitter that was just swept up? Can't flush it down the drain because it has been determined to contribute to the problem of microplastic marine pollution. There is however recent development that offers a solution to the problem: Eco-friendly glitter made from cellulose, a fiber found in the walls of plant cells.

All the plastic that gets tossed into the garbage without a second thought enters the waste stream and ends up in landfills where it hangs out for a long time. Most plastics take years to decompose. Instead, it gets broken down to smaller and smaller pieces, the action of rain washes these small pieces of plastic to the streams and rivers and eventually into the ocean. Powerful ocean currents locally concentrate them and deposit them in sedimentation drifts sometimes reaching several kilometers long (Amos).



Microplastics are defined as tiny plastic particles less than 5 millimeters in dimension. To see exactly how microplastic pollution harms aquatic ecosystems, scientists set up six miniature ponds in the lab, and introduced varying quantities of six different types of microplastics including glitter and examined where the microplastic ended up. In every case, microplastics altered the food chain by diminishing the abundance of algae and duckweed, removing an important source of food for many fish (Briggs).

The problem with glitter is that it starts out as microplastic from the outset so the minute it enters the water ways, it sinks and immediately contributes to this problem. When people wash glitter down the drain, it contributes to the issue of glitter harming marine life. When microplastics reach the ocean, they are consumed by plankton, fish, and birds, causing it to be exceedingly harmful for marine life.

Glitter is not only damaging to life in the water but also life on dry land, as it is made with plastics that are bad for the environment. As plastics slowly break down, they emit harmful toxic contaminants. Studies have also shown that these chemicals can affect our body by interfering with various hormones. What these chemicals do to the body can be passed down, as these plastics can attach to the fetus and affect future generations (Ragusa). It can take part in harming chronic disorders such as reproductive, metabolic, and degenerative diseases (Gruber). In addition, plastics are made from fossil fuels, and their manufacturing process contributes greenhouse gasses into the atmosphere, a major cause of global warming (Dodgson).

Scientists have recently discovered microplastics in a different aquatic environment: human blood. These microplastics can get stuck in our organs and cause harm to human cells. The microplastics are being consumed through the intake of air, food, and water. A recent study showed that microplastics can limit our red blood cells ability to transport oxygen by latching onto their outer membranes (Carrington).

Because of harmful, traditional glitter, cosmetic brand Lush, most popular for it's decorative, glamorous, and eye catching bath bombs, recently announced that they will no longer be using plastic glitter in their products as it is harmful and detrimental to the environment. Other researchers agree with this and also believe that glitter should even be banned for those same reasons (Matei; Wetzel.)

Microplastics, the primary ingredient of glitter, find their way into the oceans, but with biodegradable glitter, this problem will hopefully be minimized and even eradicated. The alternative to traditional glitter made of plastic was found in cellulose, located in the cell walls of plants. The cellulose in plants is able to make exquisite colors, and scientists realized they could mimic the nanoscale patterns that the cellulose creates and use it to make all different shades of glitter.

This eco-friendly glitter was inspired by the *Pollia condensata*, an African plant. This plant grows iridescent berries, and within these berries are cellulose fibers which create metallic hues visible to the eye when hit by light in a certain way. Chemists poured a liquid mixture of these tiny rod-like fibers and spread it across a plastic sheet. As it was drying, the cellulose fibers formed structures that looked like spiral staircases, and by adjusting the steepness levels of the staircases of cellulose fibers changed the wavelengths of light the cellulose emitted, changing the color of the film. They ground up their shiny product to make the glitter. Scientists remain hopeful that this new form of glitter will be better for the environment as it is made from plants and not plastics (Temming). Aside from glitter, the environmentally friendly cellulose based plastic is also used for eyeglasses frames, thermoplastics, and even electronics too. It is said that these plastics are lighter than regular plastic and more moldable, making them easier to work with (Innexus).

This shiny ribbon contains tiny arrangements of cellulose that reflect light in specific ways to give the material its color.

Who would have ever thought that something as seemingly innocuous as glitter can dramatically affect the environment, but that is what is so deceiving about glitter; you never can know how far it really spreads. Something that most would overlook as insignificant can have profound impacts on the world. Glitter is merely the entry point to understanding the dangers and impact of microplastics on our health. In contrast to their microdimensions, the impact of microplastics are morphing into a huge ecological and consequently biological threat.

Perhaps, stores will all switch to this eco-friendly glitter. As this discovery is quite recent, there isn't extensive research that has been done. However, there can be dramatic effects in the long run but we don't know that yet as it's only the beginning. But as for what we have now, this is a promising development that can hopefully bring great, positive, and influential impacts on the environment and future discoveries.This development gives hope that we can limit the manufacturing of the more harmful plastics which will allow improvement for many issues such as global warming, a problem connected with marine plastic pollution through filling the water with microplastics which kill marine life (Briggs).

This discovery of eco-friendly glitter sheds light on something most would overlook. It goes to show that there is nothing that is too trivial or inconsequential that it can't be subjected to scientific scrutiny and improvement.

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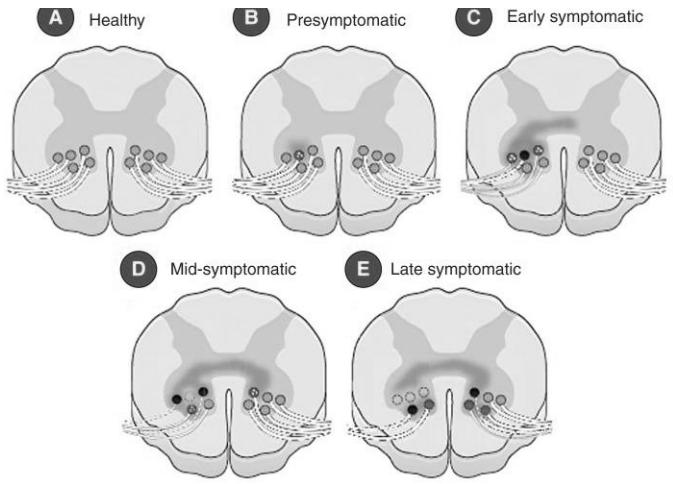
Locked-In No Longer

Tami Eberstark

Recently, scientists have developed a new brain implant which allowed a man to compose sentences and "speak" to his son, even while in the completely locked-in stage of ALS.

Imagine you are walking down a busy avenue when you trip and fall. You lie on the floor shouting and screaming for help, but countless people walk by seemingly unhearing. This is the reality for the thousands of people each year who are diagnosed with the incurable disease of ALS. But this may be changing. New technology may make it possible for a person with late stage ALS to communicate, even after losing all ability to move.

Amyotrophic lateral sclerosis (ALS) is a neurological disease which leads to the gradual death of motor neurons, the nerve cells responsible for voluntary muscle movement. There are three different types of ALS; classical ALS, primary lateral sclerosis, and progressive muscular atrophy. Classical ALS is caused by the loss of upper and lower motor neuron function resulting in total paralysis and death after about four years. Primary lateral sclerosis (PLS) involves the loss of function in the upper motor neurons, leading to loss of motor function in the arms, legs, and bulbar muscles–the muscles involving speech, chewing, and swallowing. Progressive muscular atrophy (PMA) affects the lower motor neurons and can begin in any part of the body. Nearly all cases result in paralysis and the inability to communicate, while leaving the patients with full cognitive function. In simple terms, they are trapped in their own body (3, 4).



This is a model of the spread of ALS in the spinal cord. In a normal spinal cord the neurons remain healthy and functioning (A). In the presymptomatic stage the neurons begin to degenerate, but symptoms are not yet expressed in the patient (B). The disease continues progressing and moves to different regions of the spinal cord (C, D). Eventually, the patient presents with severe symptoms, and motor dysfunction as more neurons are destroyed (E) (3).

ALS is categorized in two ways; sporadic ALS, which occurs randomly, and familial ALS, where the disease is passed down genetically(3). While there is no known definite cause of ALS, there are many hypotheses

and links between specific genes and ALS. Familial ALS is associated with mutations in the SOD1 gene, a gene involving antioxidant resistance, but there are many possible mutations which can occur on the SOD1 gene alone, and not all of them result in the same type of ALS (1). Additionally, mutations in the *C9ORF72* gene are responsible for most cases of familial ALS, but hardly anyone with sporadic ALS has mutations in this gene (3). Because of these inconsistencies and the other unknown causes of ALS, it has been extremely difficult for scientists to discover medication which can slow the progression of or cure ALS.

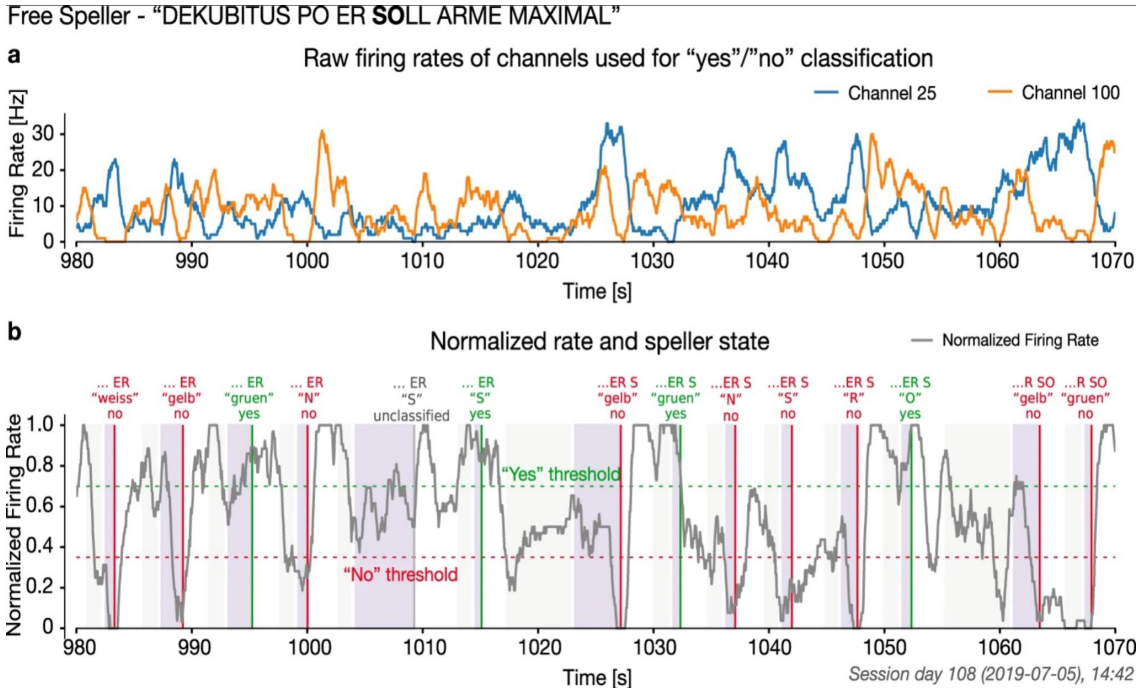
Instead of slowing progression of the disease, some scientists are focusing on developing new ways for ALS patients to communicate with family and friends before they die. One common way for ALS patients to communicate is with eye tracking devices which track patient eye movements in order to spell out words and sentences on a screen. This system works, but what happens when the patient can no longer move or open their eyes? In 2016 a team of researchers were successful in creating a system where a 58 year old woman in the locked-in stage of ALS was able to communicate through electrodes implanted in her brain. The electrodes were placed in the left motor cortex and the left prefrontal cortex of the brain, and were able to detect when the patient attempted to move her hand based on when those areas of the brain were activated. After many weeks of practice, she was able to control a computer system which was connected to the electrodes. This system worked for this woman who was still able to move her eyes and fire neurons from her motor cortex, but what about the people who are in the later stages and can no longer do the same (6)?

Recently, scientists have developed a new brain implant which allowed a man to compose sentences and "speak" to his son, even while in the completely locked-in stage of ALS. A group of researchers from University of Tübingen began to work with this man in 2018 after first establishing that he was in the completely locked-in stage of ALS, and that his eye movements were too inconsistent to use eye tracking devices to write sentences. The man had been previously communicating with his family with a "yes" and "no" system where family members asked questions and if he responded with any eye movement at all, his answer was yes, otherwise it was no (2).

By using his family's system and electrode sensors, researchers were eventually able to develop a system to communicate with the patient. Researchers implanted electrode sensors in two motor cortex areas, areas in the brain that usually control motion. They first tried to read neural signals when the patient used the "yes" and "no" system developed by his family, but did not get any definite results (2). Next, they asked the patient to imagine moving parts of his body, but again received no neural signals. After around three months of failed attempts, scientists decided to instead try auditory neurofeedback communication, a method where the patient tries to change their brain signals while receiving an auditory signal which tells them how they are doing (5). The pitch of the auditory signal increased when the patient succeeded in speeding up the firing of neural signals, and decreased when the patient lowered the amount of fired neural signals (5). On the first day using this strategy, the patient was able to change the pitch of the signal, and only a few days later he was able to match the pitch to a given target pitch (5). Each day the researchers would start by asking the patient to match certain target tones and if he was over 80% successful in matching the tones, they would continue to test the spelling part of the training (2).

While using the auditory signals to know how he was performing, the patient was able to select specific letters or words. The researchers gave a threshold of under 0.4 neuron firing rate to mean "no" and a rate above 0.7 to mean "yes." The patient would be given a letter by a computer program, and by using the auditory signals

as an indication of how he was doing, the patient increased his neuron firing rate to above 0.7 to answer yes and select that letter. That letter or phrase would then be written on a screen as part of a sentence. If the patient lowered his neuron firing rate to under 0.4, it means that he would not like to use that specific letter and the computer system would prompt him with a new letter. By using this system, the patient was able to spell sentences like "first of all head position very high from now" to help people make him more comfortable, as well as ask his wife and son if they would like "to watch Disney's Robin Hood with me" (2).



This graph shows the neuron firing rates of the patient. The green letters on the second graph were selected and written because the patient increased his neuron firing rate to above the "yes" threshold. The red letters were not selected because the patient lowered his neuron firing rate to under the "no" threshold. (The phrase the patient was asked to spell as well as the phrases which he had the option to select are in German, the patient's native language) (2).

Although this system is not perfect–it can take over an hour to write one sentence and there are days where the patient cannot write anything at all–it is a huge step for communication among individuals with ALS or other paralyzing diseases. It allows these individuals to spend their time in comfort and communicate with their loved ones. Although this auditory neurofeedback communication is not yet available for everyone in late stage ALS, it helped one man tell his four year-old son that he loved him, and will hopefully allow many others in the locked-in stage of ALS to tell their loved ones the same.

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Advances in Cancer Treatment: CAR T Therapy

Teri Ehrenpreis

The therapy worked virtually instantly and within weeks Emily's cancer went into complete remission.

Meet Emily Whitehead. At age five she was diagnosed with Acute Lymphoblastic Leukemia (ALL), a very serious pediatric cancer. After relapsing at age six and additional unsuccessful chemotherapy treatments, her parents were told that there was no hope and that they should prepare for the worst. With nothing else to lose, her parents enrolled Emily in a clinical trial for a new treatment against ALL cancer. The new treatment was called chimeric antigen receptor therapy (CAR T). The therapy worked virtually instantly and within weeks Emily's cancer went into complete remission. Emily is the first person to ever receive this highly personalized and novel drug; she is termed patient 1. In 2017, five years after the initial clinical trial, CAR T became FDA approved to treat certain types of Acute Lymphoblastic Leukemia. ("Emily Whitehead - Immunotherapy Patient Stories") ("Emily Whitehead's Story: CAR T Cell Therapy for Acute Lymphoblastic Leukemia")

To understand more about this miraculous new treatment, we must look at the basic building blocks of the human immune system. T cells are a crucial component of our immune system. They are created in the bone marrow, matured in the thymus, and are of three main types : cytotoxic, helper, and regulatory. CAR T uses the cytotoxic form of T-cells. Beginning in human infancy, T cells are trained to correctly identify antigens (proteins displayed on the extracellular surface of plasma membranes) as either foreign or self. On occasion, these T-cells are overly zealous and react to harmless antigens, resulting in allergies. On other occasions, the T-cells mistakenly identify self-cells as foreign, resulting in autoimmune disorders.

If the antigens are correctly identified as foreign, cytotoxic T cells will go into attack mode and destroy the cell bearing the foreign antigen. *(See Figure 1)* In this way, the T cells identify infection or bacteria or other harmful substances by their identifying markers or proteins and harness the immune system to attack and destroy such foreign substances. Specific T cells synthesize a specific membrane bound protein called T-cell receptor, which is a perfectly shaped "key" to attach onto the specific antigen (Ghanchi).

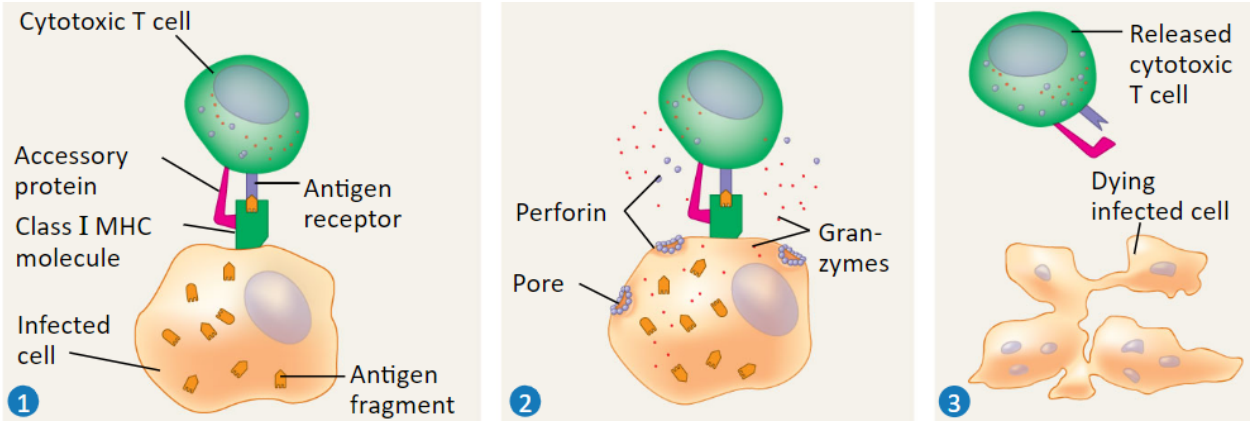
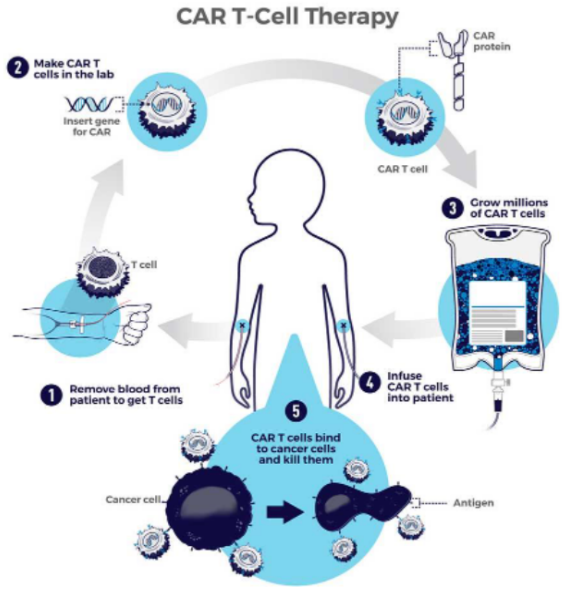


Figure 1

While T cells are usually very good at identifying the antigen markers on pathogens, when it comes to many different types of cancers, T cells are ill-equipped to recognize the specific cancer antigens and fight the cancerous cells. Part of the reason is because cancer cells are not foreign. They are "self" cells that have mutations. CAR T aims to remedy that by removing T cells from a patient's body and genetically modifying the T cells to enable them to recognize the specific cancerous antigens. Once the specific cancerous antigen is identified, the gene for the receptor protein specific for the cancerous antigen must be designed and reverse engineered. It can now be inserted into the T-cell genome using genetic modification techniques such as CRISPR. *(See Hirsch in this publication)* The modified T-cell will now express the receptor designed to recognize and bind to cancerous cells, attack and destroy them. Once the modification is complete, the modified T cells are induced to proliferate and re-inserted into the patient's blood through an infusion. At that point, the patient's newly improved T cells are able to identify the cancerous cells within the body and the immune system then attacks and destroys the cancer (NIH). The CAR T cells continue to proliferate in the body, providing long lasting immunity (Hamers). This leads to long-lasting T cells that respond to and recognize the cancer cells as bad.



In a follow-up study examining the durability of T cells in two patients who received CAR T therapy approximately ten years earlier, researchers identified 1,149 CAR T cells within the patients. Just like we build immunity to common viruses through B cells and then have a permanent supply of B cells that can destroy future viruses, the same happens with T cells and cancer cells. This is why CAR T is so successful. At times we may have antigens of influenza in our body, but T cells recognize them as a threat and kill them before we even know we are sick. Similarly, post-CAR T, the patient's body has T cells that recognize the cancer cells as a threat, attacking and destroying them immediately (Melenhorst).

Prior to the availability of CAR T, the prognosis for relapsing, refractory ALL was less than 10% (Ronson). With the development of CAR T, these patients have new hope, as clinical trial outcomes for relapsing, refractory ALL patients who received CAR T demonstrated 88-93% complete remission rates. Such a disparity in outcomes is a very exciting advancement in the treatment of blood cancers and declared as "one of the greatest success stories of modern oncology" (Pierro). Although the results of CAR T went above and beyond anyone's wildest expectations, it is so far mostly limited to treating cancers in the blood. This is because blood cancer has a target, or special and individual markers, at which the CAR T can aim, while solid cancers often do not express one tumor-specific marker (Marofi). Also, blood cancers circulate in the vascular system thus making them more accessible. Solid cancers, on the other hand, are more often contained in a microenvironment,[2] making them more difficult to access ("A Solid Future for Cancer Cell Therapy").

[2] The National Cancer Institute defines a microenvironment as the "cells, molecules, and structures that surround and support other cells and tissues." In the case of cancer, the abnormal cancer cells "can change their microenvironment," which "can affect how cancer cells grow and spread."

Unfortunately, the CAR T treatment itself can be accompanied by severe side effects including, but not limited to, extremely high fever, low blood pressure, delirium, neurotoxicity and reduced numbers of native healthy immune cells when the patient is receiving the infusions. Because of these severe side effects, the patient may need intensive care, usually in the ICU, while receiving the CAR T. Additionally, the patient may need long-term GAMMA globulin infusions to fortify the weakened immune system (Hamers). The potential for such side effects must be considered by the patient's medical team and weighed against the potential benefit of the treatment when determining if CAR T is the appropriate therapy for the patient.

CAR T is a breakthrough therapy option due to the fact that it is tailored to the patient's cells and has a fairly high success rate in clinical trials because it is created by taking a patient's own cells and re-engineering them. The downside is that it takes time to manufacture. Unfortunately, some patients are at such a critical stage in their illness they don't survive the nine to fourteen day wait for production. Additionally, the cost of each therapy is between $373,000 to $475,000. To help address these concerns, scientists are looking to create a "universal CAR T" that would not need to use a patient's individual cells, which would mean that the CAR T would no longer have to be tailor-made for each patient. The hope is that hospitals and cancer centers will be able to have CAR T always accessible and available (Hamers; Pierro)

It has now been 10 years since Emily Whitehead received CAR T. Once she was in remission, it stayed that way. This is a miraculous recovery for a child who was literally at death's door. This is the extraordinary capability that CAR T has demonstrated so far, and with the continued research that scientists are doing with CAR T, including "universal" CAR T, there is hope for a brighter future in treating many different forms of cancer. Some labs have already reported cautious optimism over their success in developing this second generation of treatment (Vasic). Cautious optimism is infinitely preferable over the alternative.

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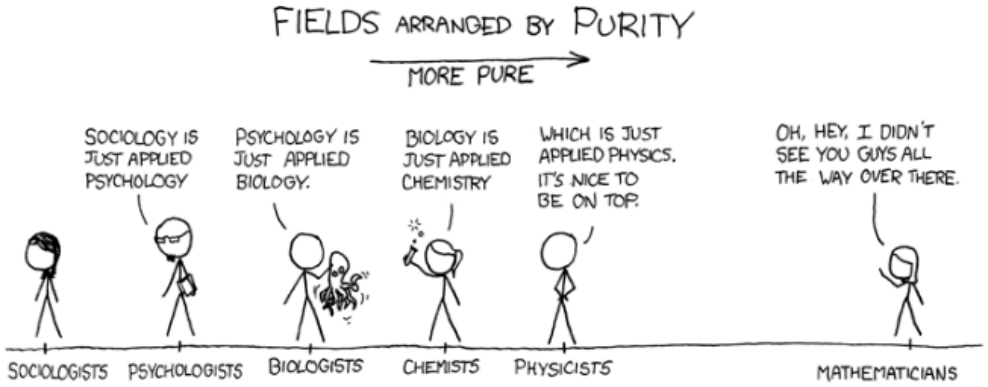
The Mother of All Cognition

Matea Frieber

The importance of the study of mathematics to the sciences is so fundamental that it is called the mother of all sciences.

The importance of the study of mathematics to the sciences is so fundamental that it is called the mother of all sciences. However, even if you don't plan on going into engineering, medicine, or any other STEM subject, a recent study suggests that you still should not give up on math. The study of mathematics has been previously established to be advantageous in areas such as future employment, mental and physical health, and socioeconomic status (Science Daily.) It is now found to be equally important to ***all*** areas of cognitive development.



High schools in the United States often require their students to take three years of math education as a graduation requirement. But in several other countries, including India and the United Kingdom, 16 year old adolescents may choose to stop learning math as one of their individually selected advanced, or "A level" subjects (Science Daily). Of course, if a student is pursuing a career that doesn't involve or require advanced math education, this decision offers the advantage that it allows the student to better focus on their other studies. But, more often than not, teens haven't decided on a career yet, and haven't had enough exposure to choose a suitable field of study wisely. Is this policy truly in the students' best interest?

Important cognitive and neural changes occur in adolescence, and because of neuroplasticity (the brain's ability to create and reorganize neural pathways), the brain is profoundly impacted by education (Marks). So what might the neural repercussions be of withdrawing from math education as an adolescent? Does the decision to quit math lead to any meaningful differences in brain chemistry or organization? While the disadvantages of a lack of education are undisputable, the impact specific subjects have on cognitive development is not.

Brain imaging studies do implicate neural changes in brain regions associated with mathematics education. The researchers were testing for the possible role math education has on the levels of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), and the excitatory neurotransmitter, glutamate, two major factors of cognitive development and neuroplasticity during adolescent development and education.

Based on existing literature, the team hypothesized that math education may lead to increased glutamate, which plays an important role during brain development, and helps with learning and memory. They also predicted higher levels of GABA, an inhibitory neurotransmitter that decreases brain and nervous system activity, thereby increasing focus and self-control in adolescents. Higher levels of GABA are generally a good thing, while lower levels have been shown in previous studies to be associated with less impulse control and poor cognitive functioning during adolescence (Zhou).

In order to test this causative association, the researchers saw the United Kingdom as an ideal setting to explore the neural repercussions of withdrawing from math education as an adolescent. They divided 87 A-level female students between ages 15 and 18 into two groups: the math group, with 49 students who were studying A-level math, and the non-math group with 38 students who had not chosen it as an advanced subject. In the first experiment, students participated in a brain imaging session using MR spectroscopy, which is executed on an MRI machine with added diagnostic tests to measure biochemical changes in the brain (Mayfield Imaging Services). The team scanned the intraparietal sulcus (IPS) and middle frontal gyrus (MFG), both frontoparietal regions of the brain that play a central role in mathematical learning.

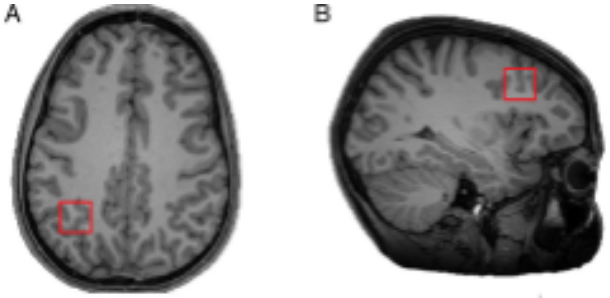


Fig. 1. This figure, produced by the researchers using a standard display of MRI images of the brain from different perspectives, shows (A) the IPS and (B) MFG regions.

The results of this experiment gave solid evidence in favor of the original hypothesis; the math group indeed had raised levels of GABA ; however, it was not clear that studying math was the cause for this rise in GABA levels. Were the adolescents who pursued math as an advanced subject simply smarter beforehand? If they had already had higher GABA levels, and tended to like math more, maybe that was the root of their decision to choose it as an A-level subject. To eliminate this competing hypothesis and control for these additional variables, the scientists ran another series of tests using a second group of pre-A-level students, 21 of whom expressed willingness to study math as an advanced subject, and 21 who expressed the opposite. They found that there was no difference in GABA levels between the groups, and that they performed equally well when tested on their abstract problem solving ability.

Based on the results of this experiment, it was deduced that adolescents don't begin having higher GABA levels until after they begin math as an advanced subject. This indicates that the neural changes in the first studies are, in fact, evidence of neural plasticity, as math education affects development in the MFG. Zacharopolous and his team also found that the link between GABA levels and math education still held after controlling for the total number of A-level subjects each student was taking (Zacharopolous).

The study further provides evidence that a lack of math education may alter cognitive and neural development. Adolescents who did not pursue math as an advanced subject had lower levels of GABA in their MFG compared to those who continued studying math. The results also indicated that GABA can benefit future math achievement. Zacharopolous and his colleagues asked the young adults to take a test of mathematical ability about 19 months after their brain imaging scans. The results showed that generally, higher

concentrations of GABA at the beginning of the study predicted better mathematical performance 19 months later. Significantly, GABA concentration did not predict students' advancement in other classes. The GABA levels in the MFG can predict whether or not a student was studying math, and their future math ability. This ability to predict through GABA concentration is suggested to be specific to math education, and was not evident in other subjects usually taken by math students such as biology, physics, and chemistry (Zacharopolous).

Where does all this leave us? Zachoropolous's discoveries are groundbreaking, but this is a single study that needs replication and leaves us with unanswered questions. The experiment was performed exclusively on female test subjects, which may skew the data due to hormones and differences in pubertal development among the subjects. Would the same results be obtained with male test subjects, who are traditionally thought to be better at math? We are also still unsure how math education impacts the brain over the long term, after high school. That would require a long-term study, and this article came out only around a year ago. Another area worth exploring is what possible alternatives there may be to math, if any, that engage the same regions in the brain for those who don't enjoy studying math.

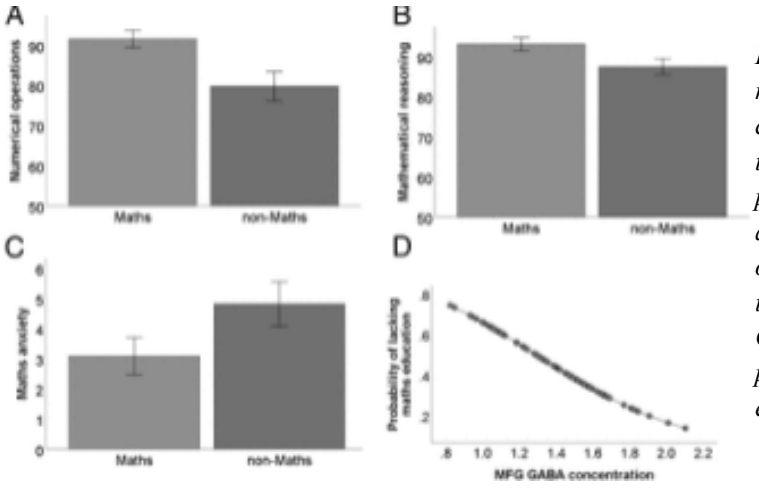


Fig. 2. These charts, produced by the researchers, show the performance results, comparing adolescents who studied math to those who did not. Chart A compares the performance on a numerical operation attainment test, B compares the performance on the mathematical reasoning attainment test, and C the math anxiety assessment. Graph D shows GABA levels in the MFG predicting the probability of lacking math education.

This study underscores the importance of math, whether or not it is students' primary interest, as it has neurological benefits that go beyond the subject itself, and may shape a more efficient and effective brain. It also brings to light the advantage students in schools that require math study until graduation have over those in schools that don't, and the implications this has for providing equal opportunity to all students, maximizing human potential. The findings of this study also usher important concerns about distance education during the COVID era, and raise questions about the impact it may have had on the cognitive development of children today. While we were previously unaware of the true extent of the effect math education has on the brain, we must now further explore how to mitigate the negative impact of this loss, as well as the loss occurring in the countries that do not enforce or even offer advanced math study.

In summation, this study strongly suggests that if you don't include mathematics in your curriculum as an adolescent, you might end up with lower levels of GABA in your middle frontal gyrus, and not reach your full cognitive potential. Go figure!

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Back to the Future

Chaya Friedman

Nearly all events in nature will only happen in one direction: a melted ice cube won't spontaneously sprout from a glass of water

Time is defined by its arrow; it has a specific direction, pointing from the past to the future. This idea, formally stated by English physicist Arthur Eddington in 1927, offers a metaphor regarding time's asymmetric "movement." The arrow stems from the irreversible processes overwhelmingly prevalent in day-to-day life. Nearly all events in nature will only happen in one direction: a melted ice cube won't spontaneously sprout from a glass of water, all the king's horses and all the king's men can't put humpty dumpty together again,, and a shattered window won't suddenly reassemble itself. This notion that events occur in one order, and one order only, is consistent throughout the universe and is deeply rooted in our experience and understanding of the world. Yet, why is it true? Why does this arrow exist? (1, 6)

The very root of time's arrow, the reason events occur in a specific sequence, is entropy, the measurement of disorder within a system. As an irreversible system progresses from order to disorder (black coffee and milk are mixed, for example), the entropy increases. The separate liquids have a lower entropy as the molecules are divided neatly into "coffee" and "milk." However, when combined, the entropy increases as the molecules are removed from their orderly separation and mixed. This is encapsulated by the second law of thermodynamics, which states that the entropy within a closed system will always increase (or stay the same.) Since the universe is a "closed" system, in any spontaneous process, the entropy of the universe increases, a one-direction arrow (6).

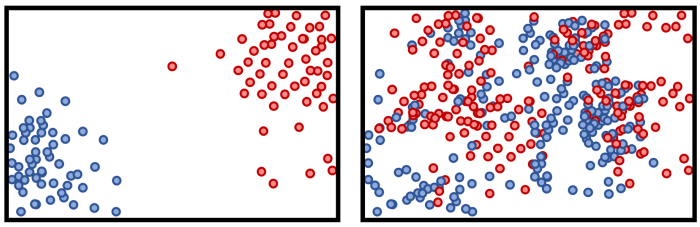

Figure 1: Systems in low and high entropy states, clearly showing how a system of higher entropy is a system with more disorder. Another way of looking at entropy is the probability of locating a particular particle. When a system is highly ordered, for instance, a neat library, it is easy to locate a particular book.

The origins of the second law stem from French military engineer Nicolas Carnot in 1825 who sought ways to maximize the efficiency of steam engines. He discovered that the most efficient engines were those that generated the least amount of heat waste (heat is a form of "useless" energy that can't be fully converted to other forms of energy to do work), yet he also found that no matter what, every engine will lose some energy (in the form of heat or other waste energies) as it burns fuel. What Carnot had realized was that the burning of fuel was an irreversible process: as the gasoline is burnt, its energy becomes increasingly and permanently useless. The heat is dissipated into the universe and cannot be spontaneously retrieved or converted into other "useful" forms of energy (1).

These discoveries were furthered by the findings of German physicist Rudolf Clausius in the 1850s. In stating that heat will never flow spontaneously from colder to hotter objects, Clausius recognized Carnot's ideas

as a reflection of natural phenomena. When a hot object is placed next to a cold object, heat will flow both objects have reached equilibrium, the same temperature. Clausius later restated this law using entropy, stating that entropy will never spontaneously decrease. How are these laws the same? According to Clausius, entropy is the measure of a certain amount of energy's uselessness. While the entropy of the hotter object (which has more entropy because heat is useless energy) decreases as it lessens in temperature, it decreases less than the colder object's increase in entropy as it becomes hotter. Therefore, the amount of entropy in the total system sees an overall increase. When a system is in equilibrium, it means that the entropy has reached its highest value because all objects are the same temperature, meaning they all contain the same amount of waste energy. The thermal energy within the system has reached the highest level of uselessness and has nowhere else to go (1).

To summarize, Clausius states that entropy is the degree of uselessness in an amount of energy, which will always increase within a closed system. But why is this? Why must the entropy always increase? Modern understanding on this point was provided in 1877 by Ludwig Boltzmann, who examined entropy in terms of particles. Boltzmann realized that the way a sample appears to us (its macrostate) doesn't necessarily change when the arrangement of its atoms (its microstate) changes. He also noticed that this was especially true of systems with high entropy. Such a system could undergo many changes in its microstate (arrangements of its individual atoms) that wouldn't affect its macrostate (appearance). This is in stark contrast to systems of low entropy, where a change in microstate would lead to a change in the macrostate as well.

For example, if someone was able to change the microstate of coffee mixed with milk (a system with relatively high entropy), without changing any of the atom's properties, an observer would be unable to tell the difference. However, if the microstate of black coffee (for the sake of example), somehow just lying next to milk was changed, its macrostate would differ–the appearance would noticeably change as the exchanged atoms cause the liquids to mix and form a new color. In this way, Boltzmann showed that systems increase in entropy because statistically, there are so many more ways for a system to be high entropy rather than low entropy. The lower entropy macrostate of unmixed black coffee and milk has limited microstates because the atoms are relegated to their original liquids. While there are still many potential ways for the atoms to arrange themselves within their liquids, they are severely limited in that the black coffee molecules are isolated from the milk particles. It would be much easier to find a specific molecule of black coffee when it is not mixed into the milk. In contrast, the macrostate of mixed coffee and milk has many more microstates. If the atoms can move around from side to side, in any way they choose, there are infinitely more possible ways in which these atoms can arrange themselves (1, 2, 4).

Boltzmann's discovery revolutionized how entropy and the second law are viewed. Before his discoveries, early physicists like Clausius saw the increase of entropy as a natural phenomenon that would occur without exception. However, Boltzmann revealed this law to be a statistical probability; he showed that a macroscopic system will likely, rather than definitely, increase in entropy. To understand this concept, picture within half a container. When the valve is opened, the gas will begin to expand spontaneously throughout the rest of the vessel. It is technically possible for the gas atoms to spontaneously reassemble in their original position–filling exactly half of the container–yet this is extremely unlikely, as there are so many more potential disordered states compared to the single ordered position with which they began. However, the same is not true of a simple, microscopic system.

Imagine there were only three particles of gas in the aforementioned container. The likelihood of the atoms' spontaneous movement back to their original position becomes much higher. The macrostate of the low entropy configuration (the atom's original positions) and the high entropy configuration (the atoms' positions after they move) have a relatively similar amount of microstates, and therefore the probability of both macrostates occurring is very similar. Hence, a lessening of entropy in a microscopic system is not only possible but probable. In fact, a microscopic system can just as likely evolve towards lower entropy (backward in time) as it can towards higher entropy (forward). At its most simple level, nature doesn't prefer one direction of time over the other, and both arrows are indistinguishable (1, 4, 5).

In a recent study conducted by the Universities of Bristol, Vienna, the Balearic Islands, and IQOQI-Vienna, physicists have applied this phenomenon to the most fundamental level of the universe, the infinitesimally small quantum realm. Rules such as the second law fall into the category of classical mechanics, which provides an understanding of macroscopic systems and how they operate. Yet, classical mechanics falls short in regards to the most elementary systems at the subatomic particle level. The irregular behavior of microscopic particles, specifically electrons, necessitated the development of quantum mechanics. However, as macroscopic systems behave according to the laws of classical mechanics, quantum mechanics has virtually no effect on our everyday experiences. One could easily live their whole life without any knowledge or understanding of quantum systems and laws; it's only when scientists begin examining the most elementary systems, such as electrons, that the limits of classical mechanics no longer suffice (2, 4, 5).

To understand the concept of quantum superposition, (which is necessary for the comprehension of the study regarding time), it is useful to examine the example provided by physicist Sean Caroll. Imagine you had a cat. Cats are macroscopic systems and are therefore governed by classical mechanics, but for the sake of example, this cat behaves like a microscopic system. Imagine there were only two places your cat could be, and you were able to specify her precise location: on the window sill or in the chair. In classical mechanics, if you didn't know where the cat was, you could conjecture that there's a 45% chance she's on the chair. This statement is simply an indication that you lack information because whether or not you're aware of it, the cat is either on the window sill or in the chair. In quantum mechanics, however, there is no fact about the location of your cat. There is no "true" place where she is; she exists simultaneously on the sill and in the chair. In other words, her quantum state is a superposition of these locations. However, if we were to observe (observe and measure are being used interchangeably) this cat, we would find a definite result: she is either in the chair or on the window sill. In quantum mechanics, measuring a system has an integral effect, removing it from its state of superposition. See Figure 2 for a discussion of superposition in electrons.

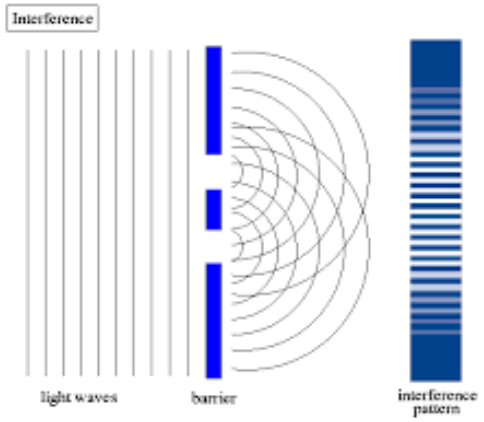

Figure 2: Quantum superposition is famously demonstrated in the double slit experiment. This image demonstrates a version of the experiment in which electrons are fired through two slits in a sheet of metal at a screen. If particles like paint were to pass through the slit, the paint would cover the screen uniformly where it hit the screen. You would be hard pressed to find areas on the screen absent of paint. However, when light, a wave, passes through the slits, the two beams interfere and create a checkered pattern of light and darkness. Electrons behave similarly to light, demonstrating the wave-particle duality of electrons, a superposition of both states (3).

This essential role played by this observation may seem jarring as we're accustomed to a world behaving predictably as dictated by and adhering to the laws of nature, whether or not we're cognizant of it. So, what actually occurs in a quantum system when it's measured? According to the Copenhagen Interpretation developed by Neils Bohr and Werner Heisenberg in the 1920s, when a quantum system is measured, its wave function (which defines states in quantum mechanics) collapses from a state of superposition and becomes a wave function with 100% probability for the outcome seen when measured. This kind of wave function is called an eigenstate. Though we don't know what eigenstate the system will exhibit when observed, we can create probabilities regarding the potential outcomes due to the original wave function. The wave function truly behaves like a wave, oscillating through the space of all potential results of a measurement, with each wave corresponding to a potential outcome. Every wave has an amplitude, a number which, when squared, specifies the probability of that result appearing when the system is measured. So, going back to our cat, her wave function might tell us that there's a 45% chance she is on the chair and a 55% chance she's on the window sill. These are probabilities about the result that will appear when the cat is observed and removed from her state of superposition (1, 5, 6).

Physicists applying these principles to time's arrow have discovered that certain quantum systems, which can evolve towards higher entropy and towards lower entropy (due to their submicroscopic size), evolve in a superposition of both directions. The researchers found that measuring the entropy production in such systems removed them from their state of superposition and placed them back onto a defined time's arrow—either forwards or backward. However, under certain conditions, both processes interfered and the researchers could observe the consequences of this evolution along both temporal directions through the amount of entropy produced by the system (2, 4, 5).

This study offers new information regarding time within quantum systems, which comprise the most fundamental level of the universe. Quantum mechanics, while having no effect on day-to-day life, reveals the true nature of the world. Its strange laws oppose understanding of the most fundamental concepts, sparking the realization that all we intuitively know may not be as obvious as we think. With experiments like this one, scientists make strides in their attempts to uncover the often mystifying and mystical nature of nature and gain a richer understanding of the phenomena that, whether or not we're aware of it, dictate our world.

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Protein the Musical

Nechama Friedman

Science doesn't have to be complex to the point of being frustrating, it can be turned into something enjoyable and perceivable.

Can proteins be Broadway's next big hit? A recent advancement in the study of protein-music is pushing proteins to obtain higher levels of enhanced musicality. Proteins are being translated into music and portraying the vast range of connections found between science and music.

Proteins are molecules composed of chains of amino acid subunits in a precise, designated order, which then fold into complicated shapes. They play vital roles in our lives, assisting many of our bodily functions. Enzymes, for example, help speed up chemical reactions to enable the cell to carry out its jobs more conveniently. They form cellular support structures like collagen in the skin. The structure of a protein can be mapped (using advanced techniques such as x-ray crystallography), showing the amino acids in their order and three dimensional space, giving rise to the myriad of protein shapes (Figure 1). But maps of proteins are foreign to the general public; their complicated depictions are inscrutable to the uninitiated in knowledge of amino acid chemistry.

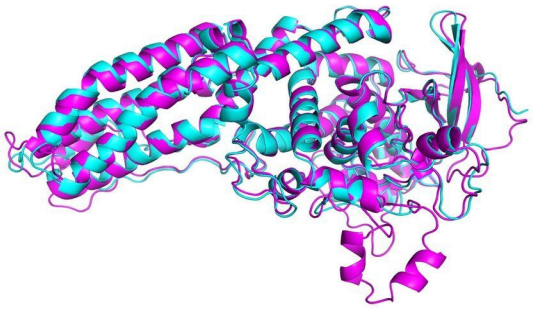

Figure 1 depicts the shape and structure of the protein lipase, which assists in the digestion of fats. The specific conformation, which determines its function, is determined by the particular sequence of amino acids in the chain.The structure includes "lids" that selectively allow certain molecules to enter the active site, and local hydrophobic/hydrophilic concentrations guide the movement of molecules to their proper location within the enzyme, to facilitate the reaction (4)

Researchers at the National University of Singapore and at the Rockefeller University began investigations to make the understanding of protein structure more accessible on a visceral level to individuals curious about science. Towards this goal, the researchers crafted a plan to translate the patterns and properties of the amino acids within proteins into something more regular in most people's daily lives–music (5).

This idea originates from the fact that there are many similarities between features of protein structure and musical structure, the first being their origin. Scientists suspect that the spectral and temporal aspects of music emanate from human biology. The DNA codes for proteins as music notes code for a song. Both music and proteins are composed of building blocks that dictate the aspects of the final product they create in a specific orientation. As a consequence of this structure, music and proteins contain recurring patterns; music in melody and proteins in secondary structure and tertiary (3-D) fold (1).

To achieve the feat of protein-music, the scientists created an algorithm that interprets a given aspect of the protein structure into a corresponding aspect of music. Note lengths, for example, might be determined by the size of the amino acid. They created the algorithm by comparing properties of musical notation with

properties of protein structure and finding the closest factors that aligned with one another. The algorithm they designed is essentially a dictionary that would tell what each property of an amino acid in a sequence would get you in a sheet of music. Each amino acid was picked to represent a quantized aspect of the music when its properties matched up effectively to the value of that musical feature. So, for example, one amino acid could be taken as the definition for the pitch value of a note, like C (1). An entire protein string would code for one song, and as each protein is unique, subsequently, every song made would be too.

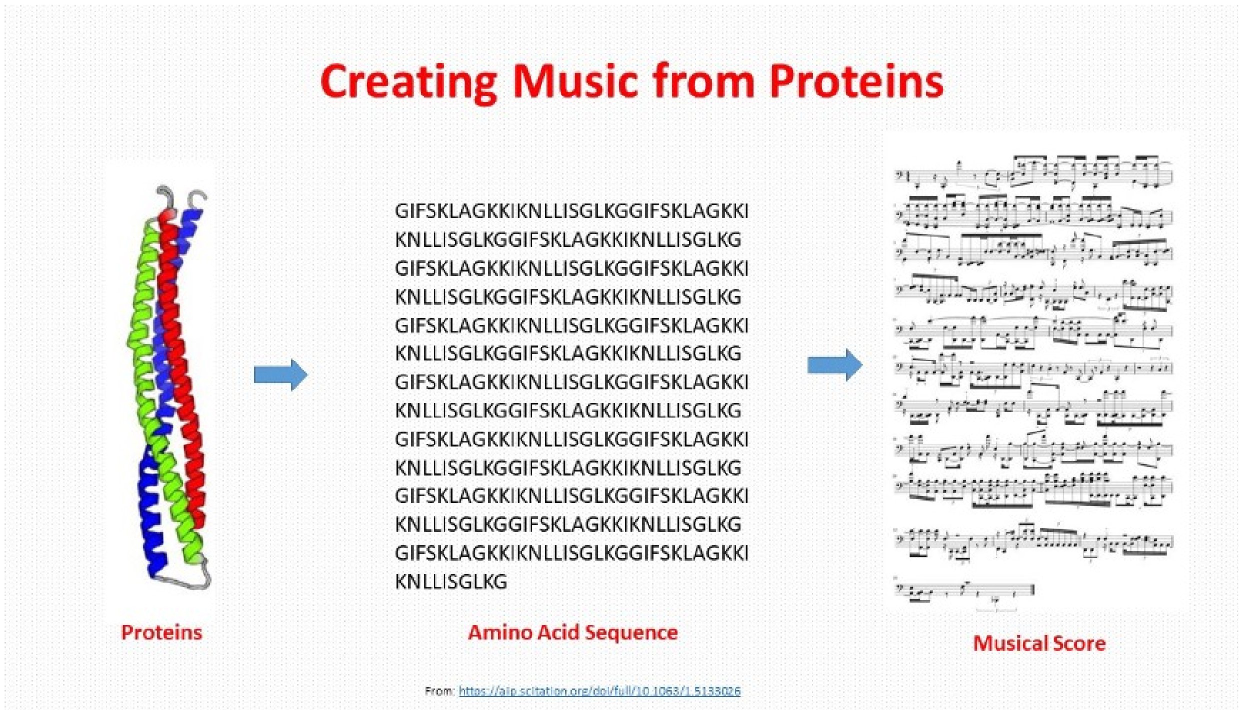

Figure 2: The algorithm developed made it possible to re-identify a given protein as a piece of music. A protein is also known as a polypeptide chain, as it's a string of amino acids joined by peptide bonds. These amino acids individually define different features of the musical piece to collectively compile it in its entirety.

After many proteins had been transcribed using this set algorithm, the researchers noticed that the music created was much less pleasing to the ear than "human music". They inferred the possibility that perhaps the patterns of the algorithm they used didn't cause the proteins to form patterns in the music that were alike to patterns of human music, despite the features they'd matched up. In pursuit of enhancing the quality of the music listening, the scientists concluded that creating algorithms that focus on specific genres could help improve the music. This entailed reconstructing a code with patterns specifically tailored to the pattern tendencies of a chosen musical genre. After constructing a new algorithm that was genre-styled, new music was generated from the same proteins, affirmatively concluding that enhanced music quality could be attained. One of the subjects of the experiment, a protein receptor for oxytocin, specifically portrayed the success of this new method of protein-to-music mapping, having been judged as the one with the greatest increase in musicality compared to the previous algorithm (1). Although the nature of the music generated showed overall improvement in contrast to the previous trial, protein-dictated music still has miles to go before it resembles the music we're used to. Scientists hope that with additional research of a broader range of musical genres, and the help of artificial intelligence to formulate algorithms that properly coordinate amino acid properties with musical features, further improvement in the quality of protein-music can be made.

This article provokes many new insights into the way the world views science. We now see how tightly correlated every aspect of nature is with one another; through their equatable features and patterns, they can all be arranged to complement each other. Acknowledging this can help ease the confusion and misunderstanding inherent in certain aspects of science. If we choose instead to express the same idea in the form of something we can better understand, we can be motivated to learn more than what we believe we can. This was the goal of the researchers that began this study. Being able to express protein structure in musical notation makes the understanding and visualization of protein structure more available to people that aren't necessarily studying this area of science or regular to its terms and style (6). Framing something complex into something more common makes it possible for many more people to fathom the concepts behind protein structure.

That something as daunting and confusing as protein structure and amino acid patterns can be explained through something as universally loved as music is inspiring. Science doesn't have to be complex to the point of being frustrating, it can be turned into something enjoyable and perceivable. Music is also shown to have various uses and purposes, beyond what meets the eye. By finding an instance where music helps interpret the complexities of science, we're shown that music can be influential in even more areas, as well as the possibility of turning many things we're used to into something that can further benefit our world. Perhaps the process could be reverse engineered, where a curative protein drug can be synthesized from already existing sheet music. Beethoven was really a molecular biologist before his time.

This topic creates many openings for future scientific breakthroughs. Understanding protein structure and relating it to similar subject matter can perhaps benefit how scientists create proteins or utilize them in scientific discovery. Proteins are commonly designated towards aiding our health through medicine, and hopefully this research can facilitate the making of new drugs and antibodies that would support the well-being of our society.

Can protein-music still be further improved? Need it be? So much still remains to be seen and discovered about this unique development. Scientists might try to continue the research by encrypting more algorithms based on musical genres. Time will tell if their experimentation will truly help or motivate society to understand proteins. Proteins are truly on their way to becoming the next hit sensation!

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Porky Pig to the Rescue?

Sara Fried

Many see this as a dramatic move, risky and uncertain, and as of yet, an unproven therapy that offers the tantalizing promise of great potential.

In recent events, a middle-aged man is reported to have been living for over three weeks with a heart transplant from a genetically engineered pig. With an organ shortage crisis, the doctor of this man stated that such an accomplishment is a "breakthrough surgery." Xenotransplantation, as it is known, is specifically transferring a non-human organ to a human. Many see this as a dramatic move, risky and uncertain, and as of yet, an unproven therapy that offers the tantalizing promise of great potential. While close to major advancements in xenotransplantation, the developments underway could take years to be finalized (Beil). However, various experiments, such as transferring a pig's kidney to people kept temporarily alive on ventilators, may prove that something formerly thought to be way out of the bounds of science, might finally be possible.

Transplantation generally is the transferring of tissue, organ or cells, from one area to another to rebuild or repair organs and tissues which have been damaged or deemed incapable of working productively. Each year, countless lives are saved by operations involving organ donors. The main difficulty is that such operations only are made possible using a drug regimen to fully insure the immune system will not reject the new transplant. This is the reason why a recipient and their donor are always meticulously matched for transplantation, using similarities from blood-types to the way in which the recipient's cells react generally to newly identified cells. However, the immune system poses a threat to the transferring of organs belonging to different species. More well known as rejection, the immune system may view the transplanted organ as foreign, and ultimately cause destruction to the organ, which can be fatal to the human body.

To detour around the immune system's barrier, intervention is required to increase chances for longer term survival with the newly implanted organ. Immunosuppressive drugs are administered to block the response of the immune system and avoid rejection; however, this poses a huge risk of succumbing to relatively mild infection. Research is continuously conducted to discover the best and most innovative strategies for preventing rejection, allowing for smoother, more concise transplantation and diagnosis with relevant treatment. The more foreign the species, however, the more difficult it may become to devise the best plan to successfully integrate the foreign organ into the human body (immunology.org).

It is interesting to note that one might believe monkeys or apes should be the most useful in terms of effective xenotransplantation, since these species are seen as very closely related to the human itself. To provide animal organisms free of potential viruses that could be life threatening to humans, monkeys would have to be birthed by c-section and then raised completely isolated from other specimens. This poses various issues of animal cruelty; there would be a requirement to raise the monkey in isolation. Evidently, this would prohibit the apes from psychologically developing naturally, being unable to interact daily. Pigs on the other hand, are produced in multitudes and can be raised in a way in which they will be free of treacherous viruses and other damaging diseases; isolation wouldn't be a mainstream issue in terms of these species. Most importantly, their

organs are more unlikely to pose harm to humans by the human body rejecting the xenotransplant; their organs are found to be quite alike to humans' in shape and specific functions (Weiss).

This knowledge would have been vital to researchers and doctors in the mid twentieth century, when xenotransplants were even more astounding to the public. Since the 1960s, xenotransplants have made headlines, with reports detailing the risks which were undertaken in the operation. In an attempt to save a near-dead man, acclaimed surgeon Denton Cooley used the heart organ of a sheep as a solution to organ failure. Unfortunately, rejection of the newly identified organ by the body was quick in coming. Additionally, in 1984, Loma Linda University Medical Center in California endeavored at xenotransplantation when doctors attempted to save a two-week-old baby with a cardiac defect, resulting in a baboon's heart sewed into the infant. She only survived twenty-one days. At the time, reports such as these were referred to by some people involved in the medical profession as "beastly business", and in fact, it caused such a controversy that the 1995 report of the Journal of American Medical Association asserted to the fact that the scientists involved in the experiment left their standing posts and "beat a hasty retreat back to the laboratory" (Beil).

Despite being constantly pushed away by moralists who stated arguments against their endeavors, and after countless trials and errors, in the 2000s a group of researchers created genetically modified pigs that were engineered in such a way that removed the alpha gal sugar molecule coat around the cells. This coat can trigger rejection in the human immune system. In addition, they also took into account the swine genome in the pigs containing embedded viruses. These are viral genes woven into the genetic material; they don't affect pigs, but in other species such as humans the effect is inconclusive and can prove threatening.

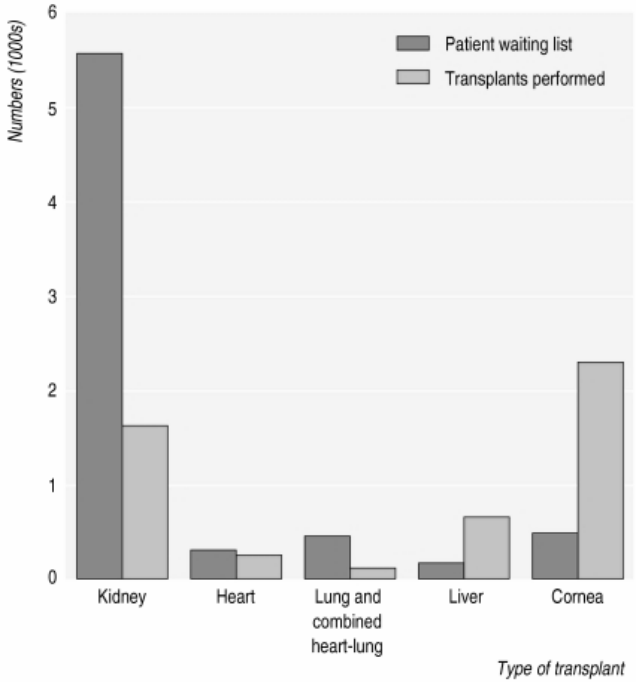

Figure 1 demonstrates a significantly large number of organ transplant operations that were performed in the United Kingdom in 1997 and the comparable size of the waiting list. Unsurprisingly, the request of organ donors for kidney transplants overtook the rest. Surprisingly, transplants of corneas and liver meet the demand and the number of patients on the waiting list is low. Perhaps the reason for corneas is that they have limited vascularization, which limits rejection. Livers can regenerate making the transplantation of an entire liver unnecessary.

Making these species genetically compatible with humans was a big enough feat on its own. In 2020, Revivicor pigs were accepted for transplantation of their organs into humans by the U.S. Food and Drug Administration. In October 2021, NYU Langone Health in NYC had a Revivicor kidney transplanted into a "brain-dead" patient who was then observed for 54 hours which is considered enough to see if there were early signs of rejection. After two months, the experiment was repeated, and a third transplant by the University of Alabama at Birmingham was made to a man into his abdomen which kept him alive temporarily, though only

on a ventilator (Beil). In the late twentieth to early twenty-first century, numbers of requests for organ donations are quite high and continue to grow, making these xenotransplantations a significant development.

Due to the huge gap between need for transplants performed and requests for donors, as new diseases begin to be treated more often by xenotransplantation, the need for organs will continue to rise. It is simply impossibly difficult to find enough organ matches from humans to completely support the increase (Weiss, 1998). The organ-shortage crisis was a main reason for the modification of a pig in order to use its organ in the first place. In another transplantation of Revicocor organs, the kidneys of a clinically brain-dead person were extracted and replaced with two xenotransplanted kidneys from a genetically modified pig. When they reattached the blood vessels, the blood flow was adequate despite the human blood pressure's exposure to the implants. No rejection of the newly identified organs was seen, and the kidneys functioned until approximately 74 hours after, and it was found that no viruses were detected. Although the kidneys could produce varying quantities of urine, the full function of the kidneys did not return.

The possibility of brain death or microvascular injury could prove an interfering factor with xenotransplantation, although the explanation is not known. This further raises questions of which patients are the best candidates for such operations. Major obstacles concerning such xenotransplantation and its complication may have been somewhat resolved. Xenotransplantation is proven to be capable of producing desired results, and in addition, usage of specifically modified pigs is a step forward in ensuring that the body does not dangerously react in rejection. This has been one of the major issues surrounding the throngs of Xenotransplantation for decades (Porett).

In August 1999, a study was conducted in which over 100 people were given medication with living pig tissue. There was zero observation of the suspected possibility of infection, proving that it may be possible to survive with pig cells with no long-term negative effects. Several people were additionally considered to be at higher risk of infection. Despite jumping through multiple hoops to remove possible dangers certain organs might pose, the eventual response of the body to the new organ is still relatively unpredictable and unknown, and so this idea must be further studied (archive.bio.org).

As we go deeper into the 21st century, humans have been able to make significant comparisons between animalistic and human characteristics, which has contributed to the understanding of xenotransplantation. In the future, the understanding of the similarities between the way a human's body functions versus the way an animal's body functions will hopefully increase and continue to help people who need organ replacements. Not yet ready for prime time, with more research, this might be the best solution to the problem.

In the Jewish realm, xenotransplants should raise red flags of halachic ramifications. According to the Torah, a pig has split hooves but does not chew its cud and is therefore excluded from the list of kosher animals, making them forbidden for Jews to eat. The Sages expressed disgust at this animal, and set a prohibition on raising pigs. On the other hand, there is no problem with receiving insulin from pork. When saving a life, in fact, Judaism allows consumption of non-kosher food by mouth (Brody). With all intricacies of discerning halachic issues, hopefully there will be an unambiguous conclusion which will be of assistance in this groundbreaking research of xenotransplantation, saving countless lives in the future.

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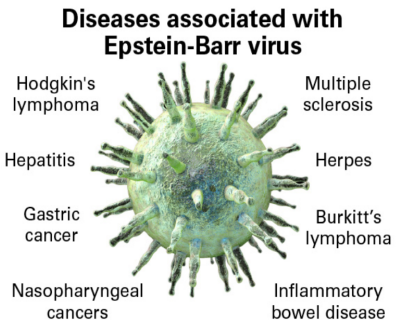
The Stealth Bomber Virus

Devorah Ginsberg

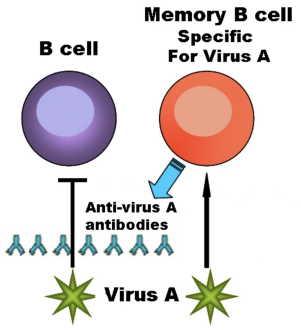
Some people jokingly say that EBV stands for "everybody's virus" since essentially everyone in the world gets it.

Chances are that you or someone you know has been infected with the Epstein-Barr virus. By the age of eleven years old, half of the world's population has been infected. Many get it as a toddler in school or from sharing a drink with a friend, but by adulthood, 95% of the world has had it. Some people jokingly say that EBV stands for "everybody's virus" since essentially everyone in the world gets it (11).

In 1964, pathologists at Middlesex Hospital in London, Michael Anthony Epstein, Yvonne Barr, and Bert Achong, received samples of tumor cells from their colleague Dr. Denis Burkitt. While in Uganda, Dr. Burkitt noticed that an unusual number of children were developing jaw tumors, a phenomenon later named Burkitt's Lymphoma. When Epstein and Barr looked at the samples under an electron microscope, they found a new member of the herpes virus family and thus established this virus as one of the causes of Burkitt Lymphoma. This was the first time that a virus was discovered to cause cancer. (6) The Epstein-Barr was later shown to be definitively linked to other cancers like Hodgkin's Lymphoma, as well as certain stomach, head and neck cancers. EBV is linked to 1.5 percent of cancers worldwide (3).



Most childhood infections of Epstein-Barr are either asymptomatic or very mild. However, when acquired during adolescence (the age of the students at MHS), it often causes Mononucleosis or Mono. You or one of your friends have likely had Mono. The symptoms are fever, sore throat, swollen glands (hence the nickname glandular fever), and a possibly swollen spleen. Most of these symptoms last only about two weeks; however, another significant symptom is extreme fatigue. This exhaustion can linger for much longer, even up to six months (which is why schools often are understanding about absences when it comes to Mono (1).



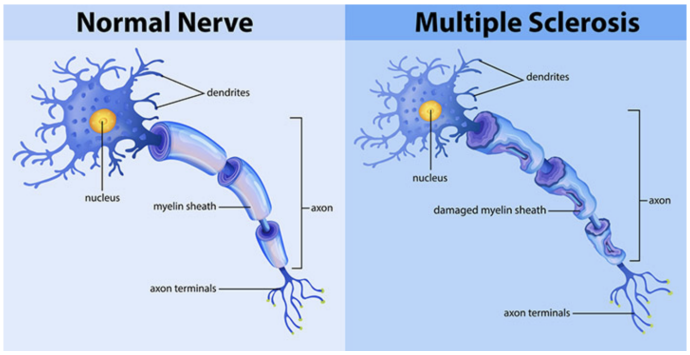
EBV is one of the nine types of known herpes viruses. It is usually spread through saliva, or sharing food, but can also be spread through a cough or sneeze. First, it infects the epithelial cells in the throat and then moves on to infect B-Cells, a type of white blood cell that makes antibodies. This virus does something pretty remarkable: it keeps itself hidden for decades by concealing itself ironically in the one place our immune system would never look, ***inside*** the immune cells themselves.

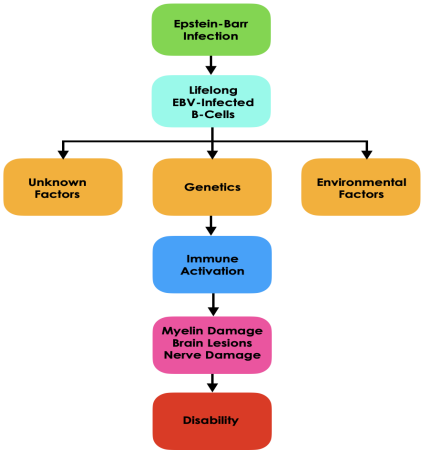
In order to understand how EBV evades the immune system, one needs to understand a little about how B-cells and the immune system work. To protect the body from foreign invaders such as bacteria and viruses, B-cells circulate around the body looking for antigens, which are identifying proteins displayed on the surface of cells that allows the immune system to distinguish between foreign cells and self cells. When B-cells detect a foreign antigen, they transform and proliferate into specialized B-cells that ramp up production to make specific antibodies to fight that exact

antigen. To protect the body in the future from that antigen, as it finishes up fighting the infection, some of these specialized B-cells turn into memory B-cells. These cells are there forever to protect the body if that antigen appears again. They are like the army in reserve that can be called up at a moment's notice to begin fighting the familiar invader immediately (10).

After EBV infects the epithelial cells, it deviously infects the B-cells. And when those B cells turn into memory B-cells, the Epstein-Barr virus has found a place to hide and lays dormant, biding its time, waiting to attack. EBV is a DNA virus, and like other DNA viruses, it can ingratiate and integrate itself into the host genome, like the mole in an espionage thriller. It remains hidden under the radar until triggered to reactivate. Until the trigger, the viral DNA lies dormant and when the host cell replicates its DNA, the viral DNA is replicated in tandem. RNA viruses, such as COVID and SARS are cleared relatively quickly because RNA lacks the stability of DNA and is degraded. The chickenpox virus (Varicella), another DNA virus, remains inactive in the nervous system after an infection. A reawakening of the Varicella virus in the nerve cells later in life results in a very painful illness called Shingles. A reawakening of Epstein-Barr can result in different types of cancers and, as has recently been discovered, autoimmune disease (9).

For many years, scientists have thought that there was a possible link between the Epstein-Barr Virus (EBV) and Multiple Sclerosis (MS), an autoimmune disease affecting 2.8 million people (10) worldwide; until now, however, scientists had not been able to prove this. Two recent studies finally prove the link that Epstein-Barr causes Multiple Sclerosis. Multiple Sclerosis, like other autoimmune diseases, is where the immune system mistakenly attacks healthy cells in the body, believing that they are foreign. Many autoimmune disorders attack specific types of cells, such as in Type 1 Diabetes, which targets the pancreas, and in Rheumatoid Arthritis, which attacks joints. In the case of MS, the immune system strikes the central nervous system. It attacks the myelin, the insulation cover of the axons of nerve cells, disrupting the communication of nerve signals. The name Multiple Sclerosis refers to the lesions or scars ("sclerae") that develop from this damage. An MS attack or relapse, which occurs randomly, can cause motor, sensory, or visual problems and can last for days or weeks. These symptoms can either disappear entirely or leave permanent impairment. MS is an unpredictable disease with no cure that can affect each patient differently, leaving some with almost no symptoms and others with disabilities like losing the ability to walk (4).





The cause of MS is unknown. Scientists think it is a combination of multiple factors that trigger MS. Firstly, there is a genetic component. It is not an inherited disease which means it is not passed down from parent to child, but 200 genes have been identified that each can contribute in a small way to developing MS. Secondly, there is an

environmental component, such as smoking or vitamin D deficiency. Thirdly, an infectious factor is also suspected, like a virus or microbe, and for many years scientists have believed that the ubiquitous Epstein-Barr virus was the culprit (10).

How do you create a study that shows a link to a virus that all of humanity is infected with? EBV and its antibodies have been disproportionately found in people with autoimmune diseases such as lupus, rheumatoid arthritis, and MS. There have been suggestions of a correlation, but firstly, how do you come up with a control group when everyone has had EBV? Secondly, the study would take many years since it takes about ten years from an EBV infection to the onset of MS symptoms. One would need a control group that consisted of people before they caught EBV. The researchers at Harvard were able to use a massive archive of 10 million serum samples taken over 20 years from the Department of Defense that routinely tests for the unrelated disease, HIV. This solved both issues that the study might have (2,8).

From there, the researchers were able to find several hundred thousand people that tested negative for EBV, and of those, 955 people eventually tested positive for MS. The results showed that people infected with EBV were 32 times more likely to develop Multiple Sclerosis (5). A second study explains how Epstein-Barr might cause MS. Scientists discovered that roughly 20-25% of MS patients have antibodies that bind to a protein from the Epstein-Barr virus, called EBNA, and the protein GlialCAM that is made in the brain and spinal cord (7). What these studies strongly suggest is that an Epstein-Barr infection is a prerequisite for developing Multiple Sclerosis. Since only a tiny fraction of people who get Epstein-Barr get MS, it must be a combination of EBV, genetics, and environmental factors, but Multiple Sclerosis will not develop without having first gotten Epstein-Barr.

The question remains what do we do with this new information? The idea that a vaccine might prevent Multiple Sclerosis is really exciting. Currently, there is no vaccine for Epstein-Barr. Maybe it is because it is such a common infection that we thought rarely caused severe illness. As long as the evidence between EBV and MS was not proven, there was not an overwhelming amount of commercial interest for an incredibly common infection that rarely caused serious illness. There are two current clinical trials for an EBV vaccine. Since cancers and MS take years to develop from an Epstein-Barr infection, it will be a long time before we see if the vaccines for Epstein-Barr works at preventing these illnesses, but even the prospect of having a vaccine for MS – an incurable, debilitating disease – is thrilling.

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Skinny Mice Pay the Price: The Cost of Vision Acuity

Zippora Harris

Despite representing only 2% of the body's weight, the brain uses a disproportionately large share of the energy–nearly 20% of the caloric intake.

Despite representing only 2% of the body's weight, the brain uses a disproportionately large share of the energy–nearly 20% of the caloric intake (Herculano-Houzel). This energy use is critical during periods of starvation; glucose is diverted from other body parts to ensure that the brain maintains its energy supply (Watford). However, it is not clear exactly how the brain uses that energy. Specifically, how is energy allocated among the various brain functions? Previously, it had been shown that energy was needed for fruit flies to form memories (Placais), but until now, no one has demonstrated how energy impacts brain function in mammals.

Dr. Padamsey and colleagues set out to find out the relationship between energy use and neural processing of information. To do so, they examined the energy consumption and neural processing of visual cortex neurons in food restricted mice compared to normally fed mice. The experimental mice were food restricted over two to three weeks until they were at 85% of their normal weight. The authors then implanted microscopes and glass electrodes into the mice's brains to record the activity of visual cortex neurons while the mice watched a movie containing nature scenes. Importantly, the mice were fed as much food as they wanted to eat just before they were tested, so the results were not affected by the distracting effects of hunger (Padamsey).

Neurons communicate with each other by a combination of electrical and chemical activity. A neuron excited beyond a threshold develops a brief, intense, surge of electrical activity called an action potential. *(See A. Cohen, "Seeing the Light," in this publication)*. The action potential causes the neuron to release chemicals known as neurotransmitters which bind to receptors on a neighboring neuron. When neurotransmitters released from the first neuron bind to the receptors on the second neuron, the channels open, allowing a flood of charged ions to enter. This changes the electrical state of the second neuron, initiating an action potential in the next neuron along the pathway.

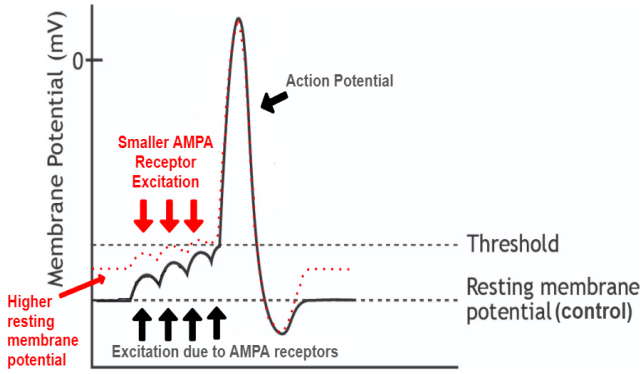
One example of a neurotransmitter is glutamate which binds to AMPA receptors and excites neurons by allowing positive ions into the cell. When AMPA receptors excite a neuron sufficiently to cross its threshold, it fires an action potential. *(See L. Borenstein, Laughing Through Depression in this publication)*. By placing a glass pipette (connected to an electrical circuit) up against the cell and poking a small hole in the membrane, the authors could measure both action potentials and the excitatory currents due to the binding of glutamate to AMPA receptors. Excitatory currents are known to use 57% of the brain's adenosine triphosphate (ATP, the body's energy currency) and action potentials use 23%.

Interestingly, in food-restricted mice, the AMPA receptors generated smaller excitatory currents in response to visual scenes, resulting in 29% less ATP use than in control mice. What is more surprising, even though the visual cortex neurons of food deprived mice received less excitation, visual scenes induced similar rates (and heights) of action potential activity (Padamsey). Figure 2A illustrates that visual stimuli induced similar action potential firing rates in control and food deprived mice. This finding suggests that even though

food deprivation reduced excitation to the neurons, which should have made it difficult for visual scenes to activate neurons, somehow the neurons compensated and could detect the scenes regardless.

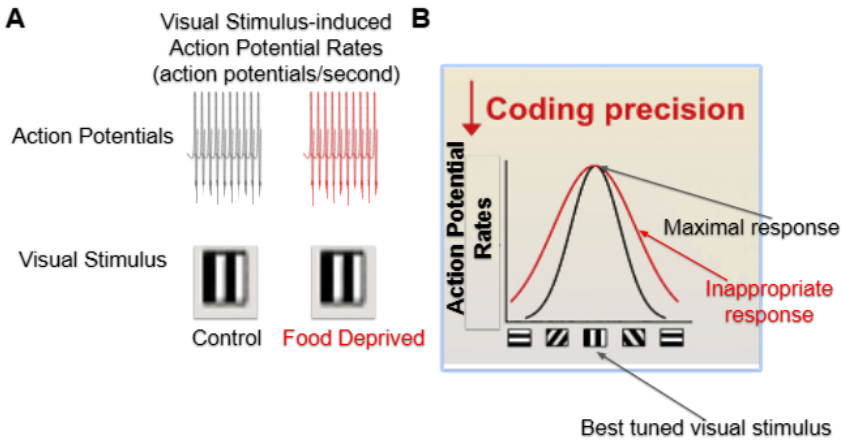
These findings raised a question: if visual scenes induced less excitation of visual cortex neurons, why was not the rate of actional potential activity in response to the movies similarly reduced? Why did it remain the same? It turned out that the membrane potential in the neurons of the food deprived mice were constantly resting at an elevated excited state, so it took less excitation to reach the threshold for generating action potentials *(Figure 1)*. This adaptation saved energy under conditions of starvation (Padamsey).

Figure 1. Glutamate binding to AMPA receptor causes excitatory currents (black vertical arrows) that move the neuron from the resting membrane potential (lower black dashed line) towards the threshold (upper black dashed line). When the membrane potential crosses threshold, the neuron fires an action potential (diagonal black arrow). When the mice are food deprived, glutamate binding to AMPA receptors causes smaller excitatory currents (vertical red arrows). However, the neuron rests in a more excited state (diagonal red arrow) making it easier to reach threshold. Figure adapted from https://openbooks.lib.msu.edu/neuroscience/back-matter/additional-review-answers/



This strategy of saving energy had downsides. Since it was easier to trigger an action potential, even visual stimuli that normally wouldn't drive a neuron to fire an action potential would do so in the food deprived mice. As a result, while normally there would be a narrow bell-shaped curve of the rate of action potentials in response to visual stimuli, in the case of the food-deprived mice, that bell-shaped curve became 32% wider. As can be seen in figure 2, while in control conditions, a neuron might have unique action potential responses to vertical vs diagonal lines, allowing for visual discrimination between the two, in food deprived conditions both of these stimuli would trigger action potentials. As a result of this broader tuning curve, the food restricted mice had decreased ability to distinguish subtle visual differences. For example, they were not able to get a reward that depended on differentiating between vertical and diagonal lines (Padamsey).

Figure 2. ***A)*** *Firing rates of action potentials are similar for control (black) and food deprived (red) mice when presented with the same visual stimulus.* ***B)*** *A schematic of action potential responses to different visual stimuli during control (black) and food deprived (red) conditions. Under control conditions, neurons are tuned to fire the maximum rate of action potentials to the correct visual stimulus and to fire very little to other visual stimuli. However, in the food deprived condition (red), the neurons fire action potentials both to the correct visual stimulus and inappropriately high to other visual stimuli. Adapted from Padamsey et al. 2021.*



The authors were still left with one major question: what was it about starvation that caused the neurons to change the way in which they functioned? Leptin is a hormone released by fat cells that regulates metabolism by monitoring energy state and controlling appetite (Kelesidis). Since there were fewer fat cells in the food-deprived animals, there was less leptin. The authors hypothesized that this decrease in leptin is responsible for the changes in the way the neurons functioned. To test this idea, they gave the food-restricted mice supplemental leptin and found that doing so restored normal visual abilities, supporting their hypothesis (Padamsey). However, it remains unclear by what mechanism leptin is able to improve vision.

This article demonstrates how the brain conserves energy to maintain intellectual function even under prolonged conditions of starvation. It also reveals the negative consequences of that conservation strategy. This topic is important because it can add to the understanding of how nutrition impacts our ability to think properly. Since it shows that ATP is critical for precise cortical functioning, these results open the question of whether eating properly on a daily basis could help people solve intellectual problems. However, in order to address this question several outstanding questions need to be addressed. For example, do the findings in the visual cortex apply to other brain regions which process more abstract reasoning about concepts? Do small changes in nutritional status such as those that result from skipping breakfast impact precision or do these effects only develop when the individual is starving? Most importantly, do the findings from this study apply to humans (such as those with anorexia) or are they only true in rodents?

In addition to these outstanding questions, future experiments need to be done to understand the role of leptin in mediating the effects on the neurons and to discover what is responsible for depolarizing the resting membrane potential? Discovering these relationships may help us understand fundamental features of nutrition and how the brain processes information efficiently.

In summary, food deprivation causes the neurons to be unable to distinguish between subtle visual differences. The Gemara rhetorically asks (ירושלמי ברכות פ"ה ה"ב) אם אין דעת הבדלה מנין, without knowledge, can there be distinction? This research highlights this concept perfectly by showing us how the brain needs to function properly (דעת) in order to properly distinguish between different visual stimuli (הבדלה).

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Smoky Has a Helper

Yael Herskovitz

Despite all of these advancements in predicting forest fires, they still happen, and it is important to find a way to finally control them and limit the resultant damage to the ecosystem.

In the summer, this city gal travels 3 hours just to be upstate. The fresh air, animals, and forests full of trees are breathtaking.The sublime beauty of untouched nature leaves me awestruck in contemplation of *'Mah Rabu Maasecha Hashem!'* The intricate patterns and coherent interconnected processes of nature prove that every blade of grass is under the control of Hashem's guiding hand. My *kavanah* during davening is intensified. Unfortunately, forests around the world are at risk. Because of global warming and the associated rising temperatures and decreased rainfall in certain areas, uncontrolled forest fires are increasing in frequency, intensity and proving to be a growing international threat. Many species of trees are naturally adapted to recurring fires. Some have a very thick bark that shields the cambium in the trunk from fire. In some kinds of pine, cones open because of the heat from the fire, causing the seeds to come out and allowing for a quick recovery. However, not all trees are naturally so fortunately endowed. Therefore, the long-term impact of the increasing number and intensity of forest fires on the forest's ecosystems is being estimated with Artificial Intelligence to help vulnerable trees to survive (Seidel).

Artificial Intelligence (AI) is a software that mimics parts of human intelligence and makes predictions based on data, learning from the world around it. It has been demonstrated that computers are learning to read CT scans and learning to diagnose medical conditions with astounding accuracy, surpassing that of human pathologists (Mukerjee). Computers have moved beyond simply following the instructions spelled out in the programs designed by human engineers; they are now capable of learning from the patterns of the data that they are fed and applying those patterns to novel situations to make accurate predictions.

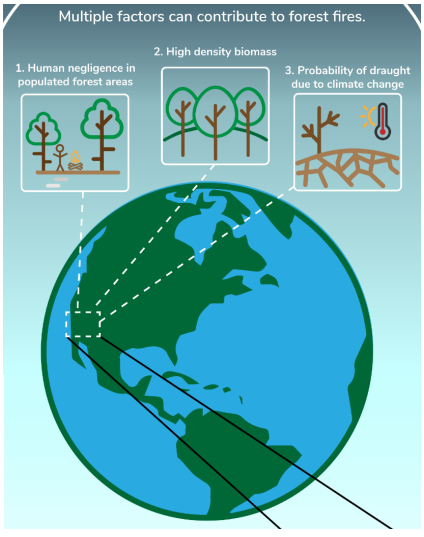
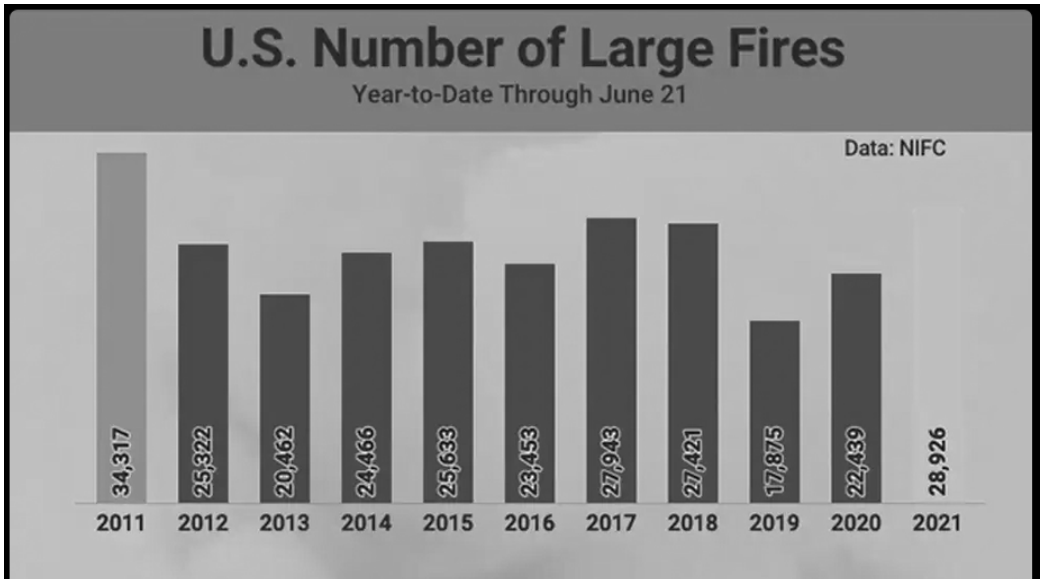


Figure 1: AI generated map of potential fire "hot spots."

Results of these simulations show that in the United States, Yellowstone Park's currently untouched vast forests in all likelihood have fewer trees by the end of this century. Advanced simulation models are needed to

calculate the many complex interactions between forest fires, the climate, and forest ecosystem processes. To effectively mimic the behaviors of the complex simulation model, researchers implement a deep neural network that learns based on how ecosystems reacted to environmental changes in the past, in order to make projections for the future. The great thing is, it only takes a small fraction of computing power that most large-scale simulations otherwise would. This enables researchers to analyze larger areas with higher-resolution simulations (Seidel, *see Figure 1*).

Simulations of Yellowstone Park were performed across 8 million hectares to calculate how different climate change scenarios in the 21st century would change the repetitiveness of the forest fires and determine which parts of the forest will not be able to regenerate. Using these predictive models and algorithms, the researchers have discovered that by the end of the century, 28%-59% of the forest will disappear. Most of the tree species that are not naturally adapted to forest fires, and the flat landscapes that cannot stop the spread of the fire, will be lost. Forests are threatened because not many seeds will make it to the ground. The drier and hotter it is, the fewer young trees will survive and won't be able to grow enough to produce seeds at all. In addition, trees need more water than grasses and small shrubs to grow. Destruction of the trees will encourage the growth of these understory species and the forest ecosystem will be altered in their favor (Durgadas). *(Figure 2)*



All the services provided by the forest will be gone. With the performance of photosynthesis and its relatively slow turnover, forests provide carbon storage in the form of organic compounds, which protects against future global warming. With the extensive underground network of roots and mycorrhizae fungi, soil erosion is minimized and soil fertility is enriched. In comparison to grasses and shrubs, forests provide much biodiversity and recreational value. Forests provide habitats for many species of animals, birds, and essential fungi. These studies and simulations are created to educate visitors to Yellowstone Park about the dangers of climate change and the importance of protecting our forests.

AI is not limited to predicting forest fires but can also be utilized to predict other natural disasters and potentially prevent tragic loss of life and property. If we know what will happen in advance, we can prepare and react with the proper measures; to be forewarned is to be forearmed. For instance, it has been used to make

better predictions about where earthquake aftershocks are going to hit. Scientists have found that AI predicted where these aftershocks would be better than the way seismologists normally predict them (Gramling).

In addition to the new AI fire predicting technology, Portugal's Compta Emerging Business and IBM have teamed up to create something different, that not only predicts forest fires with AI, but their device, Bee2FireDetection, detects and alerts firefighters and communities when there is a fire. To fight these fires more quickly and efficiently, it uses AI from IBM Watson, The Weather Company data, and IoT data. Bee2FireDetection is a spectrometric camera that analyzes thermal imaging and chemical components and can identify the signs of a possible fire whether it be heat spikes or smoke column patterns. Bee2FireDetection can detect fires over nine miles away and alert the necessary people in real-time to contain the fire (Correia, Figure 3).

Figure 3: The Bee2FireDetection camera, currently available worldwide, is saving lives with its brilliant fire detecting technology.

Since forest fires are common and dangerous in the United States, the federal government should assume greater responsibility for the damages that forest fires cause on private and public forests. The government should be putting more funding into research like IBM's. This is something everyone wants to stop, and using AI helps prevent damage that is bad for the people and the country (Wiener).

Not only are forest fires on the rise in the US, but in Europe as well (Figure 4). Plans are already underway to introduce this AI technology globally. Israel is another country that has been recently plagued with forest fires. In the north, between Har Carmel and Har Hermon there are many forests which makes this area highly vulnerable to forest fires. In 1991 there were around 274 forest fires in northern Israel and a lot of the forests were burnt. How can these fires be prevented? Other solutions have been proposed that do not involve AI but are just as helpful. Suggestions include dividing forests into smaller parts that are broken up by roads that do not have any vegetation, pruning trees about 13 feet above the ground so that there is less-flammable substance on the lower part of the trees, and planning controlled fires that rid weeds and leaves from the forests before the summer and planting trees that can quickly recover from forest fires (Harpaz).

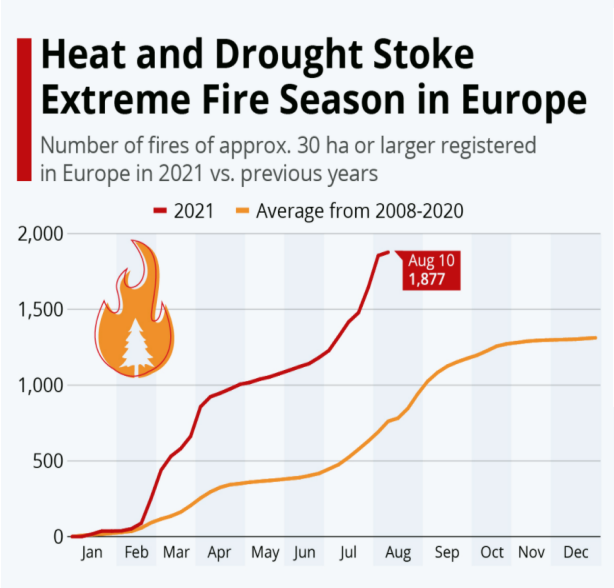


Figure 4: This chart stresses the rising frequency of Europe's forest fires in 2021, compared to 2008-2020.

Despite all of these advancements in predicting forest fires, they still happen, and it is important to find a way to finally control them and limit the resultant damage to the ecosystem. A question that still needs to be addressed is whether there is a way to improve the precision of the predictions made on forest fires. This can help us take the proper precautions if we know exactly when and where a fire is likely to happen. Looking at the fascinating research of these scientists, it is clear that humans have the brainpower to solve the problems that come their way and although something may seem unsolvable to one, with collaboration and cooperation, another will find a solution. There is something everyone can do to put an end to unnecessary forest fires caused by rampant climate change.

On the other hand, there are those who argue that we should not be overly zealous in our firefighting activity. Periodic fires are essential to the health of forests. Fires open the forest up to sunlight, nourish the soil, clean debris from the forest floor, and take away low-growing underbrush. If there is less competition over nutrients, a tree can grow healthier and stronger. Hundreds of years ago, before humans interfered with forest fires, the forest ecosystem was more resilient and healthier (Benefits of Fire).

The researchers at the Technical University of Munich plan to use Artificial Intelligence to analyze the effect of climate changes in Europe's forests too. If the university can disperse their technology over the globe, most of the world's fires can be avoided before they even start. We must spread awareness of the dangers of climate change and continue to research ways to put an end to catastrophic forest fires once and for all.

Forest fires don't just affect the environment but also the humans that live in and near the forests. Trees provide us with oxygen, stabilize the soil, and store carbon. They also supply us with matter we can use as tools and as shelter. Without trees, the survival of animals and humans would be at risk. If forest fires burnt down all the trees because of carelessness or because we didn’t take the proper precautions, our quality of life would be severely impacted, not to mention all the other non-human inhabitants of the forests.

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Copycat Science: Twins Born of Different Mothers

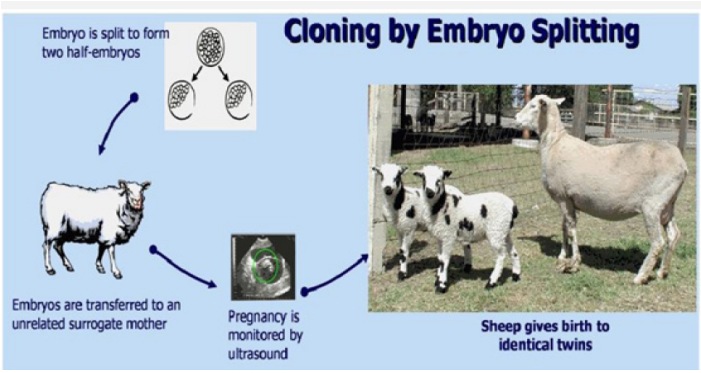
Aliza Herzog

It is extremely difficult to successfully clone an animal in entirety; the failure rate approaches 90%. When successful, well-deserved celebrations are in order.

Solve this riddle: My daughter is my identical twin, yet we were born years apart. How is this possible? Through cloning a replica of DNA, scientists are attempting to create genetic copies of an organism of a species that nearly became extinct and provide it with a possible source of genetic diversity. Genetic diversity is important to the survival of a species as it allows species to adapt to any environmental changes and it ensures that they can be brought back from the brink of extinction. Researchers were able to successfully clone and breed this animal, a black-footed ferret named Elizabeth Ann, by using preserved cell samples.

Cloning is a technique scientists utilize to create precise genetic copies of an entire living organism. To the uninitiated, it appears to be a relatively straightforward procedure; however, there is actually a lot of work and understanding that is required, and many pitfalls that must be avoided. It is extremely difficult to successfully clone an animal in entirety; the failure rate approaches 90%. When successful, well-deserved celebrations are in order (Center for Food Safety).

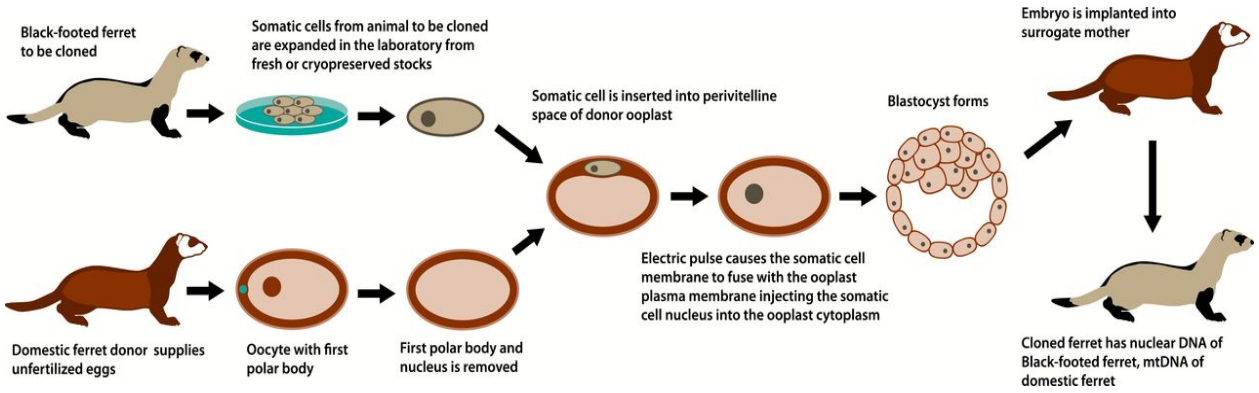
There are two methods of cloning. The first is called Embryo Splitting or Twinning. This refers to the formation of twins or multiples, through the splitting of an animal embryo in the early stages of development. An embryo is split, and both separated halves of the embryo are inserted into the female's uterus, where they develop into individual animals, both sharing the exact same genes. Embryo splitting is extremely efficient to assist reproduction and has been developed into the animal system. This is analogous to what happens naturally in the case of identical twins, only here the separation is deliberately purposeful.



The second, more complicated method of cloning, is called somatic cell nuclear transfer. In order to clone, scientists must first collect a single body cell from the animal they wish to create a replica. This somatic cell has the complete complement of homologous chromosome pairs, and is termed diploid. They then remove the nucleus from an egg cell from the ovaries of a second animal. Egg cells have only 1 set of chromosomes and are termed haploid. Only when fertilized, do egg cells become diploid and only then can they proceed to grow and develop into a fetus if they are provided with the proper environment. The researchers fuse the enucleated egg cell with the diploid somatic cell. This fused egg cell has the nucleus and all the genetic information of the donor animal only, and is now diploid so it will then proceed to grow and develop when implanted into a surrogate host female. The offspring

is a genetic replica of the animal from which they originally retrieved the somatic cells. The offspring will have none of the genetic endowment of the animal that provided the egg cell (Brown).

In 1979, a plague spread to the black-footed ferret species, and they were subsequently declared extinct. Oliver Ryder, a scientist who specialized in chromosomal evolution and endangered species, decided to collect cell samples from several animals, one being the black-footed ferret, with the hope it would one day become of value. Decades later, scientists stumbled upon these preserved cell samples of a ferret named Willa. They were able to use these cells to captively clone and breed a black-footed ferret named Elizabeth Ann. The success of cloning Elizabeth Ann was a triumph, as it prevented the extinction of the entire black-footed ferret species.



Previously, the Roslin Institute, while researching more efficient ways to produce animals, cloned the first ever mammal: a sheep named Dolly. She was cloned using the cell of a six year old Finn Dorset sheep, and a Scottish Blackface sheep. The outcome was not so rosy for her. Dolly aged prematurely and developed tumors growing inside of her lungs. She was put to sleep on February 14th, 2002 at the age of six to prevent further suffering. The scientists mistakenly retrieved the cells from an adult sheep, resulting in her telomeres being much shorter than usual as they were never fully renewed. Telomeres are tips of DNA molecules that protect the DNA from damage. With age, the telomeres shorten and function as a molecular timepiece. Researchers have learned from this error the importance of retrieving cells from young animals, rather than adult animals (Bioscience for the Future).

The U.S Food and Drug Administration discusses the reasons for cloning and what can go wrong. Health problems do not commonly occur when cloning, aside from when attempted on calves and lambs. This is because cloning interferes with the normal genetic functioning of these animals. Many scientists have deeply researched this topic, and after hundreds of tests, can safely say that clones are perfectly healthy and behave just like conventionally bred animals (U.S. Food and Drug Administration). Since there is not a high risk in the safety and health of cloned animals, there is an intense interest in cloning.

One crucial reason for cloning is to prevent the loss of nearly extinct animals. The scientists who cloned Elizabeth Ann did so to prevent the extinction of the black-footed ferrets. Another reason for cloning farm animals is to propagate disease resistance and suitability to climate. Sometimes there is a need for an animal that is not originally bred in a particular climate and cloning is an efficient way to breed one's desired animal (Food and Drug Administration). However, it is not entirely sensible to breed an animal in a climate it is not suited for as it introduces alien species, which are species non-native to an ecosystem (IUCN). The main issue with alien species is that it negatively impacts native biodiversity.

The concept of scientifically cloning animals has immense benefits because the process recreates the healthiest possible animals. An area of concern is that some animals are easier to clone than others, primarily due to the animal's reproductive patterns. Dogs, monkeys, and mammals are proven to be some of the most difficult animals to clone. This is because they don't experience regular ovulation cycles, resulting in difficulties producing an egg (How Stuff Works). Chickens are also yet to be cloned. This is because they lay their eggs externally, and once an egg is laid, the necessary nutrients are already inside the shell.

Scientists are continuously discovering more information about this topic. Would the cloning process remain harmless if performed on humans? There are many ethical issues regarding cloning humans and should be vigorously regulated. Who should pay for it? Can it be executed more quickly? Which humans would be chosen for cloning and for what purpose? One could envision a nightmarish scenario, where a depraved megalomaniac creates a human clone of himself, or an entire herd of human clones, specifically designed to provide perfectly matched replacement organs with no possibility of rejection, thereby ensuring his longevity.

There is a lot of controversy over the idea of human cloning. On the one hand, it brings forth great medical potential. On the other hand, many ethicists, lawyers, and scientists argue that human cloning is beyond the pale human ethics. When Dolly was cloned, constant arguments arose over whether or not one should rightfully be allowed to clone humans. UNESCO, the United Nations Educational, Scientific, and Cultural Organization, set up an investigation. There is a lack of clarity in the international law on regulations on this topic, which makes it difficult to determine whether or not it should be allowed. As a result, the members of UNESCO refused to hold a convention for multiple years. In the year of 2005 this changed; however, there was not any sufficient progress. This topic has been revisited multiple times by multiple different organizations. The most recent was in 2014 by the Bioethics Programme, however there remains to be no progress on this case.

Researchers successfully cloned an animal using preserved cell samples. It is the scientific trick of producing a living organism from past living organisms, which by the way, nature has been accomplishing for millenia . Cloning has become extremely popular as it prevents extinction, helps scientists study diseases within animals, and it upgrades the overall quality of the animals. Researchers are continuously discovering more about this fascinating topic.

The Torah perspective is that a human being with a *guf* and *neshama* which are inseparable can never be entirely cloned.

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CRISPR: Beware of Greeks Bearing Gifts

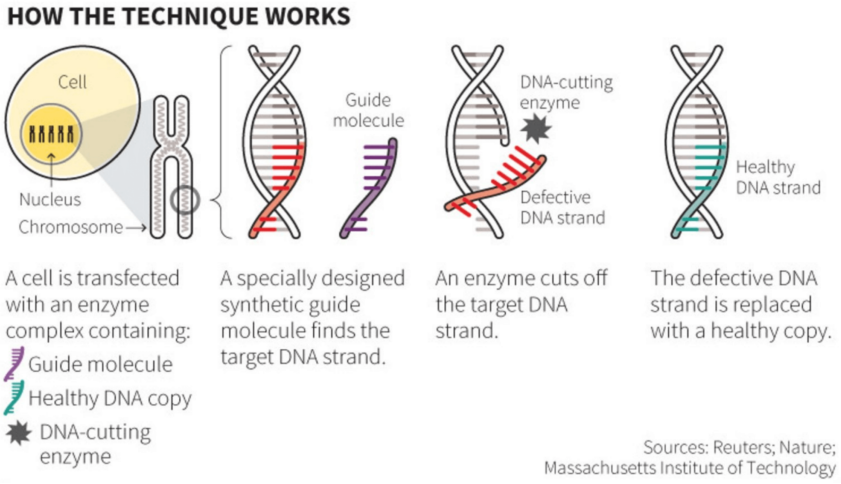
Ayelet Hirsch

Now, they are discovering things people in the past would not have been able to imagine in their wildest dreams and would have relegated to the realm of science fiction.

The past several decades have witnessed a dramatic increase in the fields of technology and science. Just a few hundred years ago, knowledge and research on human biology and anatomy were hardly as extensive as they are today. Even the basic principles of inheritance were only discovered by Gregor Mendel as recently as 1865. Now, they are discovering things people in the past would not have been able to imagine in their wildest dreams and would have relegated to the realm of science fiction.

In 2020, two female scientists were awarded the Nobel Prize in chemistry for their efforts on creating one of the most powerful genetic tools the world has ever seen (5). Jennifer Doudna, a scientist based at the University of California, Berkeley, and Emmanuelle Charpentier, a researcher at the Max Planck Unit for the Science of Pathogens in Berlin, met at a science conference in 2011, discovered they had common interests and jointly published a paper on their findings the following year (4). Referred to as CRISPR, these "genetic scissors" have the ability to edit DNA sequences in the genome, which may allow scientists to cure rare genetic diseases in the near future.

CRISPR is a genetic tool, originally evolved in bacteria, that employs the Cas9 enzyme to modify strands of problematic DNA. It is a defense mechanism that protects bacterial cells from the harmful effects of viral infection. When a virus enters a cell, the CRISPR machinery takes a part of its genetic information and stores it in its own DNA. If the same virus or a similar one attacks the cell later on, the cell will recognize it and send the CRISPR-Cas9 enzyme to destroy it. Piggy-backing on what nature has already devised, researchers use this mechanism to search out specific sequences of DNA in a cell's genome, cut it out completely or insert replacement sequences that have been designed to accomplish a specific goal. Scientists originally thought CRISPR would be able to differentiate between the DNA in question and similar sequences, but they have since discovered that it sometimes removes DNA that is mostly the same but with a few different letters. This can lead to some issues, which will be discussed later on.



There are many fascinating applications of CRISPR in today's world. Although the technology seems complex and difficult to implement, it can greatly improve our daily lives. For example, pet breeders can utilize the tool to remove common genetic diseases that plague purebred animals, like bladder stones in Dalmatians. It

can also be used to create allergy-free foods, so that they no longer contain the protein that causes dangerous allergic responses. Scientists may be able to modify foods such as peanuts, milk, and eggs so they can be consumed by a wider range of individuals. Another implementation of CRISPR sounds like something straight out of science fiction: de-extinction. Scientists have already begun working on this, introducing DNA from the extinct species of passenger pigeon into a living modern-day relative, the band tail pigeon, and breeding it until it essentially becomes no longer extinct. They expect the first generation of the pigeons to hatch sometime in 2022 (2). *(See Herzog in this publication.)*

Despite its allure, scientists will have to tread with caution regarding the accessibility of this tool. There is an obvious danger that comes with such a powerful device: gene editing in humans. One Chinese scientist has already slid down this slippery slope and used CRISPR to genetically modify embryos that produced fully-developed twin infants. After this experiment became public, many people called for a ban on genetically modifying humans. In fact, the original article published by the Chinese scientist was retracted; it was simply too controversial. People believe that scientists are trying to "play G-d" and take over the role of designing humans' genetic makeup (7). Moreover, they claim that using CRISPR to alter the genetic makeup of embryos is unethical; scientists may abuse their power and create powerful and potentially dangerous genetically altered humans, alongside the fear that they may unintentionally introduce a new chronic illness or disease to the population.

CRISPR can also unintentionally change the DNA around the segment that needs to be edited and cause even more harm, which is called having off-target effects. CRISPR on occasion will cut a sequence of DNA that resembles the target. This quirk is actually beneficial for bacteria in their defense against constantly mutating viruses, but can also be disastrous for humans. In three separate studies, scientists introduced specific mutations into embryos to test the abilities of the CRISPR-Cas9 machinery to recognize and repair these mutations. It should be noted that these embryos were specifically created for research purposes only, and not for reproductive purposes. They found that at times, the enzyme will cut in the wrong place and reattach the pieces together incorrectly. This resulted in large swaths of changes in the chromosomes, consisting of additions, deletions and inversions. Sometimes entire chromosomes went missing. These changes occurred near the target site and further removed from the target site. The error rate varied and sometimes reached as high as 22%. Scientists are working on models that will define the likelihood of these errors and under which conditions these errors occur (3).

As can be seen from CRISPR's numerous implementations, the technology has proved itself to be extremely useful in the genetics field. That being said, scientists and governments must ensure that it does not allow society's established moral and ethical boundaries to become blurred. Only time will tell how this groundbreaking tool is used in the future. In the meantime, perhaps we should take a lesson from the inhabitants of Troy and be very careful with what we allow to breach the walls of safety.

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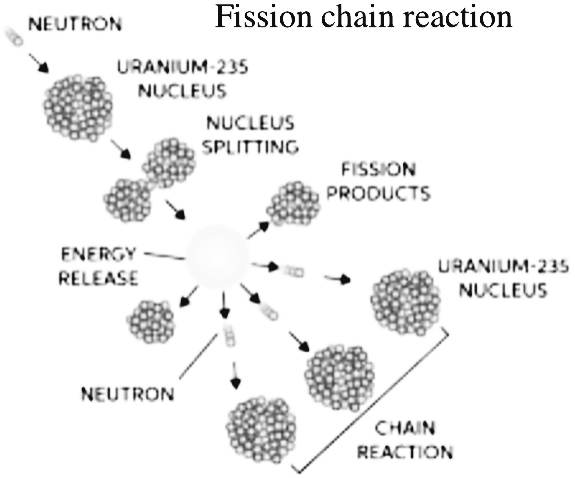
The Secret of the Stars

Zeldy Itkin

The 1.3 million joules of energy this experiment produced has led us close to ignition, a feat scientists have struggled to accomplish for years.

August 18. 2021. 2:06 pm. A record breaking nuclear fusion experiment was achieved in the world's biggest laser facility. The 1.3 million joules of energy this experiment produced has led us close to ignition, a feat scientists have struggled to accomplish for years (Conover). In order to appreciate the magnitude of this event, it is important to understand some underlying concepts. What is nuclear fusion and why is it so important? How does it work? What is the difference between nuclear fission and nuclear fusion? What are the benefits of fusion over fission? What is ignition?

On September 27, 1907, Einstein published his equation on the relationship between energy and mass. It was the famous equation, $e = mc^2$, energy is equal to the mass of any object multiplied by the speed of light squared, and is one of the key foundations of our understanding of physics. This simple yet genius equation shows that energy and mass are flip sides of the same coin. A small quantity of mass can be converted to an enormous quantity of equivalent energy and explains why the sun and stars glow. It is because of a process called nuclear fusion (Prager & Najmabadi).

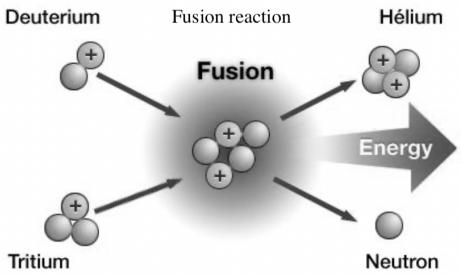


In the 1920s scientists thought that they had a good understanding of matter. It was simple after all, electrons with a negative charge surrounding a dense nucleus containing a number of positively charged protons. The neutron's existence was yet to be revealed. The discovery of the neutron by James Chadwick in 1932 unlocked a whole new world of possibility for science (Basher & Green). The neutron is the "velcro" that prevents the positively charged protons from repelling one another, thereby holding the nucleus together (Williams). Since neutrons are lacking in charge, and will not be repelled by the positively charged nucleus, accelerated neutrons can pierce the atom's heart and split the nucleus, releasing energy. This is the essence of the fission reaction. During this reaction, a small amount of matter is "lost," called the mass defect and instead, converted to a huge quantity of energy in accordance with the prediction of Einstein's equation.

Just a year after the neutron was found, the idea of nuclear bombs took root. Hungarian physicist Leo Szilard proposed that if they could find an element that could be split by neutrons and then release neutrons, it would initiate a chain reaction. The liberated neutrons would go on to split more atoms, which would then release additional neutrons, and each splitting would expel enormous quantities of energy that would be the makings of an atom bomb. In the following years, scientists worked toward achieving just that. They bombarded

all different elements with neutrons which produced all manner of radioactive and stable isotope by-products. (Isotopes are atoms of the same element that have the same number of protons but different numbers of neutrons. Some isotopes are unstable/radioactive and therefore prime candidates for fission. *See Mendelovitz in this publication.)* Finally, in 1934 the first fissionable artificial radioactive isotopes were produced by pelting elements with the helium nuclei. Fission was then used to create the devastating nuclear bombs that ended World War II with the destruction of Hiroshima and Nagasaki. It is also used in peacetime to power nuclear power plants (Conover). For the past 50 years, all our nuclear power plants produced energy through this process.

In recent years, a new reaction called fusion was unveiled. As science began to progress, scientists began to uncover many secrets of the universe in the 20th century, but the secret of the sun and stars remained a mystery. The concept of nuclear fusion became known when British astrophysicist Arthur Eddington proposed that these glittering lights derive their energy from the fusion of deuterium (a hydrogen isotope with one proton and one neutron) to tritium (a hydrogen isotope with one proton and two neutrons) into one helium nucleus with two protons and two neutrons ("History of Fusion"). The leftover neutron can then initiate a fusion chain reaction and the mass defect to be converted into energy following the equation of $e=mc^2$ (Prager & Najmabadi). However, in order to "ignite" the fusion reaction, such high temperatures are required that the expenditure of energy required to reach ignition is greater than the energy recouped by fusion.



As the world around us advances and changes, there is a need for an even greater energy source. While nuclear fission power plants are cheap, reliable, and can sustain a chain reaction for extended periods of time, they create a lot of toxic radioactive waste, are very harmful for the environment, and may not contain enough energy for future technological advancements (Verlini). Fusion, however, is not beset by these problems. If fusion is reached, it would create a possibility of a huge, sustainable, and safe source of energy (Kiger & Freudenrich). Fusion does not release CO2 ,or any other harmful by-products into the environment. It would also be inexhaustible, once the chain reaction is achieved, it will continue as one adds deuterium and tritium–both isotopes of hydrogen which are most effective and create the most energy in the fusion process (Verlini). When Time magazine asked Stephen Hawking, a theoretical physicist, what scientific discovery he would like to see in his lifetime, he immediately answered that he would like to see fusion become a viable source of power ("Stephen Hawking")

There are many different types of fusion reactions though most contain deuterium and tritium. Firstly, there's the proton-proton chain, which is the reaction used by the sun. The proton-proton reaction is when four protons form to create two deuterium atoms, the two deuterium atoms then combine individually with a proton forming helium-3 atoms. The two helium-3 atoms then unite to create an unstable atom called beryllium-6 which then decays producing energy. The second type of fusion reaction is the deuterium-deuterium reaction, when two deuterium fuse to form a helium-3 atom and a neutron. Lastly is the deuterium-titanium reaction. This reaction is when one deuterium and one titanium atom combine and

configure a helium-4 atom and one neutron (Kiger & Freudenrich). Though this process sounds fairly easy in theory, scientists have struggled to make long lasting fusion a reality (Ashish).

Why? Like fission, in order to create a constant energy flow with fusion, one must create a self-sustaining fusion chain-reaction, which is called ignition. Unlike in the sun and stars where the gravitational forces make fusion easy, it's extremely difficult to achieve here on earth. There is a powerful repulsive electrostatic force between nuclei, preventing the prospective fusionable nuclei from colliding/fusing. However, if the temperature increased sufficiently, it could speed up the atoms and they can get close enough for the attractive nuclear force, the force that holds protons and neutrons together in an atom, to overcome the electrostatic repulsion and fusion could occur (Orbach). In theory, when ignition is achieved, the fusion reaction releases four times more energy than fission!

Despite all these challenges, scientists are getting closer to making ignition a reality. On August 18, 2021, scientists paved the way towards a nuclear fusion climax with a dynamic laser blast at the National Ignition Facility, or NIF, at Lawrence Livermore National Laboratory in California. The scientist had bombarded a small cylinder which contained a tiny fuel capsule made of deuterium and tritium with 192 laser beams. When these beams were focused on a target the size of a BB, it produced a hot spot that was the diameter of a human hair, collapsing the fuel inside the capsule, reaching the right temperature and pressure to fuse the hydrogen atoms into helium, and setting off a chain reaction. The fusion reaction produced 10 quadrillion watts of power in over 100 trillionths of a second and produced five times as much energy that was absorbed in igniting it. If the NIF does end up reaching ignition, there will still be many other challenges to be able to make fusion available for constructive use (Conover).

The NIF isn't the only facility that has invested in attaining fusion. Many others have joined the quest to make fusion feasible as a clean, healthy, safe and powerful source of energy. Nuclear fusion is a proverbial double-edged sword and it is incumbent upon society to ensure that it is used responsibly. The promise of nuclear fusion is no longer a theoretical dream of a scientist, it's a reality that lies in our near future.It is incumbent upon us to safeguard it and use it with a measured dose of caution. As we are admonished in *Pirkei Avot, Asu S'yag*.

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Music Magic of Micro RNA

Yehudis Kundin

Music's ability to alleviate depression or any mental illness has been discovered thousands of years ago.

Can music truly do magic? Agreed, music is beautiful and transportive, but can it also be transformative and have an impact on the way your body works? Can it wave its imaginary wand and heal a sick person? Music's ability to improve various functions of the body has been a topic of great interest to me mainly because I play several instruments and music is an important factor in my life. A recent TED talk discussed the different parts of the brain that are activated when listening to music, but even more parts are activated in the musician who plays music. It described the immense cognitive benefits of music on musicians, such as enhanced memory, ability to solve problems, and higher levels of executive function (includes planning, strategizing, and attention to detail) (Collins). This paper aims to tease apart the various intersecting threads of molecular biology, music, and health.

Music has been known to have many beneficial uses in the medical world. It is interesting to note that music has been known to be beneficial long before modern medicine and science. In fact, it has been used long before drug medication was even created. This can be proven by looking in *Tanach*. Firstly, when Yaakov was in the depths of mourning since the "death" of Yosef, Serach bas Asher played the harp while breaking the news to him that Yosef was in fact alive. Dovid also used the harp to ease the "רוח רעה", or depressed spirits, that descended on Shaul. Music's ability to alleviate depression or any mental illness has been discovered thousands of years ago.

In modern medicine, music has been used for motor and cognitive rehabilitation in neurological diseases (Nair.; bioRxiv), oncological treatment to improve psychological well-being (Köhler), to reduce fatigue in women with breast cancer (Alcântara-Silva), alleviate psychological symptoms in Alzheimer's Disease (Gómez-Gallego), etc. In one particular 2001 study1, PET (positron emission tomography imaging technology) was used to measure the neuronal activity in a person while listening to music chosen to elicit pleasure and chills in his/her body. Researchers found that this music activated brain regions that are typically involved in reward/motivation. It elicited a similar response with other euphoria-inducing stimuli, such as food and drugs. However, the usual stimuli for reward system activation are biological necessities for the body or pharmacological interventions. These findings offered an added perspective on music. Researchers suspect that as human cognition improves as a result of evolutionary development, humans become more capable of deriving pleasure from more abstract stimuli. Although music is not necessary for survival, perhaps it will indeed benefit humans both mentally and physically (Blood and Zatorre).

Another crucial advancement was the discovery of the role of music in recovery for middle cerebral artery stroke. After performing several studies testing the effectiveness of music for recovery from this disease, researchers found that when patients listened to their favorite music, it led to cognitive improvements such as verbal memory and focused attention. These findings strengthened the idea that music can recruit certain neural circuits underlying some forms of attending, working memory, semantic and syntactic processing, and imagery (Särkämö).

The information that scientists have discovered throughout history on the subject continues to have an influence on current studies. This article will focus on one recent study, the effect of music on microRNA. Gene expression is the term used to describe how the information encoded by a gene is used to create a product. First, the process of transcription copies the DNA into a messenger RNA. The mRNA will leave the nucleus and enter the cytoplasm where it will direct the synthesis of the product in a process called translation. This process must be tightly controlled or regulated for a cell to function properly. MicroRNA can be used to control gene expression. A microRNA is a single-stranded non-coding RNA that prevents the production of a certain protein by silencing the messenger RNA. It does this by using a complementary sequence to bind to and block the mRNA from doing its job of creating a protein. (*See figure 1 below*) The biogenesis of microRNA is still unclear, but the basic understanding is that the RNA creates the first form of microRNA and after several cleavage events, they become mature microRNA. Upregulation of a certain microRNA increases its production or quantity and downregulation decreases its production or quantity. One of the various mechanisms of upregulation and downregulation will be explained later on.

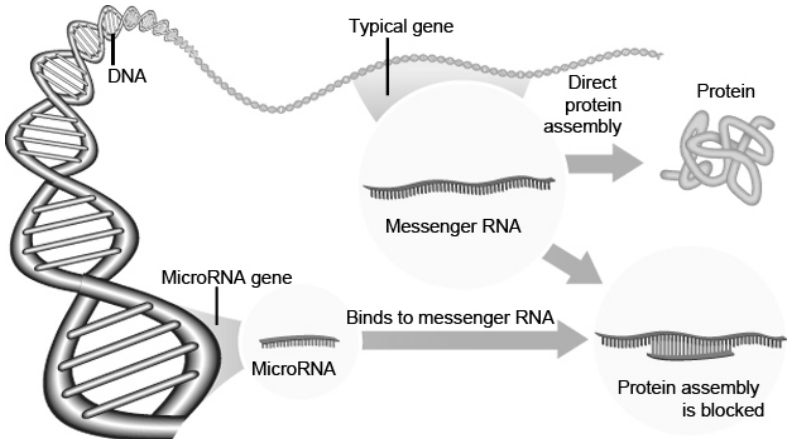

Figure 1: A section of DNA, gene, is transcribed to messenger RNA. The mRNA enters the cytoplasm where it directs the synthesis of a particular sequence of amino acids of a protein. MicroRNA is complementary to a segment of DNA just prior to the gene and blocks transcription, essentially stopping the expression of the gene.

Researchers examined studies of musical animals such as songbirds and zebra finches. The studies on songbirds have shown that music-listening can activate genes that are associated with synaptic plasticity (the ability of synapses–junctions between neurons—to strengthen or weaken over time), long-term potentiation (a persistent strengthening of the synapses between neurons based on recent synaptic activity), and dopaminergic transmission (the transmission of dopamine which is both an excitatory and inhibitory neurotransmitter that impacts functions such as reinforcement and reward, thoughts and emotions, etc.). Results of the zebra finch studies have shown that music-listening can upregulate certain microRNAs. (Nair; bioRxiv)

If such are the effects of music on musical animals, they wanted to examine whether music can have similar cognitive benefits on humans who also tend to be more musical. Researchers conducted their own study testing the effects of music-listening on the microRNA transcriptome (the full range of microRNA in an organism) of people with musical education or musical aptitude. They found that high scores on the musical aptitude test correlated with upregulation and downregulation of certain microRNAs, leading to the idea that

music has a neuroprotective role. For example, upregulated miR-23a and miR-23b repress the gene APAF1 which activates neuronal apoptotic processes. Apoptosis is an essential part of the cell cycle because it gets rid of damaged cells that are beyond repair and gets rid of unwanted cells. Additionally, miR-25 inhibits the pro-apoptotic gene TP53, reducing neuronal apoptotic processes. Their findings also pointed to the idea that music-listening affects memory. For example, upregulated miR-23a regulates the gene PTEN which activates MAPK (a type of protein) activity. MAPK plays a big role in memory consolidation and synaptic plasticity. Music-listening has also been shown to protect from Alzheimer's disease and Parkinson's disease based on their findings of upregulation in neuroprotective microRNAs. Low expression of miR-132, for example, can lead to neurodegenerative disorders, so upregulating this microRNA can definitely prevent such diseases. (Nair; bioRxiv)

Additional microRNAs that were upregulated by listening to music include microRNAs that regulate Central Nervous System myelination. Myelination, or wrapping a membrane around the nerve cell axons, increases the efficiency of transmission of electrical impulses through the nerves, long-term potentiation, neuronal plasticity, inner ear and auditory system development, cell death, and wound healing. The target genes of these upregulated microRNAs control several things. Firstly, some of them control cell-cycle inhibition. The cell cycle is the process of the cell getting ready to divide into 2 daughter cells. This reproduction is essential in the organism's survival. However, regulation of the cycle is necessary because sometimes there is damage to the DNA which must be fixed, and regulation is needed to prevent uncontrolled cell division. Some other target genes control neuron apoptosis, sensorimotor learning, auditory perception, vocal plasticity, and repression of myelin proteins (proteins that play an important role in creating the myelin sheath on nerves). MicroRNA downregulation from listening to music was seen in microRNAs in charge of angiogenesis (the development of new blood vessels), cell proliferation, and adiponectin signaling (a protein hormone). (Nair; bioRxiv)

Based on all their findings, researchers concluded that music-listening can greatly affect the microRNA responses and gene regulation in people with inherent musical aptitude. No significant microRNA changes were exhibited in people with just music education, or low musical aptitude. Therefore, for musically apt people, listening to music can in fact be very healthy and beneficial for their bodies. (Nair; bioRxiv)

For those who *play* music and were wondering whether all those years of practice benefitted their health in any way, the answer is a most definitive YES! Another study was done testing the effects of music on *musicians*. This time, they tested the effects of music performance, specifically Western classical music, rather than music-listening. Interestingly enough, very similar results were found to those of the music-listening study. Several microRNAs were upregulated and downregulated in very beneficial ways. The effects can be seen in the figure below.

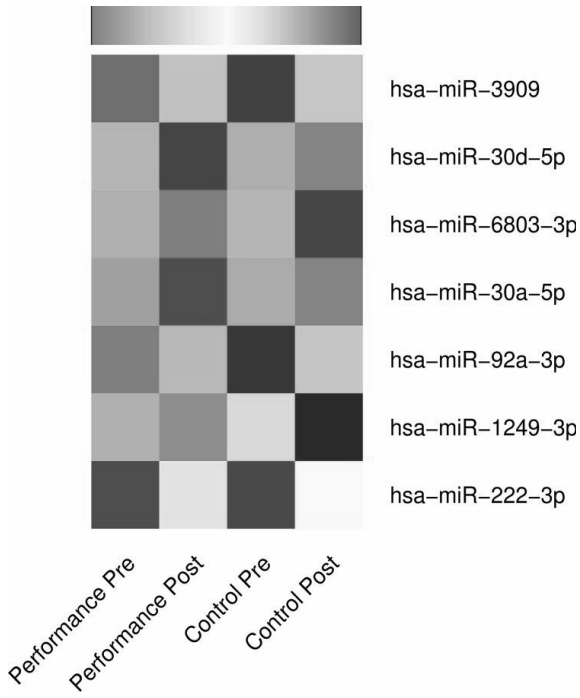

Figure 2: The effects on the microRNA of musicians who performed versus the control group which consisted of musicians who neither performed nor listened to music during the time of the study. Grey, white, and black colors indicate low, moderate, and high expression of microRNAs, respectively. The majority of the 5 microRNAs depicted show an increase in expression of that microRNA between pre-performance and post-performance while showing a decrease from before and after for the control group. For example, hsa-miR-222-3p starts out as grey, or low expression, but becomes white, or moderate expression, post-performance, as opposed to before and after the control group, which goes from black to white.

One example of the beneficial effects of music performance on musicians is the upregulation of hsa-miR-222-3p and hsa-miR-92a-3p, 2 of the microRNAs in the figure above. These microRNAs target PTEN, a gene that produces an enzyme that is part of the chemical pathway that signals cells to stop dividing. By targeting PTEN, these microRNAs activate AKT signaling. A signaling pathway is a series of cellular reactions which occur as a response to a certain signal received by a cell. The AKT signaling pathway is important for cell survival and cellular proliferation (the process of a cell growing and then dividing into 2 cells, leading to exponential cell growth). Therefore, its activation by these microRNAs is extremely beneficial to musicians (Nair; Peer).

In summary, music can facilitate cognitive and emotional functions in the body. These findings add validity to the theories of music's beneficial nature to the human body. In addition, they also show that not only is music beneficial to people in general, but it also has effects specifically on musically apt people and musicians who play music. This topic is extremely important because it opens up possibilities for a whole new set of non-pharmacological therapies without the attendant side effects. In so many instances, music has been proven to improve sick patients of various conditions and alleviate symptoms. Perhaps it is time to add it to the physician's toolbox.

Of course, aside from the medical benefits, music should be integrated into people's daily lives to *prevent* illnesses. There have been ample studies that prove how music can be extremely beneficial for mental health, and what better time than now? Especially with the onset of COVID-19, depression rates in adults have shot up from 8.5% to 32.8% (Crawford). Music can be crucial as a preventative measure against depression and other mental illnesses.

Future studies are needed to look at specific factors such as the genre of the music, the duration of listening, and personal preference to determine the microRNA changes in these specific circumstances (Nair et al., bioRxiv, 2019). In addition, more studies can be performed targeting the non-musical. Perhaps there is something to be found regarding changes in their microRNA in response to music that this study may have overlooked. There may also be other changes not related to microRNA that occur in people with low musical aptitude but that are beneficial. Of course, more needs to be explored regarding the exact effects of music to pinpoint where in the recovery processes of various diseases music-listening should be implemented. The

intersection of music and medicine leaves much to be explored. However, with the novel effects scientists have already discovered, it is clear that to some degree, music can be dubbed "magical".

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Unlocking the Secrets of Irregular Nuclei

Tzivya Mendelovitz

Symbolic of unity, this is a metaphor for the common phrase "all for one and one for all.

What is the connection between an old Italian family's crest *(figure 1)*, a particle accelerator, and the possible cure for cancer? In the mid 1980's scientists made a discovery that shocked and confused them; they had discovered a rare isotope of lithium, called lithium 11, consisting of 3 protons and 8 neutrons, with a highly irregular nuclear structure. What was so interesting about Lithium -11 is that it has a Borromean nucleus, meaning its nucleus is made of 3 interlocking parts. The first main cluster making up the nucleus is packed with 3 protons and 6 neutrons. The second two are two separate neutrons flanking that cluster of protons and neutrons, forming a broad halo around the core. In addition to this irregular structure, what's even more interesting is that if one of these 3 pieces is removed the whole nuclear structure would fall apart and disband. The structure of this nucleus is also extremely large, and because of its large halo it's the same size as a lead nucleus despite having almost 200 more protons and neutrons *(figure 2)* (Conover).

Figure 1

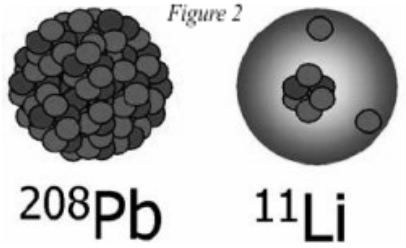
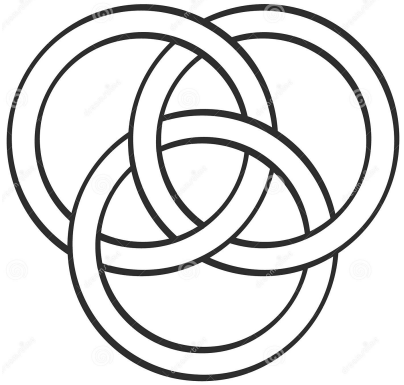


Figure 2

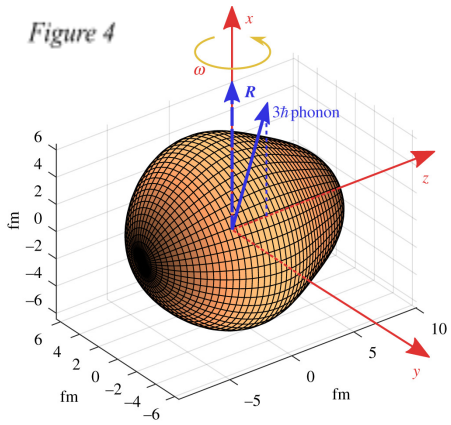
This is analogous to the Borromean rings studied by mathematicians *(Figure 3)*, where three rings are linked and non separable until one of them is opened and released. At that point, the other two rings are no longer linked. Symbolic of unity, this is a metaphor for the common phrase "all for one and one for all," –either all three are simultaneously interdependent, or none of them are.

Figure 3



But Lithium-11 is only the beginning. Nuclear theorists say there are many more examples of these strange nuclei; some which are distorted into weird shapes (for example a pear-shaped nuclei, *Figure 4*) (Butler) or those which are wrapped in a skin of neutrons almost the way a peel would encase a fruit, as in Lead 208 (Conover).

Figure 4

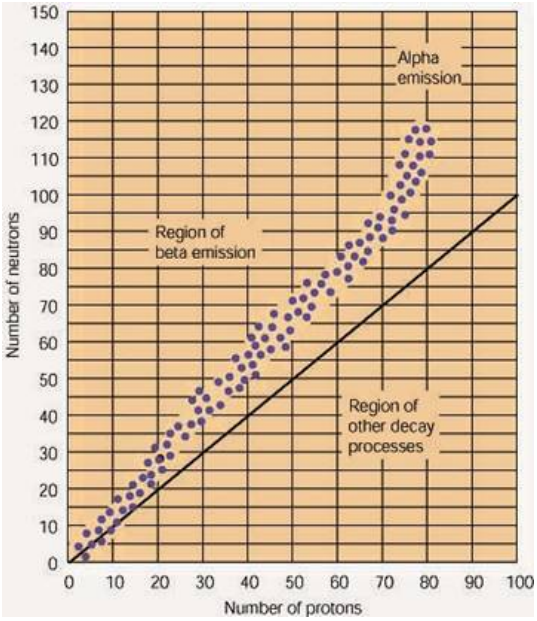


To find more of these irregular nuclei and research into the strange behaviors they exhibit, scientists at Michigan State's FRIB (facility for rare isotope beams) are working on building a new kind of particle accelerator which will significantly assist with the project, but to really understand what FRIB is trying to accomplish with their particle accelerator one must first go back and understand the basics; isotopes.

Isotopes are different versions of an element with varying numbers of neutrons within that atom's nucleus, but that have the same number of protons, a basic characteristic of the element, known as Atomic Number. As of now there are 118 known chemical elements and each of these elements has a variety of isotopes. Scientists hypothesize there are at least 8,000 isotopes of the known elements but only around 3,300 have been detected. FRIB is trying to discover many more of these isotopes by using their particle accelerato them. The researchers on the team believe they can even identify 80%, or maybe even more of the missing isotopes! (McEntee)

Figure 4

Out of all the known isotopes there are only about 250 which are stable, and these are the ones which contain the nuclei scientists are the most familiar with. These stable isotopes include the Oxygen-16 in the air we breathe, the Carbon-12 found in all living things, and basically your "every day elements". The reason the nuclei within them are stable is because they contain exactly the right balance of protons and neutrons, one too many neutrons would cause a nucleus to be unstable and decay, emitting radioactivity (whether over a long period of time or mere seconds). Generally, as the imbalance between protons and neutrons increases so does the instability of the nucleus, and the more unstable the nucleus the weirder its properties tend to get (Conover).



(Figure 5) below shows the band of stability for nuclei versus the 1:1 ratio (solid line) of neutrons and protons. Until atomic number 20, a 1:1 neutron:proton ratio is sufficient for stability. As atomic number increases past 20, an ever larger neutron:proton ratio is required for stability. Past atomic number 82, all nuclei are unstable and there are no stable isotopes.

Once the basics are understood, it's now possible to understand the actual process FRIB is using for their experiments; At first elements are vaporized and ionized and then accelerated to make them start moving just a little. Then using electromagnetic forces, the particle accelerator will "herd" the ions into a finely focused beam. The atoms must be ionized so that the electromagnetic forces can operate on charge particles and "herd" them into a straight coherent beam. This beam will then enter the linear accelerator which can super-accelerate the ions using rapidly oscillating electromagnetic fields. The way it does this is by winding the facility (almost like a cargo train) in a paper clip shaped route so fast that the particles are moving around half the speed of light *(Figure 6)*. Acceleration to such a high speed is necessary to overcome the natural repulsion between the positively charged protons in the nucleus and

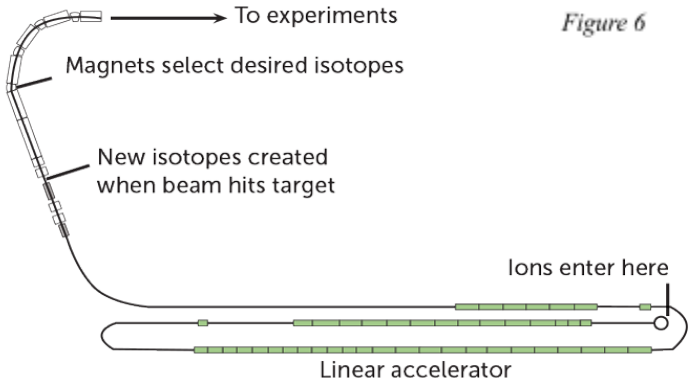


Figure 6

positively charged particles being aimed at the nucleus. The speeding particles will fly into the nucleus at such a high speed and either fuse with the nucleus or split it apart. Either event results in the creation of novel nuclei.

Scientists can extract the particles they actually want to study by using magnets, which separates particles based on their mass and electric charge. When the scientists extract the particles they want, they send them to an experimental area which uses detectors to study things like their properties, the rate at which they decay, what reactions they undergo and more, to hopefully eventually come up with an all-encompassing theory for nuclei (Department of Energy; Conover).

The reason FRIB's beam is so complex is because there's a very specific amount of energy needed for this complicated process. Too little wouldn't work but too much energy would blow the nuclei apart once they collide with the target, therefore FRIB's particle accelerator is designed to reach less than a hundredth of the energy of the world's largest particle accelerator at CERN in order to produce these rare isotopes. How does the accelerator work with so little energy? Instead of relying on a lot of energy, the accelerator relies on the huge quantity of particles in its beam (for example it can slam 50 trillion ions of uranium into its target at once), and as a result of this, FRIB's accelerator can do something its predecessors couldn't; produce much more intense streams of rare isotopes. Even though it's difficult to make these isotopes and they might only appear successfully once a week, or even once a month, it is still much more often than in any other facility due to the fact the beams are greater in quantity of particles rather than in energy levels (Conover).

FRIB's accelerator will be extremely useful for pinpointing the boundary of the neutron drip line. The neutron drip line is basically the boundary line of the maximum number of neutrons in a nucleus before it bursts from too many. So far, scientists only know this crucial threshold up to the tenth element on the periodic table; neon. The scientists at FRIB hope to find the drip line for at least up to zinc, the 30th element on the table (Nunes; Spyrou). A big reason why the drip line is so important is because the closer nuclei get to that threshold, the more irregular they become. Lithium-11, with 3 protons and 8 neutrons, or Magnesium-40, with 12 protons and 28 neutrons, are extremely close to the drip line and their neutrons greatly outnumber the protons in their nuclei. Both isotopes act and look extremely irregular, with their Borromean nuclei.

Probing the structure and inner workings of the most basic particles of the universe is a fundamental quest of scientific inquiry. The knowledge gained from this line of pure research, knowledge for knowledge's sake, can be utilized in many practical applications, such as medicine, radiation treatments, and as of yet, unimagined applications (Conover; Spyrou). Terbium-149 is one of the isotopes that could be hopefully harvested in sufficient quantities by the accelerator. It emits alpha particles as it decays which can kill targeted cancer cells. What makes it so suitable for this job is its half-life of 4.1 hours. It decays fast enough and with such intensity that it obliterates cancer cells without hanging around to overstay its welcome, but not too fast that it disappears within seconds, leaving some of the cancer still active. Hopefully FRIB will be able to extract enough of this isotope for cancer treatment (Conover).

With time and lots of work FRIB's new particle accelerator can revolutionize chemistry, physics, the medical field, cosmology, and even more. The hopes and expectations of the facilities scientists, researchers, investors, and even outside spectators are extremely high, and hopefully FRIB will be able to fulfill the promise of its expectations.

So, the connection between an old Italian family crest, a particle accelerator and the possible cure for cancer? The 15th century Italian family crest, in the shape of the Lithium-11 Borromean nucleus, and cancer

cures developed covered through FRIB's particle accelerator are all undeniable signposts to a previously undetected sublime structural fingerprint of the supreme architect.

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Migraine Headaches: It's Not All in Your Head

Lily Notkin

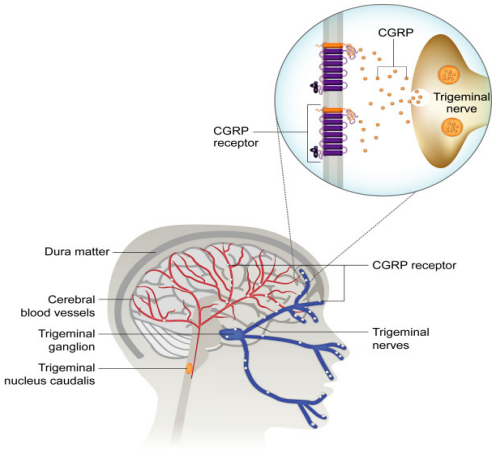
Now, imagine that two days later, the entire cycle begins again. This is what it is like to experience migraines.

Imagine waking one morning with a feeling of dread. Within a few hours, your vision disintegrates into a field of sparks and every sound causes stabbing pain. Soon, you start vomiting and take to your bed, your head gripped by pain that does not respond to any over-the-counter medications. The pain lasts for 24 hours. Now, imagine that two days later, the entire cycle begins again. This is what it is like to experience migraines. In the United States, 35 million people suffer migraines each year. Migraines are the second leading cause of disability worldwide and the number one cause of disability in younger women. Migraines affect twice as many women as men, most commonly aged 35-45 (Pietrasik).

Migraines occur in stages. They often start with a prodrome which is the feeling of the onset of an illness within a day of a migraine attack. One may experience sensitivity to light, sound, or smell, and usually fatigue. Within an hour of a migraine, some people experience aura. Auras are visual disturbances stemming from the nervous system and appear as flashes of light, wavy lines, black dots or tunnel vision. Next comes the migraine which consists of an ache leading to a pulsing throbbing sensation, many people experience nausea or vomit (WebMD). A migraine can last hours to even days.

With a growing number of people burdened with the debilitating symptoms of migraines, it is crucial that scientists find a cure. But how? Nobody knows exactly what causes migraines. Until about 2010, migraines were thought to be caused by constriction of the arteries in the head followed by dilation of arteries elsewhere in the body. This hypothesis was debunked and now doctors accept the neurovascular hypothesis, which says migraine pain stems from the trigeminovascular system which are the blood vessels located on the side of the face which provide blood vessels to the nerves on the side of the face. This system transmits nerve signals from the blood vessels in the skull to the brain using vasoactive neuropeptides (CGRP, neurokinin A, and substance P), which are neurotransmitters that can contract the blood vessels. These neuropeptides trigger nerve inflammation and these nerve impulses are then transmitted along the trigeminovascular system until they are perceived as pain by the brain (Peters).

Historically, there haven't been great treatments for migraines. In the late 1930's, a medication isolated from moldy wheat (ergotamine) was found to relieve the pain of migraine, but later trials found it just as active as placebo (Goadsby) *(See Rosenberg in this publication)*. In the 1950's, a combination of nervous system stimulants, anti-nausea medication and caffeine was developed, but overuse worsened migraine attacks and the combination caused a lot of side effects (Ctrl M Health Migraine Team). In the 1960's, antidepressants and antiepileptics were given for migraines and the also cause serious side effects, including suicidal thoughts (Kanner). In the 90's, a novel class of drugs called the triptans were developed and the first triptan was approved in 1991. The triptans revolutionized the acute treatment of migraine, but still could not prevent migraines (Ghoshal). So, the research continued to find a more suitable treatment.



In the mid-2000's, researchers started to develop novel migraine treatment options such as the CGRP receptor antagonists. An antagonist is a substance that stops the effect of another substance in this case, vasoactive neuropeptides (NCI Dictionary of Cancer terms). GCRP receptor antagonists prevent the inflammatory peptides from binding to their GCRP receptors and starting the pain cascade. In early 2019, the first CGRP receptor antagonist injections were FDA approved. Acute oral treatments were also approved. In clinical trials, 60% of patients reported that at least half of their weekly migraines were gone and 16% of people were migraine free. These treatments are revolutionizing migraine care.

The discovery and development process of novel drugs takes at least 10 years and costs, on average, $2.6 billion (Carroll). Bringing the CGRP antagonists to market took 25 years, a typical timeframe for novel drug development. It began in 1976, when Lars Edvinsson discovered that CGRP receptors were located in trigeminal sensory nerves on cranial arteries in humans. In 1984, his research group found that CGRP was a dilator of cerebral arteries. This led Edvinsson to first propose that CGRP may be a key factor in regulation of cerebral blood flow and the migraine syndromes, especially after his research group found that CGRP was the only neuropeptide released during migraine. Later, they proved that sumatriptan prevented the increase of CGRP levels at the same time that it stopped a headache attack. This strongly implicated the crucial role CGRP has with migraine symptoms. Once the target, the CGRP receptor, was identified, a multitude of research teams began the development of small molecules and antibody drugs that could block CGRP from binding to its receptor and initiating the pain cascade (Penttila). Today, six drugs blocking CGRP are approved by the FDA and more are in development. Unlike CGRP antagonists which were deliberately designed to treat migraines other drugs were found to treat migraines by accident.

You've heard of Botox, the injection that the beauty industry has used for decades to eliminate wrinkles. Some patients noticed that after they got Botox injections their migraine symptoms eased. But why do botox injections lessen migraine pain? Because no one knows exactly what causes migraines, no one knows exactly how Botox therapy prevents them. If the neurovascular hypothesis is correct, Botox injections into the areas innervated by the trigeminal nerve inhibit release of CGRP from peripheral neurons, which interferes with their ability to transmit the sensation of pain. In other words, Botox is thought to reduce the transmission of pain impulses by trigeminal neurons to the second order neurons in the brain stem, so the brain does not perceive pain.(Agostoni).

These therapies have benefitted countless sufferers of recurrent migraine headaches but there is still work to be done; not everyone responds to these new treatments (Samson). Research continues to develop treatments to help people whose migraines don't respond to the currently available medications. Effort is continuing to answer the questions like: Why aren't some people helped by the new drugs? What kind of medications can help them? Will these new drugs benefit people who suffer from other types of headaches or even other pain syndromes?

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Speaking Your Mind

Ariella Paneth

Most human beings produce intelligible speech at the rate of 150 words a minute. That's 9,000 words an hour, and approximately 108,000 words a day!

Imagine life without speech and efficient communication. Speech is what elevates us from the rest of the animal kingdom and makes us human. Most human beings produce intelligible speech at the rate of 150 words a minute. That's 9,000 words an hour, and approximately 108,000 words a day! Life can be very frustrating for people who suffer from anarthria. They lack the ability to intelligibly speak due to the inability of the brain to control the muscles involved in articulation.

There are many types of speech production difficulties that stem from the brain. A prime example is amyotrophic lateral sclerosis, or ALS *(See Eberstark, BenAmi in this publication)*. Speech capacity in patients suffering with ALS is damaged due to issues relating to radial diffusivity in the frontal, parietal, and right temporal lobes of the brain. Radial diffusivity is the extent to which water diffuses perpendicular to a white matter tract, or axon fibers. When a patient suffers from ALS, the water diffuses irregularly in these specific parts of the brain resulting in lack of volitional control of speech and sensory feedback (4). Other speech production issues stem from muscles, such as articulatory issues with the tongue, lips, or jaw. This includes people suffering from paralysis, whose minds are racing but cannot verbally express what they are thinking about.

Lucky for people with these speech limitations, there are certain processes of decoding thoughts through a machine so people with these limitations can communicate. The downside is that these machines work using letters. A person has to repeat a letter in their head numerous times until the machine picks up which letter the person is trying to articulate. This goes on until a full message is complete., This process is quite time consuming, as about only ten words can be produced in a one minute period, leaving those with anarthria very frustrated (2).

A new invention by Gopala K. Anumanchipalli has the power to enhance many people's lives, by creating a quicker, more efficient way to decode the thoughts of those with anarthria (1). Anumanchipalli discovered this by taking advantage of subjects who are treated for epilepsy using micro-acupuncture in the upper cerebellar cortex, and inserting electrodes into the part of the brain responsible for translating thought to record activity (5). The sensory motor cortex (SMC) was used in recording the intentional message, the IFG or inter frontal gyrus, which is involved in planning brain activity, and the STG which is the perception area of the brain (2). By analyzing how the brain forms words, scientists including Anumanchipalli were able to imitate how the brain actually creates spoken words. This entire process is called Electrocorticography, or recording electrical activity in the brain by using electrodes in direct contact with the cerebral cortex or surface of the brain (3).

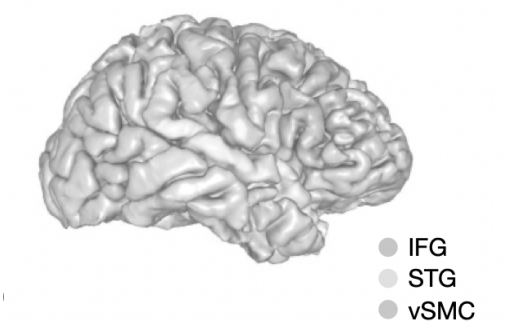

Figure 1: Depicted are the parts of the brain that makes this experiment possible. The IFG plans the sentences, the vSMC is responsible for recording the message, and the STG perceives the message

Rather than decoding through letters, this process takes strings of sentences and translates the sentence using the pattern of the wave frequency of the entire thought generated in specific parts of the brain. Before we speak, the thoughts in our brains are made of electric waves, and these waves act as communicators between different neurons located in the brain. When we speak, these waves are naturally transformed into acoustic waves, and sound waves by our oral machinery. Anumanchipalli monitored the brain's wave activity by means of the electrodes, which allowed him to decode the electric waves and convert them into acoustic waves. He was able to record kinematics, or the motion of the thought of speech, and translate those waves into acoustics, and finally translate the acoustics into decoded speech waveforms.

To test this invention, researchers gathered many listeners to see if people untrained in this technology would be able to translate the waves. Specifically, they used a group of people found on a website called Amazon Mechanical Turks, a network of randomly chosen adults who test out experiments for which computers are ill-suited. They started out by using this method to translate overt speech, or actual spoken speech. Researchers gathered 50 words, and gave the subjects 60 sentences of spoken speech which they needed to decode from sound waves, using the word bank of 50 words. Additionally, they gave 25 words in a bank to people who would need to decode 82 sentences. Of all the responses, 21% and 43% transcribed the sentences perfectly, and there was a median word error rate (WER) of 31% - where the people translated the word wrong, for example mistaking 'rabbits' for 'rodents'. They compared known waves previously generated and then compared these test waves to see if they could be "translated" into words, kind of like a dictionary. Overall, the main purpose of this experiment was to establish a baseline error rate for words correctly interpreted (1).

In a second experiment, researchers experimented with decoding mimed speech, or lip-reading with no voice production. Again, the same list of 60 sentences were given to subjects to decode, this time from a brain wave spectra. They had to read the spectra, and choose a sentence of the available 60 sentences which with the spectra correlated. Even though the decoder wasn't trained on mimed speech, they were still successful in translating the words correctly, even though it was more difficult to decipher what the subject was mouthing. To test this out, a subject who was treated with these electrodes first said the sentence using overt speech, and repeated the sentence this time only mouthing it. The waves were much lighter than the overt speech but the pattern remained consistent. This proved that whether or not the sound actually came out of the vocal cords, the thoughts are what create the waves (1).

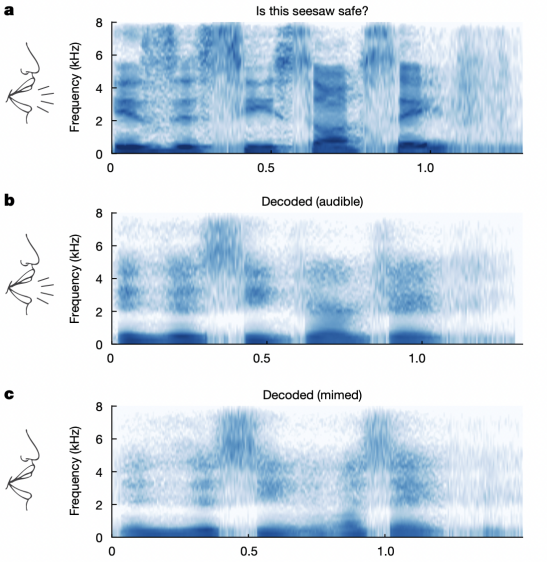

Figure 2: Depicted is the sentence "Is the seesaw safe?" in acoustic waves. The top chart shows overt speech, the middle shows whispered speech, and the bottom shows mimed speech. Clearly there is a big difference between the clarity of the top and bottom chart. The clarity is compromised but the waves stay the same.

Although this experiment opened many doors for the future of people suffering from anarthria, researchers are still working on translating the brain waves to sound in real time and more importantly, working on translating the waves without even needing to mime the words. However, researchers are confident that this will be achieved within the next five years with the help of Neuralink, a neurotechnology company developing implantable brain–machine interfaces. It is also in the future of this invention to teach methods of decoding speech by means of computers, making it more accessible to common people who need the help of this invention Additionally, Anumanchipalli hopes that in the future they will be able to translate sentences not only using electrodes in the brain, but possibly also using other biometrics such as heart rate or body movement (3).

This differs from the technology that Stephen Hawking uses to communicate, because that uses means of alternative and augmented communication, or AAC. That includes signing, gestures, symbol charts, and large pictures or objects for reference. In other words, by means other than a decoding machine. They also use methods of eye gazing devices, however those people need to be able to use the muscles controlling upper, lower, and lateral eye movements (6).

The tools of science, when wielded properly in skillful hands can do wonders for the disabled and disadvantaged. To return the power of communication to those who thought that there was no hope, is a tremendous chessed and shows that anything is possible. With this invention, there is hope of communication even for those who don't have a voice.

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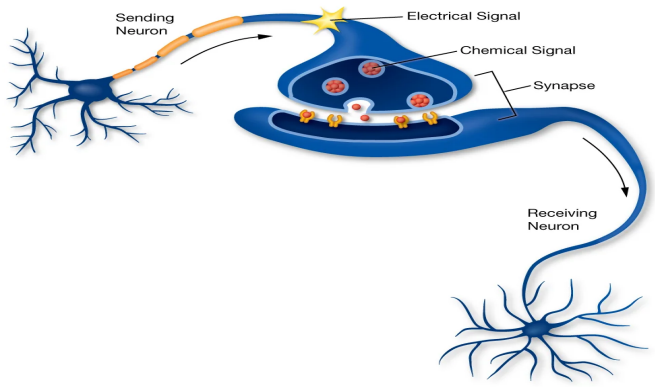
Brain Computer Interface:
The Good, the Bad, and Truly Ugly

Rachel Leah Perlman

For the past few decades neuroscientists have been recording and eavesdropping on nerve cell activity with altruistic goals, but the specter of nefarious outcomes looms.

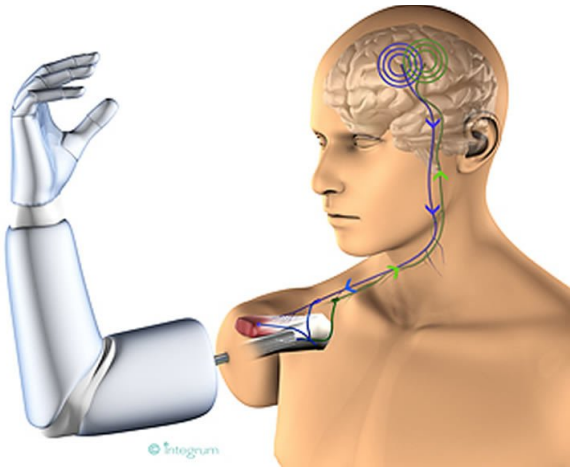
Does the greater good supersede the need for individual privacy? The innermost sanctum of our individual privacy is our thoughts, ensconced and protected in our brains, safe from outside intrusion. Or are they truly? For the past few decades neuroscientists have been recording and eavesdropping on nerve cell activity with altruistic goals, but the specter of nefarious outcomes looms.

Neuron communication utilizes chemical messengers and electrical signals along pathways of the brain. The job of the nervous system is to collect information from the environment and initiate an appropriate response by innervating muscles and glands. The nervous system is also the repository of our memories and thoughts. Within the neuron itself, impulse flow is electrical in nature, but in order to traverse the small gap between neurons, the impulse flow is converted to one of chemical neurotransmitters. Once they get to the other side, the signal becomes electrical again. Neurons are constantly multi-tasking; a neuron that's sending information can connect to several neurons receiving information, and a neuron receiving information can connect to several neurons sending information (Cherry; Learn.Genetics). By monitoring the electrical and chemical activity within the brain, scientists can track and trace the flow of information. But the more ominous question hovers. Can scientists redirect the flow of electrical activity and control our thoughts?



Entrepreneurs, and researchers aim to listen in on people's brains and hope to change thinking. Ilan Musk hopes to link human brains to computers using neurotechnology and Brain Computer Interface (BCI). Advances are in the works and in many different areas, including external headsets that may be able to distinguish between hunger and boredom; implanted electrodes that translate intentions to speak into real words (see Paneth, Eberstark in this publication); and bracelets that use nerve impulses for typing without a keyboard. A bracelet bejeweled with electrodes can detect tiny nerve impulses on the wrist. The bracelet uses electromyography, which picks up the behavior of nerve cells that control the muscles, to eavesdrop on signals that move from the brain to hand muscles. Another invention is a laser helmet which emits laser beams through the skull and enters the brain. After bouncing off tissue and blood, the particles of light return to detectors that measure the oxygen levels. Those levels indicate where the active nerve cells in the brain are, which gives clues about mental processes (Sanders).

At first glance, one might question the utility of all of these technological advances. However there are disabled people who can really benefit from it. The goal for researchers and doctors had been to be able to directly get information from the brain to help people whose bodies can't speak or move. Implanted electrodes are able to record signals from the brain's intentions which allows people to control robotic prostheses. In order to improve the flexibility of prosthetic links, scientists linked electrodes directly to the muscle. The muscle signals, which informs how much force was needed to use the particular muscle, is measured on the skin surface with two electrodes. But it's hard to detect the signals through the skin because it's weak and unstable. The solution is to directly attach the electrodes to the muscles under the skin. Prosthetic arms have two electrodes attached to itself and when an amputee flexes a muscle adjacent to the amputated limb, the electrodes detect the signal and convert movement into the artificial hand. When signal problems occur, the prostheses are prevented from functioning well. By implanting the electrodes into the muscle itself, rather than placing them on the prosthetic limb they can make the prosthetic movements easier to control (Osborn, Lykkegaard).



As the figure to the right shows, the implanted muscle electrodes are linked to nerves that can control the prosthesis.

Paraplegics are testing out brain computer junctions to connect the brain to the digital world. Using brain signals, users are able to do online shopping, use an artificial body part to eat and drink and even communicate. Research has decoded speech from the brain signals of a paralyzed man who is unable to speak. When he saw the question, "Would you like some water?" on a computer screen, he responded with the text message, "No, I am not thirsty," only using signals in his brain. This is another example of the tremendous progress underway in linking brains to computers (Sanders).

Another useful invention for disabled people is a speech interface. A speech interface is a software application that facilitates linking between humans and voice-enabled-applications, such as virtual and voice assistants. However, speech interfaces presume the ability to create comprehensible speech which people suffering from locked-in syndrome are incapable of doing. Because of this, the best would be not to speak but to simply envision oneself to say words or sentences. Interfaces that are fixed on imagined speech would enable fast and natural communication without the need for audible speech and would give a voice to otherwise mute people. Brain computer interfaces are currently only used by a small number of patients. This is due to the unnatural way the machine is set up where users often have to focus on a single letter at a time which is then selected. A BCI based on brain activity for thoughts would promise communication without the need for auditory voice production. Only a silent speech interface based on brain activity would enable severely disabled persons such as people suffering from locked-in syndrome to communicate with the outside world. A downside

to this invention is the fear often associated with BCI that private thoughts could be read and thereby freedom of thought not be guaranteed (Schultz).

Neuralink is a company founded by Ilan Musk to allow the brain to interface directly with a computer. The company is working towards developing an easy to implant brain to computer interface that could do everything from healing brain injuries to greatly enhancing our perceptions. But the technology has also created an ethical and legal danger. While a brain to computer interface could help disabled people control everything from a computer cursor to a wheelchair, there is also a dark side. BCI could have valuable therapeutic effects including treating depression and Alzheimer's disease. However over or under stimulation to the brain from the BCI may have the capacity to alter ourselves and our personalities. Brain stimulation could address many aspects of a person's mental condition that are undesirable to them and provide them a means of alteration other than therapy or medication.

Additionally, those kinds of alterations might go wrong by having unintended side effects, like generating impulsivity. Furthermore, what does this mean for prosecution of crime and for offenders who have aggressive and violent impulses due to these external brain manipulations? On the flip side, a person equipped with BCI who has violent tendencies and is in danger of taking inappropriate action, could use BCI's counter violent impulses to produce a calming effect. There are those who would argue that this takes away human free will and personal moral accountability. Another ethical issue raised is the possibility of using a BCI to download memories onto a computer, which raises the issue of who has access to those memories, and the haunting nightmare of computer manipulated memories (Stuart).

These abilities also raise ethical questions about who gets access to our brains and for what purposes. When surveyed, many people expressed skepticism because it's a breach of privacy. The idea of allowing the government, businesses and even medical staff access to the brain's inner thinking didn't sit well with them. The potential for a BCI to alter thoughts and behaviors is frightening. What if further improvements would reveal even subconscious thoughts to the light of day for public scrutiny (Sanders).

The desire to persuade and change a person's mind is not new. Winning hearts and minds is at the center of advertising and politics. Technology's ability to manipulate hearts and minds with a subtle nudge is a threat to the underpinnings of our democratic society. A doctor might use precise brain-modifying technology to ease anorexia's grip on a young person, but the same might be used for money-making purposes: Imagine driving past Starbucks and suddenly you have an irresistible urge for a coffee. Is the craving caused by real thirst? Or is it the result of a tiny neural nudge just as you drove near the lady with the long hair? (meaning the Starbucks symbol). That neural intrusion might cause uncertainty over where that urge came from, or might even escape notice altogether. This is dangerous because once you start stimulating the brain, people's minds will be changed, and they will never know about it because they will think it's coming from themselves. One might not know if the thought or feeling came from his own brain or put by someone else.

As neurotechnology marches ahead, scientists, ethicists, companies and governments are looking for answers on how, or even whether, to regulate brain technology. This is something that will need to be further explored as more inventions are coming to light. What still needs to be resolved is how to handle the privacy issue. Some have proposed strict regulations around privacy that would treat a person's neural data like their organs. Just like a heart can't be taken out of a body for medical purposes without pre-approval, neural data shouldn't be removed either and should be protected from companies seeking to use it. Others say that people

should be able to profit from selling their brain data hence neuro-capitalism. A central agency composed of representatives from the world of scientists, academia, and government is needed to tackle these and future difficult questions that loom on the horizon. If each company is allowed to independently work through ethical issues, it would create a labyrinth of regulatory processes that anyone would be hard put to successfully navigate. The potential for this technology to help people with mental illness and disability is too important to let our fears of privacy violation undermine its advance but lack of ethical clarity is unlikely to slow the pace of the coming neurotech onslaught. Ethics must illuminate the murky path ahead and protect what makes us most human (Sanders).

In Judaism, deceiving someone falls under the prohibition of לא תגנב. According to the Sforno "Even deceiving your fellow man deliberately is called "stealing" גנבת דעת הבריות, "stealing people's minds, misleading them to believe that lies are truth." Companies can use new technology to literally change people's minds but that is misleading them and considered stealing. This is because the victims don't know that the thoughts are not their own and they're original thoughts are being "stolen" and replaced by new ones. A consumer might think they want to buy a product when really they don't and it's a neural intrusion in their brain telling them otherwise. Jewish producers and companies have to be careful to not let money get to their head by misleading people to buy their products. As Jews we have a special obligation to ensure that clients\customers are properly respected and feel that they can trust us to keep their data private and not be tempted to sell or tamper with it. We must respect that everyone has the right to privacy and can feel comfortable knowing that our data is safe when using these new inventions.

George Orwell's novel, *1984*, describes a dystopian society where mind control by the government is the order of the day. The nightmarish phrases, *big brother, newspeak* and *doublethink* were introduced into our lexicon. Throughout the cold war of the 1950's, readers assumed the protagonists of this novel were stand-ins for Soviet era communists and the democratic United States. In light of recent technological advances, a rereading of the novel might be in order.

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Can You Hear Me Now?

Devorah Pluchenik

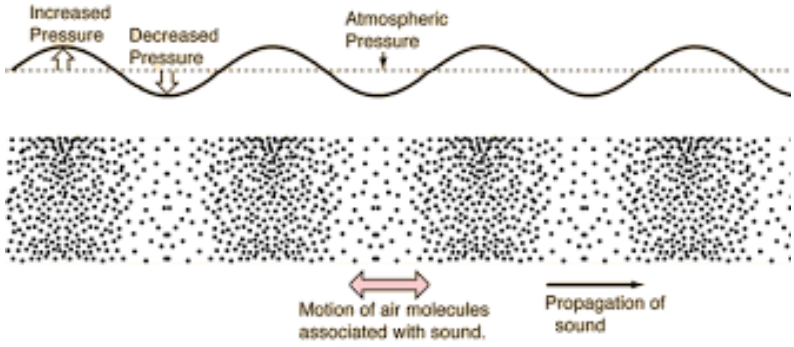
Too embarrassed to keep saying "What?" you just nod your head, agree and hope you have not committed an egregious faux pas.

Imagine sitting in a restaurant but you cannot make out the conversation around you. Everything sounds muffled and indistinct. Too embarrassed to keep saying "What?" you just nod your head, agree and hope you have not committed an egregious faux pas. You are probably not aware of NIHL, especially if you like to turn up the volume when you listen to your music. Noise-Induced Hearing Loss (NIHL) is a condition that comes from listening to noise too loud for the human ear to handle.

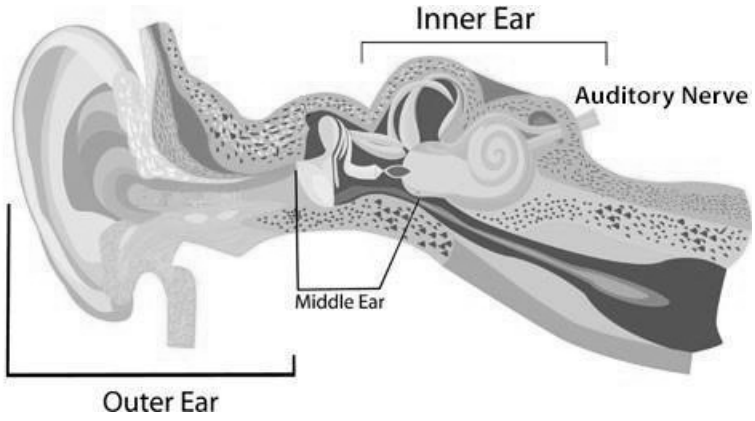
Loud noises can lead to permanent hearing loss. People can be exposed to loud noises in their day-to-day routines without even realizing it. Being at a construction site, listening to loud music, drilling into the wall, and being on a noisy helicopter are just some examples of daily volumes too loud for the health of our ears. One would think that "too loud" is all relative, that a simple accountant wouldn't be at as high of a risk to get NIHL as rock band leaders, however, no matter what your profession, everyone, be it in the daily commute, occupation, or night-life is susceptible to NIHL (Fink and Mayes).

It's common to get NIHL if your cumulative A-Weighted Decibels (dBA) level is too high. dBA is the term to measure volume. On a day-to-day basis, the volume in a library is 30 decibels. In a restaurant, having a conversation is about 60 decibels. A vacuum cleaner is about 75 decibels, and a jet engine is about 130 decibels. The Environmental Protection Agency (EPA) and The World Health Organization (WHO) both say that the highest daily dBA should be 70 decibels (Redmond). At a recent concert at Louisiana State University, the decibel level reach 95 dBA which set off seismographs indicating vibrations reached earthquake levels (Paul).

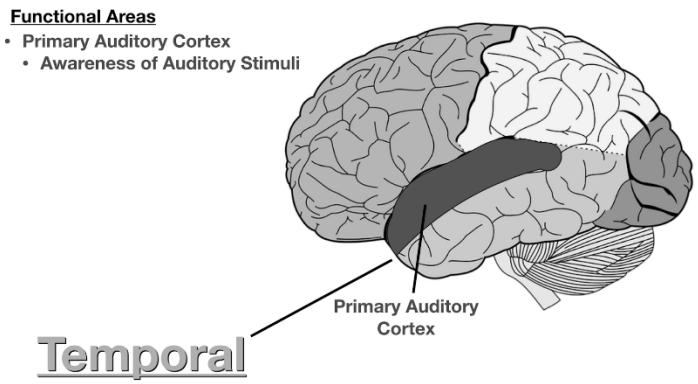
Many would think that their daily routine would not allow them to be exposed to volumes over 70 decibels. A librarian may be exposed to only 30 decibels at work, but her commute on a rowdy subway could force her to dangerously increase the volume on her headphones. On the flip side, a construction worker is always exposed to high decibel levels, yet if he is careful to always wear earplugs, that may soften the intensity of the volume and decrease it to a healthy level. Preventing hearing loss is easy if you have the right tools to apply to your daily routine. For example, one could wear earplugs to a wedding to help decrease the level of dBA that the ears are exposed to. In 1979, Dr. Amar Bose invented noise-canceling headphones so that pilots could concentrate. Headphones with noise-canceling capabilities block out sounds around you, so you won't hear anything but what's in your ear. The headphones started selling commercially in 2000 (Hlt). With that recent invention, when traveling on the subway you don't have to raise the volume so high in order to comfortably hear your music.



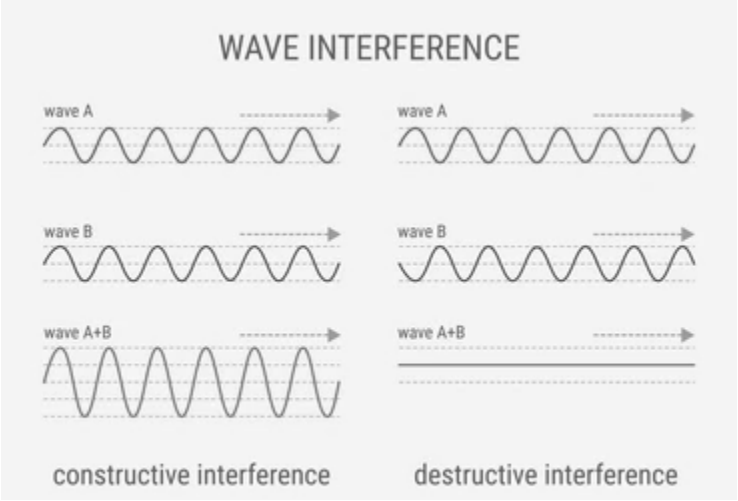
In order to understand how noise canceling technology works, one must understand the basics of sound. When one strums a guitar it causes the strings to vibrate. These vibrations make nearby air particles to alternately compress and rarefy, which creates a longitudinal sound wave (BBC). Sound waves travel through the air, and enter our body through the outer ear heading straight to the eardrum, which causes the eardrum to vibrate. The eardrum forwards these vibrations to three small bones in the middle ear, which in turn vibrate in sequence which increase the amplitude of the vibrations and send them to the inner ear. The waves continue through the inner ear to the cochlea, which is a fluid filled shell figure deep in the inner ear. The vibrations continue through the fluid, and as each wave peaks, the tiny hair cells that line the cochlea bend, and turn the waves into electrical signals. This bending causes a conformational change in the receptors from which the hairs emanate. At this point, the physical events are transduced to an electro/chemical nervous impulse within the auditory nerve. The auditory nerve transmits these electrochemical signals to the primary auditory cortex of the temporal lobe of the brain, where they are interpreted as meaningful sound.



When it comes to sound waves the bigger the vibration, the louder the sound. Sound waves are measured in decibels, therefore, when the vibration is bigger it will create larger sound waves which measure to high decibel levels, which can cause damage to the delicate mechanism of the eardrum, inner ear and cochlea ear because it's too loud. (Redmond).



The vibration of a sound wave can be depicted by looking at the amplitude and frequency of the sound wave. The amplitude is the measure of the height from the center of the sound wave to its peak or trough, and the frequency is the measure of how often a wave length is completed. Amplitude corresponds to the loudness of the sound and frequency corresponds to the pitch of the sound. Noise cancellation technology works to cancel out a sound wave by creating an identical sound wave that starts playing at half a wavelength later so that the two waves are out of phase. When one amplitude is at its peak, the other is at its trough. When the amplitudes of the two waves are combined, they add up to zero, canceling each other out in a phenomenon called destructive interference (Soundguys).



Listening to loud volumes can lead to NIHL, but there have also been other causes for the condition that have nothing to do with volume at all. The elderly are more susceptible to loss of hearing by way of falling, developing dementia, getting into an accident, or surprisingly when they live at home by themselves with no one to talk to. Most hearing loss that the elderly experience is from one of these causes and not from exposure to high volume (Fink and Mayes).

Another type of hearing impairment that can result from volume issues is tinnitus. Tinnitus is a disease where people hear a persistent sound that is not really there. It can last for a few minutes or a few hours, it can be loud, soft, low, or high. It sounds something like a ringing in your ear. Some people have it for years, and unfortunately it can be a sign of hearing loss. It is common for people to get tinnitus for a few minutes after listening to really loud music (Brookshire). Jan Mayes, an audiologist from British Columbia spent most of her career helping people who suffered from on-the-job induced hearing impairments, often tinnitus. Mayes' work shows how valuable the sense of hearing is. The fact that she dedicated her life to fixing something so small as a ringing in the ear proves that even minor hearing loss can be life altering (Redmond).

While NIHL is preventable, it is not curable. When the ear is exposed to sounds that are too loud, the tiny hairs in the cochlea get damaged and sometimes die; they do not regrow. This is the issue with listening to amplified noise because without the hairs, our body cannot convert these vibrations to electrical signals for the brain to recognize as sound. Cochlear implants bypass the problem but do not regrow the damaged hair in the cochlea. The cochlear implant works by having receptors placed behind the ear which receive the sound waves, convert them into electrical signals, and transmit them to the auditory nerve directly, bypassing the ear. One in the auditory nerve, these signals continue on their merry way to the brain. Although cochlear implants help restore partial hearing for those with hearing loss, it requires surgery and a training and adjustment period. It also comes with many side effects and does not actually cure the issue (Mayo Clinic).

A drug that can cure NIHL would be ideal. Stem cell therapy has met with limited success. Identifying the signaling pathways which would induce mitosis and differentiation in the stem cells lining the cochlea is being sought (Xu, Yang). A research team from Nanjing University has used cochlear organoids (see BenAmi in this publication) to screen a library of FDA approved drugs to identify a possible candidate that can promote the regeneration of hair cells. An anti-cancer drug called regorafenib showed some promise. Trials on rodent models are currently underway and hopefully will lead to a drug to cure this condition (Landsdowne).

Our delicate sense of hearing is too important to be treated in such a cavalier manner. The more we get comfortable with lower volumes, the safer our ears will be. If we get used to it, it can become the new norm and we can say goodbye to the abuse to which we subject ourselves by blasting loud music in the car. Instead, we should pray for the time when we can soar to the spiritual heights from the songs of the *L'viim* once again.

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The Nothing Cure

Michali Rosenberg

Surprisingly, the open-label placebo group achieved the same level of relief as the closed label placebo group.

Did you ever kiss a boo-boo and relief was immediate? No, your kisses are not dispensing a pain relief potion. This is a bona fide manifestation of a real measurable objective phenomenon, not limited to the junior set. Even adults will demonstrate relief from the Placebo Effect.

It is a situation where practitioners give patients a look-alike fake pill or treatment from which patients benefit. The idea is that your brain can convince your body that this treatment is authentic, causing you physical relief and healing (Brookshire). Placebos are usually used in clinical trials where patients are given pills, some of which consist of a new form of therapeutics, and others have no actual medicinal value in them. These patients are completely unaware of which pill they consumed. Afterward, scientists look at the results of these patients and sometimes see that placebos often produce an outcome similar to the treatment it is being compared to (Harvard Health). The results were due to these patients' belief that the treatment is legitimate and should heal them, tricking their bodies to behave accordingly.

A new discovery is that mild electric zaps to the brain could make the placebo effect stronger (Rocheleau). This is the first study to increase placebo and nocebo effects by altering brain activity. The nocebo effect results in the experience of negative side effects of a medication just from the mere suggestion that it might occur (Stromberg). Kong and his team conducted an experiment where 81 participants endured painful heat on their forearm through a thermal stimulator. Each participant received three creams to place on different parts of their arm. They were told one was a numbing lidocaine cream, one was a regular cream, and one was a pain-inducing cream. These participants did not know that all these "creams" were the same inert lotion dyed into three different colors (Rocheleau).

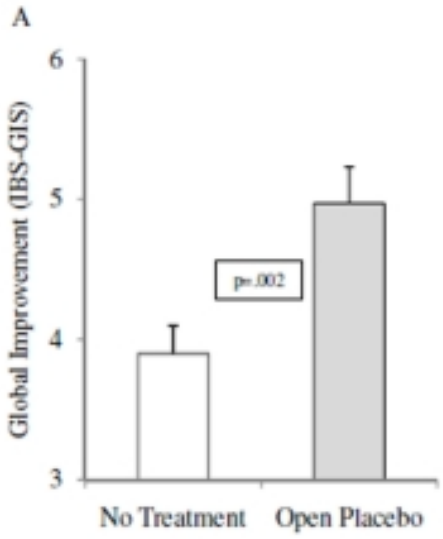
Before applying the heat, researchers had delivered electric currents to some participants' brains with a method called transcranial direct current stimulation, or tDCS. They used two different types of current: positive anodal tDCS, which typically makes nerve cells more active, more likely to fire off signals, and negative cathodal tDCS, which usually makes cells quieter and less active. They found that people who received cathodal tDCS described stronger placebo effects when they applied the "lidocaine" cream on the burn of their skin, while for people who received anodal tDCS, the stimulation dampened the nocebo effect of the "capsaicin" cream (Rocheleau).

This discovery gives researchers insight into how brain stimulation affects neural pathways and can significantly affect placebo and nocebo effects. For example, cathodal tDCS increases connection with the targeted brain area and a nearby area in the brain involved in cognition and emotion. This connection correlated with people reporting a more substantial placebo effect. The question now is to what extent can these electric zaps help people through the placebo effect? Doctors and researchers are using this discovery as hope to perhaps in the future heal patients in need of an impossible or unknown cure.

Another aspect to consider is the ethics and psychology involved in placebos. When a doctor prescribes a placebo to a patient, something with no sound medical reasoning why it should work, s/he technically breaks the doctor/patient trust and faith. While it's true that not many doctors will actively and knowingly engage in

this deception, doctors around the world routinely prescribe medication they know won't medically change their patient's condition.

The story gets even more bizarre. A randomized control trial was conducted involving people who had Irritable Bowel Syndrome. They were divided into two groups with one group receiving no treatment, and the other group receiving an open label placebo. The goal was to see if the effect of placebo is due to deception, or is the effect due to the fact that they received something, even knowingly a placebo. They randomized the group, gave some participants no treatment as a control, and gave the other half open-label placebos. Surprisingly, the open-label placebo group achieved the same level of relief as the closed label placebo group. Their study suggested that when an intervention is described clearly with a supporting rationale to their patients, placebo responses reflecting symptomatic improvement can be produced without dishonesty and deceit (Kaptchuk).



The relevance of the placebo effect cannot be overestimated. It provides relief for many people in pain and demonstrates the true effectiveness of new drugs brought to market. Pharmaceutical companies hate the placebo effect since it cuts into their profits. It is also important to note that while placebos have an excellent reputation for reducing symptoms such as stress and pain (Brookshire), they also have a measurable effect on physical problems such as lowering cholesterol and shrinking tumors (Harvard Health).

The power of the mind-body connection is a wonderment. While science today has gained tremendous insight on the significance of the placebo effect, there is still more to learn and further research to be done. For example, scientists must still figure out to what extent the placebo effect works. Additionally, it's still hard to understand how much the placebo effect is dependent on the individual patient, his health status at the time, and whether or not it can be consistently considered a standard rule. It has been found that there are genetic signatures to individuals who respond more or less strongly to the placebo effect. This should come as no surprise since pain is modulated in the nervous system by neurotransmitters through neural pathways. Since the type and quantities of neurotransmitter synthesis is under genetic control, investigation of variation in these genetic markers (termed the placebome) should lead to improved outcomes for patient responses. To date however no wide-scale genome-wide association studies have been performed (Hall). How many people are unaware that the key to their own healing lies in their own brain, if they just put their mind to it.

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The Mama Bear Phenomenon

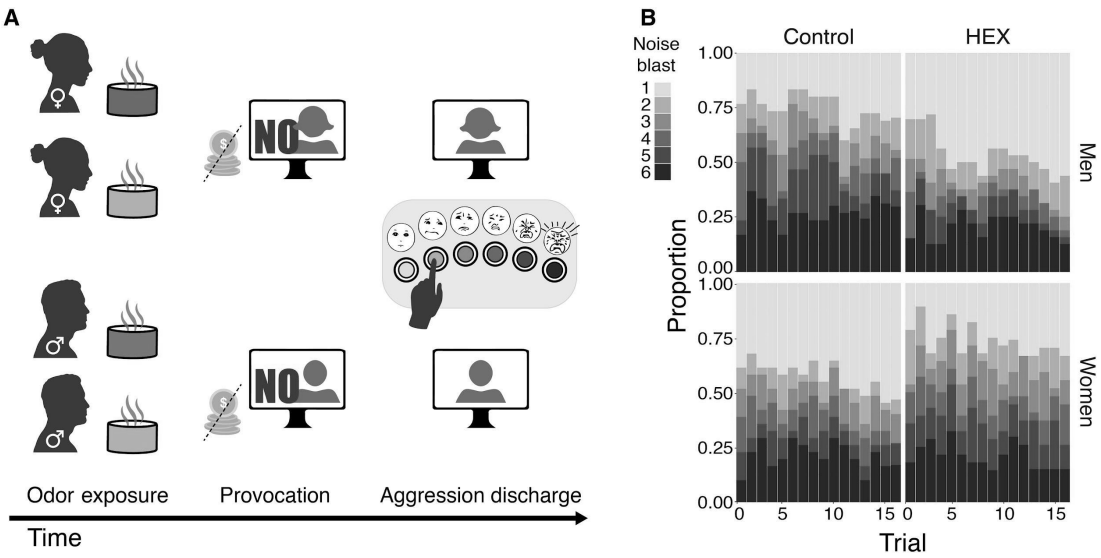
Rikki Schreiber

Scientists have found an odorless compound, hexadecanal, otherwise known as HEX, which increases aggression in women and decreases aggression in men.

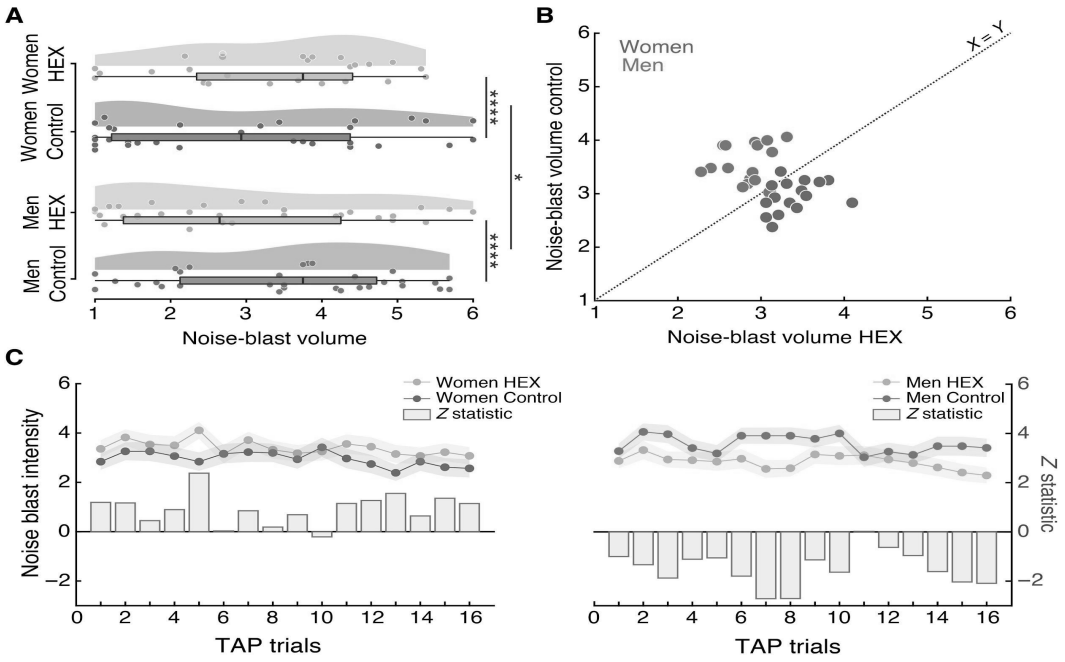
Which gender is more aggressive? Most would place bets on the brother building battle bots over the quiet, doll-playing sister, right? Contrary to popular opinion, in certain instances, females can actually be more aggressive. Scientists have found an odorless compound, hexadecanal, otherwise known as HEX, which increases aggression in women and decreases aggression in men. HEX is emitted by humans from their skin, saliva, waste products, and most notably from babies' heads (Underwood).

Researchers found that HEX can be aggression-inhibiting after piping HEX into mouse cages and that it caused them to be more relaxed. Release of corticotropin hormone is a stress indicator (Backström), and in this case, the activity of corticotropin-releasing cells in the nucleus of the mice hypothalamus (PVN) was reduced compared to when the mice were put in a clean box (Klein).

A study was conducted to test the effect of HEX on people by creating a series of computer games that were designed to engender extreme frustration. Half of the 126 participants were given HEX infused strips to wear on their top lips while the other half were given an identically smelling but HEX free strip to wear. First, the participants were asked to divide a specific amount of virtual money with an unseen player that they thought to be another human, but was in fact a computer. The computer was extremely frustrating and didn't allow them to give anything less than 90% of the money to their unseen player, preventing them from making any money. Once the participants were extremely agitated, they earned chances to blast noises at the same unseen partner by pressing a button with emojis alongside it, to describe the level of pain the noise would cause, demonstrating the participants' levels of aggression. According to the results , the women who smelled the HEX infused strips were 19% more aggressive whereas the men behaved 18.5% less aggressively (Mishor). Maybe try piping HEX into your brother's bed next time he gets mad at you.



This image graphically demonstrates how women overall blasted larger waves of sound to their unseen player which demonstrates that the HEX caused women to behave more aggressively than when they smelled the control odor, and it caused the men to behave less aggressively than when they smelled the control odor. On the spectrum of yellow to purple, the closer the emoji's corresponding sound was to purple, the louder the sound was blasted, and the closer the emoji's corresponding color was to yellow, the milder the sound was. As is demonstrated by the mens' graph, there are more yellow noise blasts and less purple noise blasts blasted by the men who smelled the HEX than by the men who smelled the control odor indicating that the men overall blasted milder blasts after smelling the HEX. Additionally, on the womens' graph, much less of the yellow, the quieter blast, and much more of the purple, the louder blast, were blasted by the women who smelled the HEX compared to those who smelled the control odor indicating that the women on average blasted stronger blasts after smelling the HEX.



These graphs demonstrate how women over all blasted larger waves of sound to their unseen player than the men. The graph on the top left demonstrates how men mostly blasted more intense noise blasts after smelling the control odor compared to smelling the HEX. The bottom left hand graph demonstrates how women blasted noises with higher intensities after smelling the HEX rather than the control odor. The bottom right hand graph demonstrates that the men overall blasted louder noise blasts after smelling the control odor than after smelling the HEX.

Scientists conducted another experiment where they compared the different behaviors of people while smelling the actual HEX as opposed to the control odor by monitoring their brain activity using an MRI scanner. Here, HEX increased aggression in women by 13% and decreased aggression in men by 20%. Additionally, HEX also decreased neural communication between places in the brain which regulate aggression in women and increased neural communication between these areas in men (Mishor).

In another test, where players can earn money, keep their current amount of money, or deduct money from their opponent by repeatedly pressing the appropriate buttons. The scientists used fMRI to view the brain during provocation to see how and in which areas of the brain HEX affects aggression. They substituted buttons with fist-clenching pressure detectors and found that HEX increased aggression in women and reduced aggression in men. For women and men alike, the HEX chemical increases activity in the area of the brain that is involved in the perception of social cues, the left angular gyrus. HEX regulated the functional connectivity, interactions between different areas of the brain (Park), between the angular gyrus and regions of the brain involved in social assessment such as the amygdala, orbitofrontal cortex, and the temporal pole which is involved in aggressive execution. The temporal pole, amygdala, and orbitofrontal cortex are parts of a brain network that controls aggressive behavior by evaluating emotions and making decisions. The HEX chemical regulated the functional connectivity in a gender-based way such that under provocation, it increased connectivity in men and decreased connectivity in women. Increased functional connectivity with these parts comes from reduced aggression as the aggression is being more regulated, which happens in mens' brains, however, decreased functional connectivity comes from increased aggression, as the aggression is being less regulated, which is what

happens in women's brains (Mishor). Additionally, under provocation, there's an increase in activity of motor and premotor areas of the brain which are the parts of the brain that create signals to control the movement in the rest of the body (Yip).

Men and women clearly respond differently to stimuli, which is interesting, because according to the biggest brain imaging study ever conducted, while there are some gender-based patterns in the brain, male and female brains are more similar than different. There are some differences, for example, that females tend to have thicker cortices, the folded gray layers outside the cerebrum, which is associated with performing better on cognitive learning through experience and general intelligence tests. Additionally, males have greater brain volume for subcortical areas of the brain such as the hippocampus, which is very involved in recollection and spatial awareness; the amygdala, which is involved in emotions, recollection, and decision-making; the striatum, which is involved in learning, inhibition, and reward processing; and the thalamus, which is involved in processing and communicating sensory messages to other areas of the brain. The cortical thickness of the male brains varied a lot more than with the females which makes sense as demonstrated by the IQ tests previously taken where mens' scores varied a lot more than womens' (Price). Most parts of the brain, although there might be slight gender-based differences, have overlapping features and aren't limited to their gender, meaning that it's not unlikely for a female's brain to have some male characteristics and vice-versa. There are additionally only a few parts of the brain that are dimorphic, meaning that there are two completely different types that the female and male versions minimally share features or don't at all (Wheeling).

In conclusion, which gender is really more aggressive? The answer is that it depends upon the circumstances. Although it may seem that men respond to some aggression-triggering stimuli more shrewdly than women, in the case of female aggression stimulated by hex, there is a clear beneficial adaptation. Women will fight tooth and nail to protect their infants. The lesson to be learned: when walking in the woods and you come across cute bear cubs playing, don't mess with the mama bear.

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Tiny Tools for a Big Job: Harnessing Nanopower to Cure Disease

Golda Schuster

Interestingly, DNA bots move similarly to humans—a process called bipedal walking.

The mere thought of a spider is enough to make some of us run and scream. Now cover your ears and imagine microscopic robots crawling around inside your body. Research is taking robots to a whole new level—a submicroscopic nanoscale level. Robotic technology is miniaturizing, advancing and being channeled to cure diseases and disorders.

When asked to imagine a robot, many people may think of an industrial robot, or a humanoid robot, or even a Roomba. But what about DNA? Traditionally, robotic engineering and robots were associated with metal, nuts, and bolts; however, with advancing technologies, robotic research has turned to other building media and materials, including biological components such as DNA. Until recently, DNA was viewed exclusively as an information storage molecule that contains the program for living beings to function. But now, with the changing technology, the uses for DNA are being stretched further than they have ever been before. The idea to use DNA in robotics was invented out of the necessity for targeted cures. DNA began as a material to store information, then expanded its use to build structures, kind of like bricks, and then physicists found that its self-assembling abilities can create very complex shapes. This opened up a whole new realm of scientific study and changed the world of robotic science forever, all with the hope to eradicate disease within humanity.

To better understand how robotics and DNA combine, a quick review of DNA's structure is in order. It is made out of four small components called bases, which are adenine represented by A, guanine by G, thymine by T, and cytosine by C. DNA also has a phosphate and sugar backbone, which together with the bases form a nucleotide. These nucleotides line up A with T and G with C, and together they give rise to the iconic twisted ladder double helix structure that we are familiar with (MedlinePlus) *(Figure 1)*. Roboticists used these DNA structure rules to create microscopic DNA robots called nanobots.

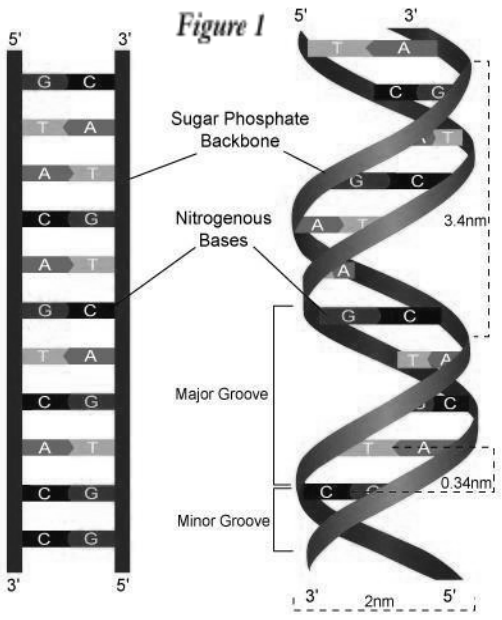
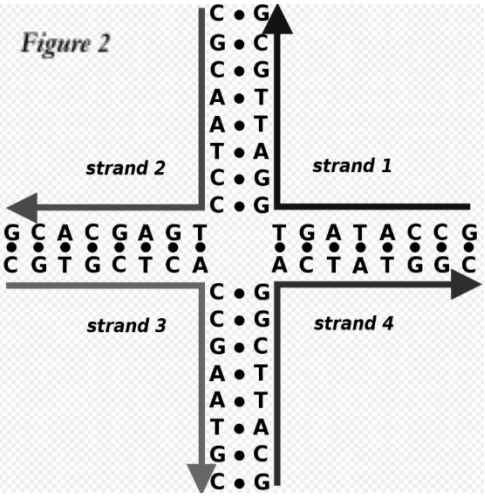


Figure 1

What exactly is a nanobot and why is it so important to science? A nanobot is a microscopic robot, made out of many different materials, one of which is DNA (Techopedia). Because of their small size, nanobots are extremely useful in many areas of study including astronomy, security, defense, and most importantly, medical sciences. In this essay, we will look at the lifesaving potential provided by these nanobots.

The formation of DNA bots can be understood analogously on a macro scale. When two magnets align next to each other, the rules of polarity allow you to predict exactly how they will connect. The same thing occurs on the nanoscale. DNA has 4 base pairs, A T C G, and each of

these will only pair with one another - A with T and G with C. If you lay out a single stranded DNA that has a specific order of base pairs, you can accurately predict how the strand will shape itself because of DNA's structure rules. This is illustrated in *Figure 2* where the 4 strands associate into a 4-arm structure. The order of the base pairs in the original single stranded DNA will determine full control over the end product. With the help of computer programs, engineers, physicists, and scientists are able to work together and sequence the base pairs for single stranded DNA that allows them to create amazing self-forming shapes with DNA that can fulfill a variety of functions (Kearney).



How does a DNA bot move to its target location? Interestingly, DNA bots move similarly to humans—a process called bipedal walking. When we walk on our two legs, we pick one leg up, move it forward, and put it down in the place that we want it to go. We then lift our other leg, and repeat the process. DNA bots also have "feet." Like magnets, DNA bases in the DNA molecules are attracted to some other molecules, so when the DNA is at rest its 'feet' are stuck in place because of the attraction to what's beneath it. However, when something in front of it has a greater attraction, the DNA will lift its 'foot' up and put it back down in the spot with greater attraction. It then does the same thing with its other 'foot', enabling it to move across the surface (Li).

While the knowledge of how DNA bots can move was an incredible advancement in robotic technology, scientists needed to establish how much control they can actually have over the DNA. Programmed objects like computers are coded to be 100% responsive to our input and are also coded not to act without our command. Computers have two inputs that go through logic gates, which determine the output that will travel on to the next gate in the logic pathway. Every time the inputs pass through the same gate, the same logic rules will apply, with no change. The important question for roboticists to figure out was if DNA bots can follow the same process of logic rules.

Plato famously said "necessity is the mother of invention." With the rapid evolution of disease, scientists are at a loss for how to make treatment more specific. There are times where the treatment of certain diseases and cancers can create more adverse effects and cause more harm to an already sick patient because the treatment is insufficiently localized. This necessitates the creation, or invention, of new cures. With the development of nanotechnology and the creation of self-assembling DNA, scientists saw an opportunity to create a robotic DNA that would be able to carry packages and act as a delivery system to a specific target. With the help of robotic DNA, many diseases and cellular issues can potentially be corrected, including cancer.

In order to test out the functionality of the DNA robots, scientists programmed the order of base pairs that would hypothetically release a load when triggered, and then created the DNA strand in accordance with the program. They then injected the robots into a cockroach and labeled the robots with fluorescent markers so the robots would be trackable. Upon observation, the injected DNA bots functioned exactly as it was programmed to, passing through logic gates, as shown in *Figure 3*, and reacting as expected (Amir). When these logic gates were triggered, the DNA bots effectively released their load on the target cell, with the same accuracy

as any computer (Spickernell). These incredible results proved that a biological molecule, DNA, can be successfully programmed to function as a biological robot within a living organism.

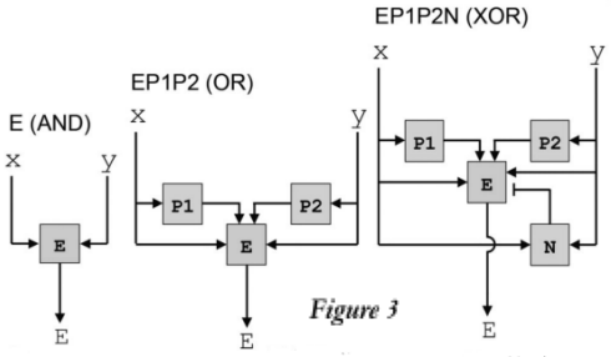


Figure 3

Previous research established that the DNA bot can move and operate as programmed by a computer. The next question that needs to be addressed is whether it can cure diseases. Scientists tested the curative properties of the DNA bot by inserting it into a mouse with cancer. The targeted cancer is developed from a mutation on the sk-br-3 gene which results in a type of breast cancer caused by an overproduction of the HER2 gene. This mutation also causes the same cancer in humans, making this a practical and informative study. The DNA bot called HApt-tFNA was injected into the experimental mouse and was observed to cause the cell to exit the S phase of the cell cycle and go into the G2/M phase. As illustrated in *Figure 4*, the control mouse had about 18% of the cells in S phase and only 10% in G2/M phase. Once the HApt-tFNA DNA was in effect, there were only 8% of the cells in S phase and 24% of the cells in G2/M phase (Ma). The robotic DNA clearly had an effect on the phase of the mouse's cells within its cell cycle, but what does it mean?

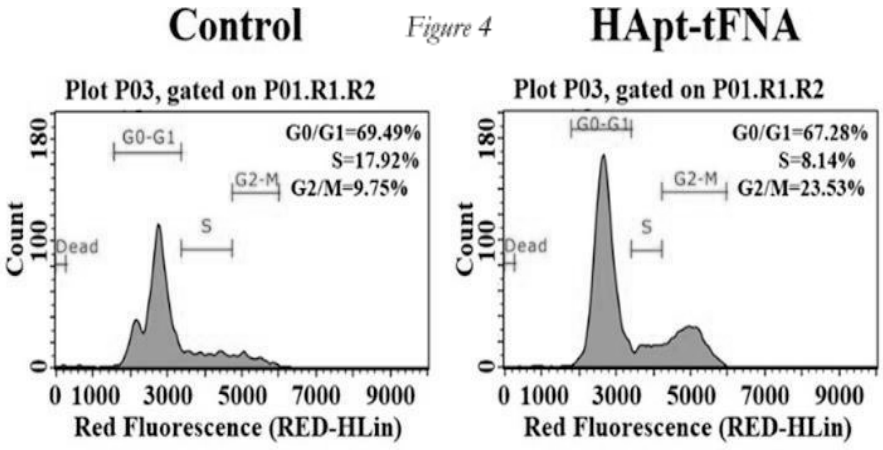


Figure 4

In order to understand the results of the experiment a brief run through of the normal cell cycle is necessary. The cell cycle is divided into four main stages: G1, S, G2, and M phase. During the S phase, duplication of DNA occurs in preparation for cell division. In a regular cell, the S phase is regulated by cell checks that control how often the DNA duplicates. However, if a cell is cancerous it gets "stuck" in S phase and causes the DNA to keep on reproducing in unreasonable quantities. G2/M phase is the phase right before a cell exits the cell cycle and dies. Cell death, also known as apoptosis, is necessary for the continuous functioning of our body and protects the body from cancerous cells. When cancerous cells get stuck in the S phase they don't pass through the regulatory checkpoint that will send the damaged cell into apoptosis. The DNA bot's ability to move a cell that's stuck in S phase to the G2/M phase can significantly lower the damage caused by cancer cells, because there won't be an excess of the HER-2 gene product caused by the cancer (Ma).

In addition to assisting cells move through the cell cycle and causing damaged cells to undergo apoptosis, scientists have found other uses for mobile DNA robots. As seen in the picture of a drug carrying DNA robot *(Figure 6)*, these nanobots are able to carry packages. The robots can also deactivate genes, and monitor the cells to ensure that everything is running as it's supposed to (Huo).

Because of its ability to access the cells so directly and knowing what the cell needs, robot DNA can be very efficient, and may be the cure that scientists have been searching for. Unlike our current medications, the DNA bots can be programmed to search for any abnormalities and therefore don't need to be specific for each disease it encounters. The bots can also adapt to conditions within a cell and react to outer stimuli. Because they are made out of genetic material, they are completely biodegradable and the cells already know how to dispose of them when necessary. DNA bots can be completely autonomous drug dealers, providing the safest and most effective treatments our planet has ever seen.

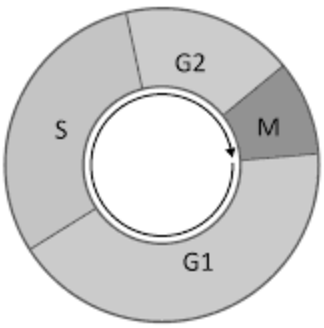


Figure 5

What are the *Halachic* ramifications of using DNA robots? Robots are obviously prohibited for use on *Shabbos* due to a myriad of reasons including *muktza*. Yet DNA robots, as we discussed, are not the traditional kind and don't have problems with outlets or battery power. So can these DNA bots be in our body over *Shabbos*? Every action you do will cause the DNA to react and act in a specific way, and one can argue that this may be *assur*. For example, something you eat might necessitate the DNA to kill a cell, but killing anything is *assur* on *Shabbos*, even a cell. One can consider whether killing a cell would be included in the *issur* of *meleches shochet*.

The *pasuk* in *Shemos* says "וְיוֹם הַשְּׁבִיעִי שַׁבָּת ו לַה' אֱלֹקיךָ לֹא־תַעֲשֶׂה כל־מְלָאכָה," *but the seventh day is a Shabbos of the Hashem your God: you shall not do any work. The Gemara in Meseches Shabbos, daf kuf chof, amud bais* says about that *pasuk*: ----,אי הָכִי הָכָא נָמֵי, כְּתִיב: לֹא תַעֲשֶׂה [ל] מְלָאכָה עֲשִׂיָיה הוּא דְּאָסוּר, גְּרָמָא שְׁרֵי. The *Gemara* explains that the *lashon* in the *pasuk* of *"lo saaseh"* means that the action of doing a *melacha* directly is *assur*, but doing the *melacha* indirectly is *mutar deoraysa*. This is the source of extensive halachic debate of whether *gramma*, indirectly doing *melacha*, is always permissible, because that's what it seems to say in the *Gemara*. However, *Chazal* forbade *gramma midrabanan*. From this it seems like DNA bots will only be an *issur drabanan*, because there is no direct *melacha* being done. A person going about their day-to-day activities is not directly mobilizing the DNA. It's just a byproduct of their actions.

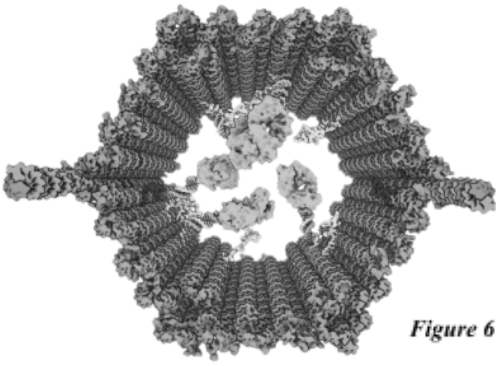


Figure 6

What are some of the factors that are taken into account for *gramma*? And what *heterim* evolve because gramma is drabanan? One factor that is used to determine if something is gramma is if there is a time lapse. If there is a delay between the action being done and its outcome then the action is considered *gramma (Shemiras Shabbos K'Hilchosa)*. Another factor to take into account is if it's visible. In *Aruch Hashulchan* it says ואין לנו להחזיק ריעותא במה שאין אנו רואים - we don't have to worry about things we don't see, so microscopic nanobots that work in your body would be fine. A third factor that is taken into account is in situations of illness even if it is not life threatening, *gramma* would possibly be permissible.

Based on this, we can understand that DNA robots inside a person would be *mutar* on *Shabbos*. There is a time lapse which causes them to be *drabanan*, but they're also not visible and so is *mutar*, and in some cases they are therapeutic.

While the DNA was tested for viability in living organisms, there is no end to the research that can still be explored. Can DNA bots mutate? If a DNA bot is made out of DNA, what's stopping the DNA bots from acquiring mutations just like the DNA in our body? If the DNA bots become cancerous, can they cause more problems than we have by having cancerous DNA try to cure cancer? This technology will most assuredly evolve at an ever accelerating pace and research will struggle to keep pace with what is guaranteed to be an exhilarating roller coaster ride.

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The Nose Knows

Serach Soloveichik

It is no small wonder that blood hounds are used by police to locate evidence and clues to solve cases.

The dark aroma of freshly brewed coffee in the morning. The refreshing crispness of brisk autumn air. The fragrance of vanilla, hot cookies, cinnamon, baking bread, the B'samim at the end of Shabbat–the list is endless. Humans can distinguish between more than one *trillion* different odors. These smells are a fundamental part of human life, mainly because our sense of smell is strongly linked to our feelings and memories. When we smell latex, we think of the dentist's office; we associate the cooling scent of mint with feelings of invigoration and energy. Moreover, the sense of smell is the foremost sense for most animals. It allows them to locate food and circumvent danger. It is how most animals circumnavigate their surroundings and build mental maps (Cepelewicz). It is no small wonder that blood hounds are used by police to locate evidence and clues to solve cases. The sense of smell, more properly known as olfaction, is invaluable.

Just as the cardiovascular system consists of the organs that serve the function of pumping blood, the olfactory system consists of the bodily structures that serve the sense of smell. One of those structures, the nasal cavity, contains the miniscule olfactory receptors which recognize chemical compounds; those chemical compounds are the odorants. When you smell something, your smell receptors are detecting the odorants. A common misconception is that a single odor–say, the smell of mown grass–is composed of merely a few chemical compounds. That premise is false; one odor alone is comprised of *hundreds* of different types of chemicals (Ruta). While receptors from other parts of the nervous system are set to bond to a few select molecules, each olfactory receptor must bond with a far greater number. Humans and animals have only so many olfactory receptors, and therein lies the question: how can our limited repository of receptors recognize such a vast number of chemical compounds?

A recent study sought to answer this mystery of odor recognition. Olfactory receptors had been discovered thirty years previously (del Mármol); however, scientists had been unable to view them up close to decipher their structures and operations, because available methods at the time were insufficient (Ruta). Additionally, receptor recognition seems to follow no specific pattern. The many compounds one individual receptor can recognize are chemically and structurally different.

At the time of the investigation, there were two prevailing theories about the interactions between odor receptors with molecules. The first was that receptors have evolved to respond to many molecules by responding to a defining feature of those molecules, such as shape and size (see Figure 3 top). The second proposition was that the receptors have multiple binding sites on their surfaces, permitting them to accommodate a greater number of varying molecules *(see Figure 3 middle)*. The findings, however, came up with a different answer.

The team set out to solve the structure of an olfactory receptor with the help of recent advances in cryo-electron microscopy, which focuses beams of electrons instead of light at a frozen specimen. This reveals molecular structure down to the atomic level. This method is becoming increasingly mainstream these days in scientific research and study (Milne). The general rule in biology is "Form Follows Function," that the structure facilitates the mode of action. This technology revealed the interior architecture of olfactory receptors thereby shedding some light on the mystery surrounding them.

Very often in biology, the success of an experiment lies with the choice of animal model and more often than not, it is the lowliest of organisms that have facilitated the major breakthroughs. Mendel had his pea plants when elucidating the mechanism of inheritance of traits, Nobel Prize winner Eric Kandel had his sea slug Alypsia when elucidating the mechanism of memory formation and storage, Nobel Prize winner Sydney Breenner used the roundworm C. elegans for his work on development. In this case, the test-subject was the jumping bristletail *(Figure 1)*, a ground-dwelling insect, chosen for its simple olfactory system, having only five olfactory receptors. Nonetheless, those receptors belong to a large family of receptors with tens of millions of variants, which according to speculation, also exists in hundreds of thousands of other insects. Despite their diversification, these receptors all function in the same way: they form an ion channel in their center *(Figure 2)*, a pore through which charged particles may flow in and out of the cell. When, and only when, the receptor encounters its target odorant and binds to it, the ion channel opens, activating the sensory cells that initiate the sense of smell.

Figure 1: The jumping bristletail, a ground-dwelling, wingless insect, and the test-subject of the experiment.

The researchers selected one of the bristletail's receptors, OR5, to study more closely. Using the procedure of cryo-electron microscopy, they examined the receptor in three structural configurations: alone, and bound to first one then the other of two chemicals, the common odor molecule eugenol and the insect repellent DEET. The outcome (depicted in Fig. 3.3) did not match the explanations of the two prevailing hypotheses mentioned above. It turned out that both the eugenol and DEET docked in the *same binding site* in the OR5 receptor, the site in question being a simple pocket lined with amino acids. Most exceptionally, the amino acids formed weak bonds with the odorants, allowing the odorants to arrange themselves in many different positions. This is contradictory to most other systems, wherein the receptors form *strong* interactions with their target molecules in what is known as a "lock-and-key model".

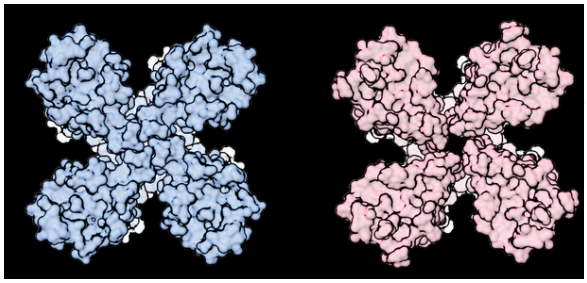

Figure 2: The channel pore (blue) dilates (pink) when an odor molecule responds to the receptor. (Ruta)

It is these weak, nonspecific interactions between the amino acids of the OR5 receptor and the odorants that allow the receptor to recognize so many contrasting molecules. The molecule can bond in different structural adaptations within the receptor; in this manner, the receptor does not select a defining feature to which to respond, but responds instead to general features of the odorant (Ruta). Additional computational modeling demonstrated that chemical compounds other than eugenol and DEET could bind with the receptor in a similar fashion. It is important to note that the olfactory receptor's ability to respond to such a vast number of molecules does not mean it has no specificity. On the contrary, there are compounds to which a receptor "prefers" to bind, and others to which it is insensitive. Furthermore, tweaking the arrangement of even one of the amino acids of the binding sites could instantly increase or decrease the receptor's affinity to a certain molecule. This could be a possible explanation as to how

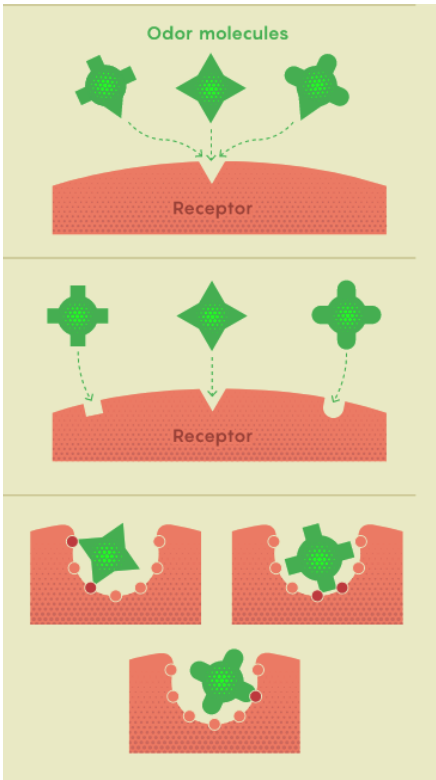

Figure 3: (Top) The receptor responds to a defining feature of the molecule, e.g. shape and size. (Middle) The receptor has multiple binding sites. (Bottom) The odorants bind to the receptor in the same location, but in a variety of orientations.

insects have successfully evolved millions of olfactory receptors to adapt to their many environments and lifestyles.

The study of olfactory receptors is far from complete, even with this breakthrough.

Insects use many other categories of ion channel olfactory receptors, including some much more complex than those of the jumping bristletail, demonstrating that there are several tools in the olfactory toolbox (Cepelewicz). These researchers believe that there are other, more general lessons to learn from OR5, such as how its operation could apply to other receptors in animals' brains. It's an excellent model for the study of imprecise binding interactions. Clearly, there are many more observations to explore and many more questions to answer.

The beauty of the olfactory system is that while we have a great deal of information about the subject already, there is so much yet to discover. And is that not the purpose of scientific study– to question, revise, and build knowledge about our natural world?

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To Touch The Sun

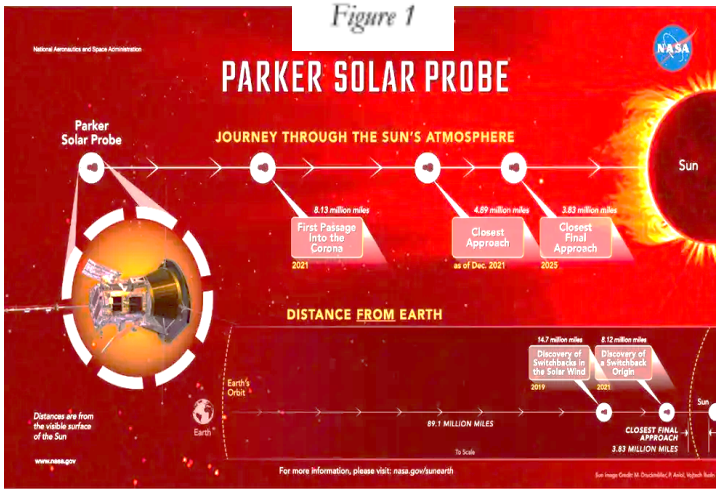
Yocheved Stein

The purpose of the Parker Probe's mission is to further expand scientists' understanding and knowledge of our Sun, as well as other stars.

In April of 2021, NASA achieved a major milestone–the Parker Solar Probe successfully "touched" the Sun by entering its atmosphere. The $1.5 billion probe was launched in 2018 and is designed to make successive circular orbits, getting closer and closer to the Sun each time (4). The probe is named after Eugene Parker, a solar astrophysicist who was first to recognize the existence of solar wind, changing the way scientists perceive the Sun and the Solar System (8). The purpose of the Parker Probe's mission is to further expand scientists' understanding and knowledge of our Sun, as well as other stars.

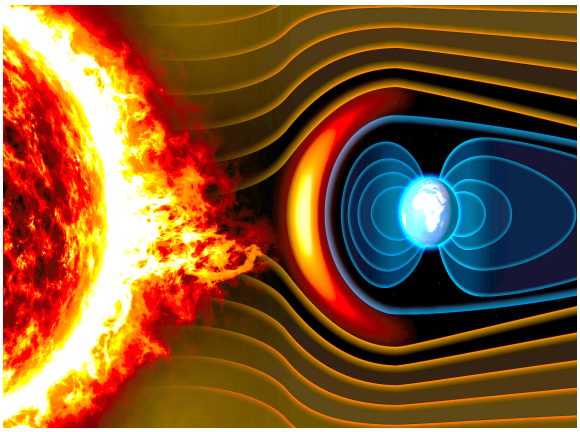
The Parker Probe was commissioned to make twenty-four orbits around the Sun over the span of seven years, using Venus's gravity to assist it in getting closer and closer to the surface each time (10). Although it has already entered the Sun's atmosphere, it has a way to go before completing its mission. Its closest pass will put it within 3.9 million miles of the Sun, the closest an artificial object has ever been (5) *(Figure 1)*. The spacecraft will be exposed to extreme temperatures over 400 times the heat we feel on Earth. In order to protect the probe from the intense solar heat, NASA's mission partner, The John Hopkins University Applied Physics Laboratory, created a carbon composite heat shield to shelter the technology and instruments that are collecting the data about the Sun and its many mysteries (5). The probe has built in sensors which direct it to shift positions, ensuring that the heat shield is always facing the Sun. Eventually though, the heat from the Sun and its atmosphere will render the spacecraft useless, but hopefully not before the mission is completed (7).

Figure 1



One of the mysteries the Parker Probe will shed light upon is how the Sun conjures solar wind. Continuous streams of charged particles and plasma, known as solar wind, emanate from the Sun's corona–the outermost layer of the solar atmosphere (10). Earth is protected from the solar wind by its magnetosphere - a magnetic field that deflects the charged particles of the solar wind (Figure 2). When the solar wind carries strong bursts of charged particles and radiation into the Earth's magnetic field, these particles get carried toward the planet's magnetic poles, causing beautiful light displays known as the Aurora Borealis, or the Northern Lights (1). Those powerful outbursts can cause disruptions to satellites, ship communications, power grids, and other technologies. They can also damage spacecraft and expose astronauts to harmful radiation (4, 6). Nicky Fox, Division director of Heliophysics at NASA says "My feeling is—if the Sun sneezes, Earth catches a cold, because we always feel the impact of what happens on the Sun thanks to the solar wind" (3). While it's known *where* the

solar wind comes from, it's unknown *how* it originates. Scientists hope that The Parker Solar Probe can help them better understand where it comes from and subsequently how to prevent the damages it can cause. Adding to the mystery that surrounds the solar wind is the temperature of the Sun's corona. The photosphere, or surface, of the Sun reaches 6,000 degrees Celsius, which is 11,000 degrees Fahrenheit (2). The solar corona however, is the outermost layer, yet it reaches temperatures over one million degrees Celsius, which is 1.8 million degrees Fahrenheit (9). Scientists are hoping that the Parker Solar Probe can help discover the solar corona's secret of how and why it's hotter than the Sun's actual surface.



The amazing feat of entering into the star's blistering atmosphere is a monumental moment for NASA. The discoveries about the mechanisms of the solar winds and the properties of the surface of the Sun are vital information for scientists. These breakthroughs can help astrophysicists understand how the Sun functions and help astronomers prepare for "space weather" that can disrupt technology and harm astronauts and spacecrafts (10).

The Parker Solar Probe is fascinating because it will open new frontiers in space exploration. Through learning more about how our Sun works and affects the solar system, we can learn more about other stars in far off galaxies that may harbor life as well. The importance of the Sun to human existence, and knowing more about an essential part of life on Earth, can lead to amazing breakthroughs.

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