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Conscious and Paralyzed
The Story of Locked-In Syndrome

Decoding the Mind
How Brain-Computer Interfaces are Challenging What's Possible

All for One and One for All
The Emergent Intelligence of Ant Collonies

LETTER FROM THE PROFESSOR

The Broad Scope of Neuroscience

The field of neuroscience is broad and includes a wide range of subfields. Neuroscientists study cellular and molecular processes, human and animal behavior, artificial intelligence, and a variety of disease states. There are even neuroscientists attempting to provide biological explanations to long debated philosophical ideas like free will. These few examples should give the reader an idea of the many subfields of neuroscience and the difficult questions that neuroscientists are attempting to answer. It goes without saying, then, that no single neuroscientist can ever hope to understand or be an expert in all of the areas of study encompassed in the field. And yet, people with expertise in these and other relate areas all identify as neuroscientists. What holds us together as members of the same intellectual family? First, we are naturalists. We hold the view that the key to understanding the simplest to the most complex processes and behaviors can be found in the natural world. Second, we recognize that the evolution of brains and nervous systems have afforded organisms with such systems increasingly more elaborate, complex, and sophisticated ways of interacting with the world. Third, we are committed to understanding how brains and nervous systems work and how they produce such complex behaviors. Neuroscientists first commit to a rigorous education in neuroscience and we use our specialized knowledge to investigate aspects of the world that is of particular interest to us. This, class of 2019, is what you have done. Having spent the last four years engaged in the rigorous study of neuroscience, you are now using your specialized knowledge to investigate the world more broadly. Your varied interests are displayed in this magazine, Volume 3 of *Scientific Kenyon: Neuroscience Edition.* In it you write about optogenetics, the cutting edge science that holds the possibility of restoring lost vision *(Let There be Light, pg. 1)* ; about near death experiences in the provocatively titled *Death is Not Always the End*, *(pg. 25)* ; about brain computer interface in *Decoding the Mind (pg. 43)* ; and about narcolepsy as an autoimmune disease *(Excessive Sleepiness, pg. 95)*. You wrote about the intelligence of birds and ant colonies, the effects of meditation on the brain, the similarities of intoxication and sleep deprivation, cellular memory, mapping the mind, locked-in syndrome, how Lyme disease mimics psychiatric illness, and yes, free will. Throughout the magazine can be found the original artwork of your classmate Samantha Montoya, beginning with the cover! We, the faculty are impressed by your commitment to the scientific investigation of difficult problems and are impressed by the broad range of your interest. You inspire us. As you leave to begin the next chapter of your life, we are confident in your success and know that whatever path you take, you will represent the yourself, the Neuroscience Department, and Kenyon College, with grace and distinction. We wish you well.

Sincerely,

Hewlet G. McFarlane
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Dr. Hewlet G. McFarlane and
The Class of 2019

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Let There Be Light:

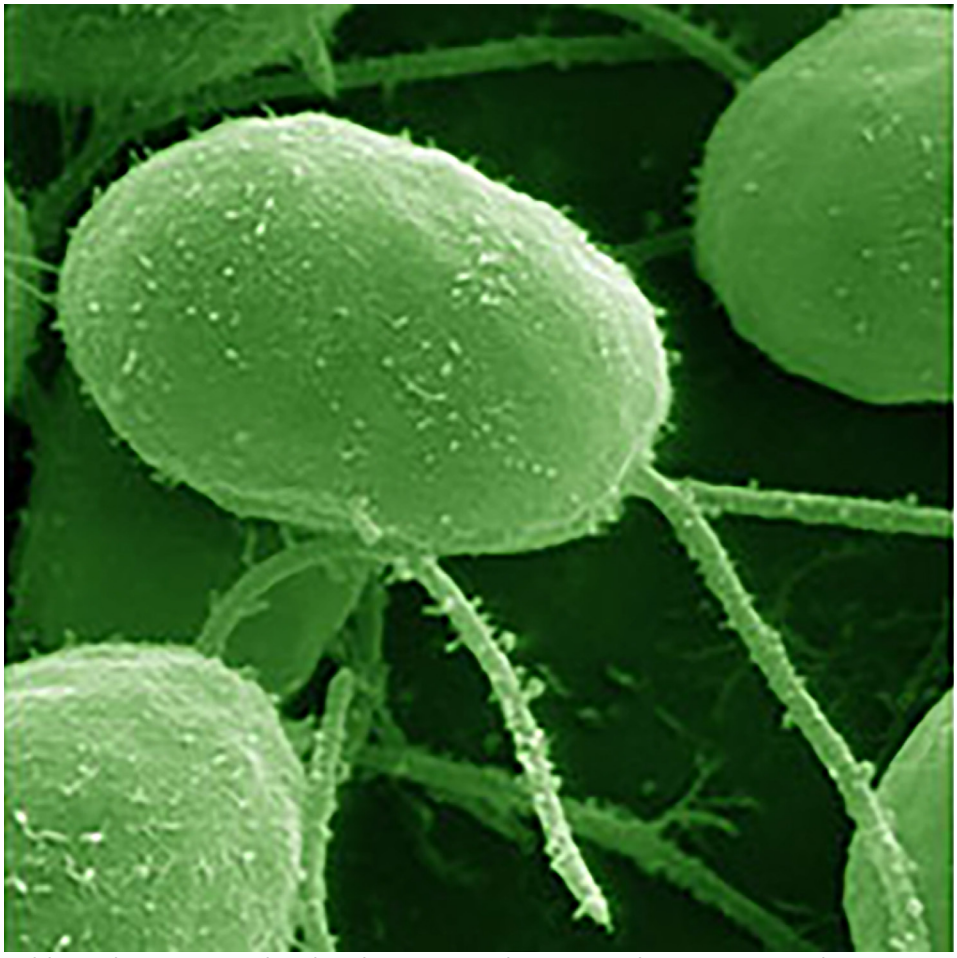
Restoring Vision With Optogenetics

By Kristin Woodard

Chlamydomonas TEM 03 oretreived from Wikipedia Commons

There's an old saying that eating carrots will improve your eyesight. Although that's a myth—more vitamin A can't actually make bad vision better—another member of the Plantae kingdom is being used to restore vision in mammals. The single-celled Chlamydomonas reinhardtii are a species of green algae that are phototactic, meaning they rely on light cues to move[1]. They contain a certain type of protein receptor called channelrhodopsins that respond to specific wavelengths of light. Although they are simple organisms, the algae use light cues in complex ways. They have an area called an eyespot, where their channelrhodopsin proteins are clustered. When these proteins absorb blue light, they signal for the algae to move towards the light source[1]. At a molecular level, humans are not so different from these microorganisms. We have similar proteins in the photoreceptor cells of our retina, called rhodopsins and cone opsins, which allow us to see many different colors, or wavelengths of light, and we also use these light cues to respond to our environment. But what happens when we lose these light-sensing proteins?

More than 1 in 3000 people are affected by retinitis pigmentosa, an inherited genetic disorder that causes the death of cells in the retina[2]. As the photoreceptors die, the brain gradually loses its only access to the visual world, and blindness creeps in. When retinitis pigmentosa advances throughout the retina, the tools we normally think of for correcting eyesight, like glasses or Lasik surgery, become useless—without light sensitive cells, the brain cannot receive light cues. Until now, that is. Scientists are currently using a gene editing technique called optogenetics to harness the power of algae and restore visual responses in humans who have lost the function of their photoreceptors. Optogenetics, a term coined by Stanford professor and researcher Karl Diesseroth, refers to a gene editing technique where genetic information for light sensitive proteins, like channelrhodopsins, is inserted into neurons in order to control neuronal signaling with light[2]. These light sensing proteins can be inserted into any neuron, and have opened the door for scientists to understand and control how the brain functions. Optogenetics is currently being studied as a tool to help reduce seizures, improve memory, relieve symptoms of Parkinson's, understand schizophrenia, and so much more. For people with retinitis pigmentosa, optogenetics provides an incredible opportunity—to experience the world though vision again, even after photoreceptors die.



Chlamydomonas reinhardtii algae. From the National Science Foundation.

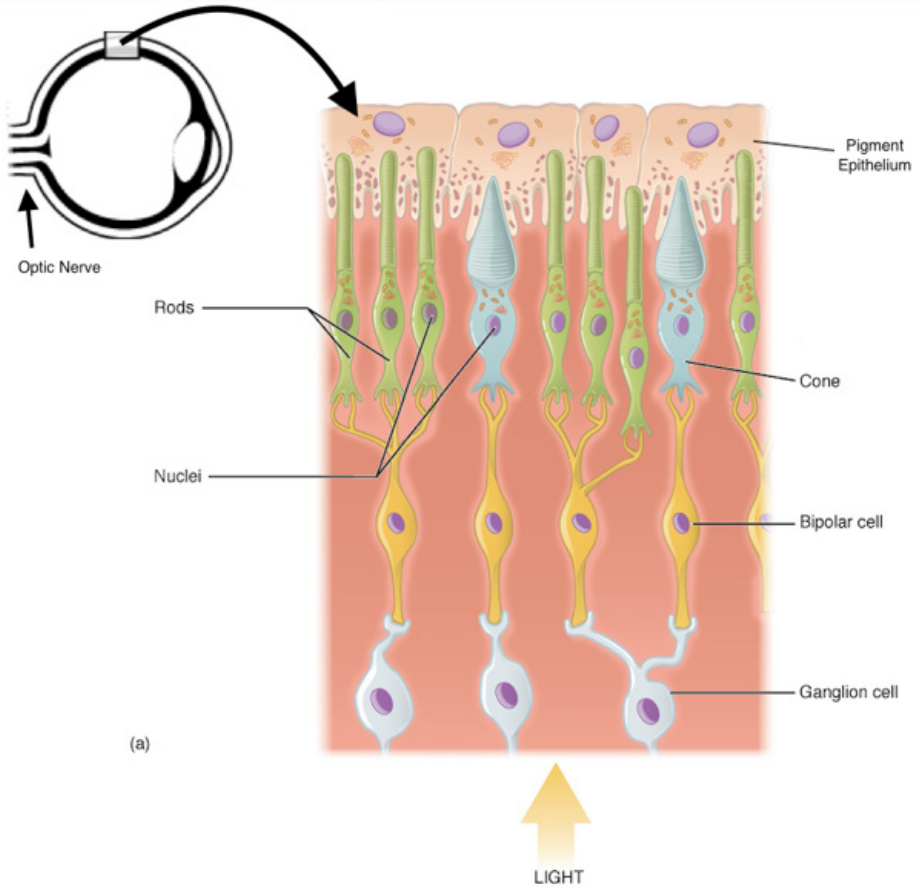
Shedding Light on Vision

There's another saying that eyes are the windows to the soul—this time, there's actually some truth to the proverb. The retina is made of layers of cells at the back of the eyeball and has a complex, organized architecture. If you were to shine a light through the pupil, you would actually see a part of the brain, because the retina is made of brain cells called neurons (I don't suggest trying this on yourself though). The first layer of neurons in the retina consists of the light sensitive photoreceptor cells, which can be divided into rods and cones. Rods contain rhodopsins that respond to the lowest wavelengths of visible light, and we have 20 times more rods than we do cones[3]. Objects don't lose their color at

night, but we see them in black in white because we use our rods to process in low levels of lighting. Cones contain cone opsins, and are sensitive to much high levels of illumination, like in daylight and artificial lighting[4]. Cones are used for color vision, since we have three different types of cone opsins that respond to short (blue/violet), medium (green), and long (red/yellow) wavelengths of light[4]. They are highly concentrated in the fovea, a small area at the center of the retina with high visual acuity[4]. Together, rods and cones help us see the visible spectrum of light, from wavelengths of ~400-700 nm[4].

When a photon of light strikes a corresponding opsin in a photoreceptor, a signaling pathway commences through the cell to a synapse where the photoreceptor communicates with its neighbors, the bipolar cells. Bipolar cells are either depolarized (positive charges inside cell cause an ON signal) or hyperpolarized (negative charges inside the cell prevent a signal, called OFF) based on the information they receive from the photoreceptors[3].

Next, the bipolar cells send signals to the third layer, the retinal ganglion cells, which project into the brain via the optic nerve[2]. Each retinal ganglion cell is sensitive to a specific region of the visual field, called its receptive field[3]. It is easiest to think of the connections between photoreceptors and retinal ganglion cells as a funnel of information: multiple photoreceptors make up a retinal ganglion cell's receptive field, and talk to bipolar cells, which talk to a retinal ganglion cell. These retinal ganglion cells process the ON and OFF signals, which contain information about shape, angle, depth, etc., and send them into the brain along the optic nerve to the visual cortex. In the visual cortex, all these individual signals carrying small pieces of information about the world are combined into the big picture[3].



The neuronal architecture of the retina. Modified from: OpenStax College, Anatomy & Physiology. OpenStax CNX.

All Eyes on Opsins

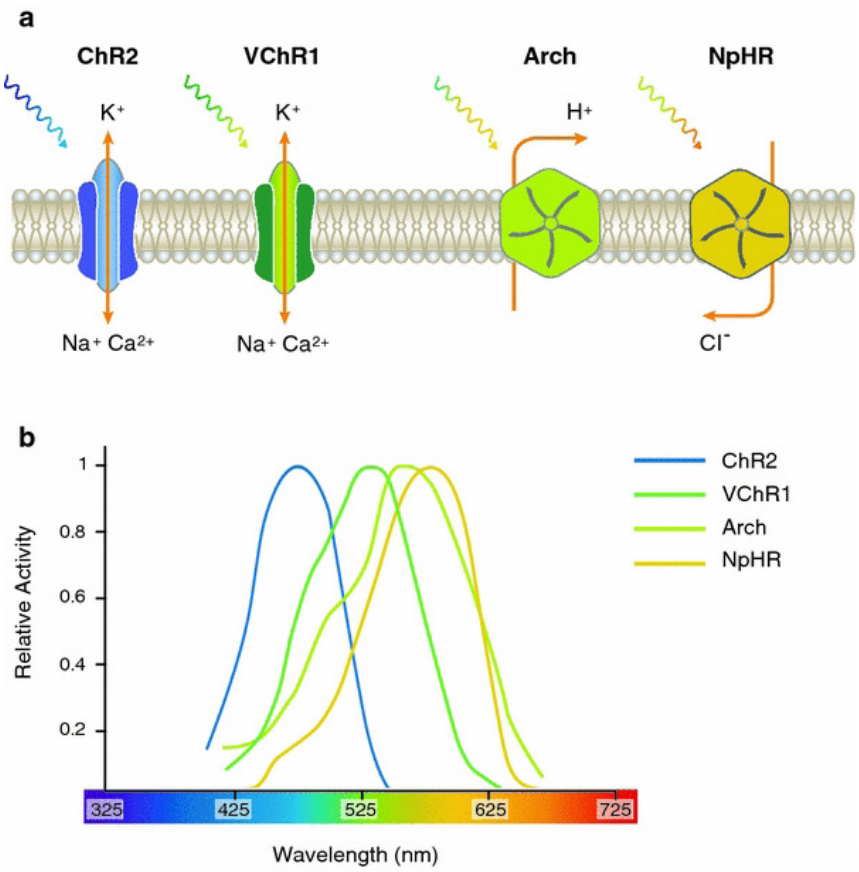
As retinitis pigmentosa progresses, the photoreceptors are the first and primary layer of neurons that are affected. Since retinitis pigmentosa gene mutations occur in the rhodopsins of rod cells, rods degenerate and die first, and then the disease progresses to the cones, leading to complete blindness[5]. Because artificial lighting mimics daylight conditions, we use color vision for longer periods of time, meaning we use our cones more frequently than our rods. Unfortunately, this also means that many patients with retinitis pigmentosa do not notice the onset of the disease until the majority of their rod cells have died, in the late stages of the disease[5]. Because there are fewer cones in the retina, gene therapies to save the opsin proteins are often ineffective as the population of cells is too small to treat by the time the disease is caught[5]. Unlike other gene therapies and interventions, by using optogenetics, scientists are able to focus on the surviving cells of the retina, not just the photoreceptors. While the bipolar cells are a candidate for intervention, the death of photoreceptors can often lead to remodeling of the retina, meaning the connections between the bipolar cells and retinal ganglion cells may have changed[6]. Therefore, retinal ganglion cells are targeted most often in optogenetics because their connections to the rest of brain are the most reliable.

The history of optogenetics has been relatively short, but very successful. In 2006, researchers Bi

et al. restored cellular responses to light in mice with cell death patterns similar to retinitis pigmentosa using channelrhodopsins[7]. Though rodents are not visually oriented creatures, a lot of optogenetic techniques have been tested in mice because they have similar neurons in their retinas and process information in a visual cortex, just like humans. Bi et al. showed that after expressing channelrhodopsins from C. Reinhardtii algae (ChR2) in the retinal ganglion cells of the mice, stimulation with light successfully mimicked the ON response in retinal ganglion cells, and were able to trace these light signals into the visual cortex. Since channelrhodopsins allow positive ions to enter a cell, the ChR2 expressing retinal ganglion cells were able to be depolarized and send an ON signal to the brain[7]. This pathway is exactly the same as in a normal, functioning retina, but optogenetics allows us to bypass the dead photoreceptors and activate the retinal ganglion cells directly.

To make retinal ganglion cells express a foreign protein, scientists take viruses carrying genetic information for a specific protein and introduce these viral vectors to the retina by injecting them into the eye with a needle. Bi et al. (2006) used this technique, injecting the mice retinas with an adeno-associated viral vector (AAVV) carrying C. reinhardtii channelrhodopsin genes[7]. The safe use of AAVVs has been widely established in animal models, and leads to long lasting expression of opsin proteins in retinal ganglion cells8. In mice models, expression of stable, functioning ChR2 proteins was observed for up to 18 months, an average lifespan for laboratory mice[8].

The next obvious step was to find a way to simulate OFF responses using optogenetics. This



Examples of light sensitive proteins commonly used in optogenetics. Source: Rein, M. L., & Deussing, J. M. (2011). The optogenetic (r)evolution. Molecular genetics and genomics : MGG, 287(2), 95-109

time, scientists found their answer in a different single-celled organism. In the oxygen-free salt lakes of Africa, the halobacteria Natronomonas pharaonis uses yellow-light sensitive halorhodopsins (NpHR) to pump negative ions into their cells[9]. This process hyperpolarizes the N. pharaonis, allowing processes like respiration to occur[9]. Halorhodopsins have been studied as a potential optogenetic tool for mimicking hyperpolarized OFF responses. However, while ChR2s allow positive ions to flow freely and quickly depolarize a cell, NpHRs are ion pumps, and only move one negative ion at a time. A large number of these proteins are required in order to hyperpolarize a cell at the same speed as ChR2s, but when NpHRs are expressed at high levels, cell toxicity is a common side effect[9]. In 2008, a team of scientists engineered a modified version of N. pharaonis halorhodopsin they called eNpHR[9]. This enhanced protein could be expressed in large quantities without harming the host cell[9].

So, the problem of mimicking OFF responses had been solved—scientists now had all the tools in place to make retinal ganglion cells function, in a simplified way, as the processing cells for light cues. Though ChR2 and eNpHR are the most commonly used opsins, there have been many other types of microbial and animal opsin proteins that have been utilized in optogenetics, all of which respond to certain wavelengths of light in a different fashion, depolarizing or hyperpolarizing a cell. By expressing a combination

of these proteins in the remaining cells in the retina, scientists are attempting to mirror the natural firing pathway of the retinal layers in the surviving cells of retinitis pigmentosa patients.

These early studies were primarily performed on mice, which, as mentioned, are not visually oriented animals. Since they have similar retinal cells, however, problems like the safety and reliability of expressing foreign opsins in mammals translate from mice to humans very well. Studies were next performed on non-human primates to explore how optogenetics affects the perceptual aspects of vision, as primates like marmosets and macaques have the most optical characteristics similar to humans. Non-human primates have a retinal architecture composed of multiple layers of neurons and a similar periphery and fovea to humans[10]. Visual cues are also processed along a similar pathway into the visual cortex, meaning non-human primates process visual cues the same way humans do[11]. Although the safe and reliable expression of microbial opsins in non-human primate retinas has been established[12,13] the cognitive effects of optogenetic intervention have been observed by directly stimulating the visual cortex. Surprisingly, very few studies have studied the behavior response of primates who have had light sensitive proteins expressed in their retinas.

Using AAVVs, Ju et al. 2018 expressed ChR2 in the primary visual cortex of blind macaque monkeys[14]. By implanting a blue light laser in the cortex, they were able to stimulate the cortical cells while the macaques were awake and observe their behavior. Macaques who received the optogenetic treatment were able to move their eyes towards a visual cue in over 96% of the trials[14]. While this study used optogenetics to stimulate a location in the visual pathway upstream of the retina, the results do suggest that inducing artificial visual responses in primates is possible.

And that brings us to the most important question: if tiny proteins from microscopic organisms can allow blind humans to detect light, how much vision can optogenetics restore? What will the world look like through modified retinas?

Many Hands Make Light Work

To better understand this question, we turn to other attempts to restore vision in humans. The field of bioelectronics has made great strides in developing technology to artificially create visual sensations. The purpose of these studies has mainly been to restore aspects of vision useful for daily life that give the wearer more independence. The main types of bioelectronic devices are retinal implants, arrays of electrodes that are placed directly on the retina[15]. Electrical impulses are passed through the device to stimulate the surviving retinal cells. This process is similar to optogenetics in that retinal cells other than photoreceptors are stimulated, but is a much more invasive procedure as the eye has to be opened and the device permanently sits on the retina[15]. With optogenetics, a single small injection with a needle is all that's necessary to mimic the effects of these devices.

Early studies of directly stimulating the retina and visual cortex described how recipients of electronic implants perceived the sensations: as phosphenes. Phosphenes are described as visualizing a bright spot of light, despite the absence of a light cue[16]. One individual who received a retinal implant described these phosphenes as, "like looking at the night sky where you have millions of twinkly lights that almost look like chaos. What [he's] in the process of now is learning how to identify the different constellations"[17]. Although optogenetics uses light cues to stimulate retinal ganglion cells, because unique signaling patterns from the photoreceptors cannot be fully conserved, information such as color and acuity is very difficult to replicate. Visual perception following optogenetic therapy will most likely be very similar to the phosphene phenomena observed in bioelectronic implant patients, and it might take a very long time to figure out how to restore color vision in the absence of cone opsins.

Other studies have shown that people with microarray implants are able to discriminate between points of stimulation, suggesting that what the wearer perceives matches the patterns of visual input, and that electronic stimulation of the visual system can represent accurate images of the world[18].

Many bioelectronic devices are now being paired with a camera to take images of the field of view, which can then be converted into a pattern of electrical signals and relayed throughout the visual system16. In this way, individuals view the world as a collection of repeatedly flashing phosphenes, and must learn to interpret what those visual cues represent. These camera devices have become small enough to mount on a pair of glasses. The main success of these devices has been allowing wearers to discriminate between bright and dark areas, like windows and doors. They also help individuals notice when people enter or exit a room, and even identify forks and spoons from plates on a table. So, even if they may not be able to tell what's

The first image represents an electrode array that is placed on a retina. The image in the middle represents the input a camera might capture, which is translated into a neural code and fed into the electrodes. The image on the right illustrates the phosphenes an individual might perceive based on the pattern of electrodes.

Source: Titchener, S. A., Shivdasani, M. N., Fallon, J. B., & Petoe, M. A. (2018). Gaze Compensation as a Technique for Improving Hand-Eye Coordination in Prosthetic Vision. Translational vision science & technology, 7(1), 2.

on the plate, people can pick up a fork by themselves and look at whom they're eating with. These descriptions of artificial vision might not sound like anything close to how humans process vision with normal photoreceptors, but when you consider that in a little over two decades bioelectronic devices have restored sight to the blind, it almost sounds like a miracle.

Similar camera devices have been suggested for pairing with optogenetic therapy. Although opsins like ChR2 and NpHR can feasibly make retinal cells sensitive to light, the threshold for the intensity of light required to activate this process is often much higher than what is available in the natural world[16]. Therefore, devices to increase illumination on the retina have been developed to induce signals more efficiently in the optogenetically-modified cells. A holographic display system mounted on goggles has been suggested to present light cues at a higher intensity and in a more organized pattern[16].

For the moment, we can only make educated guesses as to what individuals might see following optogenetic intervention. Their world will be black and white, and it will take effort and practice to interpret what a collection of light points might represent in the real world. However, that answer may come much sooner than expected. In March of 2016, a woman with retinitis pigmentosa was the first human to receive optogenetic therapy[19]. She, along with 20 other individuals with retinitis pigmentosa, is part of the first human optogenetic clinical trial, which is currently underway at the Retinal Foundation of the Southwest in Dallas, Texas[19,20]. Sponsored by a company called Allergan, the study is currently testing the efficacy and longevity of expressing ChR2 in humans, after completing safety and maximum dosage studies in August of 2016[19,20].

Another company, GenSight Biologics, started human trials shortly after Allergan[21]. In May of 2018, they began gene therapy in 18 retinitis pigmentosa patients using a modified ChR2 protein that is sensitive to red light[22]. The gene therapy is paired with the use of bioelectronic visual stimulation devices mounted on glasses, which capture incoming signals with a camera, convert the signals into a neural code, and relay this code to the treated retinal ganglion cells through flashes of red light[22]. While the Allergan study is treating fully blind patients and is expected to be complete in October of 2033, the GenSight study is testing its therapy on retinitis pigmentosa patients with a range of limited visual capabilities and is expected to be complete in 2024[20,21]. These preliminary studies are mainly to test the safety and effectiveness of the treatment before it can be offered as a medical therapy. But, considering how quickly the field of optogenetics has progressed, people may be walking around seeing the world through algae proteins in the not so distant future. These studies mark the first steps towards reversing total blindness caused by retinitis pigmentosa and other degenerative retinal diseases. For people who thought they may never see again, the future looks bright.

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Photoreceptors. Page from Images Formed in Darkness By Samantha Montoya

Tired or Tipsy?

By Peyton Thomas

"Miniature Pinser Drinking Beer" on reative Commons

Imagine Steve, a 38-year-old father of three kids. His wife just had their third baby and she is still on maternity leave. Steve is working extra hours at his job at an accounting firm to help cover the medical bills and support his family. He has been working 70-80 hour weeks for a while now and has been staying up with his new baby when he gets home from work. He's been incredibly sleep deprived but does it all for his family. One Friday night, Steve leaves work around 1:30 AM to drive home, since being at work since 6:00 AM, finishing a big project for the firm in hopes of earning a promotion. Across town, Kevin, a 22-year-old student, just found out he got into law school and has been celebrating at a local bar with his friends. Kevin has been working hard through college as a first generation graduate and is celebrating his hard work finally paying off. Kevin knows he's been drinking a little bit, but doesn't have very far to drive home so he thinks he'll be fine. Kevin leaves the bar around 1:40 am.

Neither Kevin nor Steve make it home that night. They get into a car accident on their routes home. Whose fault is it—Kevin's for being a little tipsy and slightly drifting into the next lane; or Steve's for being too tired and closing his eyes for one second too long at the wheel? When the police show up to the scene, Kevin is unconscious and Steve is in a confused stupor. At the hospital, Kevin's blood alcohol content reads 0.09%, just above the legal limit. Kevin is still unconscious and unable to give a police statement, while Steve is getting treated for mild head trauma and keeps insisting that he wants to talk to the police. Steve tells the police his side of the story and contends that the whole accident was his

fault, even though he can't prove it was the sleep deprivation. He closed his eyes for a second and ran through a red light right into Kevin, who was swerving slightly, but not the cause of this accident.

Everyone knows that drinking and driving is a bad idea, let alone illegal. When you're drunk you have delayed reaction times, impaired decision making, and a slew of other cognitive deficits that make safe driving impossible. This has been proven time and time again, leading to federal laws restricting the amount of alcohol a person can have in their bloodstream so that they do not become a danger to themselves and others around them on the road. However, most people don't realize that we put ourselves under similar cognitive impairments just by staying up late at work or pulling an all-nighter to finish a paper before getting behind the wheel. Staying awake for 17-19 hours straight produces cognitive deficits equal to having a blood alcohol content of 0.05%[1], which equates to about two average drinks within an hour. In comparison, the legal threshold for alcohol impaired driving is only slightly higher at 0.08%[2]. We all think that we know our own bodies and abilities well enough to be able to judge when we should or shouldn't get behind the wheel, but if our cognitive abilities are impaired then we don't have full control over our minds or our bodies. Society is constantly being warned about what drugs and alcohol can do to us and why we should never put ourselves at risk with things such as driving, but sleep has never been a part of this discussion.

Sleep is not something we choose to participate in, but rather a biological necessity that has more effects on our bodies and minds than we realize. Knowledge about the importance of sleep and implications of a lack of sleep could lead all of us to make better decisions about when to call it a day, when to call a taxi instead of driving home from work, and even when to stop working on your paper because you're going to sound drunk.

How Are Alcohol Intoxication and Sleep Deprivation Similar?

The physiological and behavioral symptoms as well as the cellular mechanisms of alcohol intoxication and sleep deprivation (a lack of sleep) are fairly similar. Common behaviors that are easily recognizable in people that are heavily intoxicated can be seen in cases of severe sleep deprivation as well. Some of the negative results of either intoxication or lack of sleep will be discussed in following sections, and include decreased cognitive control, slower reaction times, and increased errors in cognitive tasks. Behavioral and personality effects have also been directly analyzed in relation to both alcohol intoxication and sleep deprivation. Based on the cumulative results of various studies, alcohol intoxication can increase impulsivity and aggression while decreasing inhibition, creativity, and abstract thought[3]. Alcohol intoxication and crime rates are also extremely highly correlated. Many different types of crimes are associated with alcohol use and include robbery, sexual assault, aggravated assault, intimate partner violence, child abuse, and even homicide[4]. Of people incarcerated for violent crimes, about 40 percent were significantly under the influence of alcohol at the time of their crime[4]. Interestingly enough, a behavioral study on sleep deprivation and conduct revealed a similar negative effect of lack of sleep on the behavior of the participants. In this study by Barnes *et al.*, multiple behavioral studies were utilized to test the correlation between the amount of sleep and unethical behavior. Unethical behavior was characterized by behaviors such as cheating on survey results or taking credit for other's work[5]. They found a direct correlation between a lack of sleep and an increase in reported unethical conduct in

Drunk Cat by ParoleMusica on pixabay

Tired Cat by wilkernet on pixabay

the workplace. This increase in unethical conduct also paralleled an increase in cognitive fatigue as a result of sleep deprivation[5]. Based on these studies, sleep deprivation and alcohol appear to have similar effects on behavior, since they both have the ability to draw out an array of various undesirable behaviors in people.

At a more physiological level, both sleep deprivation and alcohol can impair basic functioning of the brain in similar ways. One of the most significant impacts of severe sleep deprivation and alcohol intoxication is on memory. The specific impairments of alcohol on memory are examined in a study by Lister *et al.*[6]. This study utilized various memory tasks within two categories, explicit and implicit memory tasks. Explicit memory is measured through tests that require conscious recollection of information, whereas implicit memory does not rely on conscious recollection of information. A combination of explicit and implicit memory tests were presented to groups of participants who were given various levels of alcohol (0-0.6 g/kg). The results revealed that alcohol decreased performance on explicit memory tasks but not implicit memory tasks[6], meaning that conscious recollection of events and information is more difficult to accomplish under the influence of alcohol. In another study by Van Dongen et al. on sleep deprivation, they used a specific computer task to measure working memory in response to sleep levels of either eight, six, or four hours of sleep for 14 days[7]. Both the six- and four-hour groups experienced decreased working memory from the computer task compared to the eight hour group. The four-hour group exhibited the most significant impairment in memory at levels that were experimentally equal to two nights of complete sleep loss[7]. Both of these studies indicate that the processes of memory within the brain are somehow disrupted by both sleep deprivation and alcohol consumption. This could have many different implications on how we function under both conditions. These data could suggest that pulling an all-nighter to study for an exam, for example, could negatively affect how much you remember for the test the next day compared to getting a good night of sleep instead. This also could help to explain why memory of events that occur during a night of binge tend to get fuzzy.

On the cellular level, similar types of neurological receptors are implicated in sleep and drinking as well. Neural receptors are protein complexes in neurons (brain cells) that bind to different chemicals to elicit a variety of responses throughout the body. Dopamine is one of many different chemical signalers in the brain that binds to specific dopamine receptors. Dopamine is used within the brain in many different regions that control motor activity, cognition, emotion, eating behavior, cardiovascular function, and positive reinforcement[8]. One specific type of dopamine receptor, D2 receptors, are essentially blocked in their function by both alcohol intoxication and sleep deprivation, but in different areas of the brain. In one study by Volkow *et al.*, there was downregulation of D2 receptors after sleep deprivation in human participants, which means that there were fewer receptors available in the dopamine pathway compared to the non-sleep-deprived control group[9]. This occurred in the ventral striatum of the brain, which is involved in motivation, decision-making, and the reward pathway[10]. Alcohol has produced similar disruption of the normal dopamine pathways within the prefrontal cortex, which is the area of the brain responsible for planning complex behavior and cognition[11]. These studies combined illustrate the similarity in cellular response in both sleep deprivation and alcohol intoxication.

Although both alcohol and sleep deprivation appear to significantly disrupt dopamine functions within the brain, sleep itself has also shown indications of disrupting dopamine activity that occurs during wakefulness. In a study using a fly model, sleep mechanisms actually blocked some dopamine signaling in the brain,

which had a positive effect on memory. Without this blockage of dopamine during sleep, the flies had significantly worse memory of motor tasks[12]. This study indicates that normal inhibition of some dopamine pathways during sleep is necessary for normal cognitive functions. However, sleep deprivation causes abnormal inhibition of other dopamine pathways that creates negative effects on cognition. Across various areas of the brain, dopamine is a key player in both alcohol intoxication and sleep deprivation, but in a variety of different processes.

What Does Alcohol Do to Us?

In a specific study of the effects of alcohol on behavior and physiology of the body, participants were given different doses of alcohol and performed tests of reaction time, arithmetic, standing steadiness, and physiological recordings (electroencephalography, electro-oculography, and eye movement). This study concluded that performance on most performance tasks declined as blood alcohol content increased[13]. Another more recent study conducted by Bailey *et al.* (2014) also examined the cognitive effects of alcohol using electroencephalography (EEG) recordings, which show changes in the brain in response to different tasks over time[14]. They gave the participants alcohol and using the EEG recordings, were able to quantify their relative amount of cognitive control and response time as they performed a basic computer task. The results of this physiological study showed both a longer reaction time and a decrease in cognitive control from the alcohol. Both of these specific studies, as well as many others, have similar results indicating that drinking alcohol affects your physical abilities as well as mental control.

The direct physiological effects of alcohol on the brain are well established. Alcohol is classified as a depressive drug, meaning it directly decreases stimulation of the brain. Alcohol activates multiple types of chemical receptors in the brain including GABAA and NMDA receptors. Alcohol molecules bind a specific portion of the GABAA receptor protein, opening the ion channel, as shown in Figure 1. When GABAA is opened, there is a negative flow of chloride ions into the neurons of the brain, which decreases the signaling rate of these neurons to other neurons in the brain. Ethanol molecules also have the opposite effect on another prevalent receptor type in the brain, NMDA. NMDA is a type of glutamate receptor, which indicates that the molecule glutamate is necessary to activate or open up the receptor. Glutamate binds to one of the protein subunits of an NMDA receptor, just as ethanol does to GABAA receptors in Figure 1. When glutamate binds and the cell membrane reaches an ideal charge, the receptor opens and allows positively charged calcium ions to enter the cell. The positive charge of the calcium ions increases the overall charge of the neuron and activates the neuron by allowing it to send signals to other neurons in the brain[15]. However, when alcohol is involved, the ethanol molecules bind to the NMDA receptor and blocks the binding of glutamate, therefore keeping the receptor closed. Both mechanisms of ethanol on GABAA and NMDA receptors keep the neurons from firing and sending a normal amount of signals to other neurons in the brain, which causes the symptoms associated with alcohol intoxication.

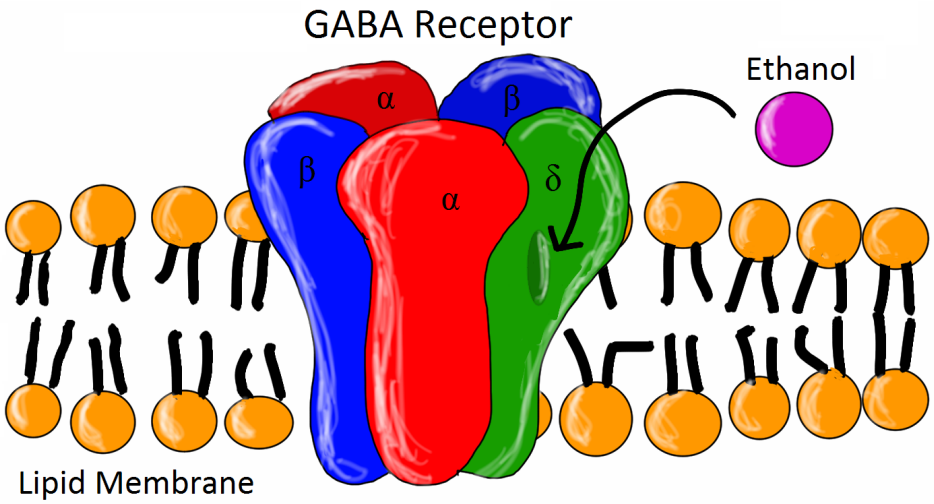

Figure 1: "Alcohol Binding to GABA Receptor" on Wikipedia Commons

Alcohol has many common effects on the functions of the body and brain as well. Moderate alcohol intoxication causes noticeable physical symptoms including general disorientation, slurred speech, loss of coordination, and impaired attention and memory[16]. Severe alcohol intoxication can cause stupor, slow breathing, hypothermia, and rapid heart rate[17]. When you are drunk, you also have delayed detection times to changes in your body position and therefore delayed response times[18]. Sleep comparatively follows a very different mechanism of action on the brain.

How Does Sleep Occur?

Sleep is a naturally occurring physiological process induced by the brain. Throughout the day, we are in a constant state of wakefulness, during which time our brains are being constantly stimulated. While we are awake, our brains are also producing a type of sleep-inducing chemical called adenosine. Adenosine accumulates in our brains throughout the day and the longer we are awake, the more adenosine is being produced. By the time we go to sleep, we have enough adenosine buildup to inhibit neurons, put our bodies to sleep, and let our brain rest[15].

There are multiple phases of sleep that we go through every night. We transition from being awake to being in slow-wave sleep to eventually falling into rapid eye movement (REM) sleep. There are five distinct stages of sleep, within these broad categories. These stages represent the different types of brain activity (as shown on an electrophysiological recording) that occur during sleep. Figure 2 represents a typical cycle of sleep stages over the course of seven hours. Both slow-wave and REM sleep serve different purposes for the brain. During slow-wave sleep, the brain is relaxing and recovering from the day. Specific patterns of brain waves called sleep spindles during this phase also indicate consolidation of memories. The specific functions of REM sleep are not as well understood. There is some evidence for REM sleep playing a role in brain development and learning. However, we do know that REM sleep is vital to the brain for survival. When it's time to wake up from a night of sleep, our brain induces an arousal mechanism to take us out of a sleeping state. This mechanism of wakefulness includes an assortment of chemicals that are released in different parts of the brain. These chemicals are all neurotransmitters released by neurons to send a signal to other neurons in the brain. Each of these five chemicals are produced and distributed in different parts of the brain to constitute an overarching arousal of the entire brain[15].

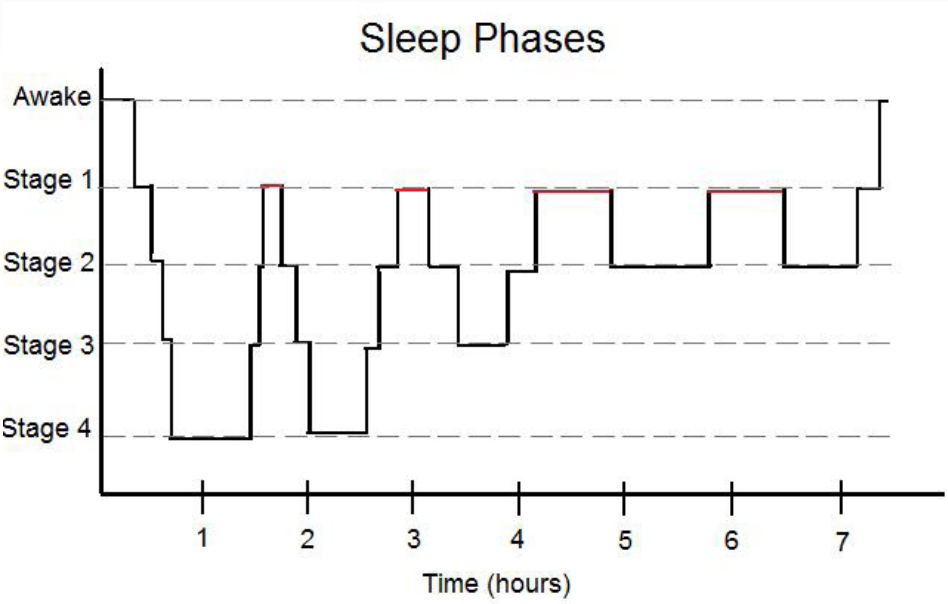

Figure 2: Adapted from "Simplified Sleep Stages". On Wikipedia Commons.

What Happens When We Don't Get Enough Sleep?

As stated in the previous section, sleep is necessary for basic cognitive functioning. On average, most people need about seven to eight hours of sleep per night[19]. Below this amount, people begin to have symptoms of sleep deprivation. Many studies have been conducted to measure the specific impairments on physical, behavioral, and mental performance from sleep deprivation. One study by Van Dongen *et al.* controlled the amount of sleep in participants at incremental levels of eight, six, and four hours for a total of 14 days and measured cognitive ability over the course of the experiment[7]. The participants of both the four- and six-hour groups performed worse than the eight hour group on the cognitive tests. Complete sleep deprivation (for 88 hours) in this same study resulted in more severe cognitive dysfunction in the participants, specifically impairing their processes of attention and memory. In another study, ultra-marathoners were monitored for physiological effects of sleep deprivation during a 168 kilometer race. Some of the athletes exhibited physical symptoms of hallucinations, extreme tiredness, loss of balance, and partial amnesia. The cognitive impairments of this combined sleep deprivation and extreme physical activity were measured by pre- and post-race tests. After the race, participants had increased reaction times, reaction time lapses, and number of errors, denoting impaired cognitive function[20]. In this specific study, there is no way to differentiate between the effects of the race itself or the sleep deprivation caused by the race, but the general

"Doze" by dannyworking on pixabay

decline in cognitive performance is consistent with other complete sleep deprivation studies as well.

There are various neurological disorders that directly affect sleep patterns. One of the more common sleep disorders is insomnia, which affects about 25 percent of people at some point in their life[15]. People with insomnia have issues either falling asleep or staying asleep for the whole night, which causes prolonged sleep deprivation for the duration of the disorder. After long bouts of insomnia, people can be at an increased risk for other health issues as a result of prolonged sleep deprivation including obesity, cardiovascular disease, and diabetes[15]. The most severe form of this sleep disorder is fatal familial insomnia. As the name suggests, this disorder is a version of insomnia that is genetically influenced and always fatal. This disorder is an incredibly rare form of insomnia with and average onset of 49 years of age, in which people completely lose the ability to sleep. Individuals with fatal familial insomnia first experience a decrease in slow-wave and REM sleep in the early stages of the disease. In later stages, any form of sleep is minimal and more severe cognitive symptoms occur including hallucinations, deficits in memory and attention, stupor, and coma at the terminal stage. This disease generally lasts for about 12-13 months from the onset of symptoms to the terminal stage[21]. The disease is the direct cause of death, but the specific mechanism remains unknown and untreatable.

What are the Implications of All of This?

If alcohol intoxication and sleep deprivation both present with very similar behavioral, cognitive, and even cellular deficits, then why do we have strict laws around drinking but not sleeping? In the state of Ohio, common penalties for driving with a blood alcohol content above 0.08% for someone over 21 years old, over 0.04% for a commercial driver, or over 0.02% for someone under 21 years old include fines ($375-$20,000), time in prison/jail (3 days-15 years), suspension of the driver's license, mandated alcohol treatment programs, and more[22]. However, sleep deprivation can cause the same driving impairment as alcohol, can pose the same safety risks, and can cause you to get pulled over for impaired driving. The differences between alcohol impaired driving and sleep deprivation impaired driving have been investigated by Fairclough and Graham in a behavioral study[23]. After a full night without sleep, the number of lane crossings was comparable to legal levels of alcohol intoxication (0.08% BAC), but four hours of sleep during the night produced the highest number of near lane crossings. Moreover, both amounts of sleep deprivation resulted in a significantly lower amount of steering activity compared to the unimpaired control and the alcohol impaired participants[23]. This single study exemplifies direct comparisons of driving under the influence of alcohol versus driving while sleep deprived, and shows that sleep deprivation is just as dangerous to driving ability as alcohol.

Knowledge of the importance of sleep and the implications of a lack of sleep is the first step in preventing harmful and dangerous situations caused by sleep deprivation. Although Steve, our sleep deprived example from the beginning was only trying to support his family, he still put himself and others at risk. Steve had the best intentions but didn't know the consequences of his actions. Kevin, similarly put others at risk by driving while intoxicated, but made that decision knowingly. If Steve had known that he was essentially driving while impaired, would he have gotten behind the wheel? Is there any way to judge or quantify sleep deprivation if it isn't detectable like alcohol?

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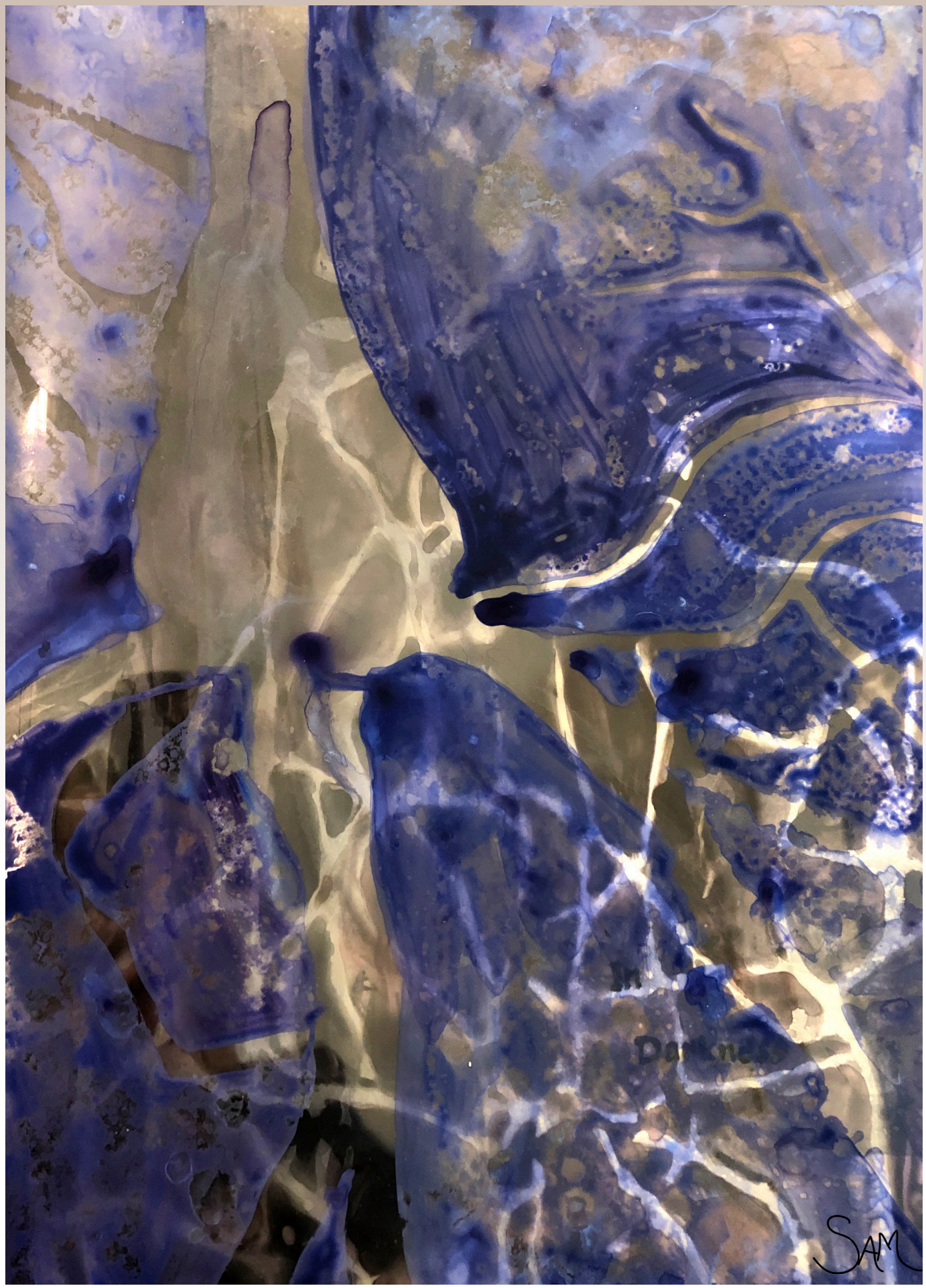


"Pyramidal Cell" from "Images Formed in Darkness" cell by Samantha Montoya

Who Are You Calling Birdbrain?

By Margie Athol

Crow by "skeeze" on pixabay

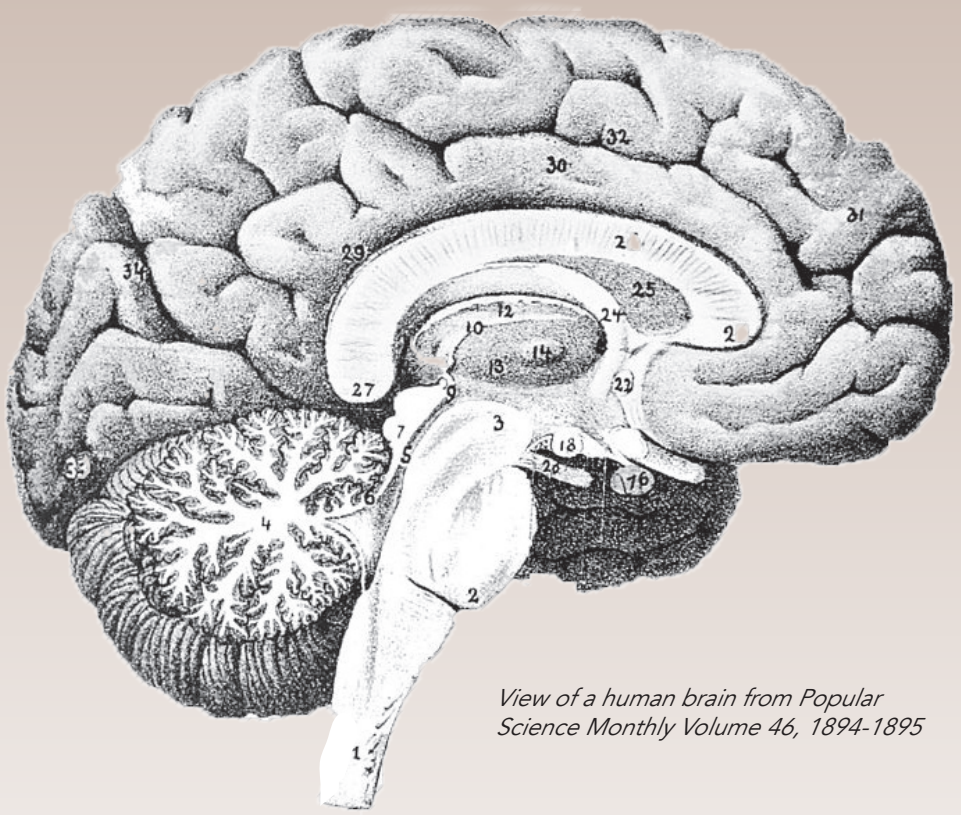
Most of us have heard or used the expression "birdbrain". Dating back to the early twentieth century, to call someone "bird-brain" is to call them, simple, unintelligent, or stupid. But despite how birds may be perceived, they aren't deserving of the moniker coined from them. From being able to navigate unfamiliar territory to using tools to hiding food for future consumption, birds engage in a lot of behaviors that require a highly skilled brain. Birds are, dare I say, very smart.

But what is "intelligence"?

When we say "smart", what does that mean? When turning to the Merriam-Webster English Dictionary, searching for "smart" lead me to "clever", defined as "mentally quick or resourceful". And what for "intelligence"? There are two relevant definitions, the first being, "the ability to learn or understand or to deal with new or trying situations" and the second, "the ability to apply knowledge to manipulate one's environment or

Image from "Illustrated British Ballads, old and new" by SMITH, George Barnett 1886 on Flickr

to think abstractly as measured by objective criteria (such as tests)". Both of these definitions have to deal with flexibility. Intelligence is all about possessing the mental flexibility to learn or to apply



View of a human brain from Popular Science Monthly Volume 46, 1894-1895

knowledge to new situations. Now the end of that second definition is critical: "measured by objective criteria". And that is where birds aren't getting a fair shake.

People are, naturally, as all animals are, centered on themselves. We think of everything in terms of how it compares to us or to humans. So when people try to study things like animal intelligence or cognition, there is a tendency to create a single scale on which all creatures are placed (and humans are at the end of "smartest"). But intelligence evolved independently among multiple taxons; it didn't evolve in a straight line culminating with humans as some theorize.

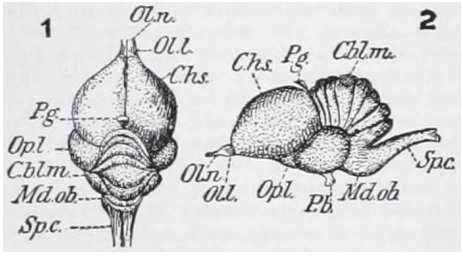
Animal cognition—the study of non-human animal mental capacities and, in some ways, intelligence—is typically studied through behavioral tasks and tests. While there is success in crafting tasks that an animal could physically do, the concept behind many tests comes down to logic along the lines of "how well does this animal do at this human task". If we are only going to use the scale of human intelligence, this isn't a bad way to do it, and is often how we arrive to conclusions like dogs having the mental capacity of a young child. Yet to really get at the intelligence of non-human animals, we should be analysing how they face challenges they might experience in their natural environment.

Yet when we talk about smarts, a colloquial analogy is "brains". If we try to define intelligence by brain properties, what do we find?

Having a lot of brains isn't the whole story…

The brain is responsible for everything we do from brushing our teeth to doing our math homework. When we talk about someone really smart we might say they have a big brain because we equate a larger brain with intelligence. The story of how we made that conclusion is an interesting one. When looking at hominid evolution, we see that the size of our brains increased rapidly and drastically. And since the increase in brain size was accompanied by an increase in hominid intelligence, it was thought that a bigger brain meant a smarter animal. We know this isn't true when we take into account examples such as the chimpanzee which is smarter than a walrus but with a brain a third of the size. And humans—supposedly the smartest animal—has a brain less than half the size of an African elephant[1]. But there is a trend you might've noticed: each of the aforementioned smarter animals is much smaller than the counterpart. So maybe it is about relative brain size. When we look at relative brain size, we see that while absolute brain size increases with body mass, relative brain mass actually decreases. What about when we get more specific?

The cortex is the thought to be the "smart" part of the brain because it is the most flexible part of the brain—it changes the most readily in response to experience. One particular area of interest is the prefrontal cortex (PFC) which is the area responsible for reason and action planning. The challenge with using the PFC as a point of comparison is that its bounds are challenging to define, meaning results aren't as accurate[1]. The next step, then, was to think not only about shape and size, but the



Drawing of an avian brain adapted from The New International Encyclopædia, v. 3, 1905, p. 102. by Ernest Ingersoll

number of neurons.

Neurons are cells of the brain that work in electrical impulses. When we talk about what the brain does, we are really talking about what a system of neurons is accomplishing. The thought is then that if you have more neurons, you could be smarter. Because neurons work in electrical impulses, when we talk about their conduction, we can think of it like wires in an electrical circuit. For intelligence, we want neurons that send signals quickly. In a wire, it will send a signal faster if the wire is thicker, if it is well insulated, and if the distance it has to travel is shorter. The same principles apply to neurons. Neurons that have thicker axons (the wire) with more myelin (the insulation) and are closer together will lead to a smarter animal. This concept is called Information Processing Capacity (IPC). IPC is a better measure than overall or relative size. And we see that animals that are more intelligent have a higher IPC. The most common comparisons are made among mammals, for example, a bushbaby has more neurons than a marmoset which has more neurons than a rat and a chimpanzee more than any of them[1]. But when we compare birds to mammals, we see that birds win each time. When comparing the number of cortical neurons, birds have over double the number of neurons of a similarly sized mammal counterpart. This is likely possible because while both "smart mammals" and birds have tightly packed neurons, birds have smaller neurons meaning more neurons can be packed into the same volume[2]. One showdown of IPC we can look at is comparing the brain of the raven to the capuchin monkey. While the raven's cortex weighs a quarter of what the capuchin monkey's weighs (10 versus 40 grams), the raven has more neurons with 1,204 million neurons in its cortex compared to the capuchin's 1,140 million[3].

Another structure we can look at when considering intelligence is the hippocampus. It's responsible for functions of memory and long-term memory and damaging the hippocampus leads to difficulty in forming new memories. And while it makes sense to look at this structure (since mental flexibility requires the manipulation of memory), when we try to correlate its overall size to intelligence, we see that it doesn't give us a clean answer. For example, birds that are able to store large amounts of food and remember the many locations don't always have larger hippocampi[3].

We could look at more subtle features such as the morphological diversity of cortical cells or we could look at cell architecture. But what would any of these differences tell us? It is difficult to say, but we can see that general trends and correlations won't tell us the whole story. So we need to take a look at what these structures allow animals to do.

And the brains of birds—despite being small—allow them to accomplish impressive feats. I'm going to look at three examples of birds that make the most of their bird brains and exhibit intelligence.

Crows

Crows are part of the corvid family which are regarded as the most intelligent birds, even displaying self-recognition in mirror tests and using tools—two skills that we thought for a long time only belonged to humans and a select few other mammals. Corvids are marked by their strong bills and feet and can be found across the world except for the polar ice caps and tip of South America. Crows, specifically, are easily recognized by their dark black feathers or by their distinctive squawking. In the last few years they have become a fascination of many and viral videos on the Internet as they display skills that we don't expect birds to possess.

Image from "B.C. 1887 A ramble in British Columbia. By James Arthur Lees. 1888. On Flickr.

Illustration from the Archives of Pearson Scott Foresman. artist unknown.

The Short End of the Twig

Many people know that crows use tools. There are plenty of videos on YouTube of crows solving puzzles, but let's stop to think about what they are accomplishing and what goes into solving a puzzle. Let's say a crow needed to choose one of three twigs to reach a rock. The crow then needs to put the rock on a lever which will open a door leading to a piece of food. First, the crow needs to be able to know how to use a twig to reach another object. The crow has to understand that it can use an object to take effect on another object. It then has to understand that twigs can be different lengths which provide a different amount of reach. The crow can do this pretty easily. The next step that the crow is able to understand is that when the lever is held down, food is revealed and the rock can hold down the lever. This requires object permanence as well an understanding of a complex relationship between two events (the pushing down of a lever and the opening of a door). The fact that the crow is able to complete a man-made puzzle with relative ease is impressive. But like I mentioned earlier, a bird wouldn't need to solve a puzzle like this in the wild, so it isn't necessarily a fair assessment.

Hunt, Rutledge, and Gray in 2006 published a study examining tool use by crows. In the study, they went into the forest and drilled a hole in some branches: large enough to fit some food, but small enough for a crow to be unable to reach inside. They then placed various twigs and leaf pieces around the branch for crows to use. What they found was that crows were able to select a tool based on length and based on the food they were trying to get. The crow would choose a twig that was long enough to reach the food while still having control. And if the crow chose a twig that was too short or long, it would adjust accordingly and pick a new tool. The food placed in the branch was either a live grub or a dead grub. The crows could use a smooth twig to get living grubs because upon being poked, the grubs would hang on to the stick. With a dead grub, however, the crows used a spiny twig to drag the grub out[4].

Crows display incredible flexibility when it comes to their tool use. They can use a twig as an extension of their own limbs but more so, they have the ability to identify the specific qualities of that tool that are effective or need to change.

Hell hath no fury like a corvid scorned

Crows are very social creatures. Cornell, Marzluff, and Pecoraro studied social learning in crows in a 2012 study. Crows engage in a behavior called scorning—when a crow will follow and squawk at animals who are a threat accompanied by wing flapping—and mobbing—when multiple crows scorn together. In the study, a person was given a human mask to wear and would then perform an aversive behavior toward a crow: catching, banding, and releasing. While this action doesn't harm or cause pain to the crow, they would rather avoid it. Over a period of five years, a person would then walk a route on which the crows were caught and wear either the dangerous mask (the one that was worn during bird handling) or a neutral mask (a mask the crows hadn't seen before).

What the authors found is that crows would scorn the dangerous mask worn during capture and over the five year period following the single capture event, the number of crows that would scorn the dangerous mask increased and larger mobs would form. What this tells us is that not only are crows able to learn and recognize human faces—which is impressive enough because we really don't all look that different (sorry)—the crows were able to learn and associate a person with a behavior. Crows worked together to scorn a person which is a protective behavior but also serves as teaching. Crows would learn threatening people secondhand; they could learn a person is a threat not through personal experience, but from a fellow crow. Crows display social intelligence which is important for survival and they were able to learn a person after a single encounter. This is called one-trial learning and has been shown to be extremely beneficial[5].

Scrub Jays

Scrub jays are what are known as caching birds. This means that they hide and store food for future use. Scrub jays are able to remember details about their caches such as what type of food they stored, if it will decay, where it is, and even if another bird was watching and might steal it. Scrub jays are able to retain this information for thousands or possibly tens of thousands of caches over a range of roughly thirty miles.

Blue Jay by Susan Young. 2018. Flickr.

Planning for the future (without a calendar)

Planning for the future is a complex task which requires the manipulation of knowledge you know into assumptions about what hasn't happened (but is assumed will). Many scientists theorize that this is such a complex task that animals other than humans can't master it. But if only humans could master it, how do you explain wolves making dens or the behavior of birds hiding before they die? A 2007 study by Raby, Alexis, Dickinson, and Clayton, showed that scrub jays are able to plan for the future in a simple breakfast experiment.

The experiment consisted of a three conjoined cages. The center cage was a neutral cage, in the left cage (what we will call the hungry side), the bird was taught over time that it would not receive food. In the right cage (what we will call the breakfast side), the bird was taught that it would be given food. A scrub jay would sleep in the center chamber then in the morning randomly be given access to the hungry side or the breakfast side. The scrub jay was able to learn pretty quickly that only the breakfast side is where they'd be given food. What happened next is what shows scrub jays can plan for the future.

Once the scrub jays learned where they would and wouldn't be given food, they were given access to all cages and food. In the bottom of each cage was a caching tray (an ice cube tray full of sand or soil). The scrub jays would cache much more food in the hungry cage. This indicates that the scrub jays know they won't be given food in the hungry cage, so they must supply their own[6]. The scrub jay understands that it will be hungry and in order to eat in the morning, he better brown bag it.

Is this wax worm still good?

Scrub jays cache various types of food including nuts, berries, and worms. If you've left a banana in your bag by mistake versus the well-intentioned bag of trail mix at your desk, you know that fruit goes bad much more quickly than nuts. As it turns out, scrub jays know this, too. Clayton and Dickinson, a decade before the above study, found in 1998 that scrub jays understand the concept of food decaying in their caches.

How they did this was by giving scrub jays the opportunity to cache both nuts (which scrub jays like) and wax worms (which scrub jays LOVE) then gave the jays either 4 or 124 hours to get hungry before allowing them to return to their caches. What they observed is that after the 4 hour delay (when the wax worms would still be good), the scrub jays returned to caches of wax worms significantly more frequently. In contrast, after the 124 hour delay (when the wax worms would no longer be edible), the scrub jays would return to the caches of nuts significantly more frequently[7].

From this we can glean that the scrub jays understand both the passage of time and what that means for the freshness of the food they've cached. They apply this information to their memory of what food they stored where and make their choice accordingly.

Pigeons

Ah the city-dwellers friend, cleaning up the dropped fries, falafel, and other street food and nesting in office buildings. Pigeons might be seen as a nuisance (and well, they are), but they are often viewed as a stupid nuisance. I'm here to defend pigeons as more intelligent than we give them credit for.

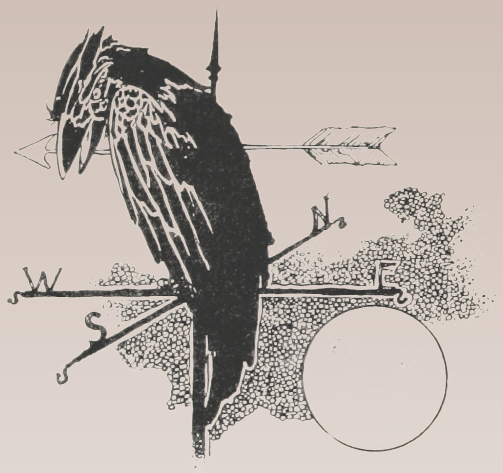
Pigeons, and especially homing pigeons, are commonly used in research. Homing pigeons are domesticated rock doves and are much like their wild counterparts, except they have been bred to be more motivated to return home. This is useful when using pigeons to send messages or in research to study how pigeons navigate[8].

I sort-a know what this is

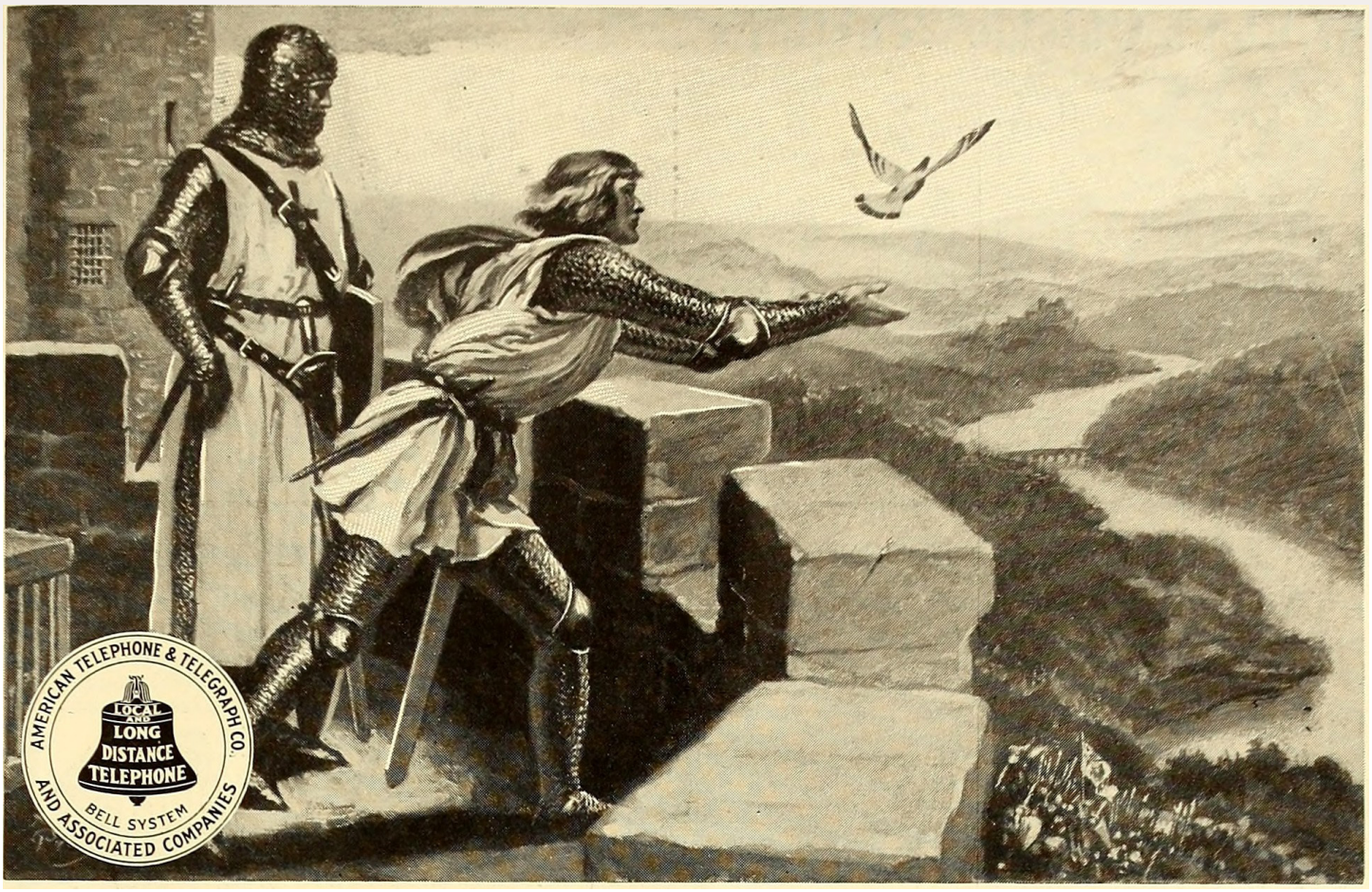
Not only are pigeons able to find their way home, but they can identify objects and create schemas or categories that they can apply to novel images. Wasserman in 1995 tested this by teaching a pigeon to choose one of two images presented on screens by pecking at it. The pigeon was then presented with an image and tasked with pecking the image that was in the same category. If it did so correctly, it was rewarded. Since there is no way to explain to a pigeon what the categories are, the pigeon learned by trial and error. Once categories were established with one set of symbols, new symbols were introduced. The pigeons were able to categorize the new symbols according to previously learned categories 65% of the time—which is impressive enough let alone when you consider the pigeon is flying by the seat of its pants (or tail feathers) with no context[9].

The boy scouts of the sky

Homing pigeons have an incredible ability to figure out where they are and how to get to their destination. There are multiple theories of how pigeons do this, one theory being the "map and compass" model. The map part is that pigeons will establish where they are in space in relation to where they want to be. But rather than a topographical map we might be used to, a pigeon's map is created using an olfactory "mosaic". Winds carry different smells toward their home and around familiar terrain that pigeons use to create a distribution of smells. Then, when they navigate, they use ambient odors to orient themselves. Pigeons will combine this olfactory map with visual cues if they are in a well-known environment. So now that they have a map, they need the "compass" part. Pigeons will establish and then follow a direction toward their goal. Their main compass is the sun, but pigeons also use magnetic fields. Birds are



From page 98 of "Lilliput Lyrics ... Edited by R. Brimley Johnson. Illustrated by Chas. Robinson" by William Birghty Rands. 1899. flickr.



From "American Homes and Gardens" page 258, 1905

able to sense magnetic fields in part due to the help of a protein in the retina called a cryptochrome, and specifically cryptochrome 4. Cryptochromes are light-sensitive proteins that help regulate the circadian clock and are significant in magnetic detection. Levels of most cryptochromes fluctuate at different times of day due to light exposure, with the exception of cryptochrome 4. Cryptochrome 4 will change shape in response to light and its levels are constant throughout the day, which would be beneficial for a navigation detector that is frequently used[10].

Pigeons are able to apply their map even to unknown territories, as demonstrated in 2013 in a study by Blaser, Dell'Omo, Dell'Ariccia, Wolfer, and Lipp. In the study, pigeons were taught a path between a home loft and a feeding loft. Once the pigeons learned the two locations, they were driven to an unfamiliar territory with no visual or olfactory cues along the way. Once at the release location, half of the pigeons were fed and half were left hungry to see if motivation impacted to which location the pigeons flew. The pigeons were able to successfully find their way back to the lofts, and it was seen that the hungry birds flew to the feeding loft and the fed birds flew to the home loft[11].

When navigating, pigeons will also fly better in a flock. The flock is lead by the pigeon with the most experience and the one who is a good leader. If the flock thinks the leader isn't being effective, then who the leader is will change. But the impressive thing about a flock of pigeons is they can navigate routes none of them has flown before to get to the same destination. Pigeons can work together to combine their maps to arrive at the destination. Flying in a flock allows pigeons to learn new routes and areas from others[8].

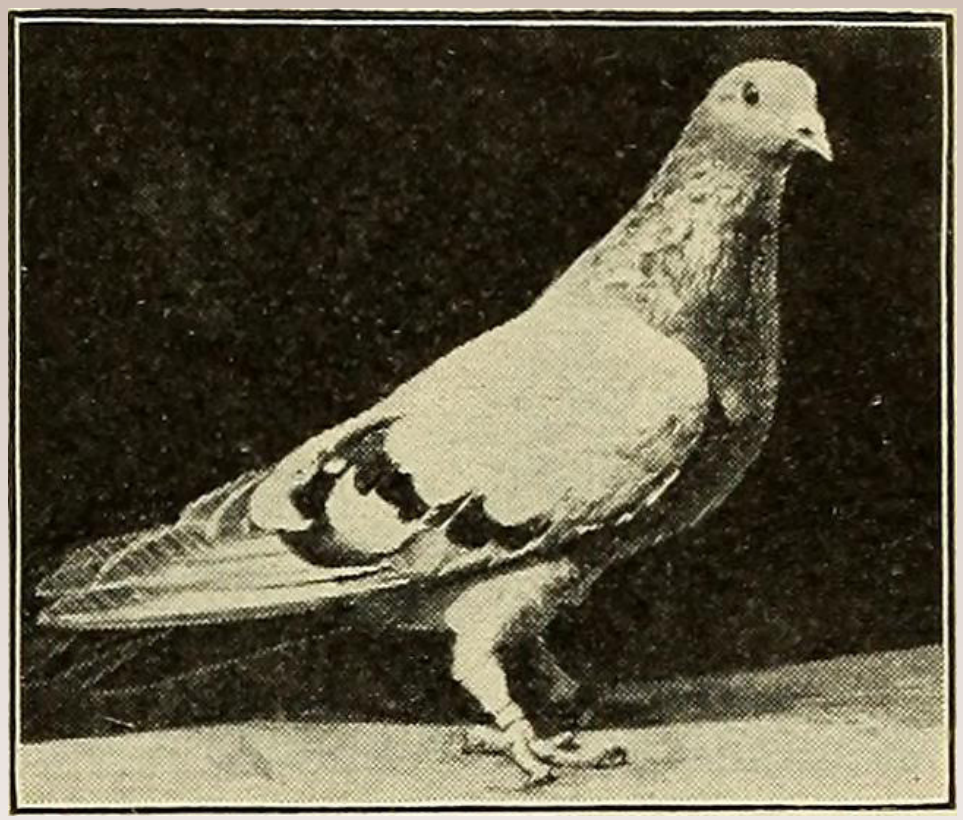


Image by John Henry Robinson from "Our Domestic Birds". 1913. flickr

So birds are smart, but are we smart enough to understand just how smart they are?

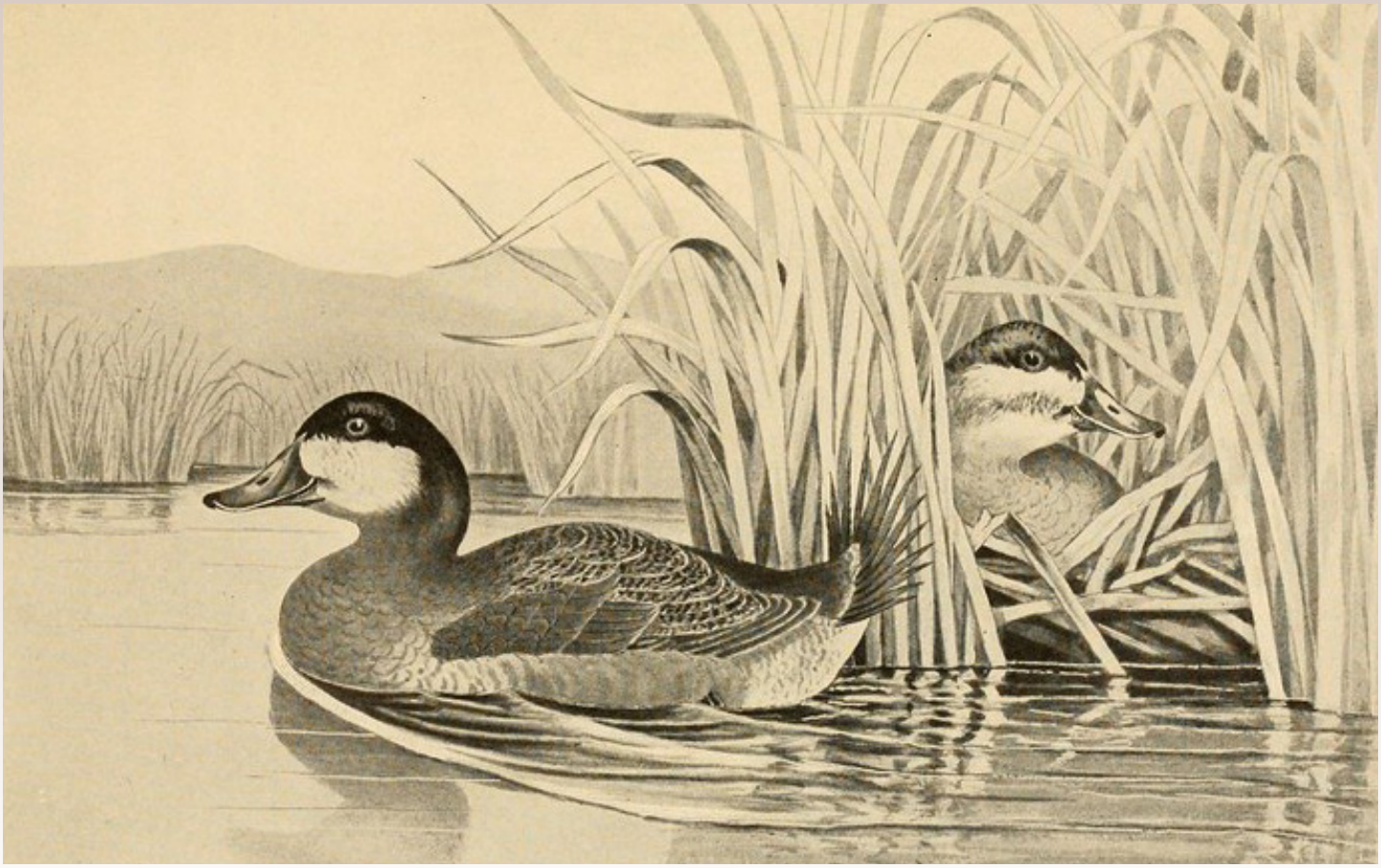
Not really. We only know intelligence from our point of view. We're operating under the assumption that animal cognition, intelligence, and logic would work like ours does. And by extension, we are making the assumption that parts of the brain which appear to be analogous do have the same function. There is actually evidence that this might be so, and for this we turn to song birds.

A walk through the woods in the spring or summer often is accompanied by the tweets of birds. Song birds are capable of complex vocal sounds and also vocal learning—skills also used by humans. Though we both evolved these skills independently, when looking at the brains of song birds and humans, similar neural pathways begin to emerge. In humans, Broca's area and Wernicke's area are highly used in vocal learning and language production, they are often called the "language centers" of the brain. As it turns out, song birds have structures that look and seem to function much like the human Broca's and Wernicke's areas[2]. This might suggest that, though evolved independently, analogous structures might exist in different taxons.

But when it comes to wondering if animals have intelligence or might use cognition like we do, we can't ask them yet, so we don't know. How do we study something that is beyond us? We apply the tools we have such as behavioral tests and brain scanning, but any knowledge we gain is built on the assumption that all brains end up working the same to some degree. When we look at human brains we see a huge variance in what they do and how they think. Can we then make the assumption that an intelligent brain that evolved independently of hominid brains would produce the

same logic? Maybe, maybe not. There are cases of the same trait evolving independently, for example, both bats and whales using echolocation and humans and koalas both having fingerprints. What if intelligence is another example? Perhaps one day we will be able to answer these questions.

Just be careful because next time you call someone a birdbrain—it might just be a compliment.



"n610_w1150" by BioDivLibrary from CC

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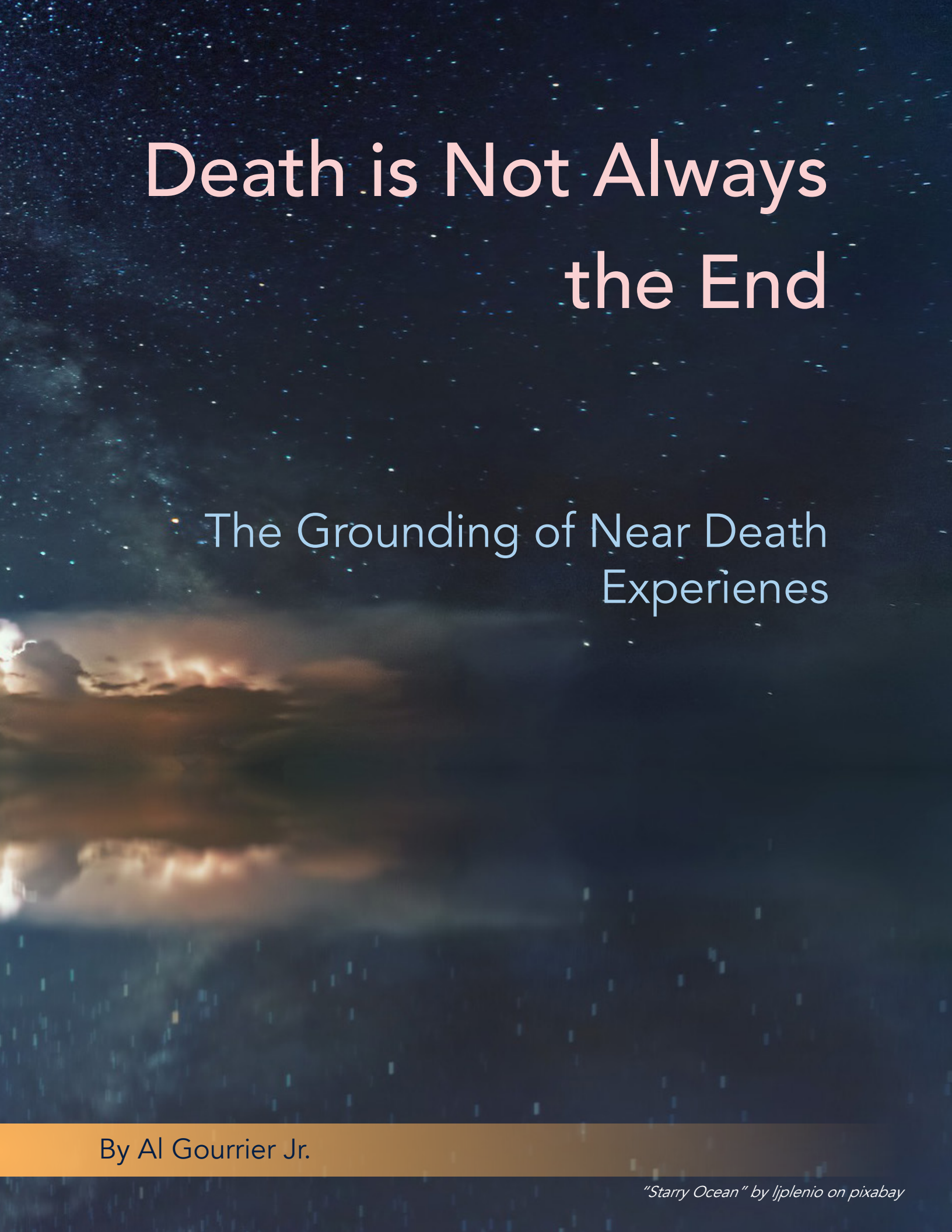

Death is Not Always the End

The Grounding of Near Death Experienes

By Al Gourrier Jr.

"Starry Ocean" by ljplenio on pixabay

Chaim Ralbag was a family man with a stable life in Rehovot, Israel. He followed a strict routine of 7:00 am work, 1:30 pm lunch at home, hour long nap, and then work again at 4:00 pm. Ralbag had excellent health but one day, he felt weary and nauseous. He awoke from his hour long nap with an instantaneous rush of dizziness and a dulled sense of vision[1]. As his senses clouded by the second, darkness accumulated and warped around him. Ralbag felt a sinking sensation and then there was nothing but darkness. He fell for an eternity. Deeper and deeper into the abyss, he reached for something—anything to brake his fall, but there was only void as his fall accelerated. At this moment, Ralbag made a decision. He surrendered the last of his free will and ceased to try.

Ralbag gave in and as he cried, his fall relaxed. He gently landed, yet was suspended in oblivion, with the void being nothing and everything at once. Escape. Escape was the only thing on his mind as he suddenly controlled his every movement. He squirmed and wailed like a mad man until he could rise. Ralbag rose and as he began to glide through the abyss, the rough edges of darkness became smooth—the colors light, and then everything became familiar. He recognized the doorframe that he attempted to grasp on his way down to the floor and at that moment, it was clear. Ralbag was in his room. As he came to this realization, he noticed someone that he recognized on the ground. To his astonishment, the person was himself.

Ralbag initially felt strange and detached upon this realization, but what followed absorbed him. Ralbag was overwhelmed with compassion and euphoria, so he soared upward through the never-ending sea of wondrous happiness. In this state of tranquility, he abruptly realized that he was not alone. Ralbag was joined in flight by many others, but they carried the light of the sun with them as they morphed into any and every form imaginable. The figures passed through each other and changed forms with every swift movement. Ralbag was astonished and radiant as he and the others attempted to transcend an endless height. He attempted to talk to one of the figures besides him, and he was amazed when he realized that the figure understood him despite his inability to form words. The figure explained that there was no dimension, no reality, and no time. Exuberant over this newly found awareness, Ralbag suddenly felt sorry for his limp body and returned to apologize.

Upon return, Ralbag enter-

"Beyond Death" by siencefreak on pixabay

ed a new reality in which he was his former self but still separate from his body. He saw a hill in the distance and as he stopped to gaze at it, he felt the ground solidify under his feet. Ralbag noticed a figure on the hill and as he walked closer, he recognized that it was his late father. His late brother was standing just behind his father. Ralbag's father disapproved of his stay and furiously spoke of his foolishness. His father told him to return before it is too late. At this moment, Ralbag reached for his father's hand and slipped as he lost his balance. With this fall, pain—real physical pain—crippled his feet as his father disappeared with a smile on his face. Ralbag crawled back to his body in pain, and as he held his body in his arms, all faded to black.

Ralbag woke up in the hospital days later. He had suffered from a heart attack. The above account was his narration of the near death experience he envisioned. Ralbag reported his near death experience in an attempt to make sense of what he had experienced. Ralbag's account was mystifying and although many of the details sound supernatural, the core features of near death experiences that he reported (e.g. out-of-body experiences) are typical of any near death experience. Thus, Ralbag's account will be used as an example to better understand the core features of any near death experience.

What are Near Death Experiences?

Near death experiences (NDE) are abnormal experiences that are the manifestations of typical brain function gone wrong during the brink of death[2]. An NDE is a subjective phenomenon that is determined by a patient or individual perceiving the experience. Traumatic, but non-life-threatening, events may even elicit an NDE or evoke NDE-like experiences. Therefore, NDEs can be facilitated by a state of extreme distress without any physical brain damage (e.g. brain death). There are many common features of NDEs that individuals have reported. These features that often discern NDEs from medical ailments and identify the occurrence of an NDE include: the awareness of being dead, out of body experiences, the perception of a tunnel of light, meeting deceased people, and positive emotions. These common features of NDEs can be biologically explained, and Ralbag's account of his NDE will be used as an example of the experiences that an individual who has had an NDE perceived.

With that being said, approximately three percent of Americans report having an NDE[3]. Ralbag, however, initially kept the accounts of his NDE to himself. He did not want his experiences to be misleading and confused for something else. The occurrence of an NDE can often be misunderstood and labeled as a psychopathological state or acute symptomology of an existing ailment. Ralbag was fearful of others' judgements because he did not know that many people report NDEs. Many reports of NDEs result from cardiac arrest and a variety of severe traumatic brain injuries.

There are also reports of NDE-like accounts in non-life-threatening events. These NDE-like accounts are often caused by extreme meditative states and emotionally intense situations, such as severe grief and anxiety[4]. NDE-like accounts are generally unclear about whether the intensity and basic features match NDEs' magnitudes. However, Charland-Verville *et al.* (2014) found that NDEs caused by brain damaged pathological comas did not differ from NDE-like accounts (e.g. severe states of anxiety) in either intensity or content. The findings also revealed that the three different coma etiology groups (i.e. anoxic [without oxygen], traumatic, and other) that compose the life-threatening NDE group in the study did not differ in their NDEs either, regardless of the severity or content of their NDE. This suggests that the prevalence of NDEs could be higher than reported if non-traumatic experiences evoke similar NDEs as individuals experiencing NDEs in danger of losing their life. Therefore, the core features of NDEs that will be described in the remainder of the article are typical for all NDEs, as seen by the shared content of NDEs and NDE-like experiences.

Near death experiences (NDE) are abnormal experiences that are the manifestations of typical brain function gone wrong during the brink of death.

The Core Features of NDEs

The first basic feature of NDEs that Ralbag reported was the tunnel of light experience. The tunnel of light perception is characterized by the awareness of traveling through darkness and reaching a luminous world of light at the end of the darkness[1]. The light is often faint in the distance and becomes more and more lucent as the individual approaches the light. Ralbag's account of this NDE feature began with an overwhelming darkness that consumed him. His dark tunnel

Figure 2: Tunnel of Light Near Death Experience Illustration. On Wikimedia Commons

was a deep abyss of never-ending darkness. As he rose through the abyss, Ralbag perceived the light sensation as the darkness faded.

Scientifically based theories generally relate the form of the tunnel to the visual cortex structure. The cells of the visual cortices process vision, both central (through the fovea) and peripheral, and that vision and cell excitation results in a dark periphery with a bright light in the center that produces a tunnel effect[5]. In other words, the tunnel of light experience that Ralbag reported could be explained by cell activation in the brain's visual cortex that "turn on" the cells that provide light in the center of the visual field while "turning off" all of the lights surrounding that center, resulting in this tunnel effect. The NDE tunnel of light perception has also been explained through observed retinal ischemia visual activity[6]. Ischemia is the depletion of blood. Therefore, retinal ischemia visual activity means that the eye is depleted of blood and oxygen. The lack of blood and oxygen in the eyes can lead to Ralbag's tunnel effect. Moreover, oxygen loss is a common feature of dying. Thus, the tunnel of light perception is consistent with dying, which explains its appropriateness as a core feature of NDEs.

The second basic feature of NDEs that Ralbag reported was an out-of-body experience. The out-of-body experience is often characterized as a feeling of disembodiment, in which one feels as if they are outside of the body and floating over it[2]. Individuals who have reported out-of-body experiences generally feel like their out-of-body "self" is alive, although they are aware that their perception of the self is not located inside of their physical body[7]. The vast majority of Ralbag's account of his NDE is an out-of-body experience, because he experiences everything besides the fall as a figure separate from his physical body. Ralbag recognized himself on the ground, and he felt strangely detached when he realized this. After contemplating his new reality, Ralbag concluded that he was the real him because he had feeling and he could think for himself[1].

Out-of-body experiences are one of the most frequently reported features of NDEs, which consequently deem them the subject of most NDE research investigations. The generation of out-of-body experiences may result from vestibular dysfunction due to the fact that vestibular

Figure 3: Hallucinogenic Out-of-Body Experience Illusion. You and You By Louish Pixel on flickr

disturbances and sensations were emphasized by every individual in the Blanke, Faivre, and Dieguez (2016) review who reported out-of-body experiences. Vestibular disturbances are generally characterized by deficits in one's sense of balance. Vestibular sensations, on the other hand, are characterized by a vast array of sensations that include feelings of elevation and floating, which are also characteristic of out-of-body experiences. The core of the human vestibular cortex is located at the temporo-parietal junction (TPJ), and damage to this region results in vestibular dysfunction. The TPJ is the area of the brain where the temporal and parietal lobes of the brain meet. The TPJ codes multisensory conflict between internal and visual information for perception of the body[8]. It's also involved in biological motion, mental imagery, and cognitive function, such as agency and self-other distinction, which determines whether one distinguishes its own body from another. Altogether, the TPJ is critical for every notion of the NDE feature of out-of-body experiences.

The critical role of the TPJ in out-of-body experiences was further demonstrated when repetitive artificial electrical stimulation of the TPJ induced out-of-body experiences[2,7,8]. Artificial stimulation of the TPJ also induced spatial illusions and body-part visual illusions, such as phantom limb sensations like the rubber hand illusion. The rubber hand illusion paradigm can cause individuals to feel like a rubber hand is their own hand by simultaneously stroking one's own hand (that is hidden inside a box) and the rubber hand (that is placed in front of them where the hidden hand would lay) at the same time[9].

Transcranial direct current stimulation (tDCS) is a form of repetitive artificial stimulation that uses constant electrical currents through electrodes on the head. tDCS maximized induction of the TPJ in regards to increased internal drift, which determines the location misjudgments from the fake rubber hand to the real hand. This suggests that individuals whose TPJ was stimulated experienced the sensation of the fake arm as part of one's own body. The TPJ is also demonstrated to evoke illusory self-locations, which is characteristic of out-of-body experiences. Furthermore, MRI analysis revealed that the right TPJ (rTPJ) was predominantly active in patients who experienced out-of-body experiences[7]. Therefore, multiple accounts of the TPJ evoking out-of-body experiences were found using different functional neuroimaging measures, which suggests that the TPJ is pivotal in producing the out-of-body experience feature of NDEs.

The third basic feature of NDEs that Ralbag reported was an intense rush of positive emotions. Positive emotions as a NDE feature is often characterized as intense feelings of acceptance, euphoria,

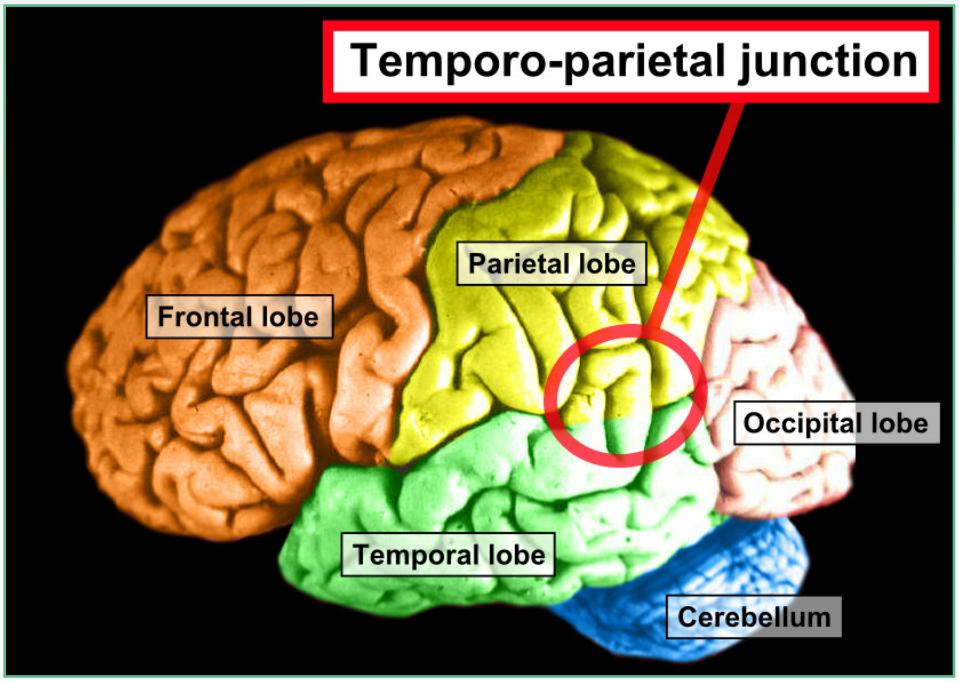

Figure 4: The Temporo-parietal junction (TPJ). The image labels the TPJ, cerebellum, and the four lobes of the brain. On Wikipedia Commons.

and pure bliss[2]. Individuals who reported having these positive feelings are also typically overwhelmed with feelings of painlessness, peace, and well-being. Ralbag was overwhelmed with compassion and euphoria and he found himself in a state of tranquility and pure happiness1. Ketamine (aka Ketalar and Special K) can mimic the positive emotion feelings of euphoria and produce spiritual awareness through binding with opioid mu-receptors and inhibiting NMDA receptors, which are important for the promotion of neuronal signaling[2]. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist (blocks the NMDA receptor), is a recreationally used drug characterized as a dissociative anesthetic, which induces the insensitivity to pain[10]. Ketamine binding activates the opioid systems reward properties to generate intense feelings of euphoria as a survival mechanism[11]. For instance, the opioid reward system is activated along with the dopamine reward system when an animal is under attack. Ketamine thus provides an example of a neurochemical approach to understanding the positive emotions feature of NDEs.

The last basic feature of NDEs that Ralbag reported was the perception of meeting deceased people. The meeting of deceased people is typical in NDEs and it is characterized by the visiting of loved ones and the souls of the past[2]. Individuals who report meeting deceased people in their NDEs often recall being surrounded by peaceful figures in a boundless realm unlike any other. Even individuals who would not consider themselves to be religious, recall being suspended in a spiritual place with an aura of peacefulness.

Ralbag had multiple accounts of meeting deceased people. His first envisioned encounter with this perception was with the figures that flew upward with him as he attempted to transcend an endless height. The figures passed through each other and changed forms with every swift movement as they carried the light of the sun with them, which is a very god-like quality. Ralbag was astonished and found himself at peace in their presence. He was even able to communicate with the figures without the use of words, which is also very transcendental. Ralbag also got the chance to reconnect with his late father and brother in his NDE. The reconnection with fallen loved ones is one of the most frequently recalled figures that individuals report after meeting deceased people in an NDE. The meeting of deceased people is typically regarded as a hallucination resulting from the abnormal functioning of the neurotransmitter dopamine[12]. Damage to the center of the visual field (e.g. Macular degeneration) can also cause intensely realistic visual hallucinations[13]. This suggests that neurochemical dysfunction or damage to the visual field can result in hallucinations, which are characteristic of the meeting of deceased people feature of NDEs.

Hallucinations have also been speculated to be compensatory over-activation in the brain areas nearby the damaged area as a means to attempt to fix the problem and make sense of what is wrong. The angular gyrus can also be of significance in understanding the meeting of deceased people feature of NDEs. The angular gyrus is a region of the brain in the parietal lobe that is involved in spatial cognition and theory of mind. Electrical stimulation of the angular gyrus induces a sense of presence, which is characterized by the feeling that someone is hovering behind you. Stimulation of the spatial cognition correlate of the brain inducing a hovering sense of presence suggests that the perception of meeting deceased people during an NDE is associated with the altered perception of one's spatial environment.

The final basic feature of NDEs is the awareness of being dead. Ralbag did not experience this feature of NDEs. Therefore, a Cotard's syndrome patient's experience with this feature of NDEs will be used as an example to biologically explain the awareness of being dead. Individuals with Cotard's syndrome, which is characterized by the delusional belief and feeling of being dead, frequently report the awareness of being dead feature of NDE[14]. A 65-year-old female patient suffering from dementia and depression developed Cotard's syndrome. She expressed awareness of her interior bodily state, and she believed that she was dead[14]. She thought that she was infecting everyone around

Stress Induced Anxiety and NDEs

The locus coeruleus noradrenergic system is a neural circuitry that may play a large role in near death experiences through generating stress-induced anxiety. This system releases noradrenaline, a neurotransmitter that effects emotions through its involvement in arousal of fear and stress. Stimulation of this system enhances the REM sleep-wake cycle that could induce life reviews and sleep paralysis (dream-like hallcuinations) during near death experiences[15].

her, and she blamed herself for any of her loved ones misfortune. Her physical examination results were normal; however, MRI results revealed that she had bilateral insular cortex atrophy (withering away of the brain). The insular cortices (fronto-temporal) are central to interoception, the conscious awareness of internal signals and sensations, and body ownership through consciousness and self-perception[14]. The awareness of being dead is thus associated with the insular cortices that disrupt interoception and body ownership normal function. This suggests that the awareness of being dead feature of NDEs is associated with dysfunction in the insular cortices.

What's so special about Near Death Experiences?

The NDE accounts of Ralbag and the Cotard's syndrome patient provided captivating and unambiguous examples of the manifestations of typical brain function gone wrong during traumatic and intense experiences. NDE are captivating because of their peculiar nature. They are important to explore because the effects of having an NDE on an individual are still widely unknown. Individuals who have had NDEs often develop new beliefs and values as a result of their reflection on their lives and the traumatic nature of an NDE. For instance, Ralbag was not quite the same after his NDE. He physically recovered from his heart attack, but he was emotionally altered. Ralbag looked forward to the day that he could return to the never-ending sea of wondrous happiness. He yearned to be in that state of tranquility, and his heart was back in that dream reality[1].

NDEs also question our understanding of consciousness and the connection between brain function and respective awareness. The doctors told Ralbag that he was unconscious and mumbled about his experiences[1]. Ralbag, however, thought otherwise and questioned the doctors' assumption and verdict that he was unconscious. He questioned how someone else could tell him that he was not aware of anything when they do not occupy in his physical being. Ralbag understood and comprehended the events that he envisioned during his NDE. He even held a sense of accomplishment and ultimate revelation for attaining a new truth about continuous realities that contemplated the meaning of time and measurement. Ralbag felt privileged to have this insight into different realities. NDEs are therefore so special because we are mystified by their occurrence, and we question the manifestation of their existence. We look for generalizable accounts to ground the complicated nature of this phenomena. Ralbag's envisioned experience and the Cotard patient's awareness of being dead thus illustrate that the perception of death is not always the end. Through their stories, the scientific explanations for each feature of NDEs was exemplified and will not be forgotten.

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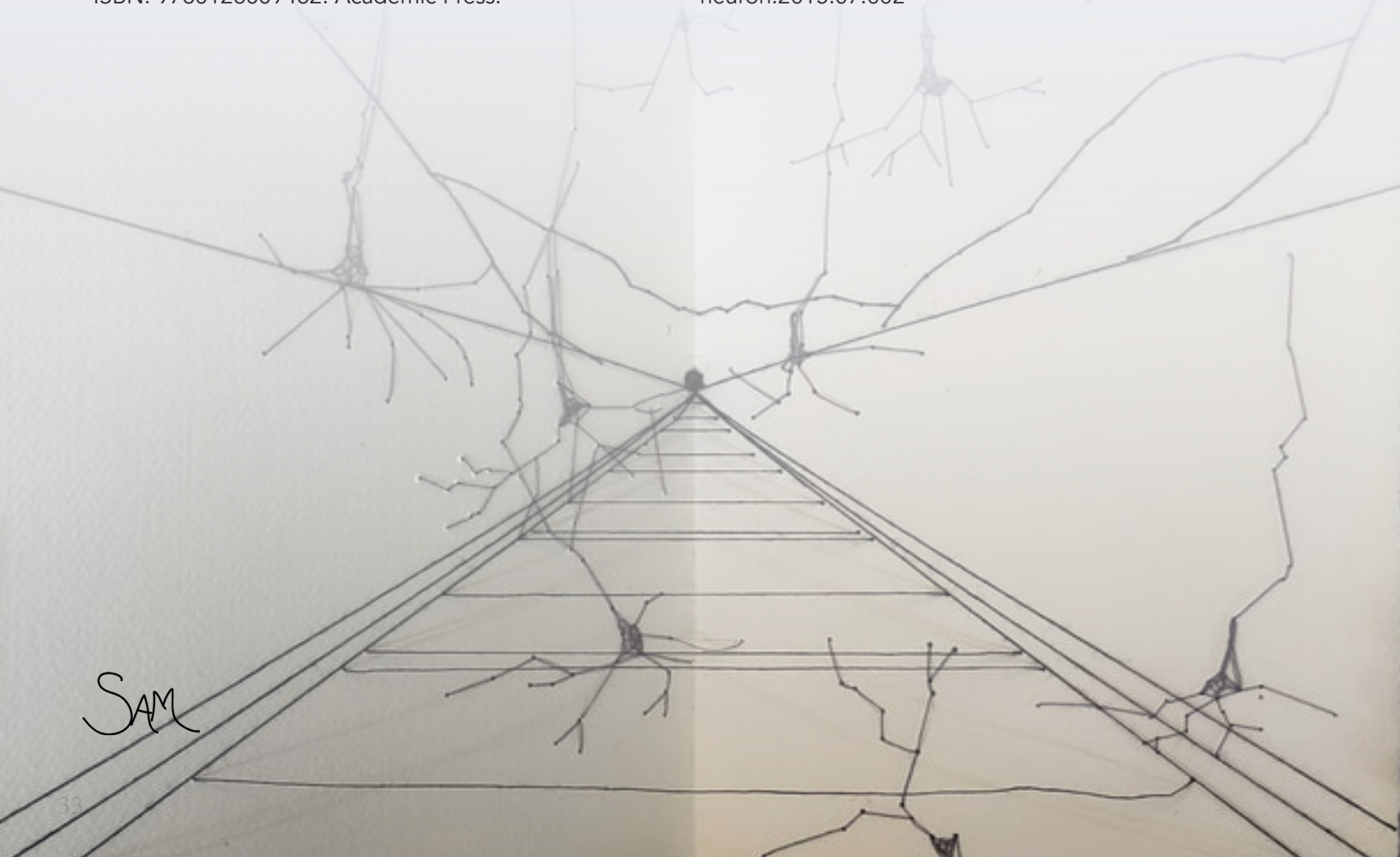

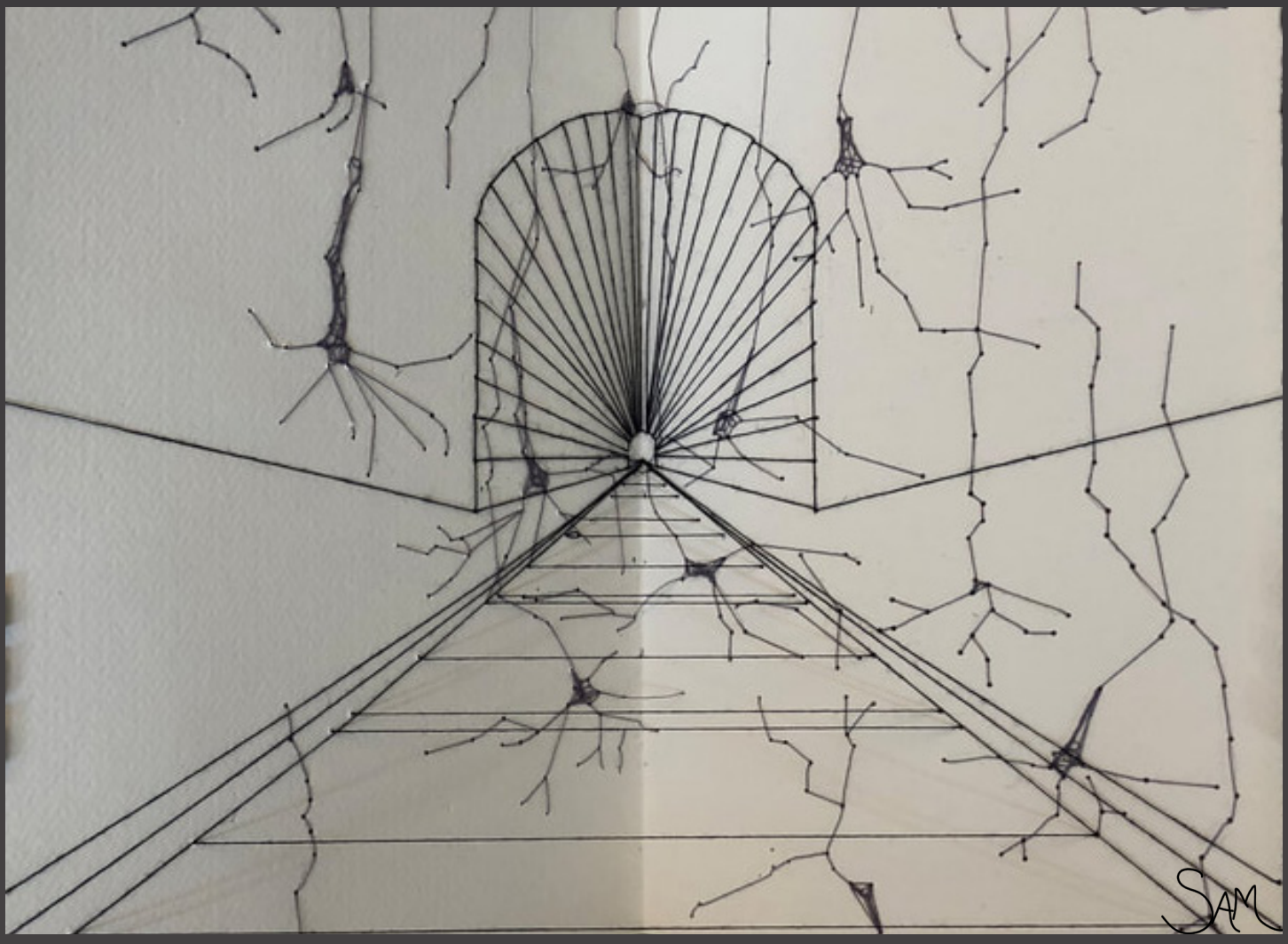

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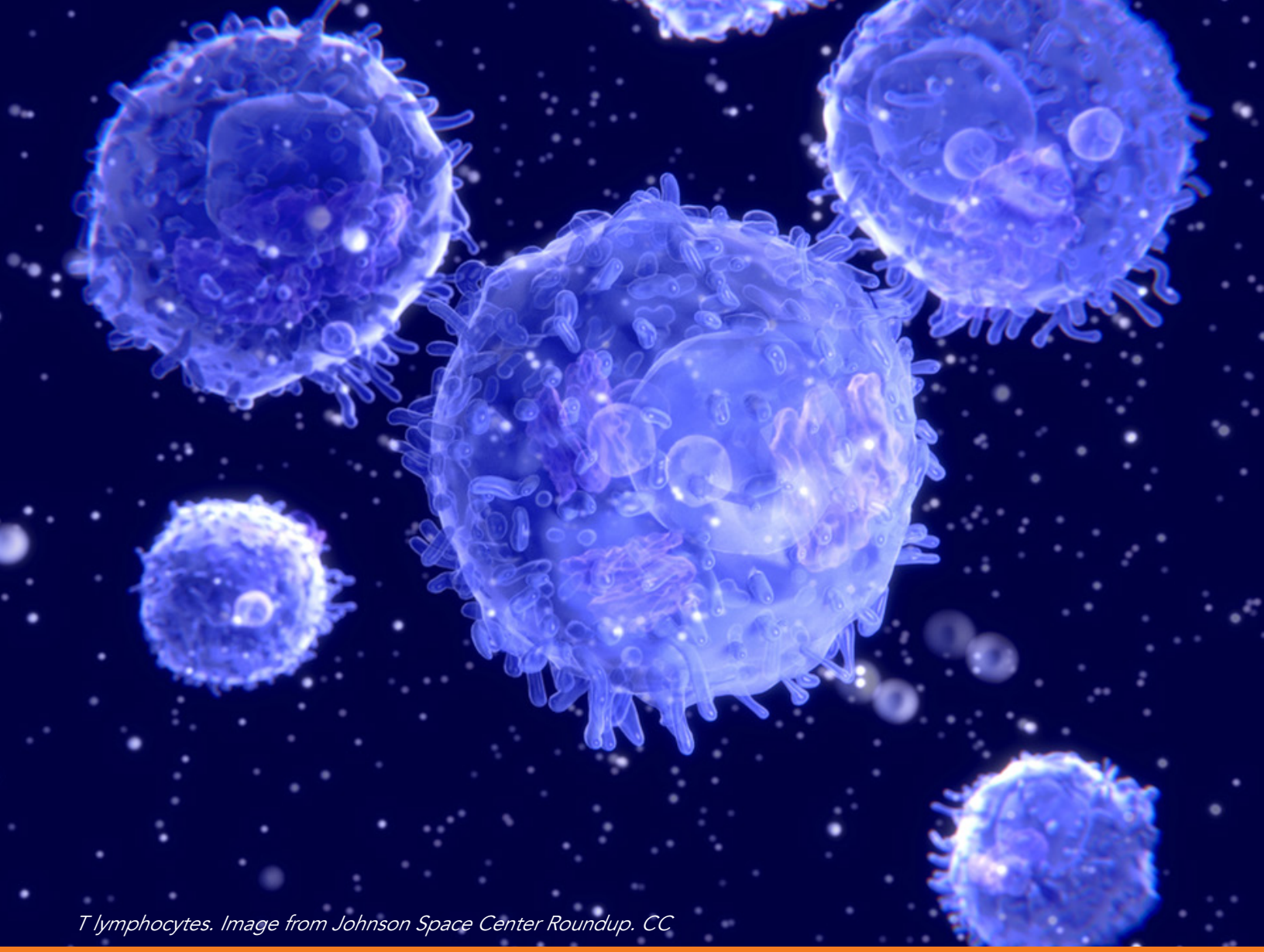

T lymphocytes. Image from Johnson Space Center Roundup. CC

Honey, are these my kids?

My hands?

My organs?

My cells?

By Anoohya Muppirala

From culture to cells, memory spans multiple levels of our lives. Recent advances in neuroimmunology suggest that tapping into "immunological memory" or the memory of our microscopic cells, may contain the answers to protecting against higher order cognitive memory decline that occurs in autoimmune disease, stress…and aging.

People often say that memory makes us who we are—and this couldn't be closer to the truth. At a macroscopic level, **cultural memory** describes how we feel connected to our families and those around us. It is defined as a cultivation of historical experiences that are passed through generations and ultimately constitute the "blood" of the people[1].

However, memory is not only how we identify with a community through our collective experiences. Cognitive memory describes how we go about our everyday lives and how we remember and know our unique place in the world—our home, our name, our identity—and without it, everything can get a bit jumbled and confusing.

Interestingly, it turns out that within our blood—our cells have memory too. Now, scientists often frown upon anthropomorphizing, but, rest assured, *hardly* any creative license is being taken. In her text, *Human Physiology: From Cells to Systems*, Professor Lauralee Sherwood defines "memory" as the ability to encode and store information from an experience and retrieve that information when needed in the future[2]. Well, this description perfectly describes how immune system cells in our bodies protect us from foreign pathogens 24/7.

The **immune system** is the body's defense to harmful pathogens, and after fighting off an infection for the first time, specific immune cells remember the pathogen and prevent any recurring infections. This is known as **immunological memory.** The cells that are crucial players, known as **memory B and T lymphocytes**, are long-lived, protect the host, and make replicates of themselves when a familiar pathogen tries to invade the body[3]. Essentially, the body has a molecular and cellular profile that defines its own intrinsic culture; the memory lymphocytes of the immune system imprint each infection as an experience and then pass on the information to new generations of naïve immune cells so they can more readily prevent the infection from happening again.

Immunological Memory:

"Essentially, the body has a molecular and cellular profile that defines its own intrinsic culture; the memory lymphocytes of the immune system imprint each infection as an experience and then pass on the information to new generations of naïve immune cells so they can more readily prevent the infection from happening again."

But sometimes, these cells get confused with their own identity and their memory marks components of the body as foreign—otherwise known as **autoimmunity**. When our immune cells can no longer tell self from non-self, it can lead to problems with a lot higher stakes. Imagine when our immune cells see the brain as foreign—the center of our thoughts and every day function? Now we have an internal fight where cellular memory gone wrong is putting our memory that defines us and how we view the world at risk too.

Multiple-Sclerosis is not MOG-nificent

Multiple Sclerosis (MS) is a chronic, autoimmune disease of the central nervous system, which is comprised of the brain and spinal cord. MS is a leading cause of disability in young adults and affects more than an estimated 2.3 million people worldwide[4]. Curiously, over the past half century, MS has become increasingly more prevalent in women, with diagnostic rates reaching up to three times higher than men. Physiologically, MS symptoms range from slurred speech, tremors, and coordination to problems with memory and concentration.

When taking a closer look, the underlying condition is due to circulating immune cells leaving the blood and invading brain tissue. The culprits—CD4+T lymphocytes—cross layers of cells that line the blood vessel and serve as the physical border to the brain. Subsequently, they enter the environment of brain tissue… and things get interesting. See, the brain is defined as an "immune-privileged" region, meaning that the brain environment is supposed to be separate from contact with immune cells. During development, B and T immune cells reside in an isolated region of the body in order to be tested with samples that mimic body tissues. This way, the immune cells that react to the body tissue are safely eliminated, allowing only non-reactive immune cells to enter the blood and circulate through the body looking for foreign invaders. Since these immune cells are supposedly never going to interact with brain tissue, the immune cells are never tested with it.

One component of the brain that is not tested with B and T cells

is the molecule known as **myelin oligodendrocyte glycoprotein (MOG)**, which makes up the fatty tissue, myelin, that wraps around neuron projections to help facilitate signaling (Imagine a rubber coating insulating the cord from a phone charger to the wall). When seen by invading T cells, MOG looks unfamiliar, and is therefore processed as harmful. The T cells then release signals to recruit B cells and other immune cells to attack the neurons, which results in progressive neuron damage and impaired overall nervous system function.

The immune system is clearly incredibly complex. Scientists have been scratching their heads trying to understand how cells handle the foreign environment of the brain in order to develop MS treatment to suppress reactivity. Turns out, mice have played a leading role in answering some of these difficult questions. Surprisingly, these common household pets have a remarkably similar immune system structure to humans, including the function of B and T cells[5]. Along these lines, we have a mouse model for Multiple Sclerosis (EAE) to thank for the advancements in therapeutic MS treatments that have been made in recent years. Interestingly, the EAE model has revealed that targeting the invading CD4+ T cells is not nearly as effective in minimizing symptoms as depleting B cells. **B cell depletion therapy** has shown promising results for MS patients, because it eliminates B cells from being able to develop into memory cells. With every infection, B cells directly become plasma cells, which secrete antibodies—proteins that target the infecting pathogen. However, some of these B cells also become memory B cells, which remember the same antibody that the plasma cells are producing but don't release it. These memory B cells then turn into plasma cells that end up secreting even better antibodies to target the pathogen more effectively if it tries to infect the body again. So, in MS, memory B cells are a problem because they keep secreting antibodies that target MOG. However, B cell depletion therapy prevents these memory B cells from forming in the first place as well as preventing B cells from producing more generations of memory B cells that will do the same[6] (Fig. 2).

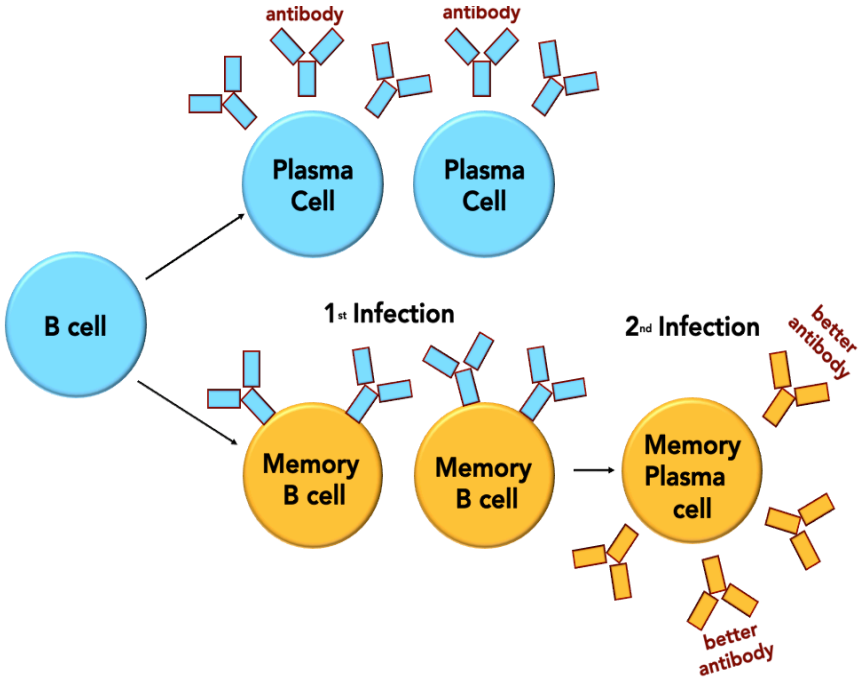

*Fig. 2: Process of B cell response during primary and recurrent infection. After first infection, B cells become **plasma cells** that secrete antibodies (Y shaped proteins) to target the infectious pathogen. At the same time, **memory B cells** that remember the pathogen are being created and rest quietly. Then, if a recurrent or second infection occurs by the same pathogen, the memory B cells respond quickly and become plasma cells that can secrete antibodies that are even better than the previous ones, using the information from the first infection. Designed by Anoohya Muppirala.*

In further support of targeting memory cells, the immunosuppressive drug alemtuzumab has been revealed to be particularly promising as a therapeutic option. Alleviating an initial immune response in MS can be accomplished by suppressing the reactive immune cells, but MS patients often suffer relapse, where their immune system is triggered repeatedly. This component often makes MS devastating, because each time a relapse occurs, the body's ability to repair neurons diminishes. Alemtuzumab inhibits relapse because the drug slows down the recovery of memory B cells after wiping out circulating immune cells[7]. This suppresses the ability of the memory cells to react immediately to MOG, buying time before new immune cells are exposed to MOG again in the brain. So essentially, new evidence suggests that targeting immunological memory may be a powerful MS treatment —perhaps saving one more patient from losing their cognitive level of memory.

NMDA Receptor Antibody Encephalitis: B a dear and turn off the Plasma cells

35-year-old Jane* sat up in her bed and blinked. She smiled, and then blinked again…slowly, relishing the fine control she had

over her eyelids. She touched her bed, soaking in the warm remnants of her body heat on the covers with her fingers. One year ago, she wouldn't have remembered where she was or been able to appreciate the feeling of being still due to her recurrent seizures and lapses in memory. Doctors even saw that her MRI revealed a striking loss of normal hippocampal volume—a region of the brain critical for memory. But after switching from her Rituximab treatment to another immunosuppressant drug, bortezomib, Jane went from bed ridden to functioning independently in little over a year! And the treatment could not have come at a better time. As her days progressed in the hospital prior to bortezomib, Jane's ability to form new memories **(anterograde)** had been fading, and her recollection of old memories **(retrograde)** had also begun to weaken.

In a similar case, another comparably aged female, Franny*, suffered from memory loss, muscle pain due to nerve dysfunction (myalgia), and involuntary muscle movement through her face and upper limbs on her right side. Franny's situation also left her bed-ridden. What was perhaps most striking about Franny's condition was that she also suffered from behavioral changes. After four weeks of bortezomib treatment, however, Franny was able to return home and regain control over much of her voluntary movement as well as both retrograde and anterograde memory[8].

Both of these cases reveal remarkable recovery—so what gives? By the looks of the situation, it is not a stretch to infer that the time spent in the hospital for these two women was fighting to not lose themselves. While they may not have known each other, Jane and Franny had a huge thing in common: they both were battling an autoimmune condition known as **NMDA receptor antibody Encephalitis.** NMDA (N-methyl-d-aspartate) receptors are expressed by neurons, especially in the hippocampus, which, again, is a region of the brain that is critical to memory formation and storage. In patients with this condition, memory B cells develop antibodies that target the NMDA receptors on these neurons, preventing NMDA from binding and inhibiting signaling. Subsequently, the connections between neurons weaken because of lack of activation, and hippocampal volume and memory loss follow. Rituximab is a drug that targets a protein found on the surface of memory B cells before they become antibody-secreting plasma cells. These plasma cells that actually secrete the anti-NMDA receptor antibody do not express the protein required for Rituximab to shut it down. Bortezomib on the other hand, directly targets the plasma cells, preventing antibody production[8].

What is curious, is that one would think that inhibiting memory B cells would inhibit plasma cell formation and therefore prevent antibody production…so wouldn't Rituximab and Bortezomib be redundant? Well, it turns out that **long-lived plasma cells** exist in our bodies following an immune response, and they continually secrete the pathogen-specific antibody even after the first infection has ceased (way to complicate figure 2, right?). So, patients treated with Rituximab may not be producing as many new memory B cells, but their plasma cells formed before the treatment are still producing the NMDA receptor antibody, rendering the drug less effective than Bortezomib. Ironically, this continual baseline level of antibody production from long-lived plasma cells is called **protective immunity,** because in healthy individuals, it helps prevent recurrent infection by immediately targeting pathogens that try to re-enter the body. But in Jane and Franny's cases, protective immunity actually caused their symptoms—because their bodies were trying to protect them from their own brains.

**Patient names changed to protect identity*

I'm stressed, I'm sick, I'm inflamed …what's an antibiotic going to do?

Many people can relate to the experience of physically getting a cold or feeling ill during an ongoing period of stress. It comes as no surprise that this is due to the immune system being compromised, rendering an individual more susceptible to infection. But what is perhaps alarming, is that individuals who suffer from abnormally ongoing periods of stress or chronic stress, can suffer from reduced hippocampal size and memory loss. In fact, even more broadly, **chronic stress** has been established as a strong risk factor for numerous mental health conditions including anxiety and depression. While research is ongoing regarding the exact biological and environmental factors that explain stress related cognitive impairment, recent evidence is demonstrating that immune system dysfunction is implicated in chronic stress-linked memory loss.

Swinging back to the mouse, researchers have been able to identify a lead on how immune dysfunction may be directly impairing memory. Scientists have utilized a chronic stress model in mice known as the **repeated**

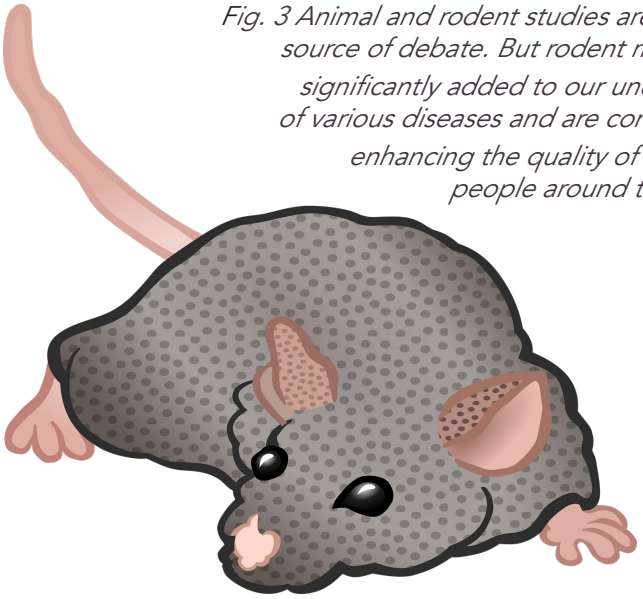

Fig. 3 Animal and rodent studies are a constant source of debate. But rodent models have significantly added to our understanding of various diseases and are contributing to enhancing the quality of life of many people around the world[9].

social defeat (RSD) model. It has been shown that individuals experiencing chronic stress often demonstrate persistent emotional and cognitive dysregulation, which the RSD model recapitulates in mice. To induce stress, male mice are essentially exposed to an emotional stressor (an aggressive male mouse) in intervals repeatedly for about a week and then given various spatial memory tasks[10].

Not only did the mice perform poorly on the memory tasks following the stress protocol, but fascinatingly, brain slices from the mice revealed high levels of inflammatory proteins, which are secreted by reactive immune cells, in the limbic region of the brain—a center involved in emotion. More specifically, the **inflammatory proteins**, along with B, T, and other immune cells, were largely accumulated in the hippocampus.

One of these immune cells, the **macrophage**, is known as a phagocyte, for it functions in consuming cellular debris and pathogens. When macrophages enter the brain environment, they respond to the inflammatory signals and attack hippocampal neurons—damaging neural circuits and signaling. In this condition, with the gathering of immune cells and inflammatory signals, the hippocampus is said to be **inflamed**. In this state, the rate of mature hippocampal neuron growth is severely hindered from damage, which was indeed found with the RSD model mice.

After identifying that the RSD mice had inflamed hippocampi, researchers wanted to investigate whether targeting the inflammation could protect against memory impairment. Therefore, prior to starting the stress protocol, RSD mice were administered a common antibiotic, Minocycline. This drug broadly suppresses immune cells. On average, RSD mice performed better on memory tasks, and hippocampal slices revealed more mature hippocampal neurons and reduced inflammation.

Ultimately, the idea that chronic stress can affect brain function may not be a new one. However, the immune system has been underappreciated in its direct role in targeting focused regions of the brain related to memory and emotion following exposure to stressors. The fact that Minocycline, a common antibiotic, can reduce stress-related memory loss, supports the model that the immune system is intimately involved in cognitive function and memory[10]. So, while stress is unavoidable during finals week, try not to get sick, because you know what they say—a healthy immune system keeps the memory intact… ok, perhaps not a catchy phrase, but it can be worked on.

As the years go on the memory (what type?) fades

In the first grade, Carla* believed her biggest accomplishment was putting her engineering skills to use by creating a Velcro attachment for her grandpa's glasses. This way, he could keep his glasses on his shirt whenever he was done using them. Otherwise, odds were, he would leave them on a counter in the house somewhere and be unable to recollect where he kept them. Whenever Carla would find the glasses for him, her grandpa would take them and exasperatedly apologize. "My memory isn't what it used to be. Thanks kiddo."

While many people may relate to having a loved one whose memory just isn't as sharp as it used to be, researchers have identified that the same can be said about memory T cells over time. Turns out, dysregulation in immunological memory is not only triggered in autoimmune diseases or psychosocial stress, but is also a normal aspect of aging.

How? Well, interestingly, (and a bit of a disclaimer), all immune cells don't have to invade the brain by crossing a physical barrier. Everyone has a pool of memory T cells that are constantly lined up in certain areas of brain tissue. These T cells would be reactive to brain tissue, but they are well contained and regulated by the tissue cells surrounding them. However, as aging occurs, the regulation by

these tissue cells worsens, and more inflammatory proteins are produced by the memory T cells. These inflammatory proteins cause the increase in chemical signals that have been linked to cognitive decline[11].

Now, acknowledging that aging changes the brain environment seems obvious, so where do we go from here? How can we pick apart the brain environment to understand causes of age-related cognitive decline? Forewarning of deja vu, but another mouse model helped researchers start attacking these questions. Essentially, scientists examined the differences in the inflammatory protein production by memory T cells in brain tissue in both young and aged mice. Furthermore, to address memory decline, the researchers investigated levels of specific molecules that promote hippocampal neuron growth and signaling.

As suspected, memory T cells in aged mice produced higher levels of inflammatory proteins than the memory T cells in the young mice. Furthermore, aged mice had lower levels of hippocampal growth factors, which explains impaired cognitive memory[11].

So now that there is evidence demonstrating a difference in memory T cell function within the brain based on age, are there any therapeutic possibilities to reduce age-related cognitive decline? To explore this idea, the researchers transplanted memory T cells from aged mice into other identically aged mice that had impaired memory. Additionally, these aged mice receiving the transplant had all of their immune cells depleted. So, the transplanted memory T cells had to replicate in a new environment free of the influences of other immune cells. Then, researchers conducted spatial memory tasks and examined hippocampal tissue. Much to their astonishment, the transplanted aged mice had improved memory, and they also expressed higher levels of hippocampal growth cues! Now, we all know the itching question here: Why would aged memory T cells be able to restore memory impairment after being transplanted into identically aged mice that had no immune cells? Curiously, upon a closer look, researchers identified that the reason the transplant may have been so successful is because the sterile, immune cell-free environment encouraged the transplanted aged memory T cells to produce signals similar to those found in young mice[11]. So aged memory T cells are capable of reversing age-related cognitive decline if they can be "tricked" into thinking they are young again. Looks like the desire to be youthful has some potential therapeutic merit—down to the cellular level.

*character name of anecdote

Let's Get Natural

Let's bring the discussion back to the way beginning where cultural memory came up. A large part of what makes a community bond is, well…food. It's a vicious cycle: at every turn of a year, it feels as though society is entertaining a new diet trend, which is subsequently invalidated by research, and then the trend finds a new focus—and the cycle repeats. Turns out though, that some of these trending diets and food crazes may actually benefit and protect against memory decline! Specifically, multiple components found in natural foods possess anti-inflammatory properties, meaning that they help regulate the immune system to prevent inappropriate reactivity. By minimizing inflammation in the brain, these compounds have been implicated in protecting against memory loss.

One trend that has gained popularity in recent years is the ketogenic diet. Individuals on this diet follow a plan of consuming minimal carbohydrates and high amounts of fats. Because ketogenic diets have been acclaimed to provide health benefits, researchers sought to ask whether the ketogenic diet could protect against inflammation-mediated memory impairment. To test this idea, mice were fed a ketogenic diet and then immunized to mount an immune response. After conducting memory tasks, the mice

Berries on pxhere

on the ketogenic diet revealed higher scores than the immunized mice on a non-ketogenic diet[12].

While much has to be done to define an exact mechanism by how this diet may protect or enhance memory, the suggested link between highly fatty foods and memory is interesting to note.

Along similar lines, berries have long been praised for their anti-inflammatory properties, and it turns out that a specific compound found in these fruits, called anthocyanins, has neuroprotective effects. Using an Alzheimer's mouse model, researchers found that administering anthocyanins provided protection against memory decline[13]. So, funnily enough, the age-old adage from our parents that "eating our fruits and veggies is good for our health" holds true—and just *maybe*, the all-natural food crazes are not as crazy as we think.

***

From neurodegenerative diseases, to stress, to aging—immunological memory plays an important role in the cognitive memory dysfunction that often occurs in these various conditions. While science has a ways to go in the journey of untapping the power of the immune system, we are making way in understanding how the memory of our immune cells can be harnessed to prevent the attack of our own bodies on our brains and ultimately …our minds.

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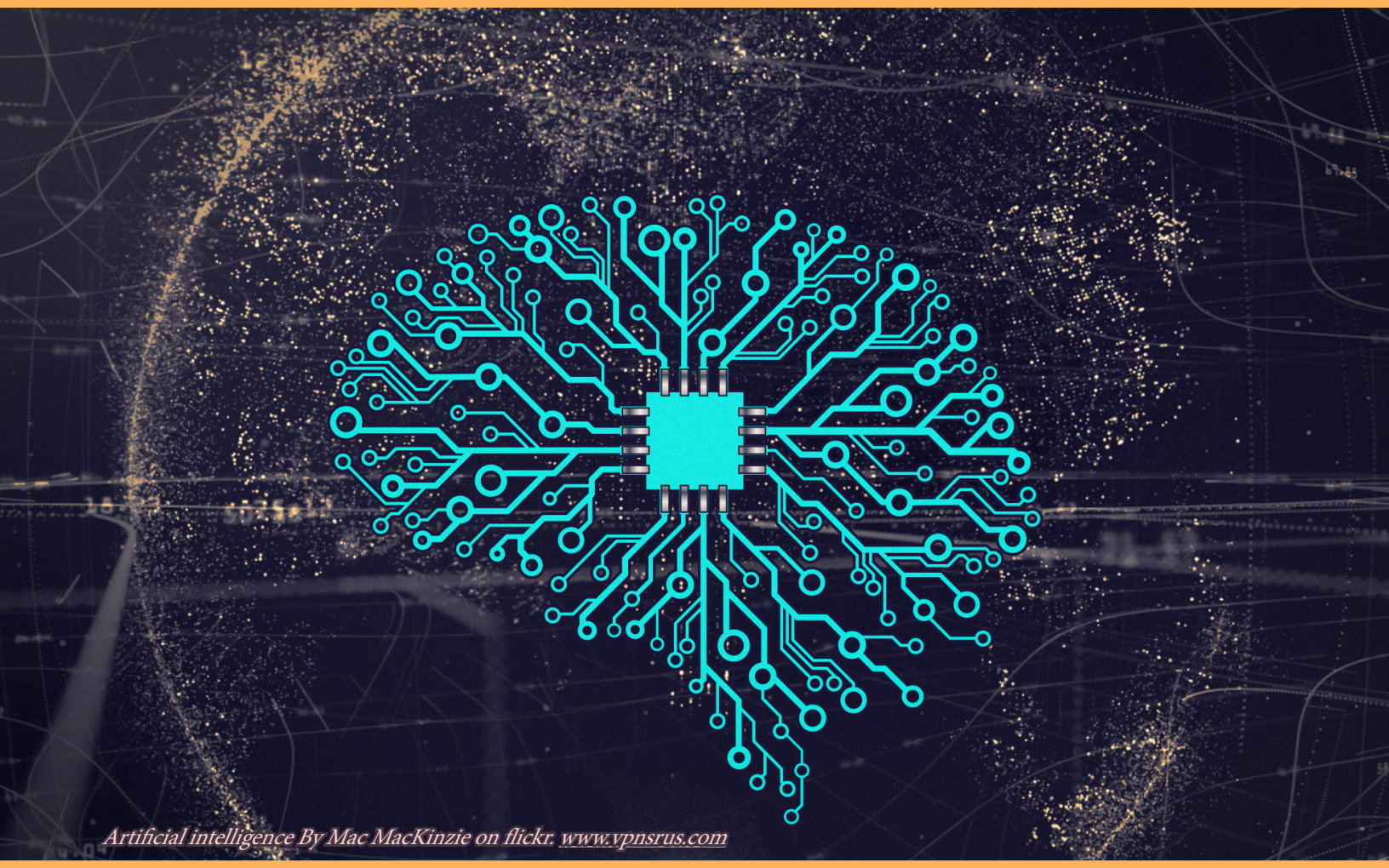
Retinal Ganglion Cell. Page from Images Formed in Darkness by Samantha Montoya

Decoding the Mind:

How Brain-Computer Interfaces Are Challenging What's Possible

By Ali Colmenares



Artificial intelligence By Mac MacKinzie on flickr. www.vpnsrus.com

Ian Burkhart was 19 when he was vacationing with friends off the coast of North Carolina. **A former athlete and self-described thrill-seeker, a single ill-fated cliff dive into the choppy waves below changed Burkhart's life forever.** Diagnostic tests would reveal that Burkhart had suffered a catastrophic cervical Spinal Cord Injury (SCI) that would leave him paralyzed from the chest down, unlikely to ever regain function of his hands or legs. That is until Burkhart was recruited by the NeuroLife Project to participate in an experimental treatment that, nearly 4 years later, has allowed him to use his hands to hold a glass, throw a ball, and even play video games[1]. Burkhart was able to perform these miraculous tasks thanks to a small device, implanted into his brain by a team of surgeons at Ohio State University Wexner Medical Center. When Burkhart thinks about moving his arm, the device decodes Burkhart's brain waves and sends the decodes messages to a specially designed arm cuff, which electrically stimulates muscles in his arm to create the desired movement[1]. The NeuroLife Project and dozens of similar projects around the country are integrating computing technology with the human brain to create Brain-

Computer Interfaces (BCI), direct communication pathways between the brain and some external computing device. These new communication pathways can and are being used to revolutionize the treatment landscape for millions of people worldwide with disabilities due to limb amputations, neurodegenerative diseases, and traumatic brain injuries, and may soon push the envelope of what the ordinary human brain is capable of.

The Electric Brain

How is Ian Burkhart's brain able to communicate his thoughts to a computer? The key to Brain-computer interface technology lies in the electrical properties of individual neurons and neuron-to-neuron communication. Neurons are the fundamental units that together, make up the complex neural networks that allow you to control your movements and experience consciousness. While scientists have known about the existence of neurons since the late 19th century, it wasn't until the 1950's that two scientists, Alan Hodgkin and Andrew Huxley, electrically stimulated a Squid giant axon to provide a conclusive answer for how neurons send communication signals: The Action Potential.

Put simply, an action potential describes the process by which a neuron transmits an electrical signal from the receiving end of a neuron (dendrites) through the cell body (soma) and along a single thin, long projection of the neuron known as the axon. Axons, which can measure anywhere from less than 1 millimeter to over a meter, are specially designed to quickly carry the electrical signal down the length of the axon. Once the signal reaches the end of the axon (the axon terminal) it triggers the release of chemical messengers known as neurotransmitters. The neurotransmitters attach to specialized proteins embedded on the surface of neighboring neurons and, depending on the types and number of neurotransmitters released may cause that neuron to fire an action potential and continue the cycle. Each action potential can be thought of as the transmission of a tiny piece of information that when combined with hundreds and thousands of other action potentials create the thoughts, sensations, and actions that make up our everyday experiences.

Scientific discovery of the action potential led to the creation and rapid growth of electrophysiology, the study of electrical properties of biological tissues. As action potentials move through the axon of a neuron, the electrical signal causes a measurable change in the flow of positive and negatively charged molecules like sodium and potassium across the cell surface. Using electrodes specially designed to measure this electrical activity produced during an action potential, researchers are able to record and stimulate neural networks in the brain.

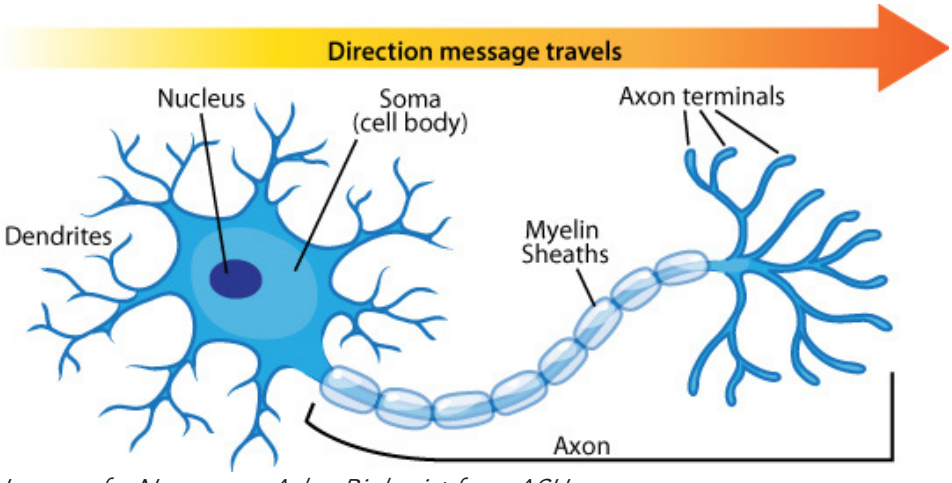


Image of a Neuron on Ask a Biologist from ASU

Recording the Brain

Different BCIs may employ different neuroimaging techniques to record and alter neural network activity in the brain. These techniques vary by scale (i.e. number of neurons being recorded), resolution (i.e. quality and precision of the recording), and invasiveness (i.e. whether the electrode recording device is implanted and if so how deep). The three most widely used techniques include electroencephalography (EEG), electrocorticography (ECoG), and local field potentials (LFP).

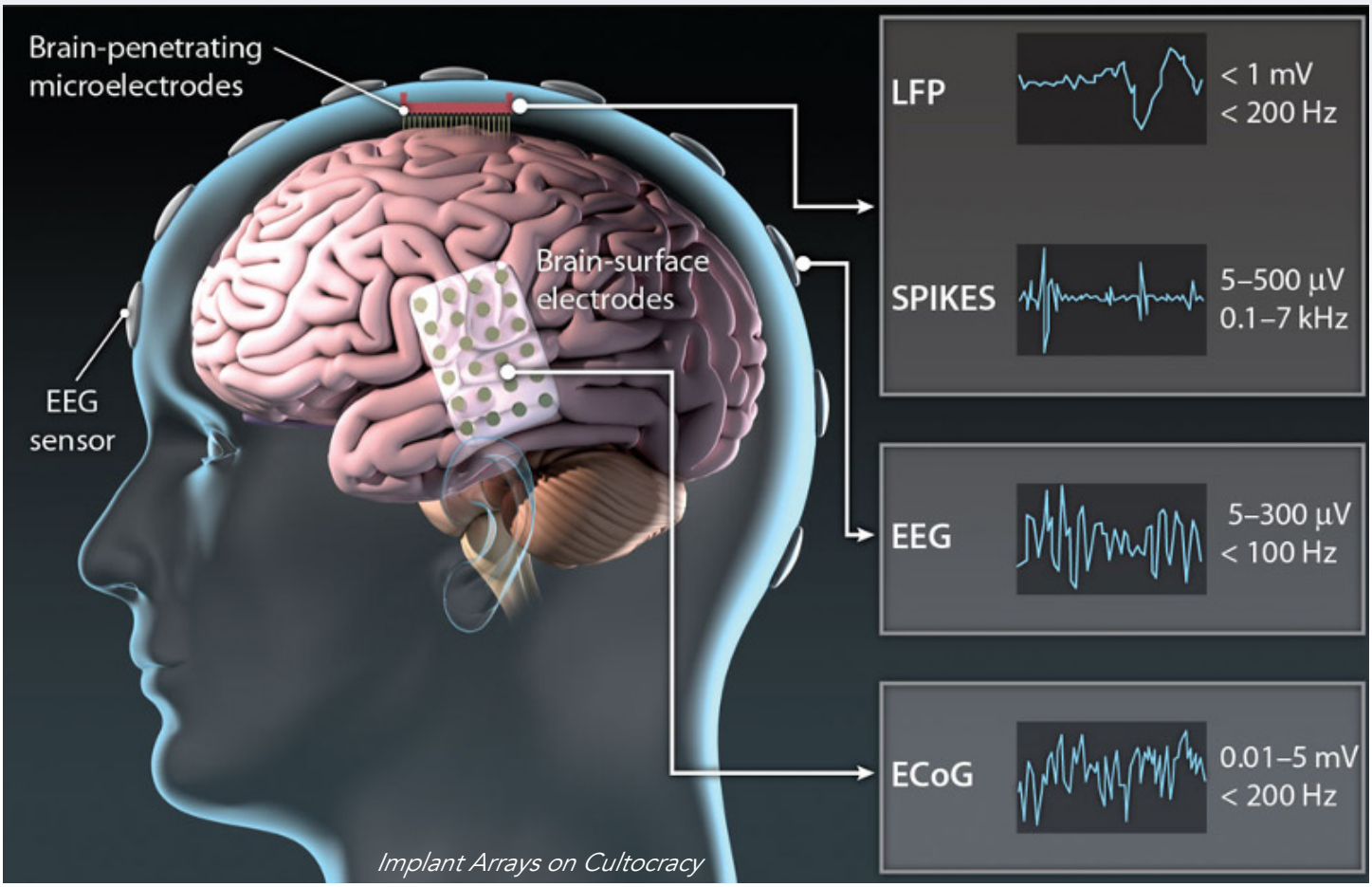
Developed during the 1920's, EEG is a noninvasive electrophysiological monitoring technique which uses a noninvasive head cap composed of multiple electrodes placed over an individual's scalp. The electrodes record electrical activity in different regions of the brain and researchers use the recordings to identify patterns of activity associated with various neurological events such as sleep cycles and seizures. EEG recordings can be decoded by BCI's with specially designed computer algorithms to perform simple computer activities and even control prosthetic limbs. However, because electrodes are placed on the scalp, current EEGs can only provide low resolution recordings of the upper layers of the brain[3]. Advanced BCI's with high precision often require higher resolution recordings collected using more invasive electrophysiological mon-

itoring techniques like ECoG and LFP.

ECoG recordings are gathered via thin, flexible electrode grids placed directly on the surface of the brain's cortex. These recordings have significantly better resolution than EEG recordings and can monitor a relatively large scale of neuronal activity. Historically, ECoG recordings have regularly been used by doctors to map the origin point of seizures in patients with severe epilepsy. In recent years, the use of ECoG to map brain activity has enable scientists to develop a deeper understanding of the patterns of neural activity associated with the planning and execution of voluntary limb movement.

The third and most invasive electrophysiological monitoring technique frequently used in BCIs is Local Field Potential, which utilizes microelectrode arrays to record the activity of precise regions of the brain with high resolution. Microelectrode arrays are composed of anywhere from tens to thousands of tiny needle electrodes arranged on a small grid that actually penetrates the brain's surface, with each electrode able to record the activity of a specific pattern of a few adjacent neurons by detecting changes in ion flow along the axons[3]. Once implanted into a patient's brain, the array can be used to create a closed-loop system between the patient's neuronal network and an external device like a computer or prosthetic.

When it comes to targeting neuronal networks for BCI research and development, scientists have tended to focus their attention on the brain's motor cortex. Deeply involved in planning and execution of voluntary movement, researchers have used microelectrode recordings of the motor cortex to observe, in real time, the specific patterns of motor cortex activation that occur as people plan, imagine, and perform various movements. These specific patterns of motor cortex activation can then be used to design computer algorithms that decode neural signals into software commands[2]. In effect, BCI algorithms circumvent the nerve damage caused by different neuromotor diseases and spinal cord injuries by creating a direct line of communication between the brain and an external computer or prosthetic. Over the past decades this technology has proved invaluable for the development of technologies that have revolutionized how scientists treat neuromuscular damage. Some current uses for therapeutic BCIs include facilitating communication, restore basic sensorimotor functioning, and improve prosthetic limb control.



Implant Arrays on Cultocracy

Restoring Communication

For individuals living with the rare neurological disorder Locked-In Syndrome, the complete loss of movement and speech capacity can leave them feeling trapped inside their own bodies. Fully alert and typically still able to hear and think normally, these are individuals left totally paralyzed due to some underlying neurological damage often caused by a severe stroke or disease like ALS. Since they are unable to move or speak, these individuals must instead rely on eye-coded communication, which requires caretakers to meticulously count blinks or eye movements which often limits communication to simple yes/no responses[4]. **Initial advancements in the BCI field towards linking the brain with technology provided a renewed hope to these individuals and their families that they might one day be able to more easily express their thoughts and feelings to caregivers or even control computer programs and prostheses.**

Today, thanks to the hard work of dedicated research groups, patients with Locked-in Syndrome have been able to communicate and interact with the external world in ways that once seemed impossible. In a study conducted by researchers at Brown University, two patients, one a man with Locked-in Syndrome due to a brain-stem stroke and the other a woman with paralysis due to advanced ALS, had their communication abilities significantly enhanced after having a 96-channel microelectrode array implanted into their brains by the researchers[4]. The patients could type messages and write emails using FlashSpeller, a typing software designed to be controlled using brain signals converted into software activity by a novel decoding algorithm uniquely calibrated to each patient brainwaves[4]. By personalizing the decoding software, the researchers were able to provide patients with a reliable BCI for everyday communication with family and caregivers.

Johnny Mathley and Modular Prosthetic Limb from US department of Defense

And while several BCIs have been developed to restore basic communication ability to individuals with Locked-in syndrome, most existing communication BCIs are limited to use with specialized software with low functionality. Seeking to develop a BCI that would expand user interface capabilities beyond simple communication, researchers from Stanford University and Brown University collaborated to produce BrainGate 2[5]. BrainGate 2 is a brain-implant system designed to enable paralyze patients to operate an unmodified Android tablet, using only their brainwaves[5]. The cutting-edge BCI utilizes recordings from microelectrode arrays implanted into the motor cortex, a region of the brain that controls voluntary movements. The recorded neural signals are processed in real time by a specialized decoding software which is able to translate brain activity into digital activity that allows patients to control a virtual mouse on the tablet screen. In their recently published study, the team reported that three research patients with tetraplegia were able to control common apps on a standard Android tablet[5]. Simply by imagining performing basic mouse commands like scrolling up and down or clicking, patients were able to type out messages, browse online, and even play a virtual keyboard using only their thoughts. Researchers hope that by designing BCI devices that can be paired with commercially available tablets and computers, they can increase the versatility and accessibility of BCIs offered to paralyzed patients.

Controlling Prosthetic Limbs

In 2005, 1.6 million people in the United States were living with the loss of a limb and most prosthetic limbs in use looked and functioned much like the prosthetic limbs of the early 1900's: hard, immobile, prostheses that offered little in the way of functionality

DARPA's Brain Initiative on CC

except for possibly a hook for grabbing[6]. In the last 20 years or so, however, the Defense Advanced Research Projects Agency (DARPA), a government agency, has provided funding that has paved the way for the development of prosthetics that integrate directly with the wearer's nervous system allowing for more intuitive control[7]. Their seminal device, the Modular Prosthetic Limb, has spent the last 10 years being developed by researchers and tested by a handful of patients like Johnny Matheny. In December of 2017, Matheny, a 63-year-old man who lost his arm during a battle with cancer in 2008, became the first individual to be given a modular prosthetic limb for real world testing[7]. The prosthetic, which attaches to a titanium joint surgically-implanted into his upper arm, is controlled using Mathney's brainwaves and has restored the ability for him perform most tasks associated with daily life. After nearly a year of pilot testing, Matheny has improved his control of the prosthetic to the point where he is currently teaching himself to play the piano[7].

Researchers' hopes for The Modular Prosthetic Limb and prosthetics go beyond improving prosthetic dexterity and patient controllability. The ultimate goal for prosthetic devices is to function as close to a natural limb as technology will permit. For researchers, that means designing BCI's that not only send command signals to the prosthetic limb, but also transmit sensory information from the prosthetic limb back to the brain. Incorporating sensory feedback into BCI's would give patients the ability to feel sensations like pressure and temperature using sensors placed on the prosthetic device and would ultimately facilitate better control of the prosthesis. Restoring sensory capabilities to amputees has long been a major hurdle for researchers, with most attempts failing to achieve feasibility beyond laboratory settings[8]. One of the first major breakthroughs towards the development of a neural interface that could provide sensory feedback came in 2005, when a group of researchers from The University of Utah showed for the first time that the severed nerves of amputees can still retain function following limb amputation[9]. By stimulating the residual nerves using implanted electrodes, the researchers were able to evoke touch sensations perceived to have come from the amputated hand or arm.

Since that discovery, scientists have worked to incorporate sensory feedback into prosthetic technology by targeting patient's residual nerves. Recently, a DARPA team further demonstrated the revolutionary capabilities of the Modular Prosthetic Limb in a 2018 study published in the Journal Frontiers in Neurology[10]. The patient, a 33-year-old veteran who lost his hand and forearm in the line of duty following an I.E.D explosion, was able to differentiate between hard and soft objects thanks to vibrotactile sensors on the prosthetic that provided sensory feedback[10]. This noninvasive sensory feedback system conveys simple force, vibration, and temperature information by physically stimulating the skin in contact with the prosthetic. In the coming years, researchers aim to provide patients with more complex and intuitive sensory feedback by developing neural implants and algorithms that can process and deliver data transmitted from sensors on the prosthetic directly to the sensory regions of the brain.

A Look to the Future

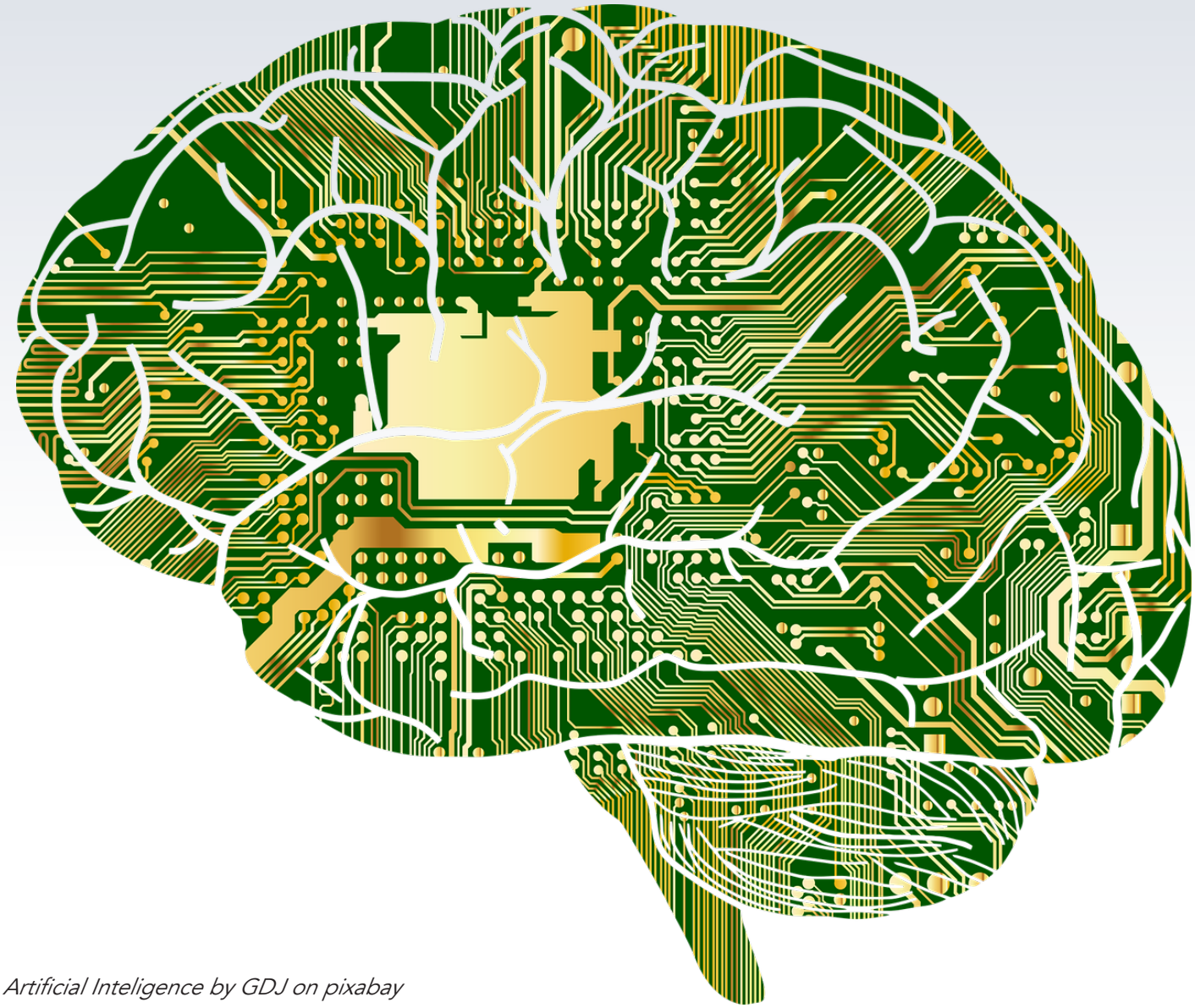
Restoring Severe Memory Loss?

As researchers continue to improve upon BCIs that restore patients sensorimotor functioning, a few ambitious teams around the country are attempting to design BCI and neural implants that would actually improve an individual's memory functioning. For the millions of people living with brain damage caused by Alzheimer's Disease, a stroke, or other forms of brain injury, damage to the neural networks involved in memory often cause significant deficits in memory formation and recall ability. By breaking

the code for long-term memory formation, researchers like Dr. Theodore Berger, a neuroscientist and biomedical engineer at the University of Southern California, hopes to create neural implants with algorithms that can help individuals with severe memory deficits form long-term memories.

In 2012 study, Berger and his team broke major ground in their endeavor to crack the memory code by designing and testing a neuroprosthesis that proved to be the first successful application of a BCI in primates to record and restore neural activity associated with normal performance on a working memory task[11]. First, the researchers used the neural recordings to create a mathematical model of brain activity during working memory activation. Then, the monkeys were administered a drug designed to disrupt the primates cognitive processing and task performance before finally the researchers used the developed model to stimulate the task-related regions of the brain[11]. The stimulation was successfully able to restore working memory functioning to the drugged monkeys and highlight the potential for BCI devices to restore complex cognitive functioning. In an interview with the MIT Technology Review, Berger expressed his vision for the future of BCIs in the treatment of memory deficits caused by brain damage:

> "I do think we're going to find a model that's pretty good for a lot of conditions and maybe most conditions," Berger predicted[11]. "The goal is to improve the quality of life for somebody who has a severe memory deficit. If I can give them the ability to form new long-term memories for half the conditions that most people live in, I'll be happy as hell, and so will be most patients."



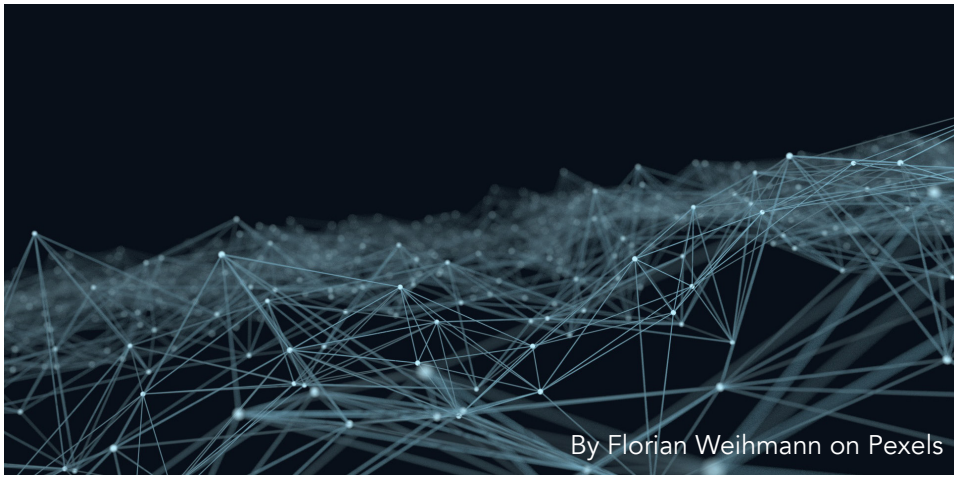
Artificial Inteligence by GDJ on pixabay

Meanwhile in another DARPA funded endeavor, The Restoring Active Memory (RAM) program, unpublished preliminary findings have already provided compelling evidence that electrode implants can be used to improve human memory formation and recall. The RAM program recruited epileptic patients who, as part of their epilepsy treatment, had microelectrode arrays implanted into their hippocampus, a region of the brain deeply involved in memory formation and storage[12]. By delivering microelectrode stimulation to patients' hippocampi while they performed a simple memory task—recalling a list of 12 random common objects—researchers were able to significantly improve patient memory performance[12]. While improving healthy patients' memory recall for a short list of words may seem like a small step towards restoring memory functioning in individuals with severe and complex brain damage, the exponential rate at which this technology has already advanced leads the DARPA's Director of Biological Technologies Office to imagine a not too distant future where memory implants can be used to deliver targeted neural stimulation that completely restores normal memory functioning to the more than 270,000 service members diagnosed with traumatic brain injuries since 2001.

Aiding or Enhancing:
Where should we draw the line?

Up to now, the majority of BCI research and development has focused on restoring function and independence to the millions of disabled individuals worldwide. However, as scientists continue to advance our understanding of the human brain, BCIs will expand to offer technologies that go beyond simply restoring lost function to disabled individuals. Whether it be improving memory capacity, increasing focus, or enhancing problem-solving ability, the development of BCIs that will serve to augment an individual's neural functioning will force governments and societies around the word to address some serious legal and ethical questions. Should neural enhancements be widely available and considered a personal choice, similar to cosmetic procedures? Or should they be guaranteed by governments as a right? Will BCIs lead to the formation of a new class system between the neuro-enhanced and neurotypical individuals? Whose responsibility will it be to make sure that neural enhancements and other BCI's are not used to increase suffering and inequality around the world?

No doubt the concerns regarding the use and regulation BCI's are going to lead some to call for heavy restrictions on these technologies. After all, media portrayals of BCI's in movies like Robocop have often created depictions of technology stripping individuals of part of their humanity. And while BCI technology is still a number of critical scientific breakthroughs away from anything closely resembling cyborg technology, the inevitably of scientific breakthrough makes this an issue that is better addressed sooner rather than later. During his administration, former president Barack Obama formed the Presidential Commission for the Study of Bioethical Issues, announcing that "As our nation invests in science and innovation and pursues advances in biomedical research and health care, it is imperative that we do so in a responsible manner"[13]. In May 2016, the Commission published a report that provided recommendations to encourage informed and just policy-making in bioethics, centered around the importance of open dialogue between experts and the public[13]. Unfortunately, these recommendations have largely been ignored by the Trump administration, which has failed to establish its own bioethics commission and has repeatedly sought to limit funding to national science initiatives. Regardless of whether our leaders choose to address the changing landscape of bioethics, breakthroughs in biotechnologies will carry increasingly profound and complex policy implications. Therefore, in the absence of political will from our leaders, we must all strive to think critically about how we choose allow BCIs to evolve and how they might fundamental and irrevocably alter the human experience at the individual, societal and global scale.



By Florian Weihmann on Pexels

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What Meditation Does to Your Brain

By Samantha Montoya

Meditation, or various forms of calming the emotions through focused thought, has been practiced since antiquity. But why is this practice so popular? And how can sitting still and concentrating physically change our brains? It turns out that the practice of meditation can cause beneficial changes in mood, decrease the natural shrinking of the brain that occurs with aging, increase levels of neurotransmitters associated with peace and well-being, alter the connections between different brain regions, and even increase the ability to fight off viruses.

What is Meditation?
A Brief History

Meditation is a means of relaxing the mind and body to find a state of calm. The English word meditation comes from the Latin meditatum, which means to "ponder"[1]. Meditation often involves clearing the mind by focusing on a mental image, saying, object, or the body. Unlike resting, meditation is an *active* process, by which the meditator concentrates on relaxation and peacefulness rather than letting their minds wander. Mediators generally sit cross-legged on the floor or on a cushion with the hands resting on the knees. There are also meditative forms that incorporate yoga and other physical movements/stances, but the lotus position is one of the most common and basic meditative pose, and is the one I have chosen to focus on in this article.

The practice of meditation is difficult to track because it was largely passed down as an oral tradition, however meditation may have been part of shamanistic practices to heal the sick as early as 200,000 years ago[1]. The first documentation of meditation is from cave paintings in India dating back to around 5,000 BCE, which depict human figures in meditative positions[1]. The first written description of meditation is from when the Vedas, or ancient Hindu scriptures, were transcribed onto paper. Hindu meditation was also adopted by the Buddha around 600 BCE, which spread meditative practice with the expansion of Buddhism to northeastern Asia[1]. Meditation was also practiced in Jainism, Taoism, and Confucianism in the East, and many forms of practice began to branch off[1]. While most of us associate meditation with Eastern cultures, meditation began to spread west as early as 330 BCE, when Greek philosophers adopted meditative practices introduced by yogis and sages from India[1]. This was largely made possible by Alexander the Great's military voyages to India in 327 BCE.

With the rise of Christianity in the West, meditation became less prominent, although some forms of prayer, such as the Hesycham Christian tradition employed meditation techniques[1]. Jewish sects also developed their own forms of mediation, such as

Avalokiteśvara sitting in meditation from CC

Balance by Samantha Montoya

the Kabbalah tradition[1]. Meditation became an intellectual topic rather than just a spiritual practice in the 1700's when many Eastern texts were translated into European languages. In the United States, mediation started to gain popularity in the 1800s, and scientific studies of mediation first began in the 1930s. In present day, meditation is increasingly being adopted by western cultures to deal with the amplified stress associated with the modernized world. Given meditation's long history, it is not surprising that there are a vast number of forms of meditation, but I will limit this article to consider the science behind meditation that is practiced without movement—simply sitting still and engaging the mind.

Evolution, Stress, and the Brain:

Why should we meditate?

Unfortunately, the very mechanisms that we evolved to stay alive continue to cause stress in the absence of the life-threatening concerns that plagued our ancestors. In order to survive, all animals, including us, attempt to maintain equilibrium, or a state of balance. For example, we avoid excess heat or cold by sweating or shivering. Our brains also help us preserve equilibrium by sending off "alarms" whenever the body perceives a threat. For example, if you see a centipede crawling up to your feet, your brain will probably send you a signal to get away from the centipede as quickly as possible. A brain network called the limbic system helps initiate the fight-or-flight reaction when we are potentially in danger, while the prefrontal cortex inhibits arousal and calms us[2]. Too much of either is detrimental, but a balance between the two is crucial to survival.

Our brains have the incredible capacity to physically change in response to experience; without this ability, we wouldn't be able to learn from our mistakes. If you eat a red berry in the woods and it makes you sick, you need to be able to learn not to eat those particular red berries in the future. The brain is constantly adapting to our experiences on molecular, cellular, and even structural levels. This means that the activities we engage in have the capacity to change our brains, and ultimately, our perceptions. A famous example of this is the enlargement of the hippocampus—a region highly involved in memory formation—in London taxi drivers. This experiment predated the GPS, meaning that London cabbies had to memorize over 60,000 streets in a six-mile radius[2]! The amount of memories that these taxi drivers made and retrieved on a daily basis required more brain matter, and their hippocampi expanded to accommodate those demands.

The flexibility of the brain helps us learn to avoid or accept opportunities. Regrettably, the brain is much more sensitive to negative experiences than to positive ones[2]. For example, fear and unpleasant experiences teach us to avoid negative consequences with greater priority than seeking out opportunities. We also recall negative events more easily than positive ones, which can be detrimental to our relationships and mental health. While we can see how this was an evolutionary benefit,

A Short Guided Meditation

Sit on a cushion with your legs crossed, or in a chair if that is more comfortable. Keep your back straight, and close your eyes. Bring your awareness to your body, starting from the feet all the way to the top of your head. Try to relax all your muscles as you think about each part of your body, yet keep your back, neck and head tall and strong. Go as slowly as you need, and return to tense areas if necessary. Now focus on your breathing. Take deep, even breaths with your diaphragm rather than your chest. This helps activate the parasympathetic nervous system, which will help calm you. Focus on the breathing, and as thoughts pop into your head, let them drift away. For example, when your mind starts wandering to the things you need to get done, or a pain in your back, try not to react to the thoughts and instead let them pass. Return your focus to your breath when you notice your thoughts drifting. Be patient with yourself and don't become frustrated if you have a difficult time at first. Meditation takes lots of practice. Eventually, it will allow you to notice when you have emotional reactions to inner thoughts, and you can practice letting go of those emotions as well. With practice, you can carry into daily life as well, beyond the practice of meditation.

Meditation Tip:

When you're stressed, try picturing a place where you feel calm and happy. Pick a place that you can recall well and conjure the image of that place in your mind. Focus on the details as you scan the scene. More than fifty percent of the surface layer of the human cortex, or the outer layer of the brain, is devoted to processing vision[2]. This dedication to vision can be used to your benefit; concentrating on visual imagery can help silence verbal thoughts.

it makes non-life threatening negative events, such as a fight with a family member, more memorable than the time they made you dinner when you were sick. Most of the worries we have about the future and past are due to our internal thoughts. A region called the **superior prefrontal cortex** is responsible for playing tiny movies in our heads. It reenacts past events and allows us to simulate future events[2]. It's clear how this was an evolutionary advantage as it helped our ancestors determine the best course of action to take in situations that might arise, but it can also cause considerable stress concerning affairs that haven't even happened! Visualizing events takes us out of the present moment, heightens our expectations to unattainable heights, and replays painful events, thus strengthening the connections that are formed from bad experiences[2].

So that's depressing. Luckily, the silver lining is that the flexibility of our brains means that we can also train ourselves to create more positive associations and physically change our brains just through practice.

A Mood Boost Without Moving

One of the primary uses of meditation today is stress reduction, but how much better is meditation than simply taking a break? Dr. Elissa Epel, at the University of California in San Francisco, set out to answer precisely this question. Her lab found that meditating reduces stress more than vacation[3]. Participants were taken to a resort to relax for a week (sign me up!). A group of the participants were taught meditation, and engaged in daily practice during their week of vacation. Dr. Epel found that the weeklong relaxing vacation alone reduced depression and stress by the end of the week, but adding meditation reduced stress and depression for a longer period of time. The novice meditators showed improvements ten weeks after the vacation, while the non-meditators' anxiety and depression scores returned to the levels they were at prior to the vacation[3].

The use of meditation as a treatment for psychological distress is not a new concept, however. Psychologists adopted meditation around the 1970s as a means of alleviating anxiety and depression. It is often used in combination with therapy to provide patients with mechanisms that help them cope with stress. These methods allow the patients to feel a sense of agency to combat the common feelings of loss of emotional control that accompany depression and anxiety[4]. Antidepressants are often a necessary ingredient in recovery because they offset chemical imbalances in neurotransmitters. Unfortunately, only about 50-60 percent of patients respond to their first medication, and some

Woman Meditating at Sunset on CC

individuals are unable to find any effective antidepressants. For this reason, psychiatrists are investigating other means of helping anxiety and depression, one of which is meditation. In 2017, a team of researchers at the University of Pennsylvania found that meditation is helpful in treating major depression when antidepressants are ineffective[4]. They gathered a group of people who had tried at least two antidepressants without adequate response, and taught half of them a breathing-based meditation. Those that meditated had smaller depression scores, while those who did not showed no improvement. Importantly, the introduction of the meditation had a high completion rate, and participants seemed genuinely interested in trying the new technique, which was vital to its success[4].

In addition to aiding in the recovery of major depression, meditation can reduce loneliness[5]. Loneliness is a predictor of morbidity, mortality, cardiovascular disease, and Alzheimer's disease in older adults. Despite the fact that meditation is largely an individual activity, loneliness scores in elderly adults decreased with the addition of Mindfulness-Based Stress Reduction meditation, which is a standard meditation technique that was implemented by psychologists in the 1970s. Remarkably, meditation also changed the immune response in these elderly adults; there were fewer inflammation markers in their blood samples compared to elderly adults who did not engage in meditation[5]. Evidence suggests that loneliness activates an inflammatory response in the body, which could be due to the social stress induced by feeling alone. Thus meditation can have a positive effect on your physical health in addition to mental health.

Meditation Every Day Keeps the Doctor Away

How can meditation make you less likely to fall ill? In addition to the study above, a number of recent studies have begun to uncover evidence that meditation increases immunity to illness. The immune system is an incredibly complex defense system against viruses and sickness, but it is also highly subject to stress-induced changes. You may have noticed that at highly stressful times of year, you are more likely to get sick, and research on the link between stress and the immune system has exploded since the 1980s. One way that we can look at alterations in immune response is to measure changes in gene expression, or how much a gene is being used as a template to make materials for the body. Genes can be turned on and off, or **transcribed**, in varying levels depending on the necessities of the system. This adaptability is vital to saving energy and resources. Our moment-to-moment experiences and bodily needs alter gene expression rapidly. Therefore, any action we engage in has the potential to change the amount of gene transcription taking place. In experienced meditators, levels of gene expression indicate an overall increase in the production of compounds associated with energy and metabolism by the end of a twenty-minute meditation[6]. They also had decreased production of compounds that cause apoptosis, or programmed cell death.

Meditation's ability to alter immune function likely has to do with the link between stress and inflammation. When the body senses a potentially dangerous stimulus, it responds by producing a short-term inflammatory response, but long-term stress can lead to many detrimental health problems. For example, chronic stress can cause thinning of grey matter (the region of your brain where neurons connect) as well as major inflammation at the cellular level. Prolonged cellular inflammation is a predictor of cancer, asthma, neurodegenerative disease, cardiovascular disease, arthritis, and psychiatric disorders such as depression and post-traumatic stress disorder (PTSD)[6]. Unfortunately, prolonged stress also diminishes the production of antibodies that fight infection, leaving you more at risk to fall ill[6]. Thus, meditation's ability to relax the body reduces stress, and therefore reduces the demands on the immune system. Of course, it is possible that those prone to meditation are more likely to attend to their overall health, and therefore their immune systems could be improved due to other factors of a healthy lifestyle.

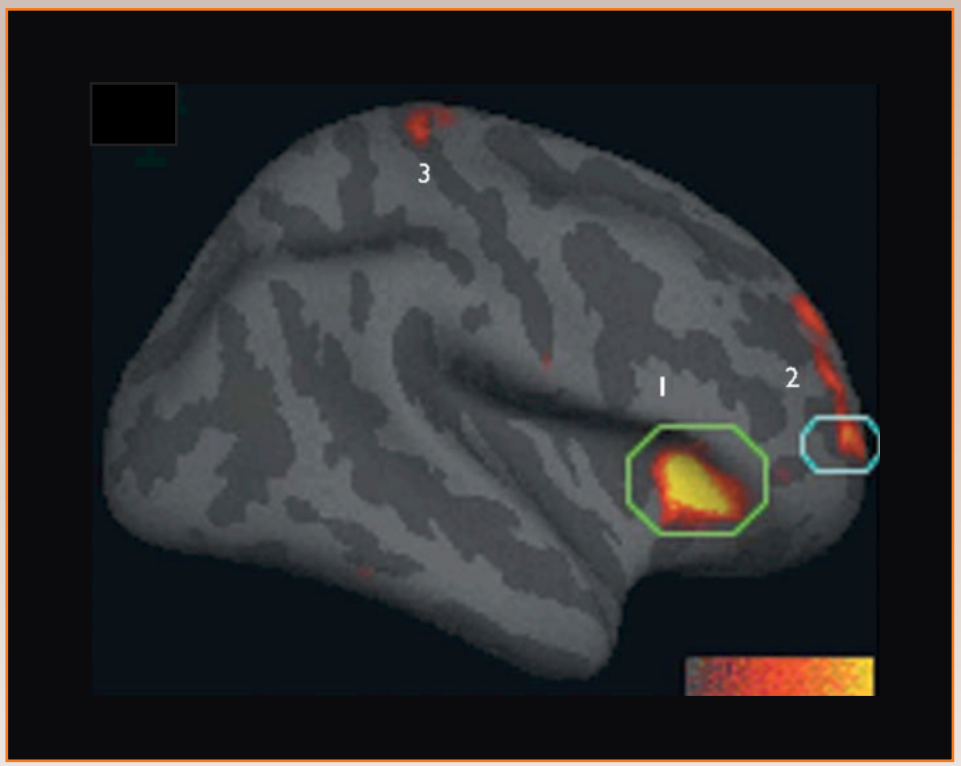
However, even short-term meditation has the ability

Meditation Anecdote:

Slowed respiration rate increases with meditation practice. The change in respiration rate between the beginning and six minutes into meditation can predict how many years someone has practiced meditation [6].

Tip:

Try taking as deep and slow a breath as possible, then relax as you exhale. This stimulates the parasympathetic nervous system, which facilitates relaxation.



A map showing regions that were significantly thicker in long-term meditators [8]. This indicates that there are more connections here compared to the average person.

to increase immune function. In a recent study, participants were vaccinated with influenza, and blood samples allowed the researchers to count the number of antibodies that formed in response[7]. Half of the participants were taught meditation, lead in an hourly practice every day, and given a three hour-class every week. The participants who meditated had significantly more antibodies, indicating that meditation either increased immune function, or sped up the process of forming defenses against the vaccine[7]. Together, these long-term and short-term studies provide evidence that meditation can be beneficial to your immune system.

As a (grey) Matter of Fact, Meditation Changes your Anatomy

When most people picture a brain, they are actually only picturing the outer, highly convoluted layer, called the cortex. The cortex allows us to adapt to situations in unique ways beyond automatic reflexes and responses. As we age, the cortex decreases in thickness—our brains shrink (sorry). While this is a natural effect of aging, recent evidence suggests that meditation helps mitigate age-related cortical thinning. Experienced meditators did not demonstrate age-related cortical thinning in the frontal cortex compared to average adults around the same age[8]. Interestingly, the meditators also had increased cortical thickness in the right anterior insula, which is associated with **interoception**, or a sense of the body's internal state[8]. If you think back to the guided meditation, focusing on the internal state of the body is one of the key ways of distracting you from your own thoughts. So it makes sense that the anterior insula would grow in response to increased use — just as with the London taxi driver example, the more you engage part of your brain, the more synapses form there, leading to observable changes in thickness over time.

In addition to changes in thickness, the brain adapts by altering connectivity between regions that specialize in specific tasks. One such region is the "**Default Mode Network**", which is a web of brain regions that activate when we think about ourselves. When we aren't focusing on a specific task, our thoughts almost always turn to ourselves —our past, or thoughts about the future. The automatic setting of our brain is a bit narcissistic, and quieting these thoughts can prove difficult. Practiced meditators have increased connectivity between the default mode network and the anterior insula, a region that is known to activate during present moment awareness and sensation of internal states[9]. The right anterior insula is also important in switching attention from mind wandering to a state of focus[9]. The anterior insula could therefore help quiet the default mode network by focusing on the present moment, maintaining attention, and sensing the body.

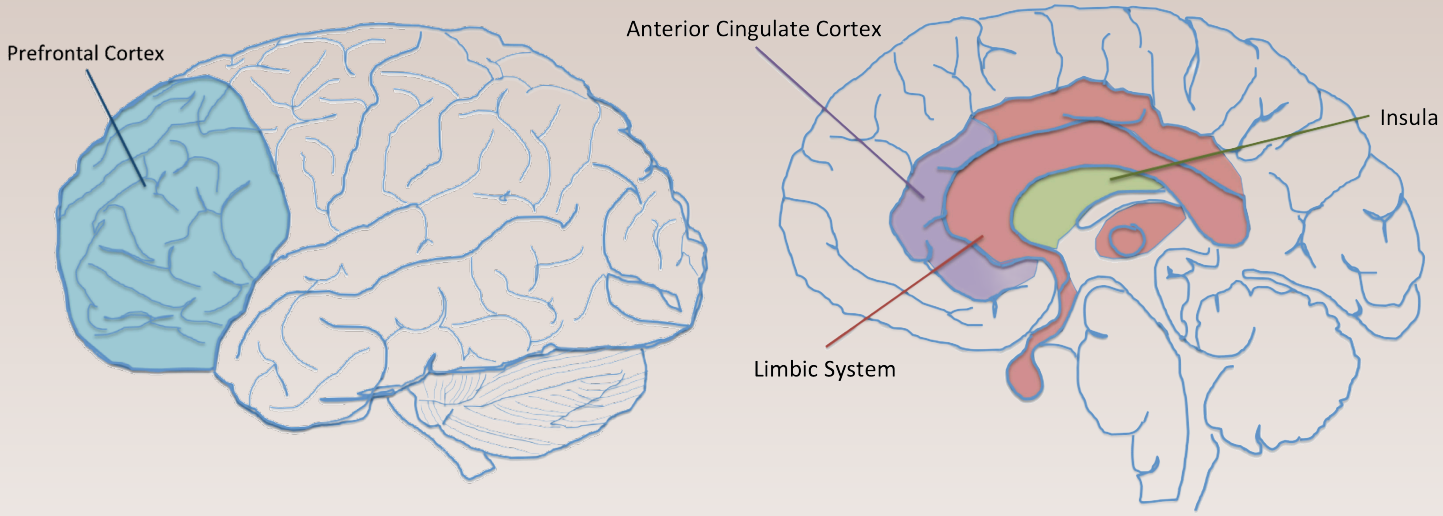
Increased connectivity between the anterior insula and

Meditation Tip:

Clearing your mind can seem incredibly difficult because of "mind wandering". When you notice a thought cross your mind, it is easy to become frustrated. Mind wandering is natural; let go of the thought and don't become frustrated when thoughts arise. Picturing a leaf floating down a river can be a helpful means of being at peace with wandering thoughts during meditation.

Parts of the Brain Involved in Meditation

Prefrontal Cortex – a logical brain region that creates plans and directs actions, part of the Default Mode Network
Anterior cingulate cortex – integrates plans with feelings, part of the Default Mode Network
Insula – senses internal body sensations and promotes empathy
Limbic System – involved in emotion and desires



Illustrated by Samantha Montoya

the default mode network may be a means of inhibiting our self-absorbed tendencies. So we would expect to see decreased activity in regions of the Default Mode Network during meditation. A number of studies have found exactly that. Long-term meditators have smaller activation in the Default Mode Network[10]. Interestingly, this finding isn't limited to the act of meditation; the experienced meditators had decreased default mode network activation at rest, or when specifically told not to meditate[10]. This suggests that engaging in meditation can help quiet worrisome thoughts about the self, even when not actively practicing meditation!

Meditation experience is also linked to decreased connectivity to primary regions of the Default Mode Network such as the anterior cingulate cortex, which integrates emotional and rational regions of the brain[10]. The meditators had greater connectivity to the orbitofrontal cortex as well, which is a region known to deal with body awareness[10]. In summary, increased meditation experience is correlated with greater connections to regions of the brain that control attention and decreased connections to the self-centered areas of the brain.

While meditation makes changes to the anatomy of the brain, what actually happens during meditation has a huge influence on the current state of mind, and can induce long-lasting anatomical changes. During meditation, Buddhist monks have heightened activity in the frontal areas, which are largely connected with attention and logic[11]. Brainwave recordings show that there is specifically more activity on the left hemisphere, which correlates with feelings of positivity[7]. It is thought that training the frontal left hemisphere to be more active could allow meditators to recover from negative experiences more quickly[7].

Neurochemistry
Keeping an "Ion" Your Inner Self

The balance of neurotransmitters and other chemicals in the brain has a profound affect on our behavior and our experiences. This is why medication that alters neurotransmitter levels is one of the

Meditation Tip:

Quieting verbal thoughts can also be achieved by distracting verbal regions of the brain. This may be the reason that mantras are a common meditation technique. Try choosing a short, positive phrase and repeating it to yourself internally.

primary means of treating disorders. Our actions can also have an affect on how neurotransmitters are released. Meditation has an effect on both increased and decreased brain activity through chemicals that excite and inhibit signals from one neuron to the next.

One of the inhibitory neurotransmitters affected by meditation is called GABA. GABA almost always decreases the chances that a neuron will fire and it therefore has the ability to quiet certain brain regions and functions. Overall, meditators have greater brain inhibition due to GABA compared to non-meditators across all brain regions[12]. This is particularly interesting because increased GABA inhibition is known to help regulate emotions and increase cognitive performance[12].

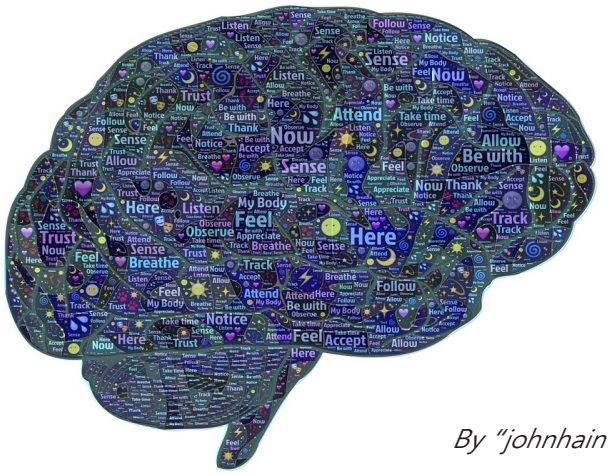
Meditation also alters neurotransmitters that tend to be excitatory, such as serotonin. Serotonin levels are linked to mood, sleep, and hunger, with increased serotonin generally contributing to positive affect. For this reason, most antidepressants increase serotonin to elevate mood. These alterations that result from meditation in serotonin don't require years of meditation practice either — a recent study on school students showed that introducing meditation reduced stress and increased serotonin[13]. The students collected urine samples throughout the day during for a week (this seems less fun to participate in than the vacation study, but *spoiler alert*—meditation decreased stress), which were used to measure the levels of chemical markers of stress[13]. 5HIAA, a precursor for serotonin, was elevated in the students who meditated[13]. The compound reflects the amount of serotonin that is being produced by the body[13]. As expected, stress and depression were lower in the students engaged in meditation[13].

Another neurotransmitter that plays a role in meditation is dopamine. Dopamine has a variety of functions in the brain, including the feeling of reward as well as controlling our body movements. The brain region where dopamine is released determines which of these roles is enacted. For example, dopamine in a region called the basal ganglia deals with voluntary movement. Individuals with Parkinson's have too little dopaminergic activation in the amygdala, while too much dopamine release in this region can cause involuntary movements as seen in Tourette's syndrome. Interestingly, meditation increased dopamine release by 65% in the ventral striatum, which is thought to result in reduced readiness for action[14]. Thus, meditation may relax the body through the release of dopamine[14]. The ventral striatum also receives information from emotional brain centers, and is vital to the reward system, which could explain the feeling of positivity and joy that come from meditation[14].

Going Forward

As research of meditation progresses, there are a number of questions that still need to be addressed. First of all, in many meditation studies, trained meditation practitioners are compared to a group of controls. The differences between the brains and behaviors of these individuals could be due to meditation, or the brain differences may have made these people more likely to pursue meditation. For these reasons, it is difficult to tease apart the benefits of meditation from a general mindset that could draw certain people to meditation more than others. Additionally, it is difficult to include a "placebo" effect in these studies—the participants knew whether or not they were meditating, which could have factored into the results.

Nonetheless, these studies show that there are numerous benefits from engaging in meditation. The attention required to suppress self-centered thoughts and focus on inner-body-awareness can help us learn how to decrease worry in daily life. Meditation helps us take time out of the day to focus on the present moment, relax the body, and recharge. The active process of relaxing helps decrease stress, which has a plethora of benefits including increased immunity, improving mood, decreased loneliness, and recovering from negative experience. So the next time you are feeling stressed, try one of these meditation techniques, and remember that you have the power to change your brain for the better!



By "johnhain" on pixabay

Serotonin Projections Embroidery by Samantha Montoya

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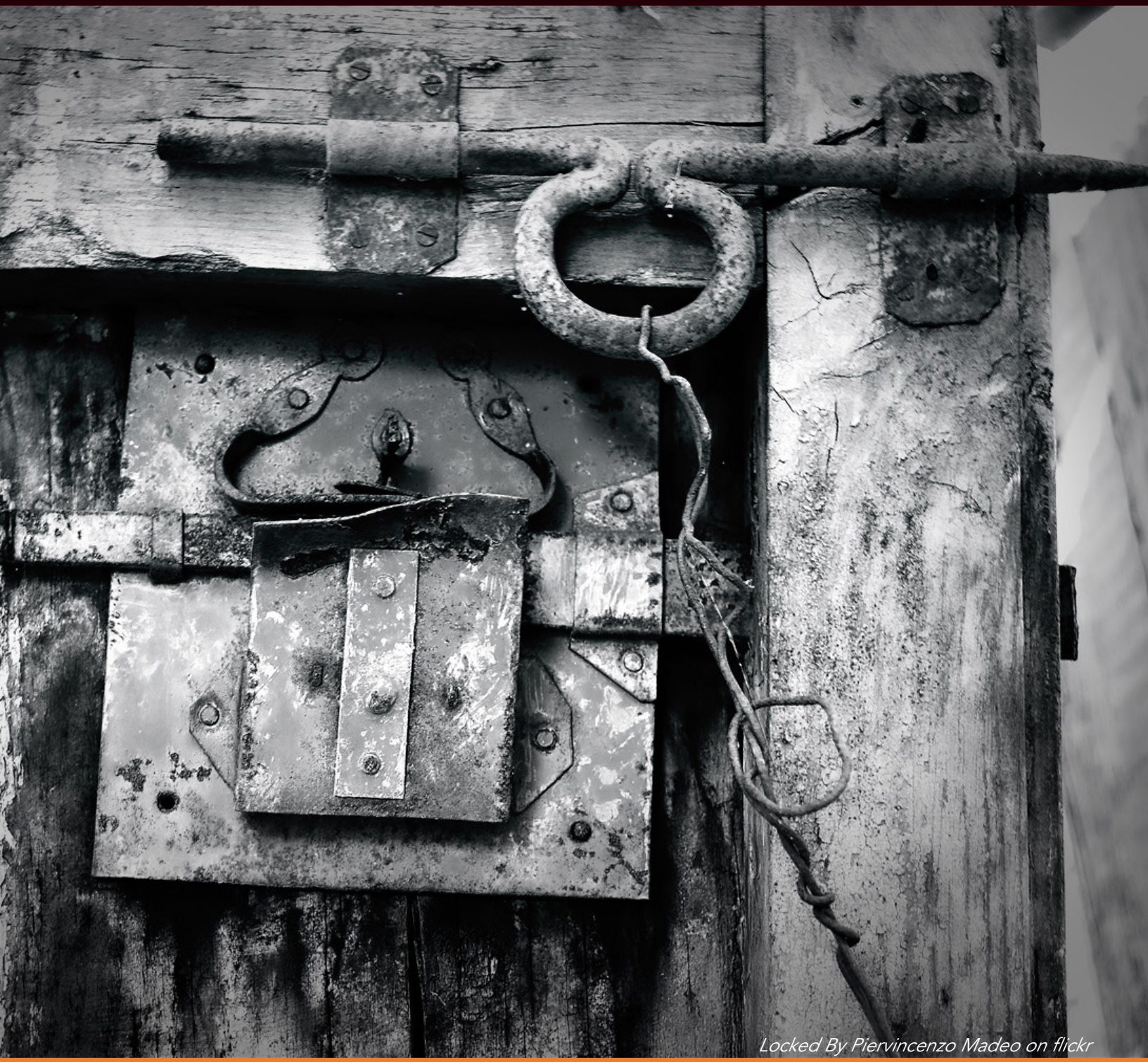
Yucca in the Snow by Samantha Montoya



Locked By Piervincenzo Madeo on flickr

Conscious and Paralyzed

The Story of Locked-In Syndrome

By Quinn Harrigan

What is Locked-In Syndrome?

What is merely a nightmare for some is a lifelong reality for others: following a critical brain injury, some people suffer from Locked-In Syndrome, a condition in which the individual cannot utter a sound or move a muscle. One individual living with this locked-in sensation has described his experience, saying,

"All my senses are normal, if not enhanced (sight and hearing). I'm just left trapped inside this body"[1]

The result of a very specific type of brain injury, Locked-In Syndrome is an example of an astonishing outcome that results from the intricacies of neural organization, and therefore is of extreme importance and intrigue.

Locked-in Syndrome (LIS) is a medical condition in which an individual loses the ability to move the body voluntarily. The immobility component of this condition's presentation is identical to that expressed in a vegetative state (VS), a minimally conscious state (MCS), or an unresponsive wakefulness state (UWS) (Figure 1). However, unlike these states, in which the patients lack cognitive brain function, patients with LIS are fully conscious; all of their thoughts and feelings are the same as any other healthy individual's. Their senses are also intact, as they are able to perceive touch and pain. Thus, an individual with LIS is fundamentally a healthy individual who is totally paralyzed. LIS has three subtypes: classical, incomplete, and complete LIS[2]. In classical LIS, the person cannot move the body in any way, with the exception of vertical eye movements and sometimes blinks. Incomplete LIS is similar, except there is a very minimal amount of voluntary movement preserved, such as toe movements or head movements[3, 4]. Finally, in complete (or total) LIS, the person is conscious, but the body cannot be moved voluntarily and there is no presence of eye movement[2, 5]. Complete LIS is the most difficult to diagnose, as the lone sign of consciousness is brain function, which cannot be detected by physicians without the use of medical tests that examine neural activity. Also of note: though they cannot move, individuals with LIS can feel both internal and external stimuli, as their ability to relay sensory information to the brain is not compromised by LIS-specific injuries[5]. In sum, all forms of this condition present with some degree of total paralysis, and individuals can communicate with eye movements in all cases except complete LIS.

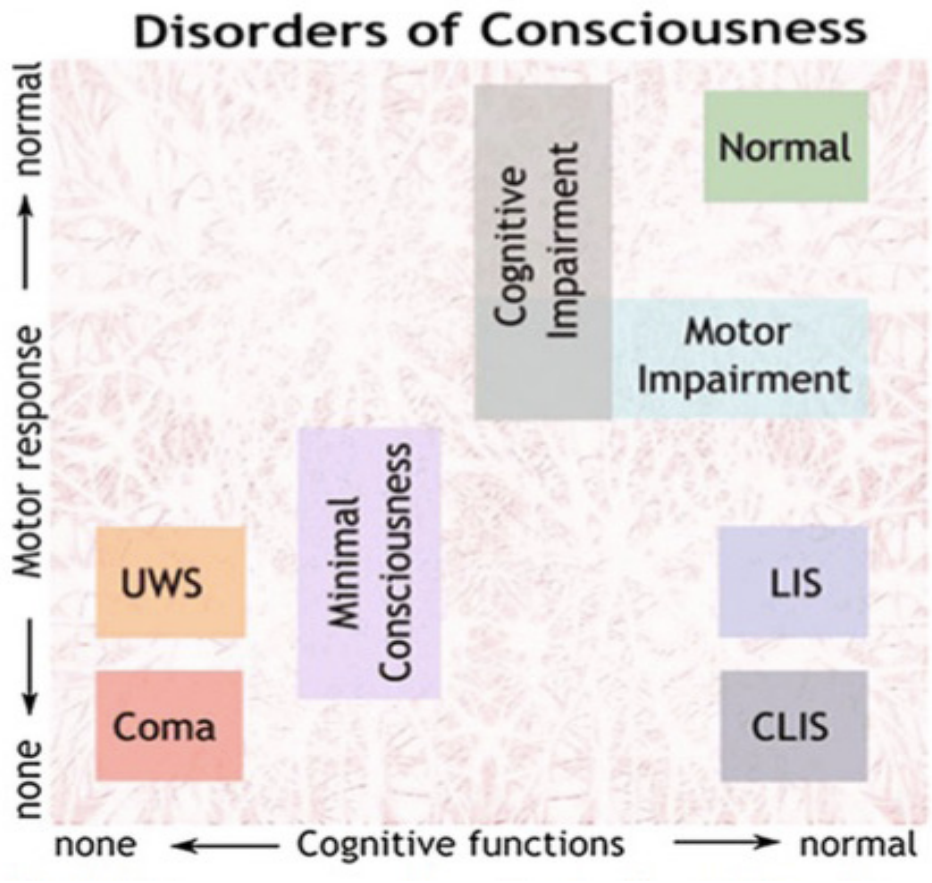
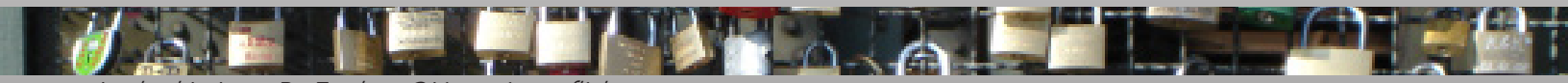


Figure 1: Motor responses and cognitive funtions in coma, Unresponsive Wakefulness State (UWS), Minimally consciousness State (MCS), Locked-in Syndrome (LIS), and Complete Locked-in Syndrome (CLIS). From Guger et al. Permissions obtained through Copyright Clearance Center

Being conscious yet incapable of movement is a frightening and foreign concept to many, and it may be difficult to truly conceptualize. Topulos, Lansing, & Banzett (1993) wanted to really understand this experience and attempted to do so in their study at Brigham and Women's Hospital of Boston, Massachusetts. In this experiment, three respiratory physiologists volunteered to be immobilized using a paralysis-inducing drug, vecuronium[6].



Locked In Love By Eoghan OLionnain on flickr

This drug blocks the chemical acetylcholine, which induces muscular movement, from the muscles. As a result, the mind is left unaltered while the body is temporarily paralyzed, just like in LIS[7]. However, unlike in LIS, participants were able to communicate with the researchers using their right fingers, which were downstream from a tourniquet, which is a mechanism that compresses the blood vessels so that the flow of blood is stopped downstream from the point of compression. The positioning of the tourniquet allowed participants to move their right fingers because the vecuronium did not reach their right hands[6]. Prior to the start of the experiment, a system of finger signals was established so the participants could indicate if they were feeling uncomfortable and required analgesic medication, which would eliminate all discomfort[6]. Heart rate, blood pressure, and a plethora of other physiological measures were analyzed during the procedure.

Immediately after emerging from the paralyzed state, the volunteers reported on their experiences. One of the complaints voiced by the participants was the discomfort of the intubation procedure (i.e., when a tube is inserted in the patient's throat and hooked up to a machine to breathe for the patient). The participants reported discomfort surrounding the insertion of the tube, and all had experienced a feeling of gagging[6]. One subject even voiced that he felt he was being inadequately ventilated, even though, as a professional, he knew this was not the case[6]. Finally, the only time the volunteers felt extremely anxious during the procedure was when they feared losing their ability to communicate with the researchers[6]. From these retrospective accounts, we may attempt to understand how patients with LIS experience their condition. The study's results indicate that lack of communication and the physical discomfort of awake intubation are some of the most distressing parts of conscious paralysis. Fortunately, LIS patients do not have to endure the stress of awake intubation forever; they are frequently given tracheostomies, which are breathing tubes inserted through an opening in the throat (i.e., the trachea) and are a better, more comfortable long-term modification. Finally, the participants of this study were experienced professionals familiar with this process; one can only imagine what it must feel like to experience this situation without this knowledge and without any way to communicate with others.

Where Does It Come From?

History and Causes of Locked-In Syndrome

Medical authors, Plum and Posner, termed Locked-In Syndrome in 1966[2]. However, this was not the first recorded account of the condition; Dumas' The Count of Monte Cristo, published in 1845, is thought to be the actual first description of LIS. In this book, the character "Herein" is a corpse that uses only eye-blinks to communicate[2]. Author Emile Zola created a similar character in his book, Thérse Raquin, written in 1868, exhibiting that this condition was conceptualized long before the name LIS emerged in 1966[2]. Since then, the conversation surrounding LIS has grown: individuals diagnosed with LIS have written books and influenced movies surrounding their experiences. One of the most famous is Jean-Dominique Bauby's memoir The Diving Bell and the Butterfly, which he wrote by blinking his left eye to indicate individual letters[8]. Bauby was the editor of the French fashion magazine, Elle, until suffering from a stroke in 1995. Bauby also notably started the French "Associate du Locked-In Syndrome," which now has a total of 367 registered patients[6, 8]. Hence, though it was only scientifically defined in the mid-twentieth century, the world has been aware of LIS for hundreds of years, and awareness is continually growing.

Although LIS is extremely rare, its most common cause should sound familiar to people from all walks of life: strokes, or cerebrovascular accidents, are decreases and/or increases in blood flow to a specific area of the brain causing temporary or permanent brain damage[8,9]. Strokes can be either ischemic or hemorrhagic. Ischemic strokes involve a blood clot that blocks an artery and cuts off blood supply to an area(s) of the brain (Figure 2; 1a, 2a). Hemorrhagic strokes are the bursting of a blood vessel due to blockage or weakness of the vessel (Figure 2; 1b, 2b)[9]. Typically, when such damage occurs, potassium increases dramatically at the point of injury; this proliferation of potassium indicates a decreased ability to maintain chemical balance within the brain. Following this occurrence, the cellular space immediately affected by the blood vessel injury begins to die[10,11]. Rescue cells (macrophages) surround the area immediately adjacent to the injury site, repairing what is possible, and the remaining damage plateaus, leaving permanent neuronal wounds[10]. In order for LIS to develop, the cerebrovascular accident has to occur in a part of the brain that communicates messages between the brain and the body: the ventral pontine region. Further, if this injury is due to a stroke

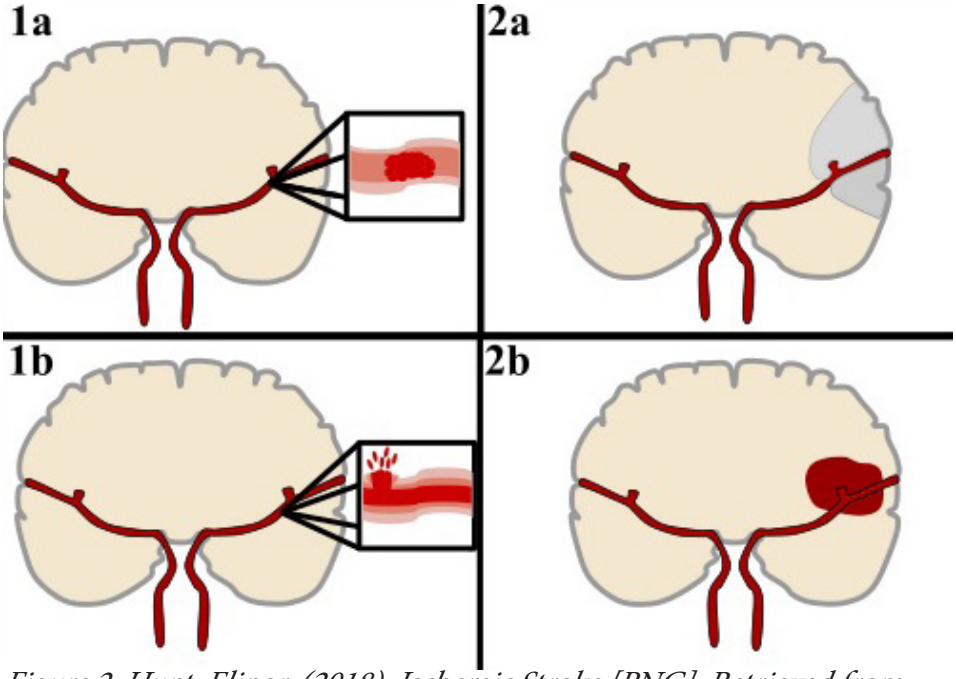


Figure 2. Hunt, Elinor. (2018). Ischemic Stroke [PNG]. Retrieved from Creative Commons

rather than trauma, the stroke must occur within the basilar artery[5,8,12]. Damage to this part of the brain is uniquely able to disrupt the signals sent from the brain to the body, by way of motor neurons, causing paralysis. However, this specific location and artery damage results in the preservation of sensory signals that travel back to the brain from the body, by way of sensory neurons[5,8,12]. Additionally, most LIS cases exhibit an ability to control vertical eye movement and blinking due to the sparing of individuals' eye-signaling mechanisms, the supranuclear ocular motor pathways[8]. Finally, LIS patients' preservation of consciousness results from the conservation of the cerebral hemispheres and the reticular formation, which are neural structures involved in higher-order cognition[8].

LIS does not always occur in an instant, but, rather, commonly transpires after initial symptoms of stroke or brain injury appear and worsen. Case studies most expertly explain this evolution from symptom appearance to development of LIS. One such example involves a 76-year-old woman with hypertension and plaque buildup within her arteries[12]. One day she discovered that she was unsteady on her feet after awakening from a nap, and that her speech had become slurred and slowed. Furthermore, she had experienced leftward deviation of the tongue and eye gaze, and her left hand and upper arm had become paralyzed. She also eventually developed left central facial nerve palsy, which is the paralysis of the left side of the face caused by the loss of central facial nerve function[13]. After being treated at the hospital, her conditions worsened, and she became totally paralyzed. When doctors discovered she could follow verbal commands with her eyes, she was diagnosed with LIS[12]. Sadly, a scan revealed that the patient had experienced a stroke that had affected her brainstem in the precise way necessary to develop LIS. Eventually she died of pneumonia. This woman's story provides an instance in which stroke symptoms materialized and eventually evolved to a LIS state. The gradual emergence of stroke symptoms and total paralysis, with the exception of the eyes, reveals how LIS can arise from minute symptoms, such as unsteadiness, and that its presentation does not dramatically differ from other stroke cases. Finally, the patient's ability to follow verbal commands with her eyes highlights the complex nature of the condition, as her mind was fully operational, though her body was incapable of function.

How Can We Tell Someone is "Locked In?"

As previously mentioned, the presentation of LIS is extremely similar to that of the "disorders of consciousness," such as vegetative states (VS); both LIS patients and VS patients cannot engage in voluntary movement or breathe on their own[8]. Yet, LIS patients are fully conscious and can perceive external and internal stimuli (including pain), and VS patients do not have either of these characteristics. Thus, the importance of being able to distinguish between these states is of the utmost significance. Technological advancements have facilitated the emergence of a variety of ways to detect if a person is conscious. One way brain function can be recognized is through patient participation in electroencephalography (EEG) paradigms that focus on the elucidation of consciousness. EEG is the monitoring of the electrical signals produced by neuronal cells (neurons), which "fire" during brain activity. In 2018, a research team compared LIS, VS, and healthy control brain activity during an examination of this type, asking participants to focus and not focus on flashing yellow and red "interlaced square" patterns, respectively[14]. LIS patients and healthy controls exhibited EEG evidence of command following,

while the VS patients did not[14]. The authors also highlighted that this type of neural examination can occur at the patient's bedside and only requires small attention spans, as each stimulus was only displayed for five seconds and each trial lasted for five minutes. Quick stimuli presentation is crucial for LIS analysis because attention for long periods of time may fatigue individuals with LIS and result in inaccurate results[14]. Thus, new methods such as this attention-based EEG paradigm provide opportunity for consciousness to be understood quickly and with ease.

However, this type of assessment is not 100% dependable; many persons experiencing LIS are not able to follow commands with their eyes right away. This is because LIS may occur following a coma period, after which the individual may spontaneously "awaken" and be fully conscious[15]. For this reason, other methods of examination are needed that assess patient consciousness without necessitating active patient involvement with a procedure. Positron emission tomography (PET) scanning has recently been used to examine neural blood sugar (glucose) metabolism in brain-damaged patients in order to reveal which areas of the brain are functioning[16]. In 2018, a research team used this method to search for neural activation in a LIS patient by tracking patterns of injected 18F- fluorodeoxyglucose, a radioactive molecule that attaches itself to glucose. When it is broken down, the radioactive molecule emits a signal that can be tracked by the PET scanner indicating which parts of the brain are using the glucose[17,18]. Analysis of a LIS patient with this method found that that all regions but the patient's cerebellar areas (which are movement-specific) metabolized the radioactive molecule, indicating this patient did not have function in this region[16].

Another promising technique that enables perception of consciousness without necessitating voluntary body or eye movement is the examination of resting-state networks, which are patterns of co-activity between the different areas of the brain [8]. A 2016 study recently proposed the examination of resting LIS patients, healthy controls, and VS patients using functional magnetic resonance imaging (fMRI)[15]. fMRI is an imaging technique that utilizes blood-oxygen-level-dependent analysis, a method that analyzes oxygen flow in the brain, therefore examining which areas are active during the fMRI procedure. Though this technology is commonly used to track brain function during paradigms, analysis of resting-state networks using fMRI looks promising. Resting-state networks can take many forms, and a frequently studied type is the "default-mode network." Default-mode networks are high-level resting-state networks that are active when a person is at rest, and, specifically, when a person is focused on the self[15]. A self-focused network may be useful for analysis of patients with LIS, as they may be focused on the self because of their limited ability to interact with the world around them. When comparing LIS patients', healthy controls', and VS patients' default-mode networks, researchers found that LIS patients' and healthy controls' default-mode networks were virtually indistinguishable, while those of the VS patients did not resemble LIS or controls participants[15]. Thus, this method distinguished between conscious and unconscious brains without necessitating active patient participation (i.e., verbal responses, active focus, etc.). Such an advancement is crucial not only because a patient may be only temporarily comatose, but also because patients with total or complete LIS may never be able to signal with their eyes.

Though the previously described analyses of LIS neural activity are exciting and promising, they are still being altered and can only be considered potential assessments. Therefore, utilizing resting-state, standard EEG activity is still the typical method of evaluation[19]. As mentioned earlier, EEG can be used to assess brain cell (neuron) electrical activity during a certain stimulus presentation. But, EEG can also monitor brain activity without stimuli presentation[19]. For example, currently, when presented with a patient who may be either in a VS or a LIS state, EEG is used to examine whether certain consciousness-indicating brain activity is present. EEG activity is displayed via oscillating waveforms, which are the compilation of continuous electrical activity produced by the brain. When brains of LIS patients are examined using this technology, physicians look for waveform responses to sensory stimulation or cognitive load, and/or alpha waves, which are characteristic of relaxed yet conscious persons (Figure 3)[19].

Finally, patients have also been discovered to be in a LIS state rather than a VS after being asked to imagine moving their limb while being monitored by EEG. Such imagination results in altered EEG activity, and, thus, patients have discovered to be experiencing LIS, not a VS[19]. Therefore, EEG is used in a variety of ways to examine the presence of consciousness in patients with possible LIS, and will most likely continue to be the standard until other methods of analysis trump its efficacy.

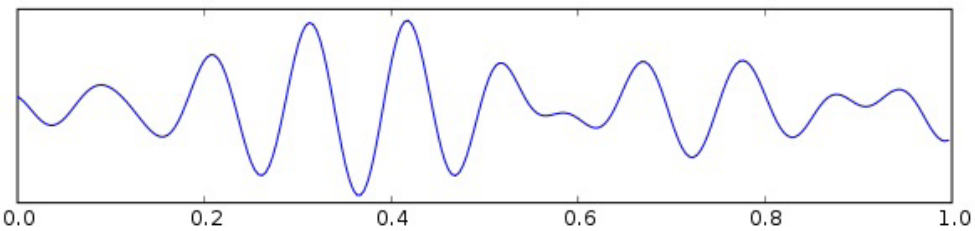


Figure 3. Gamboa, H. (2005). Alpha Waves, An EEG (electroencephalograph) 1 second sample [PNG]. On CC

Quality of Life in Patients With Locked-In Syndrome

The processes discussed up to this point are those that initiate the occurrence and discovery of the LIS condition; but there is also much to be considered after LIS diagnosis. Eighty-three percent of stable patients with LIS live 10 years after their cerebrovascular accident, and 40% live 20 years after[8]. Naturally, adjusting to their new state of being becomes a major challenge for such patients. Thus, assessments that evaluate the quality of life of individuals with LIS are factors of great importance. A 2015 longitudinal study of persons with LIS attempted to analyze patient quality of life over time, seeing which factors are most influential in life improvement[20]. Recruiting 67 participants from the French Association of Locked-In Syndrome, the researchers asked a series of questions about participants' lives once in 2007 and again in 2013. Sociodemographic information was collected (e.g., martial status, clinical data, education level, etc.) and analyzed, but the main form of quality of life assessment was obtained using the Anamnestic Comparative Self-Assessment (ACSA), which is a questionnaire that compares level of satisfaction between memories of individuals' past and present states[20]. Researchers found that most of the participants were using communication devices and electric wheelchairs that enabled relative autonomy[20]. Additionally, 70% of patients in this study described a stable or increased level of quality of life. However, 44% of patients interviewed suffered from chronic pain, 55% suffered from mood or anxiety disorders, and 27% experienced suicidal ideation. The final item proved to be a statistically significant influence on patient quality of life scores, as did patients' ability to communicate outside of a yes-no code (i.e., the use of the eyes to indicate yes or no). Finally, quality of life surprisingly did not relate to the length of time since LIS diagnosis or the extent of LIS symptoms[20]. Thus, this study revealed that LIS individuals with autonomy and relative ease of communication are more likely to have good quality of life scores, irrespective of sociodemographic measures or other disease factors. Yet, issues such as suicidal thinking and communication difficulty can lead to decreased quality of life, and should be specifically considered by caretakers of individuals with LIS.

As the previous study evidenced, individuals with LIS rate their quality of life to be relatively high, given their circumstances[8,20]. Still, another aspect to take into account when assessing LIS individuals' level of comfort is others' perceptions of LIS. In this case especially, such assessment should be taken quite seriously, as individuals with LIS must rely on others to do tasks that involve voluntary movement. Studies have shown that caretaking populations tend to believe that life with LIS is worthless, stating that they would not want to live in such a condition[8]. Demertzi, Jox, Racine, and Laureys (2014) examined this concept in detail, analyzing 3332 questionnaires concerning LIS quality of life completed by medical professionals from international medical conferences[21]. The questionnaires asked whether the medical professionals would wish to be kept alive if diagnosed with LIS, whether LIS is worse than other vegetative or minimally conscious states, and more similarly hypothetical questions. Further, questions also concerned participants' understanding of LIS as a condition and assessed whether health professionals understood LIS pain experiences. Analysis of the feedback revealed that most respondents understood LIS patients could feel pain and believed treatment should not be stopped in LIS patients[21]. Yet, most medical personnel also believed that LIS was worse than other vegetative or minimally conscious states, and, if diagnosed with LIS, they would not want to be kept alive[21]. Finally, most also believed that having a family member with LIS would be more difficult than having a family member in a vegetative or minimally conscious state[21]. As mentioned, LIS patients do not feel that their lives are not worth living, and many have stated that they would not consider euthanasia[8,21]. Therefore, the discrepancy between medical professionals' views of LIS and the patients' views of their own conditions should be reconciled to enable the most accurate assessment of patient need; medical professionals potentially interacting with LIS patients and their family and friends need to understand that this diagnosis,

though life-changing, is not life-ending. In doing so, medical professionals may be able to better present the diagnosis to these individuals and also ensure proper care and treatment.

Where Do We Go From Here?

Advancements and Future Directions

In discussing the quality of life of individuals with LIS, it is also important to note the method through which assessment is achieved. In the previously mentioned studies, questionnaires were answered using an electronic communication device or with the help of a caregiver[20]. However, issues arise when assessing other types of information outside of questionnaire capability; for instance, though the injuries which result in LIS are localized in such a way that they spare consciousness, there have been some reports of reduced cerebral metabolism in LIS patients, indicating decreased cognitive function[22]. Additionally, reports of attention and memory issues have been noted on LIS patients' self-reported evaluations. Yet, this form of report is subjective, only assessing what patients can and want to report. So, steps must be taken moving forward to facilitate more ways to assess the capabilities of individuals with LIS. Advancements have been made within the field of cognitive assessment: Schnakers *et al.* (2008) developed modified standard neuropsychological tests in order to examine LIS individuals' cognitive function[22]. Examples of such modification included altering the backward digit span task so that participants only had to indicate whether the string of numbers was the same or different. Further, executive functioning was assessed using an altered yes/no version of the Wisconsin Card Sorting Task. Finally, verbal intelligence was assessed using a Peabody Picture Vocabulary Test; the participants determining which of the pictures corresponded to a target word. Controls in this study completed the tasks using only their eyes to ensure data uniformity. Out of the 10 LIS participants in this study, four had scores in normal range for all examinations[22]. However, in the memory, auditory attention, language, and executive function categories, there were two to four LIS patients that showed impaired performance, indicating that brain damage of some type had diminished the cognitive functioning of these LIS patients. Therefore, this altered mode of cognitive assessment, made for those with LIS who cannot respond verbally or using movement, proved to be able to properly assess LIS cognitive capability[22]. Such work is one example of the necessary direction of movement toward better assessment and,

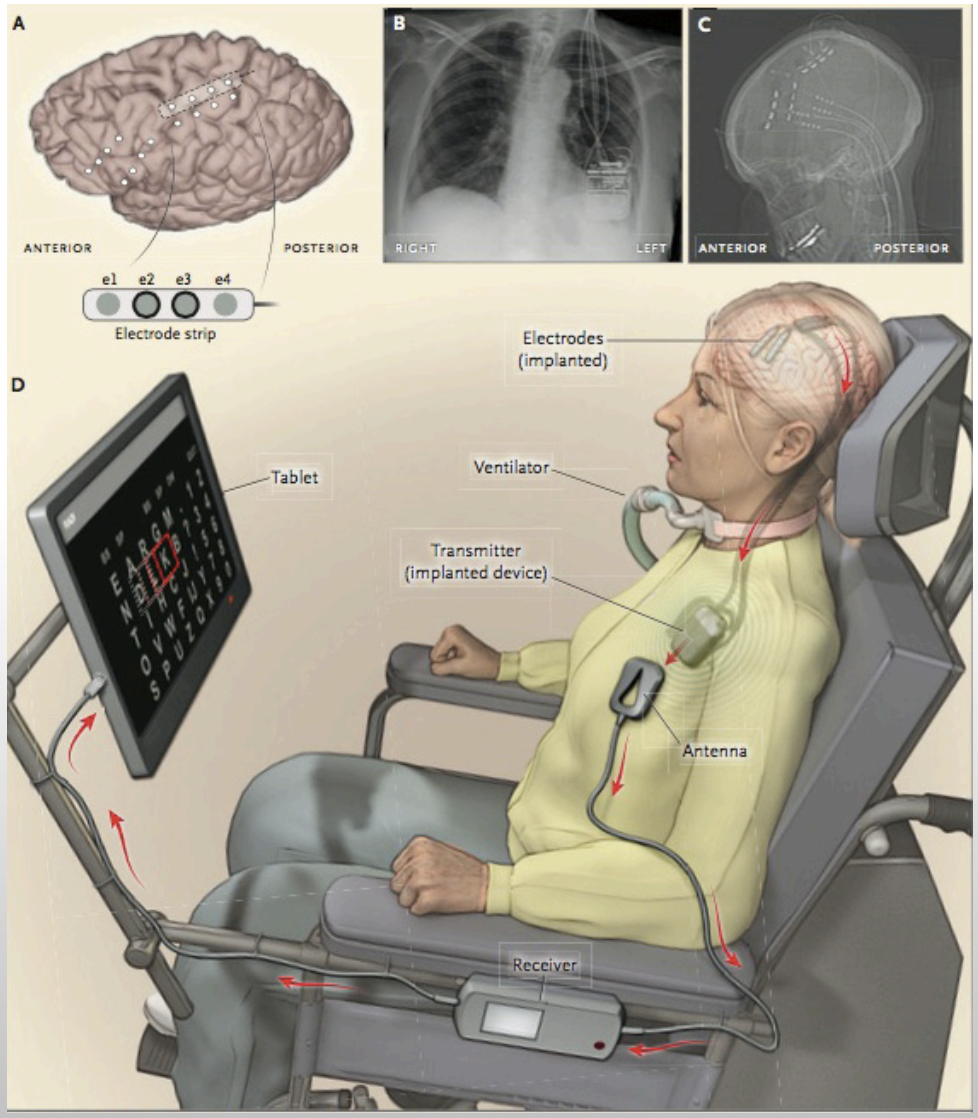


Figure 4. Pictoral representation of BCI by Vansteensel et al. (2018). Apdapted from "Fully Implanted Brain-Computer Interface in a Locked-In Patient with LIS," by M.J. Vansteensel. 2018. The New England Journal of Medicine, 375(21), 2062.

thus, better understanding of LIS patients and their predicaments. To achieve better lives for the patients post-injury, more advances of this type must be made.

Another amazing development that has been recently examined is the potential for brain-computer interface utilization in individuals with LIS. In October 2018, Vansteensel *et al.* published a piece in the renowned New England Journal of Medicine showcasing a brain computer interface that allowed a LIS patient to be able to simply think of hand movements in order to spell out a word on an computer typing program[23]. More explicitly, the subject of the study, a 58-year-old woman whose amyotrophic lateral sclerosis had progressed to the locked-in state, had electrodes implanted on her brain and a wireless radio device inserted in her abdomen (Figure 4). The devices allowed her to communicate with a computer specially designed to enable her to mentally spell out words. To do so, she had to imagine moving her arm or relaxing her arm, which would move the mouse on her computer in different directions. To click a desired letter on the screen, the participant thought of a "click" in her head, which was converted to an actual "click" on the computer. The refinement of this process took many rounds of algorithm reorganization but was ultimately successful in enabling independent communication (though at a rate of two letters per minute)[23]. The communication method created by this group could be utilized by LIS patients that cannot employ conventional techniques, like eye-tracking devices. Such work represents more necessary forward movement within the field of LIS patient care.

To some, LIS may sound like a frightening nightmare. Even in this state, however, individuals with LIS report relatively high quality of life levels. Additionally, more and more advancements are being made to ease patient lifestyle and to facilitate better understanding of the condition. To promote this forward movement, it is important for medical personnel and the general public to know about this condition, its limitations, and the remaining capabilities of these individuals. This article intended to highlight the various aspects of the condition and bring it to the attention of the public outside of the neuroscience sphere. By taking note of this condition and scrutinizing its intricacies, we give value to these individuals' lives and their pursuit of happiness despite their situation.

Hospital Room By "vitalworks" on Pixabay

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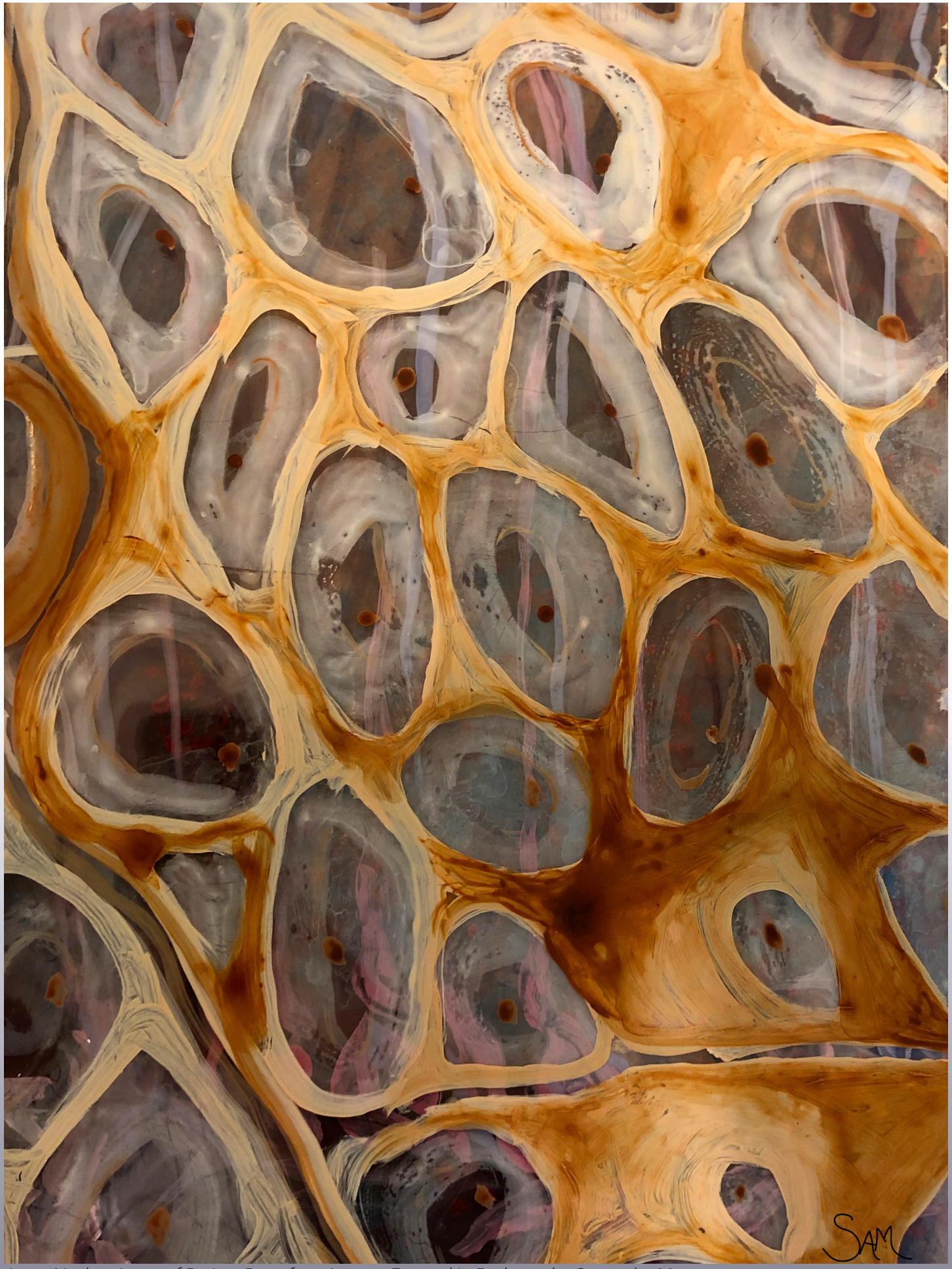


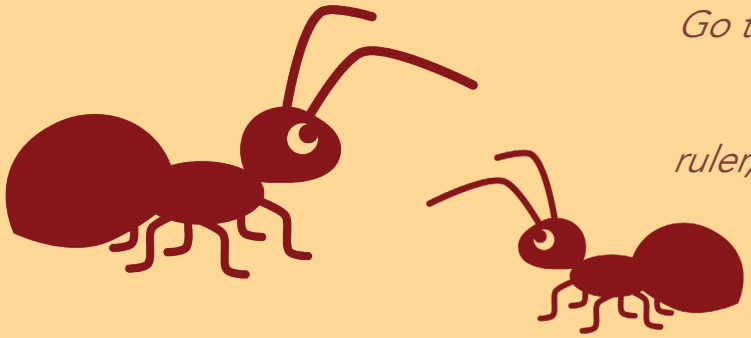
Inner Nuclear Layer of Retina. Page from Images Formed in Darkness by Samantha Monoyta

Ant by "dustonthewind on pixabbay

All for One and One for All

The Emergent Intelligence of Ant Colonies

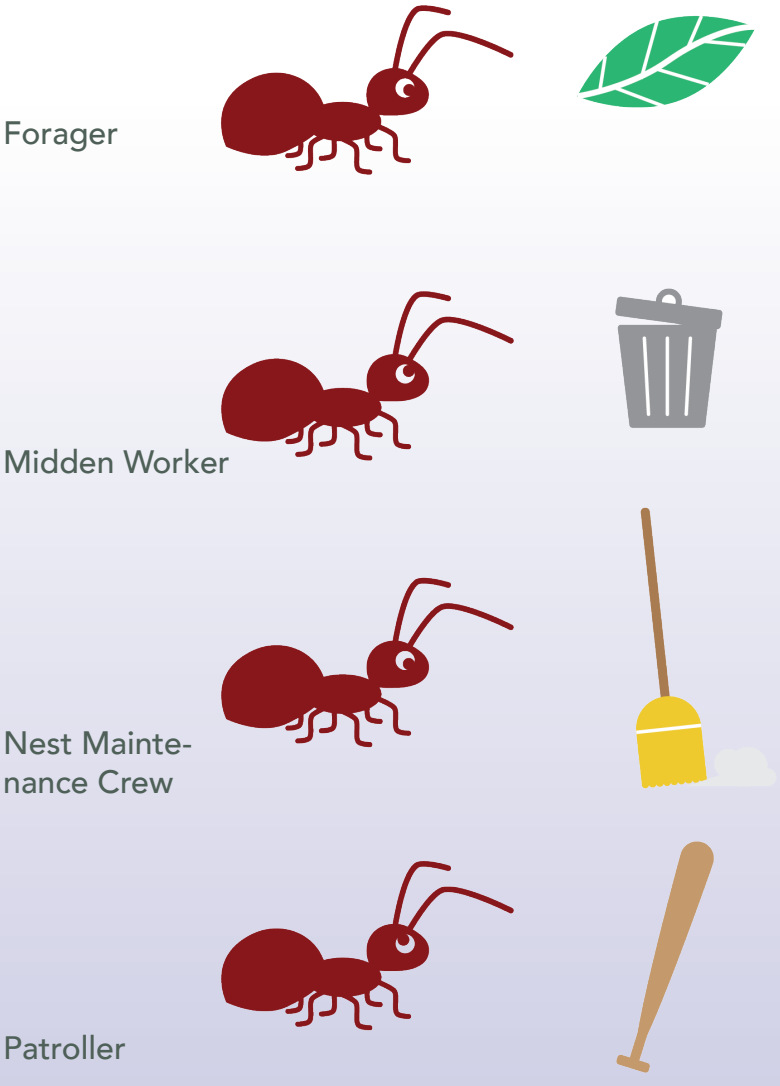
Written and designed by Kristen Pitts Illustrated by Samantha Montoya and Jacob Bergen



Go to the ant, O sluggard; consider her ways, and be wise. Without having any chief, officer, or ruler, she prepares her bread in summer and gathers her food in harvest.
(Proverbs 6:6-8)

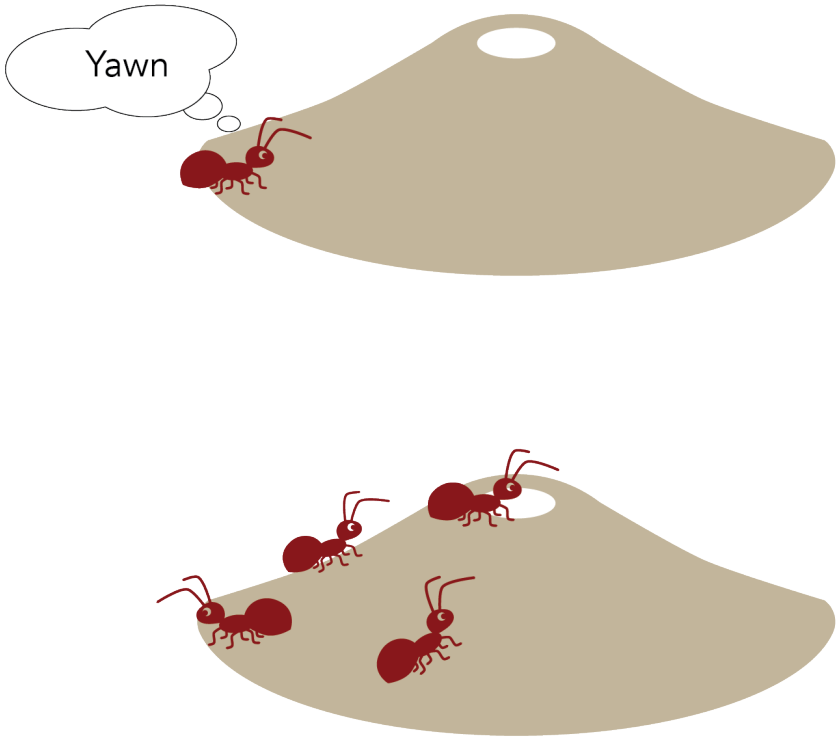
For the past thirty years, Deborah Gordon has returned to the same patch of desert in northeast Arizona to visit old friends. They are the most loyal companions, always emerging from their clay-lined huts in the earth to greet her (and the annual treats that she brings). To Gordon, the desert represents a community far removed from her home in Silicon Valley. She celebrates the birth of new members and the death of old matriarchs. She rejoices with old friends when they become mothers, grandmothers, and great-grandmothers, doting over the resemblances she observes. She takes note of those who perish to floods, droughts and famine, as well as those who survive. She is mindful of rivalries. It is a bustling village—a bustling *oikos*, to use the Greek translation of the word. There is perhaps no one better than Gordon to explain why *oikos* is the etymology of modern day *ecology*.

Deborah Gordon is a Professor of Biology at Stanford University, so perhaps you are unsurprised that her old friends are not human. You might, however, be surprised to learn that they are not individual ants, either. Gordon goes back to the desert every year to check up on. A single ant lives only for about two years, but a colony may live well into its early-30s. And, like all reproducing organisms, colonies have the potential to live on through their offspring. "Ants never make more ants; colonies make more colonies," Gordon explained in her acclaimed 2003 TED talk. Every year, on the same day, winged reproductive ants emerge from their colony and carry out a mating flight, during which a single female mates with many males before landing in the sand and burrowing into the ground. She then begins laying her eggs, and she will lay eggs from that very mating event for the next 15 to 20 years, never again emerging from the earth. She has become a queen, and a new colony carrying



the same genetic material—a daughter colony, so to speak—has been born.

Gordon is not the first scientist to consider the possibility that the colony itself functions as a unified organism. Throughout the history of biological study, there have been many definitions proposed of what it means to be an "organism." In 1852, Aldous Huxley defined an organism as "the sum of the phenomena presented by a single life."[1] This definition was amended over time to include notions such as the assimilation of substances, reproduction of similar systems and subjection to the laws of natural selection.[2,3] Perhaps the most prevailing definition today, however, is that an "organism" is any combination of parts that acts in nearly complete cooperation and has no affiliations outside the self.[4] By this definition, in particular, the ant colony certainly qualifies.



You may be thinking: What of the individual ant? Surely an ant is an organism. And while this is true by most all definitions, studying an ant in the context of its colony requires a shift in perspective. Individual ants are rather simple. They are designed to integrate local signals in order to make binary decisions—to act or not to act. Some ants patrol the nest perimeters, others forage for food. Some ants maintain the cleanliness of the nest, others take out the waste. Still others lie dormant in the earth, providing a living shield to protect the queen and her precious eggs. But all ants are dependent on other ants. In a community, they can survive. In isolation, they will most certainly die.[5]

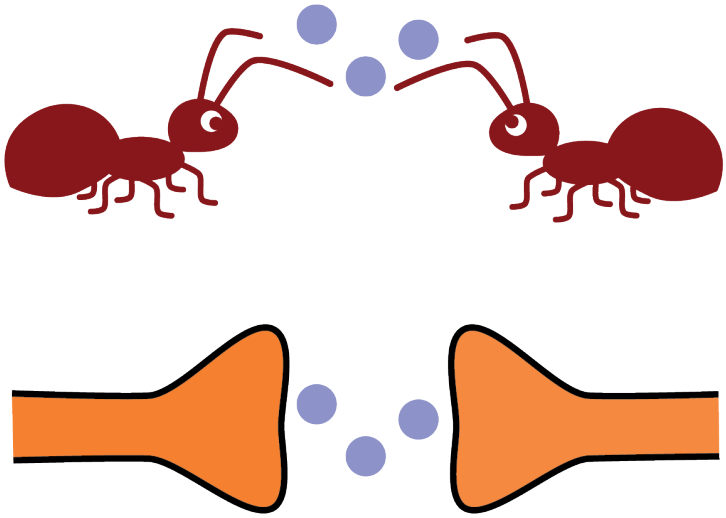
Although ants are simple-minded, the colony itself is exhibits remarkably complex behaviors. Take, for example, the way in which ant colonies respond promptly and collaboratively to the appearance of food, and in numbers that precisely reflect the amount of food present. How does a colony know how to "behave," and how is this behavior so flexible? It might seem reasonable to believe that the queen is in control, perhaps by sending out specialized chemical cues to various parts of the nest in order to govern the ants in any given vicinity. This, however, is not the case. Even if the queen were able to send out specialized chemical signals to specific groups of ants, it would be impossible for her to have enough information of the outside world (or of the nest conditions itself) to offer effective instructions to the other thousands of ants in the colony. Importantly, an ant colony is able to respond to environmental conditions without centralized control. It is an organization made of up thousands of parts all operating collaboratively within a complex network of interactions. The dynamic communication between ants in a colony allows for the emergence of collective, intelligent behavior; and in this way, ant colonies are exquisitely similar to animal brains.[6]

In order to understand what I mean, let us start by considering how a Red Harvester colony in the Arizona desert employs forager ants to find seeds. The underlying principle is simple: a forager ant will leave the nest in search of seeds and it will not come back to the nest until it finds one. If there are many seeds in the nest vicinity, then the forager ant will return quickly. Its prompt return to the nest will signal to other forager ants that there is food within close proximity, triggering their own deployment. Thus, the rate at which forager ants return to the nest determines the rate at which forager ants leave the nest. In this way, the colony does not waste individuals when there is no real promise of food in its environment.[7,8]

When this model of ant colony foraging surfaced in bio-

logical journals, it caught the attention of one prominent neuroscientist working just south of Deborah Gordon. Michael Goldman is a neuroscientist from UC Davis who has spent much of his career working to understand the decision-making properties of neurons. Before reading Gordon's study, Goldman had worked using computational modeling to understand the relationship between neuron properties and network function. Specifically, Gordon was interested in how the willingness of individual neurons to fire affected the behavior of circuits.[9] When he read Gordon's work, he was inspired by the collective behavior of the ants as well as their striking similarity to neurons in a brain. He reasoned that it was perhaps possible to use ants to study the brain—and the brain to study ants.

Imagine for a moment, that a colony is a brain and that each neuron is a forager ant at the nest. A returning forager ant is the equivalent of an incoming action potential; when it makes contact with a sedentary ant back at the nest, it "excites" it, triggering a new departure—a new "action potential," so to speak, that will eventually come back and reach another "neuron." The more food there is, the more forager ants will return to the nest to excite new waves of foragers. This positive feedback will continue until the food source dwindles, the rate of returning ants slows, and the activation of new forager ants falls back to a "resting state." Importantly, just as a forager ant might be "excited" to pursue food in its environment, it might also be "inhibited" to retreat back to the safety of the deep nest if a lack of returning ants signals that there is no food around to respond to. This operating system parallels the way in which neurons respond to environmental stimulus; through simple networks of excitation and inhibition.



Gordon and Goldman applied mathematical models to understand the dynamics of ant foraging feedback.[10] Intuitively, Gordon and Goldman found that ants that left the nest to forage had experienced a higher rate of interaction with returning forager ants than those that returned to the depths of the nest. They also found that forager ants at the nest accumulate experience with returning ants, weighing experiential evidence in order to "decide" whether or not to leave or retreat—synonymous with the "decision" of a neuron to fire or not to fire. To reflect the decision-making process of the individual ants, Gordon and Goldman developed a stochastic accumulation of evidence model to predict the rate of incoming, outgoing ants and retreating ants. Stochastic accumulation of evidence models are used quite often in neuroscience and psychology to understand how noisy environmental information is processed when deciding between two competing choices.[10] From the perspective of a neuron, "noisy environmental evidence" refers to the rate of input it receives from the hundreds or thousands of others neurons to which it might be associated, and the two decisions are to fire or not to fire. From the perspective of the ant, "noisy environmental evidence" refers to the rate at which it encounters returning forager ants, and the two decisions are to leave or to retreat.

How, though, are ants able to identify foragers that are returning versus those that are simply wandering around the nest? When observing an ant colony, the dynamic character of ants is readily apparent; what is less apparent, however, is their tendency to make direct, physical contact with the antennae of other ants in their vicinity. This finding led researchers to investigate the mode of communication employed between members of a colony during brief periods of antennal contact.[11] Scientists discovered that ant communication was first and foremost, chemical, but more specifically, dependent on unique cuticular hydrocarbon profiles present on each ant's antennae. Literature has found cuticular hydrocarbons to be critical for maintaining the social coherence of

colonies.[12,13] In the context of Red Harvester forager ants, cuticular hydrocarbon profiles are even different between those who have left the nest and those who have remained. Though the difference is subtle, it is significant enough to be detected by arrays of sensitive receptors on the surface of an ants' antennae such that returners may be identified.[8]

Cuticular hydrocarbons present on each ant's antennae allow us to complete our understanding of Gordon and Goldman's colony-brain model: each colony is a brain, each ant is a neuron, and each cuticular hydrocarbon is a neurotransmitter that serves as chemical communication. Neurons operate in complex networks of branching dendrites and traversing axons; ants operate in complex networks of random movement and stochastic interactions. Both, however, exhibit emergent intelligence as the sum of positive and negative local interactions.[6]

Let us return now to the idea of the colony as an organism—an organism composed of collaborate parts that functions much like a brain. Throughout her time in the desert, Deborah Gordon has worked to understand how environmental pressures lead to the evolution of ant colony behavior. In order to be subject to evolution, a particular trait—be it behavioral or physica—must be subject to natural selection. Natural selection was originally coined by Charles Darwin in the late 19th century and defined as "the principle by which each slight variation in a trait, if useful, is preserved."[14] In other words, a particular trait, if beneficial to the organism, will be passed on to offspring, and over generations it will become increasingly prominent in the population as a whole. Importantly, not only must differences in a trait allow for differential survival and reproductive success, but these differences must also be heritable. That is, they must be encoded in genes so that offspring may experience the same fitness benefits.

We see behavioral evolution in nature all the time: crickets tune their song in response to sexual selection; birds adjust their migratory patterns in response to climate change; squirrels modify their caching behavior in response to resource availability.[15] Although evolution can be observed by comparing traits at the organismal level, the mechanism of evolution is the propagation of certain genes in a population over time. This is perhaps easy to understand in an animal system, but it is complicated when thinking about the evolution of "super-organisms." Can ant colonies evolve in the same way as a squirrel? Is there anything about colony behavior that is, in fact, heritable?

This is a question that Deborah Gordon and her research team set out to answer in the fall of 2010. First, remind yourself that ants never make more ants; colonies make more colonies. In order to understand the family tree of the community she had been studying for decades, Gordon took genetic samples from each of the many hundreds of colonies living within her 250 by 400-meter research site. She was then able to determine which colonies came from which—in other words, which queens were mothers and which were daughters. The ultimate goal was to uncover resemblances between related colonies.

The results were fascinating. She found that one of her favorite colonies—colony 154—had recently become a great-grandmother, and that its daughters, granddaughters and great-granddaughters contributed more significantly to the community structure than any other lineage.[16] It seemed to Gordon that there must be something about colony 154 that made it particularly successful at surviving and reproducing, and that whatever this trait was must be in some way passed on to offspring.

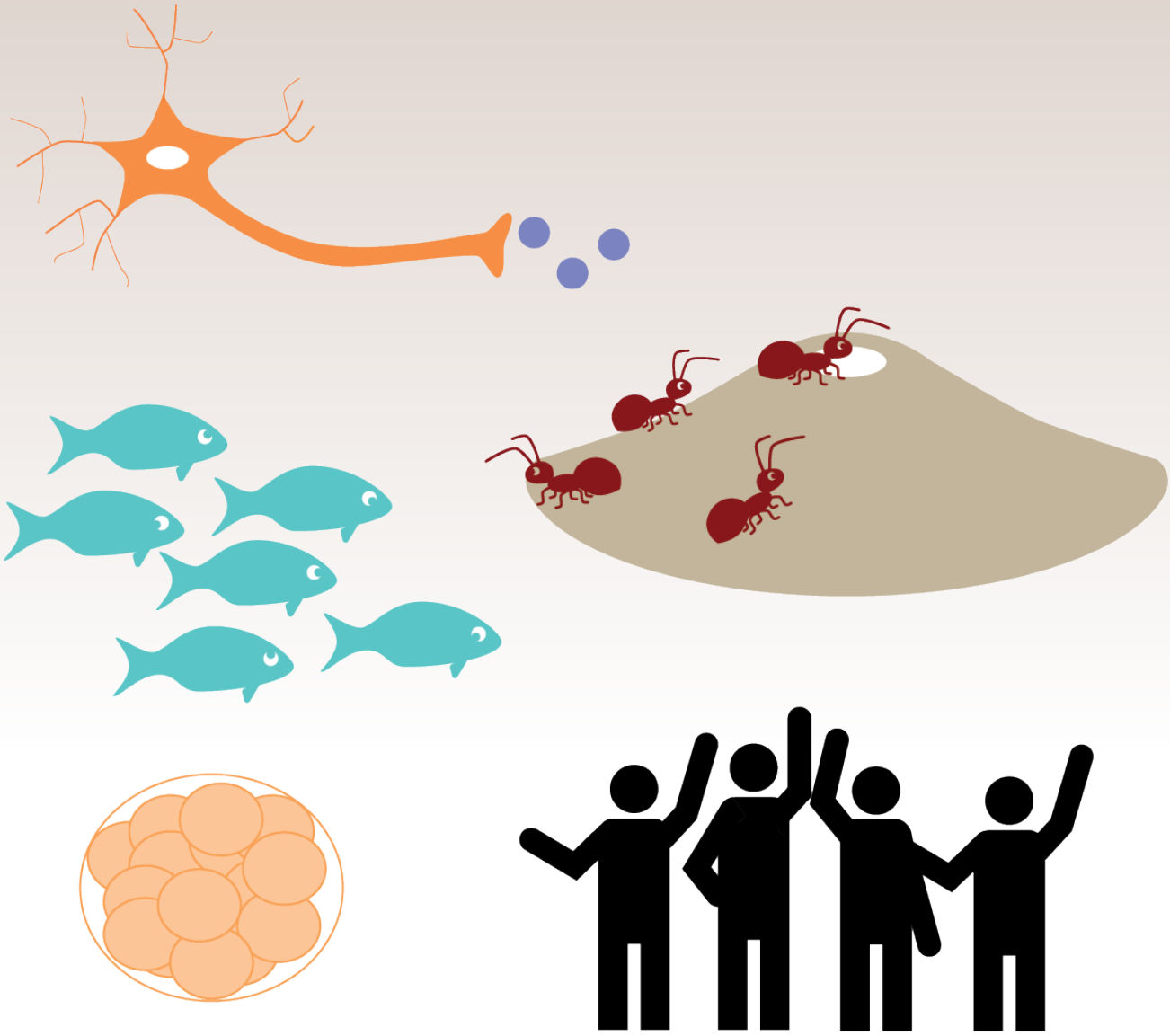
But what, in fact, was this trait? What made colony 154 so much more successful than other lineages competing for the same resources?

The answer was rather counter-intuitive. Colony 154, more than any other colony, was particularly lazy.[17] While other colonies were out and about in the heat of the day searching for food, colony 154 was resting. Its nest-bound foragers were slow to move and required a much higher rate of antennal contacts with returners to rally a search for food. The foragers of colony 154 seemed less inclined to waste away in the hot sun on a hot day than their competitors, and this, it seemed, was serving to their advantage. So, Gordon was compelled to ask: Could "laziness" be a heritable colony behavior?

She found that, indeed, it was. When it came to the willingness to forage, the offspring of colony 154 exhibited undeniable resemblance to their mothers; and when Gordon looked further, she found that these resemblances were rooted in the number of interactions forager ants at the nest must have with returning foragers before they were willing to set out themselves. In other words, the decay rate of antennal interactions was faster in foragers ants of colony 154, requiring that they experience a higher rate of "excitatory" antennal interactions before deciding to leave. Gordon further found that the required rate of antennal contacts was not only consistent between colony 154 and her offspring, but also between the mothers and daughters of other

lineages as well. She concluded, therefore, that there must be a genetic component to forager ant response, and that this genetic component offers variation in foraging behavior that produces differential fitness among colonies in a community.[17,18]

If we return again to idea that we can use ants to understand the brain, and the brain to understand ants, we might discover a whole new perspective on what it means to ask questions about collective behavior. Ants may be considered neurons in a brain, but they might also be considered cells in an embryo, fish in a school, or even humans in a mob. Taken individually, a single part means nothing, but taken together, we see patterns of remarkable emergent behavior that may be acted upon by natural selection. Ants show us how understanding the properties of parts sheds light on the function of the whole. And this might just make the thirty years Deborah Gordon spent in the desert entirely worth her time.



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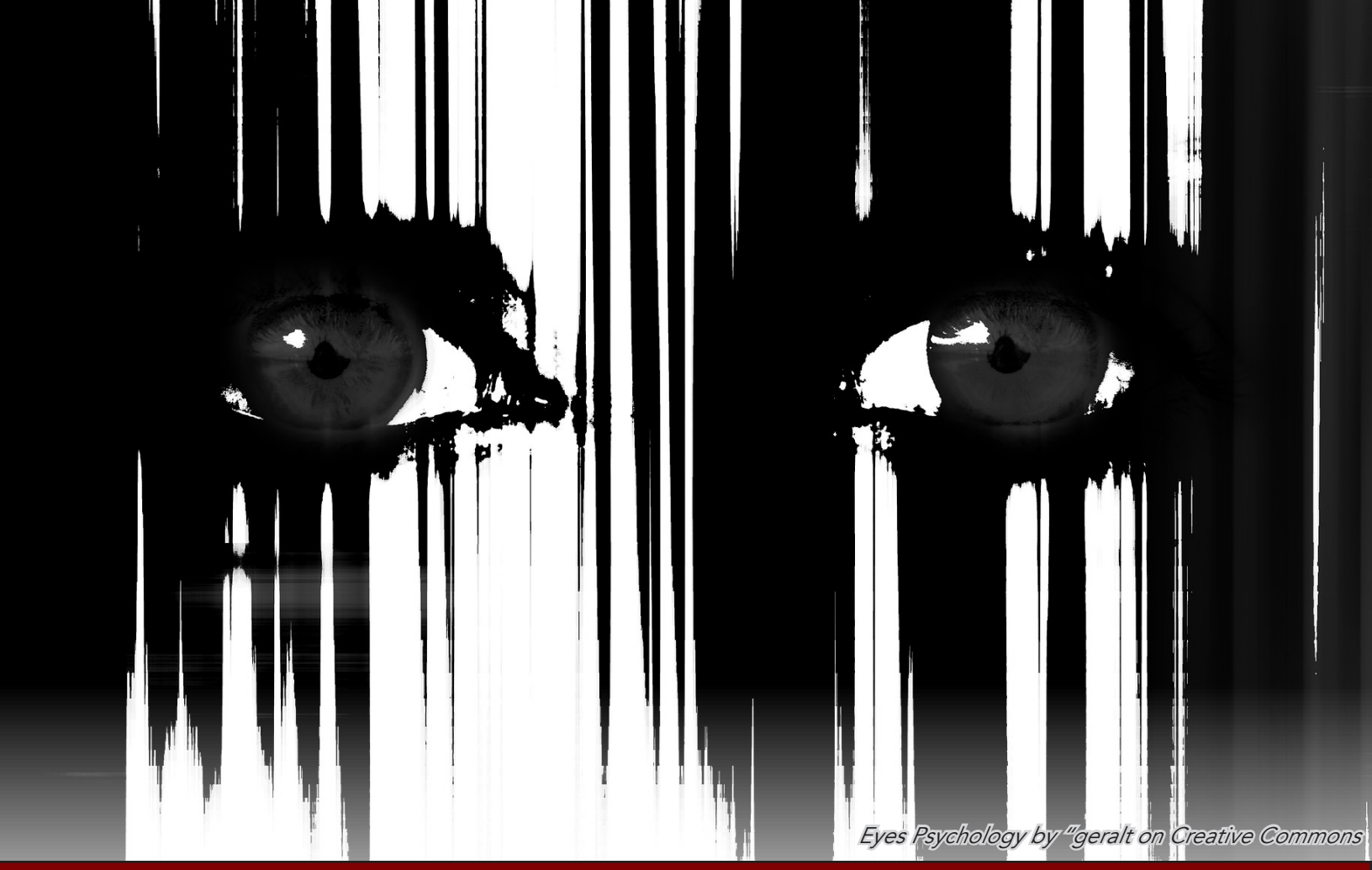

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The Great Immitator:

How Lyme Disease Can Mimic Psychiatric Disorders

By Lane Davis

What is Lyme Disease and what does it look like?

Lyme Disease is dubbed the great imitator as it's associated symptoms often mimic many other diseases ranging from multiple sclerosis to schizophrenia. When thinking about Lyme disease, I sometimes relate it to the teenage fantasies surrounding the mystical nature of vampires. Although you may think of vampires as creatures that take a human form, in my imagination vampires can be the embodiment of small insects, such as ticks. Ticks are blood-sucking creatures that live in woodsy areas, seagrass, and in the summertime, probably your dog's fur. Parasites such as these survive by attaching themselves to hosts, such as dogs or humans, submerging their fangs, or what is called their capitulum, under the skin and feeding off the hosts' blood. That being said, not all species of ticks can give you Lyme disease. Only the species of ticks known as *Ixodes* can carry the harmful bacteria that is transferred into the host during their feeding. This corkscrew-shaped bacterium is the agent responsible for the contraction of Lyme Disease and is known as *Borrelia Burdorferi*[1]. Almost always, only teenage ticks, which are called nymphs, can transfer this bacteria. Nymphs also need to be attached to their host for upwards of 36 hours in

order to successfully transfer the bacterium. All that being said, in order to contract Lyme disease, the conditions need to be very specific, so there's no need to worry over every blood thirsty tick you may find.

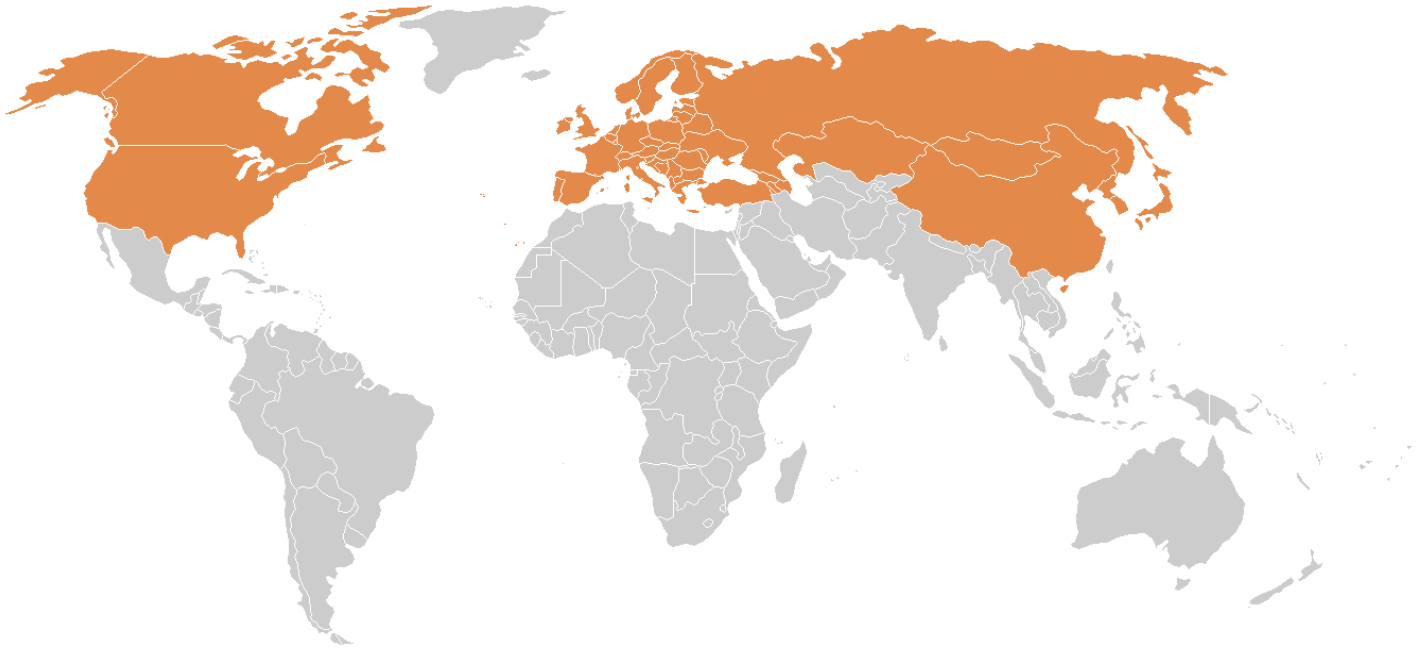
Interestingly enough, this disease was only recently discovered in the mid-1970s around Lyme, Connecticut, when multiple cases of arthritis emerged, which is known to be a prominent symptom of Lyme[2]. Since this time, the diease has been seen at an increasing rate throughout the United States in tick-infested areas. The Center for Disease Control reported approximately 36,000 cases of Lyme in 2006 in the US, however, it is likely that this is a vast underrepresentation and that number of infections should be closer to 300,000 to 400,000 cases per year[3]. This suggests that many individuals suffering from Lyme disease either go untreated or are misdiagnosed.

Today, Lyme disease has become a prototypical emerging infectious disease, however, it is commonly left untreated due to difficulty in its diagnosis. The initial infection causes an inflammatory response within the body, which usually results in a localized skin rash commonly referred to as erythema migrans[1]. Erythema migrans present as a bull's eye rash that radiates from the tick bite. Progression of the bacterial infection typically results in systematic inflammation of the body, specifically in the muscles, heart, joints, as well as in the central and peripheral nervous systems[1]. Late diagnosis of this disease allows the microbes to accumulate and travel through the bloodstream, spreading to the heart, joints, and the nervous system. When the infection spreads to the nervous system, this is when you start to see neurological manifestations. Once the infection starts to affect the brain, the infection is now referred to as Lyme neuroborreliosis (LNB). LNB causes secondary psychiatric symptoms to transpire in individuals suffering from the infection. These secondary psychiatric symptoms are caused by the *Borrelia* bacteria attacking nerves in the brain, which triggers those cells to send pain signals. The brain then enacts an immune response to these pain signals, which ultimately results in inflammation within the brain, which is responsible for the cognitive abnormalities. The neurological manifestations of Lyme can result in disturbances that present as primary psychiatric disorders. Primary psychiatric disorders, in comparison to secondary psychiatric disorders, are unrelated to biological ailments. Both primary and secondary psychiatric disorders can result in symptoms such as the following: short-term memory loss, severe depression, panic attacks, anxiety, paranoia, impulsivity, obsessive-compulsive disorder, and personality changes marked by irritability and mood swings[1]. However, more severe central nervous system symptoms such as these can be avoided by early diagnosis and treatment.

Lyme Around the World

If you live in the northeast, you have probably heard of Lyme disease, but what many people don't know is that Lyme disease is a global epidemic. The illness is not only an issue in the United States, but is also seen in over 80 countries around the world. The major infecting agent of Lyme in the US, *Borrelia burgdorferi*, is often not the bacteria we see causing

Adult Deer Tick on flickr



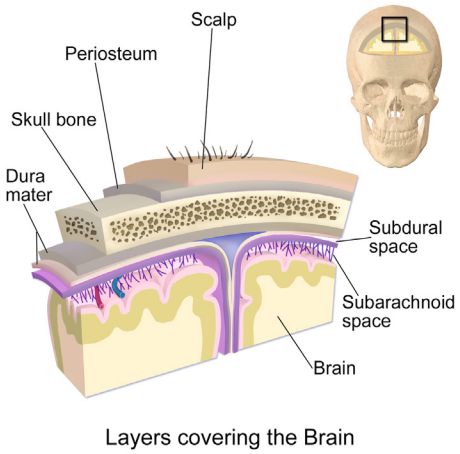
Geographical distribution of reported Lyme Disease cases (seen in orange) on CC

infections in other regions. For example, *B. afzelii* and *B. garinii* of the Borrelia family are responsible for most cases of bacterial infection in Europe and Japan[4]. The variability of the Borrelia species throughout geographical regions, results in a wide range of diverse symptoms that may characterize this infection. This is because different Borrelia species affect the human body in different ways[4]. For example, LNB is mostly caused by *B. garinii, B. afzelii* typically results in dermatological symptoms, and arthritis is mostly symptomatic of the species present in the United States, B. burgdorferi[5].

A 2010 case study examines an American 12-year-old girl who contracted Lyme neuroborreliosis (LNB) in Europe[4]. When the girl returned from her vacation in rural France, she was admitted to the hospital for cervical spinal cord inflammation and facial nerve palsy, which is a loss of movement in her face due to nerve damage. Physicians immediately tested her for Lyme, but her lab results were relatively inconclusive. The young girl did present the prototypical erythema migrans or "bull's eye" rash at the site of the tick bite, which was a key factor in her diagnosis. However, her story is often used as an example to explain why North American serological lab tests (i.e. blood tests) cannot be used as a diagnostic technique when the disease is caused by a European Borrelia species[4]. This is because European strains induce variable host antibody responses, leading to reduced reliability of serological analysis, which is the common method used in North America. In the case of this young American girl, the physicians were able to identify the pathogen of her illness solely with clinical analysis (i.e. identifying prototypical symptoms such as erythema migrans). Despite the inconsistent reliabilities of lab results, typically in the majority of LNB cases, medical tests are required for proper diagnosis.

The Difficulty in Diagnosis

The nonspecific symptoms associated with LNB make diagnosis of this illness a daunting task. In addition, the prototypical 'bullseye rash' that is specific to Lyme disease does not always appear, so physicians usually have to rely on other diagnostic measures[5]. The neurological manifestations that are presented in LNB can occur as early as one week after initial infection. These neurological symptoms typically result in response to the inflammation that occurs in the subarachnoid space, which is located in between the skull and the brain. Inflammation here causes swelling of the cells surrounding each of the brains neurons in the cortex[1]. Physicians typically resort to serological lab tests as the primary diagnostic method because clinical diagnosis can be challenging due to the wide range of potential symptoms. Most serological tests consist of a two-tiered algorithm in which a screen for B. burgdorferi antibodies detect whether the infection is present. Although this method is more accurate than other molecular tests, there are many limitations. Up to 15% of patients with neurological Lyme test a false negative[6]. Also, 5% of patients can actually test a false positive, which is usually amongst individuals living in Lyme-



Layers covering the Brain

Layers Covering the Brain on CC

endemic regions[6]. The wavering sensitivity of these serological tests are most likely due to the fact that they are not testing for the presence of the bacteria itself, but instead test for antibodies for the bacteria. When early diagnosis is achieved, treatment of a round of antibiotics, typically orally administered doxycycline, results in complete recovery[7]. Complications in treatment occur when the acute infection is left untreated for an extended period of time. When this happens, typically patients are diagnosed with chronic Lyme disease, which is a treatment-refractory illness.

Due to the irregularity of the presented symptoms and serological lab results, it has become common for physicians to mistake chronic Lyme with psychiatric disorders. A psychiatric disorder is a condition of the mind that disturbs mood, thinking, and behavior. Primary psychiatric disorders lack an underlying medical diagnosis or etiology and instead are classified through the Diagnostic and Statistical Manual of Mental Disorders or the DSM. Lyme is not the only medical illness that can be conflated with diagnosis of a mental disorder. Other illnesses such as syphilis, AIDS, viral pneumonia, hypoxia (oxygen deficiency), temporal lobe epilepsy, and vitamin B12 or folate deficiencies can all often be misdiagnosed as a primary psychiatric disorder[1]. When laboratory tests lack definitive diagnosis or when initial therapeutic interventions don't work, physicians will refer patients to psychiatrists for psychiatric treatment. Mislabeling Lyme patients has detrimental effects on the progression and treatability of this infection, however mislabeling a primary psychiatric patient with Lyme is also problematic, as administration of unnecessary antibiotic treatment can result in antibiotic resistance, and possibly lead to a superinfection. Diagnosing a neuropsychiatric disorder such as LNB can be extremely difficult, which is why there are so many reported cases of misdiagnoses.

One of the primary psychiatric disorders that LNB can imitate is schizophrenia. Schizophrenia is a chronic mental disorder that is associated with a disconnection from reality. The inflammation that can occur due to the Borrelia spirochete infection leads to neurogenerative changes that present as schizophrenia-like symptoms; such as delusions and hallucinations.

The following case studies exemplify instances where physicians can mistake a primary psychiatric disorder, such as a schizophrenia, as neuropsychiatric Lyme and vice versa. Both of the patients described below made full recoveries after correct treatment was identified.

Case Study I

Patient with previous history of Lyme Disease diagnosed with a primary psychiatric disorder

A 2015 study reports the case of David Smith* , a 41-year-old male with previous history of a Lyme disease infection, who was hospitalized for presented psychosis[8]. David had attempted suicide twice in which he stated that he was commanded to do so by the devil. In his first attempt he tried to strangle himself with his bed sheet, and the second attempt was made in the hospital when he tried to suffocate himself with a pillow. His wife explained to the doctors that over the past few weeks his symptoms had deteriorated and his hallucinations were becoming more frequent. David was also self-medicating with alcohol, which is not an uncommon behavior in patients suffering from mental illnesses. A medical workup was completed including a CT scan, however no abnormalities were shown to explain his altered mental status. Since David had previous history with Lyme disease, the doctors also completed a series of serological tests to examine any residual bacteria. An array of psychiatric symptoms including paranoia; major depression; catatonia (abnormal movement and behavior); mania: olfactory, auditory and visual hallucinations have all been documented in result of *B. burgdorferi* infection, so doctors wanted to rule that out[8]. David did in fact test positive for specific antibodies in serological testing, however, the internist determined that no antibiotic treatment was needed because there were no recent signs of infection (i.e. erythema migrans or recent exposure to ticks). The antibodies that his body produced were most likely left over from the onset of his infection

years ago. Ultimately, he was placed in inpatient care and his behavior and mood were evaluated over the preceding weeks. At this time David's auditory hallucinations did improve, but he still experienced paranoia and additionally developed manic symptoms that involved dancing around the ward for hours at a time, increased energy and decreased need for sleep. This behavioral evaluation ultimately led to his diagnosis of schizoaffective disorder as his psychotic symptoms met DSM criteria. Schizoaffective disorder is a subtype of schizophrenia, which is classified by cycles of severe symptoms such as delusions, hallucinations, and manic episodes, followed by periods of improvement. The patient was treated with 500 mg of divalproex, an anticonvulsant, once a day resulting in diminished mood symptoms. Afterwards, the patient was able to recover completely.

In David's case, his previous history with Lyme disease perplexed the physicians. His ultimate diagnosis of a primary psychiatric disorder, schizoaffective disorder, was disguised as a secondary psychiatric disorder resulting from possible neurological manifestations of Lyme disease. Despite the discrepancies of his diagnosis, today, David is able to receive the proper medication and therapy needed to manage his mental illness.

Case Study II:

A 22-year-old woman with neuropsychiatric Lyme disease

A couple of years ago, Emma Carlson*, a 22-year-old woman, was hospitalized for a flu-like illness and headaches[9]. Her symptoms quickly deteriorated, manifesting into swollen glands, painful joints, fevers, severe fatigue, stuttering, and occipital headaches. Emma also experienced hyperacusis, which is a hearing disorder characterized by an increase in sensitivity to certain volume ranges and frequencies. She also developed a sensitivity to light. Excessive auditory and visual perception disorders such as these are typical symptoms found in patients with schizophrenia. Doctors working on her case reported normal physical and neurological exams, including an MRI. At the time, Emma did reside in a Lyme-endemic area; however, upon serological examination, her tests revealed to be indeterminate for Lyme disease and there was no medical history of a tick bite or erythema migrans. The attending doctors decided on a probable diagnosis of LNB based on her physical symptoms, so she was treated with four weeks of oral antibiotics. However, Emma's condition did not improve. The doctors administered a subsequent 8-week course of IV ceftriaxone, a more aggressive form of antibiotic treatment, but only mild improvement were made.

Fifteen months later, Emma's symptoms still persisted. Her doctors were still convinced that she was suffering from LNB, so she was yet again placed on another round of antibiotics, but this time for 7-weeks. Miraculously, Emma's symptoms began to fade as she experienced a drop off in her fatigue and other physical symptoms. However, her health did not stay long as she was re-admitted to the hospital after developing irritability, panic attacks, obsessive behavior, and depression. At this time, Emma's doctors began to think that her illness may not be linked to an underlying medical condition such as Lyme disease. They treated her with the antidepressant, clomipramine. Nonetheless, her mental state continued to regress. She began to present episodes of mania with rapid mood swings as well as paranoid delusions, and auditory hallucinations. Emma was tested again for LNB, but once again serological and routine cerebral spinal fluid tests came back negative.

At this point, doctors began to examine Emma as a psychiatric patient in which they diagnosed her with atypical bipolar disorder and possible obsessive-compulsive disorder. Atypical bipolar disorder is a primary psychiatric disorder in which rapid cycling between manic and depressive states occur with little recovery occurring between each cycle10. Characteristically, classical bipolar disorder, marked by clear divisions between the two states, can be easily treated with antidepressants, however atypical patients usually respond better to anticonvulsants if previous treatment does not improve mental condition[10]. A patient with obsessive compulsive disorder usually experiences uncontrollable or reoccurring thoughts (obsessions) and behaviors (compulsions) fired by the urge to repeat these impulses over and over again[11]. Lithium, an antidepressant, was administered to help regulate Emma's manic state and the patient was once again discharged[8].

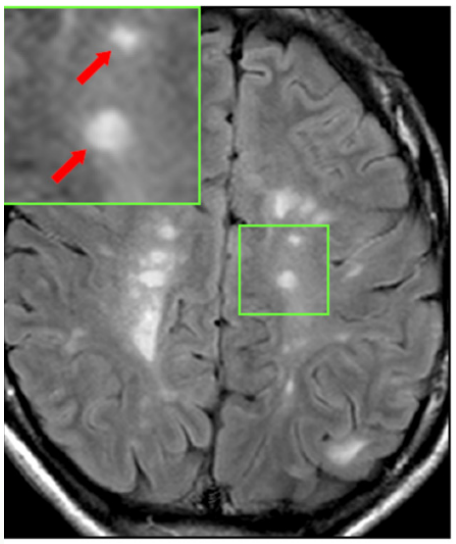
However, Emma's case was still far from being solved[9]. At home, the young women remained severely

depressed. Additionally, she began to develop cognitive dysfunction, in which she experienced difficulty spelling, writing, and speaking. These symptoms worsened, to the point where Emma was hospitalized for an attempted suicide. In the hospital, more symptoms emerged including: mania, panic attacks, paranoia, verbal aggressiveness, violent impulses, irritability, auditory hallucinations, blurred vision, stuttering, hip and knee pain, memory and concentration problems, and occipital headaches. At this point, the doctors were baffled by her case. Some of her symptoms were associated with previous Lyme cases, so once again they decided to work her up for a possible LNB diagnosis. However, just like in previous examinations, her serological tests came back negative. An EEG was also performed but it displayed normal brain activity. Stumped, the physicians placed Emma on another course of antidepressants, but no improvements were made. Eventually, after much debate, the doctors cycled back to their original theory of neurological Lyme despite the negative support from lab results. Emma's doctors argued that previous case studies revealed the link between LNB and psychiatric disorders, and the patients clinical symptoms matched this diagnosis. Once again she was placed on a trial of IV ceftriaxone. Initially, the young women's mental health regressed further as she reported experiencing horrific images of killing others. Finally, after two weeks of antibiotic treatment, Emma's symptoms markedly diminished and she was able to return home, undergoing a full recovery.

Late stage Lyme diseases' ability to mimic other known diseases including psychiatric disorders is undeniable. In the first case of David Smith, his diagnosis of a psychiatric disorder was convoluted with the his previous history with Lyme disease. In Emma Carlson's case, it was ultimately identified that she suffered from late stage Lyme disease with associated psychiatric symptoms. The underlying infection was extremely difficult to diagnosis, as the presented symptoms mostly suggested psychiatric treatment rather than a medical diagnosis. When diagnosis of Lyme is not proven but suspected, either because the clinical profile strays from the characteristic symptoms of the disorder or because of negative diagnostic tests, it is not uncommon for doctors to administer a trial of antibiotics to hopefully work as either a diagnostic or therapeutic tool[12]. Emma Carlson's infection was not able to be retorted by initial therapy of antibiotic treatment. This is likely because her infection was so widespread that the length of the first rounds of antibiotics was not long enough to fight off the entire infection. Not until the patient was treated with both antibiotics and antidepressants, did she gain her health back.

Diagnosis using Functional Brain Imaging Techniques

In both of the case studies discussed, neuropsychological testing was conducted using CT, EEG, and MRI scans to evaluate brain activity and abnormalities. EEG, or electroencephalopathy, assesses the overall activity of the brain by placing electrodes directly onto the scalp of patients. Structural imaging techniques, such as CT, or computed tomography scan, and MRI or magnetic resonance imaging, allow physicians to evaluate highly detailed, but static images of the brains' anatomy[12]. MRI scans of patients with LNB as well as other demyelinating disorders such as multiple sclerosis, sometimes illustrate punctate white lesions, or tiny white holes in the part of the brain that contains nerve fibers[12]. The white lesions, pictured as brightened areas, illustrate regions of demyelinated cells, or deprotected nerve fibers. When neurons become demyelinated, the electrical impulses that are sent are slowed significantly and



fMRI illustrates white lesions on CC

can even cease to fire completely, resulting in major neurological problems. After antibiotic treatment, these white matter lesions are typically resolved[12]. However, in patients suffering with late-stage neurological Lyme Disease and present debilitating neuropsychiatric problems such as in Emma's case, researchers have noticed that MRI scans usually appear normal[12]. On a similar note, EEG analysis can show an overall reduction in brain activity, but it is not able to localize where the issue may be stemming from.

A new method for differentiating neuropsychiatric Lyme disease from primary

psychiatric disorders that has shown promising results is use of the SPECT scan, or single photon emission computed tomography[12]. SPECT uses gamma rays to provide a true three-dimensional image of the brain while simultaneously monitoring biological activity levels. Abnormal Lyme SPECT scans show a heterogenous pattern of decreased perfusion in the cortex as well as in the subcortical white matter as previously discussed. These patterns can be visualized in up to 96% of Lyme scans, suggesting a very high sensitivity rating for this technique[12]. However, the patterns are nonspecific to Lyme disease itself, and can also be seen in patients with medical disorders that have the same underlying biology, such as chronic fatigue syndrome and cerebral vasculitis (i.e. inflammation of the blood vessel wall)[12]. Despite SPECT's inability to differentiate Lyme disease from other similar inflammatory conditions, this imaging technique has been extremely beneficial in distinguishing Lyme from primary psychiatric disorders.

How do you get the diagnosis right sooner?

That truth of the matter is that there is no easy way to diagnosis Lyme disease. When the prototypical erythema migrans do not emerge and blood tests appear negative, which unfortunately are both common occurrences among Lyme patients, diagnosis becomes a very challenging task. It's no wonder that there are so many cases each year that go undiagnosed and are able to manifest into much larger neurological problems. However, an important diagnostic clue, might be simpler than we anticipated. If assessing clinical symptoms, lab results, and functional brain imaging techniques are all inconclusive, then physicians may look for context clues. How, when, and why these symptoms occurred can say a lot about any illness that is being studied. Many Lyme disease specialists recommend asking the following questions to suggestive Lyme disease patients:

(1) At what time of year did your symptoms begin?

(2) Where were you geographically when these symptoms occurred?

(3) Have you, a pet, or family member spent a lot of time outdoors during the onset of your symptoms?

These are very important questions as they get at the true etiology of the disease itself. Did the condition start in the summer months when tick populations are at a high? Was your patient in a high Lyme endemic region at the time and could they have been exposed to outdoor conditions where ticks reside? Although these questions may seem trivial, especially in the midst of an extremely complicated and mysterious medical case such as the ones described above, they can provide vital information to the nature of the disease.

Simple tactics like these, that may seem obvious, often get glossed over in the diagnosis process, especially when the conditions are serious and have progressed into affecting the patients mental health. Something as small as three short questions could prevent early stages of Lyme disease from progressing into a chronic neurological condition. General awareness of this disease when hiking or vacationing in woodsy areas during the summer months would also be very beneficial in prevention of Lyme disease. After a hike, immediately checking your body for ticks can avoid the initial onset of this bacterial infection as it is not uncommon for ticks to latch onto you for hours before actually ever biting. If you live in a Lyme-endemic region remember these three questions because they may be the difference in preventing an easily treatable infection to manifest into a chronic mind-altering disease.

Lyme by "3smok" on pixabay

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Lyme Grass by "Karsten Madsen" on pixabay

The Fight for Free Will

By Antoinette Steely

Closed Doors by "JB_Bandit" on pixabay

The history of science has taught us that most concepts are dynamic. Society creates temporary taxonomies of words through casual language and functional context, then it is the role of science to discover the meaning behind these terms and assign them a true definition. Water was just an ambiguous phrase used to reference something unknown until scientific discoveries illuminated the complexities at work and provided the word with value. This idea that scientific explanations provide meaning by identifying the objective physical properties behind a phenomenon has been reliable, but some ideas are more abstract and cannot be fully described in purely physical terms. Free will is one of these nearly inconceivable concepts, yet it is fundamental to our understanding of both individual and social human life. In the past few decades, neuroscience has begun to address questions of freedom and moral responsibility that had previously been left to philosophy. When the natural sciences first addressed the topic, many rejected the past history of philosophical work, and came to accept that the physics and neuroscience had undermined the previous definition of agency. An agent is no longer capable of causing change through decided action. In a physically determined world, free will must merely be a perceptual illusion that we experience as a byproduct of unconscious brain activity. The natural sciences have jumped to the conclusion that the argument to best explanation must be that free will as we know it does not exist; however, this is based on a fundamental misunderstanding of what constitutes freedom.

The conviction against free will began in 1983 when Benjamin Libet conducted a series of extraordinary experiments that showed evidence that the intent for deciding is made unconsciously[1]. The physiologist at the University of California, San Francisco was enthusiastically praised for the mighty impact he

made against human free will, but the philosophical adoption of his ideas was a mistake. In his original experiment, participants were instructed to perform small finger movements, and report the moment when they became aware of the conscious decision to move[2]. This measurement showed physical evidence of brain activity before conscious awareness of self-initiated movement through a rise in an electrical potential or "readiness potential (RP)."

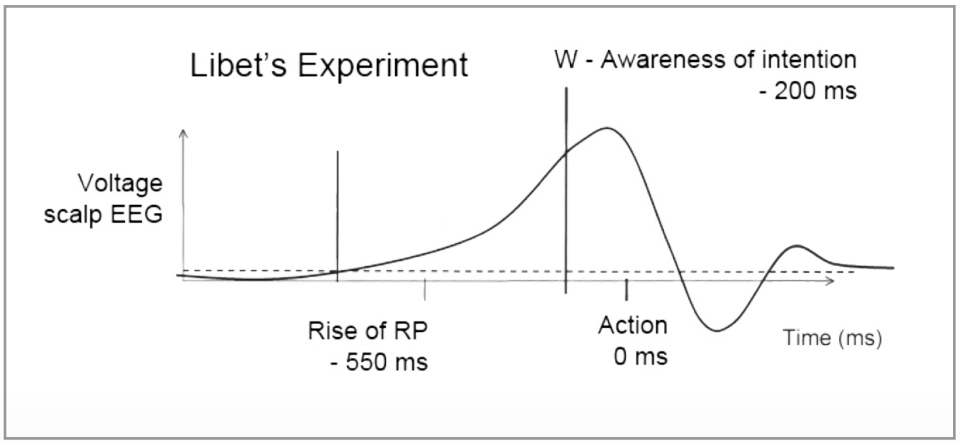

Figure 1: *A rise in the RP can clearly be shown 550 ms before a subject experienced the conscious intention to perform a finger movement. Libet Experiments. from Information Philosopher on Creative Commons*

Under this system, decision making is neither free nor voluntary, and we do not have control in the way that we think that we do. The feeling that we have the ability to do otherwise at any given moment might just be an illusion. Recent studies, however, suggest that the Libet data had been misunderstood, and readiness potentials represent a build up of activity to a certain threshold that, once passed, trigger a voluntary act[3]. The neuroscientific understanding of free will and agency is limited to willed action; therefore, it can only answer questions about executive control and the spatial and temporal components of decision making. The assumption that freedom is time independent of the will could be a mistake. In A Critique of Pure Reason, Immanuel Kant revolutionized the relationship between the internal and the external by suggesting that decisions are formed within the soul and are therefore outside of time[4]. Our perception of space and time through the senses merely cause the appearance of determined action. If an individual's sense of agency is grounded in the belief that the experience of decision making is sufficient for free action, then it is necessary for us to value our experience. This necessity persists even if it conflicts with the way that the world physically operates, implying that a metaphysics of causation is fundamental to a complete definition of free will.

It turns out that the philosophical debate on free will is strengthened by neuroscientific evidence of executive control rather than weakened by it. Regardless of whether or not our decisions are based on conscious intentions, the idea that we can decide at all already presupposes the existence of free will. In making claims about freedom without first defining the relevant terms, many experiments have inadvertently not only implied, but necessitated, the types of freedom that some philosophers do not even grant us at all. The conclusions made in empirical papers are generally too hasty and often can be weakened by counterexamples.

A preliminary definition of free will depended on an agent having a garden of forking paths available to them at any moment. This concept has long been lost due to new developments in both physics and in neuroscience, but it is not the only way that philosophy discusses personal agency and moral responsibility. In fact, many metaphysicians believe that our understanding of freedom and power differ from truly having alternate paths. While the physical sciences provide evidence that agents have no freedom at all, these empirical data are not sufficient for a necessary understanding of being. Robert Kane's theory of probabilistic causation suggests that there is a conscious effort involved in decision making that keeps our outcomes from being truly inevitable[5]. This effort of free will allows for causal outcomes which are endorsed by the agent, and an individual can fail or succeed in carrying out a chosen desire.

As discussed before, Libet conducted an experiment which made philosophers and scientists alike rethink what types of decisions are open to choice[1]. Libet evaluated spontaneous decision making by asking participants to perform self-initiated motor tasks whenever they felt an urge or desire to do so. The time of the participants awareness of intention was reported as W. Active scalp electrodes were placed over the motor and premotor cortical areas, which are known to be responsible for controlling hand movements. Scalp electroencephalography (EEG) is a noninvasive technique for recording RPs at the surface of the brain. RP's are negative spikes in electrical activity recorded through EEG to reflect event related potentials. Libet found that even when participants did not report


Which way? by Hafsteinn Robertsson on flickr

preplanning for each movement, the onset of the negative rise of the RP could be recorded around 400-700 ms before the motor act began[2]. This finding was the first to suggest that the cerebral processes that moderate motor action are unconscious and involuntary. The subjective experience of intention then, is an epiphenomenon that occurs after a decision is brought forward involuntarily by an unknown cause. Consistently and significantly, conscious intention to act occurs 350-400 ms after the onset of cerebral activity, meaning that the spontaneous voluntary acts are cerebrally initiated unconsciously.

The Libet experiments caused major doubt that we understand how the way we experience the world relates to the way that it physically exists. While it is important that these studies triggered an intense debate and a series of ongoing research to answer this question, the implications have been brought forward far too soon. EEG recordings have high temporal resolution, meaning that the accuracy of the time that an RP occurs is reliable; however, EEG recordings have low spatial resolution. Placing an electrode over the prefrontal motor area, does not ensure that the recorded RP is coming from that region. As a highly complex system, the brain is involved in many neuronal processes related and unrelated to decision making at any given moment, many of which could confound a signal to an electrode. Furthermore, the Libet experiment has been challenged many times suggesting that this type of experiment contains flaws, and that we should not be so quick to give up our fundamental understanding of human nature.

A particularly interesting experiment conducted in 2014 suggested that the Libet experiment was misguided in assuming that they were testing free will and agency, rather than an individual's ability to reflect upon inner events[6]. Jo Wittmann and his team challenged Libet's study by creating an experiment that focused on the introspective perspective when completing a motor task, and connected first person experience to the empirical brain dynamics involved in high level conscious decision making. They found that an expert meditator, who is more focused and better in touch with their mental states, could more accurately and reliably report neural correlates of intentional behavior with the subjective experience of deciding to move. When the participant accurately associated the feeling of an inner impulse to move with the RP, a recognizable pattern of similar negative deflections was also recorded, even if the participant did not immediately engage in the motor task. When there were more frequent occurrences of conscious willed movement during negative deflections of slow cortical potentials, the recorded RP was larger. This means that the negative

shifts of slow cortical potentials may promote the formation of a conscious decision to perform a motor task by facilitating a desire to engage in a movement before the conscious decision. There is an inner event, then, correlated with brain activity that both precedes and seemingly causes voluntary action.

While this first-person approach only had one participant, it brought forward an important objection that Libet type experiments do not directly record our ability to decide. Furthermore, it is in agreement with Libet type follow up studies that report that a narrowed definition of intention has resulted in a generalized sense of agency and conscious will in experiments. The sensation of wanting to move right before doing so has been accepted as the sufficient operational que for intent; however, in 2013 Vinding, Pedersen, and Overgaard found that there are actually two types of recordable intention involved in the efficacy of conscious decision making[7]. This intentional binding paradigm separated immediate proximal intention from distal or longer standing intentions. Distal intention represented the condition under which a formed self-paced intention precedes movement, while proximal intention was the condition under which participants acted as soon as they experienced the urge to do so. They found that distal intentions, which had not previously been recorded, resulted in a stronger sense of agency for participants than proximal intention, which had been the focus of other EEG experiments[8].

In a 2014 follow-up study, the group found a slow negative EEG response that could be recorded at the time when participants formed a self-initiated distal intention. This electrophysiological potential was not reported when patients intentions were formed as a response to a cue rather than self-paced, suggesting that experiments that require cued motor tasks may not be testing an individual's own agency. The temporal aspect of intention allowed the experimenters to focus on decision making and conscious intention without other confounding motor activity. If distinct electrophysiological activity that is unrelated to action generation can be elicited by slow negative electrophysiological potential found above mid frontal areas, then conscious intention is related to motor activity, and we do not form decisions fully unconsciously[7].

Free will seems to be essential for individual and social well-being; however, many experiments have been quick to undermine this concept as an illusion. Testing when intention for a motor tasks arises can only illuminate so much about an individual's subjective experience. What would happen to participants' performing Libet studies if they started to doubt their experienced freedom? A team in Berlin lead by Davide Rigoni studied just that by hypothesizing that if a participant's free will is denied, then they will become less intentional in their involvement in their preparation of voluntary motor actions[9]. They observed that the destruction of free will affects brain correlates of volitional processes even at a subconscious level. When individuals were induced to stop believing in free will, the RP was reduced before they consciously decided to move. These data suggest that the belief in free will is related to early motor preparation, not just motor execution. Abstract beliefs such as free will have a fundamental effect on our intentional actions, and manipulating these belief systems affects the preconscious stages of decision making. Self-efficacy and perceived control are likely to be important in the way we carry out motor actions and view our own agency, and the abstract belief in free will is necessary for effective planning and execution of tasks.

Unlike EEG, functional magnetic resonance imaging (fMRI) has high spatial resolution and low temporal resolution. fMRI can be used to study decision making when participants are asked to privately hold a decision

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in their mind during a delay period before acting. JD Haynes lead two fMRI experiments in which participants were instructed to view two numbers on a screen, decide whether to add or subtract the two numbers, hold this decision in their mind during a delay period, then select the intended result from a screen of multiple numbers to report which decision had been made. Haynes hypothesized that if our decisions could be predicted, we must not be free in the way that we think that we are—our casual outcomes are predetermined regardless of the experience of choice. He found that activity in medial and lateral prefrontal cortex during the delay can be used to accurately predict which decision the agent had made. These regions of the prefrontal cortex were seen to be involved in freely chosen intentions via localizable task-specific representations. When preparing to decide, the brain encodes information specifically related to that intention.

So our intentions and goals are encoded by a network of different brain regions, which can be seen by changes in task specific representations during preparation and execution of decision making[10]. Since the spatial response patterns for each task were specifically different and not merely upregulated or downregulated, intention must be highly specific. But the idea that human decisions are predictable is not novel, and hardly conflicts with philosophical assertions. To bring us back to Kane, he would suggest that there are only a few instances within a lifetime that define our identity. It is only in cases where we have equal reason to make two different choices that we would act in a way that cannot be reliably predicted[5]. Deciding to add or subtract numbers on a screen would not be one of these instances.

When the study was repeated with a focus on the frontal premotor cortex and a stronger fMRI machine, Haynes reported that when behavior is spontaneous, unconscious generation of free decisions can be observed through predictive activity patterns that increase in stability as the subject becomes closer to making a conscious decision. As the subject increased in temporal proximity to the decision, more decision related information was carried. Once the conscious decision was made, these correlations dropped off[11]. The increase in activity suggests that there may be a threshold of activity that must be crossed before we can gain conscious awareness of a decision.

In order to reconcile evidence that shows that there is no willed force involved until after or during a movement is performed with our perception that we are free agents, many labs have attempted to weaken the results and implications of Libet type experiments by altering the design. If W can be shown to be influenced systematically after a willed movement has occurred, then RPs may not be a very accurate or reliable method for determining and recording unconscious decision making. When single pulse transcranial magnetic stimulation (TMS) is applied to the supplementary motor area in Libet design experiments during the time point in which a decision is made, W is influenced. Additionally, if the experiment is changed so that the button press created a delayed tone, W is delayed respectively[12]. Even in fMRI experiments, the amount of attention placed on intention and will can skew the initial proposed results.

The manipulation of fMRI and EEG experiments suggests that we need more thorough and accurate tests before we can dismiss personal agency. Since the results of these studies can be altered, it is likely that our sense of willing is not solely related to intention of movement, and cannot be time-locked to it. A unique study conducted in 2009 by Hallett and Ellenstein directly stimulated parietal and premotor cortex regions using direct electrical stimulation. While direct stimulation techniques result in very accurate and precise data, these studies are uncommon since they require electrodes to be placed on the surface of the brain. They are commonly performed on small sample sizes of individuals who are already receiving brain surgery. In the experiment, seven individuals with brain tumors were stimulated at 57 various sites. When the right inferior parietal region was stimulated, patients experienced a strong desire or intention to move the contralateral foot, hand, or arm. When the left inferior parietal region was stimulated, patients experienced a strong desire to move their lips and speak. Increasing the same stimulation over either of these regions resulted in the belief that that motor tasks had been carried out, even though no electromyographic activity was detected. When the premotor region was stimulated, patients would not experience and even denied moving despite performing the corresponding motor tasks[3]. These results show that the conscious intention of a movement and the results that we predict from that intention are what cause the subjective experience of executing a motor task, not the execution of the movement itself.

The majority of neurological experiments conducted on intention, decision making, and free will point to the conclusion that increased parietal activity before movement execution is what triggers conscious intention

and motor awareness. The current understanding of decision making proposes that the sources of our intentions are unknown and unconscious; however, conscious motor control is active in selecting the chosen volitional process and triggering the final motor result[2]. While we may not consciously initiate voluntary motor actions, our will is active in selecting, controlling, and therefore determining their outcome. This is compatible with John Martin Fischers' definition of individual agency as "view[ing] of ourselves as agents who (help to) select the path the world takes into the future, among various paths it genuinely could take."[5] The role of consciousness and the will in motor tasks, then, is to authorize their implementation by accepting or rejecting the unconscious intention through executive control.

Even the thoroughly researched conception of executive control can be challenged by the limited capacity of the FPC. Koechlin and Hyafil argue that the FPC interacts with neighboring prefrontal regions to enable high level decision making; however, it is restricted to processing simple cognitive branching and can only maintain a pending state of a single task at one time. The prefrontal executive system is required for the materialization of higher cognitive processes, and is flexible since it is able to bear these mental tasks even though the lateral prefrontal cortex is constrained[13]. As the uppermost point of the executive system, the FPC interacts with other prefrontal regions to preserve the execution of long term decisions, particularly when they are threatened by more rewarding immediate environmental factors[14]. This evidence that the FPC is not primarily involved with complex decision making or high level reasoning processes since it acts at the end of an executive control system primarily to endorse and preserve mental plans exemplifies the sheer complexity of human reasoning.

Science is incredibly dynamic, and ideas thought to be factual are constantly undermined. No single experiment or pathway has been able to explain why humans perceive a unified conscious experience. It is unreasonable, then, to assume that one brain region alone can both fully characterize free will, and provide evidence that it does not exist. Compatibilist theories of science and free will argue that even if the source of our intentions is unknown, the laws of nature and our past experiences still contribute to the type of executive control an individual will carry out[9]. John Martin Fishcer summarizes this view and reconciles the classic definition of free will as:

> My freedom now is my freedom to add to the given past, holding fixed the laws of nature. In terms of our metaphor, my freedom is the freedom to draw a line that extends the line that connects the actual past with the present (holding fixed the natural laws). The future may be a garden of forking paths (in Borge's lovely phrase), but the forking paths all branch off a single line.

We have reasons for vetoing or endorsing actions, and those reasons are our own in the sense that they derive from our experience, even if they are unconscious. If nothing else, freedom exists as a necessary phenomenon of human nature and manifests through endorsed action. Agent control does not require the ability to do otherwise, but rather the ability to control our actions and the outcomes of our desires.

"Decisions Must Be Made" by Simon Matzinger on flickr

The philosophical conception of free will has been rejected as too vague and inappropriate for scientific and psychiatric evaluations; however, it is essential to our ethical views and structures of morality, societal life, and responsibility. Contextualizing free will in terms of decision making makes it more useful for analyzing behavior and accountability, but this scope is too narrow to include important abstract values that characterize our being. Philosophy and empirical sciences seldom coexist in intellectual discussion, and the divergence of the two fields has resulted in a language barrier. It is the scientific understanding of free will that is too limited, since it involves a heavy presupposition that control requires no predictability and conscious intention. The ability to predict which outcome an agent

will choose is not inconsistent with philosophy, since it is expected that an individual would not exercise the ability to do otherwise a majority of the time. An adapted understanding of free will that satisfies both fields could propose that insofar as an outcome can succeed in what an agent was trying for or wanting, the agent succeeds in endorsing the outcome, and this causal outcome is enough to grant freedom.

Even if human intention is merely an unconscious result of chains of necessitating causes that can be traced to the past, we can still have the freedom required for free will. As long as the domain of future reasoning contains the possible outcomes under which an individual's behavior is a function of their executive control, an individual is capable of doing whatever is a suitable function of their will. Insofar as humans have the capability to take ownership for their actions by endorsing or rejecting any given intention, those actions are up to them, and the origins of decisions are not important as a threat to individual agency. The active approval of a decision is enough to mark that decision as your own.

Decisions on Max Pixel

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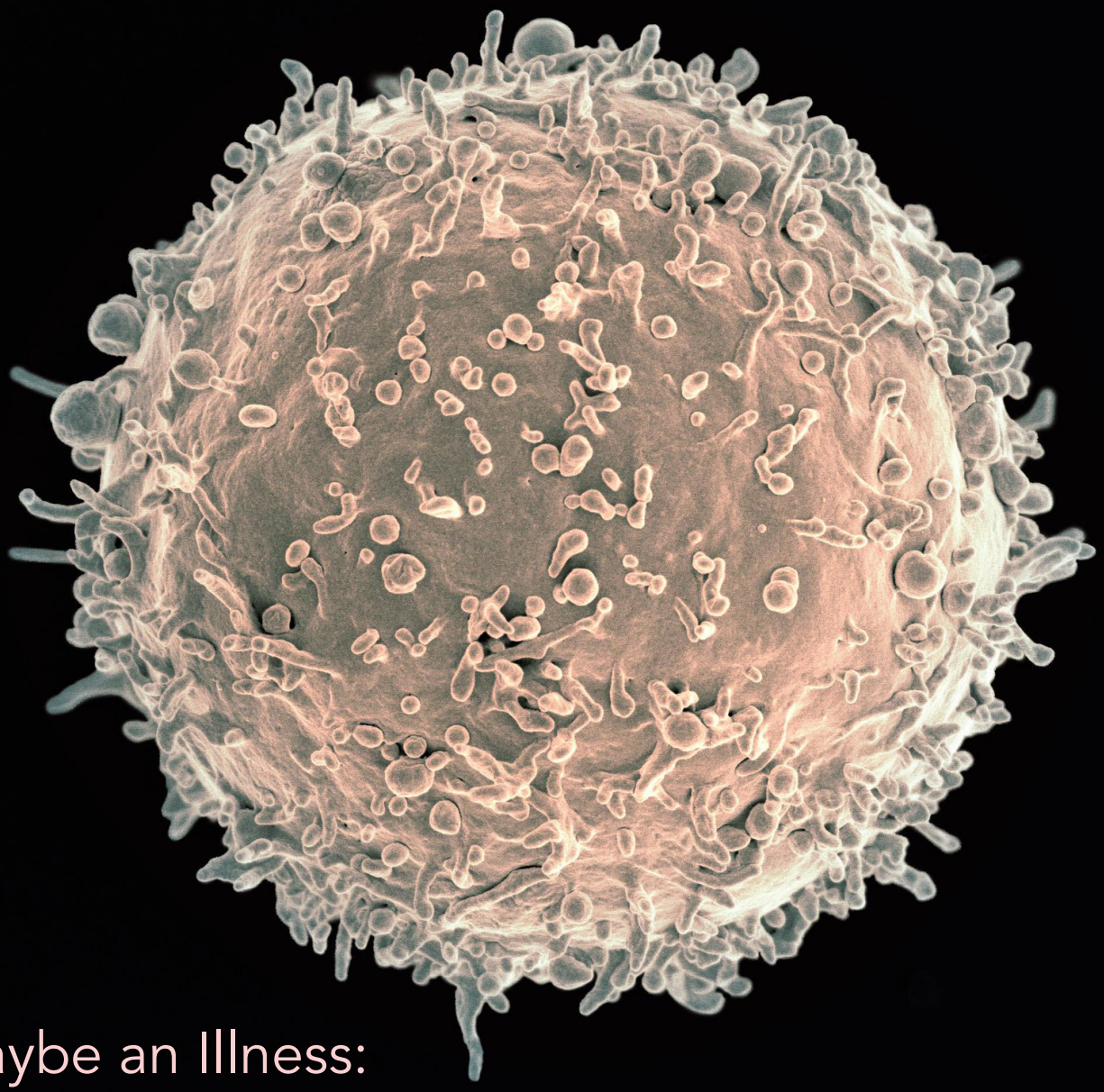
Excessive Sleepiness?



Maybe an Illness:

The Possibility of Narcolepsy as an Autoimmune Disease

By Marisol Arce

What is narcolepsy?

Narcolepsy. It affects 1 in 2,000 Americans, and over 3 million people worldwide. It is not exactly considered a "rare" disease, but it often misdiagnosed or attributed to something else. It seems like an unimaginable illness: one minute you're awake and functioning normally, the next minute you're suddenly asleep. A person with narcolepsy will suffer from "sleep attacks": unexpected episodes of excessive daytime sleepiness[1]. Often times they are triggered by intense emotions, like laughter or anger[2]. This is called cataplexy, which means that the person loses muscle tone and collapses while being conscious[2]. Currently, there is no cure for narcolepsy. Although there are an assortment of drugs and medications used to treat the symptoms, narcoleptic patients have to carefully monitor their illness for the rest of their lives. Living with narcolepsy is no easy task, it impedes everyday activities and social life, forcing many to quit their jobs and relinquish their independence.

Narcolepsy can develop at any point of a person's life. Although we do not know the definite cause of why this happens, scientists know that the loss of orexin-producing neurons result in narcoleptic symptoms[3]. Orexin, also known as hypocretin, is a hormone produced in the hypothalamus of our brain. It is essential because it promotes wakefulness and helps regulate our wake and sleep cycles. When orexin-producing neurons die, orexin production and levels drop below normal. Without sufficient levels of orexin, the body cannot keep itself awake and is thus susceptible to excessive daytime sleepiness and sleep attacks[3].

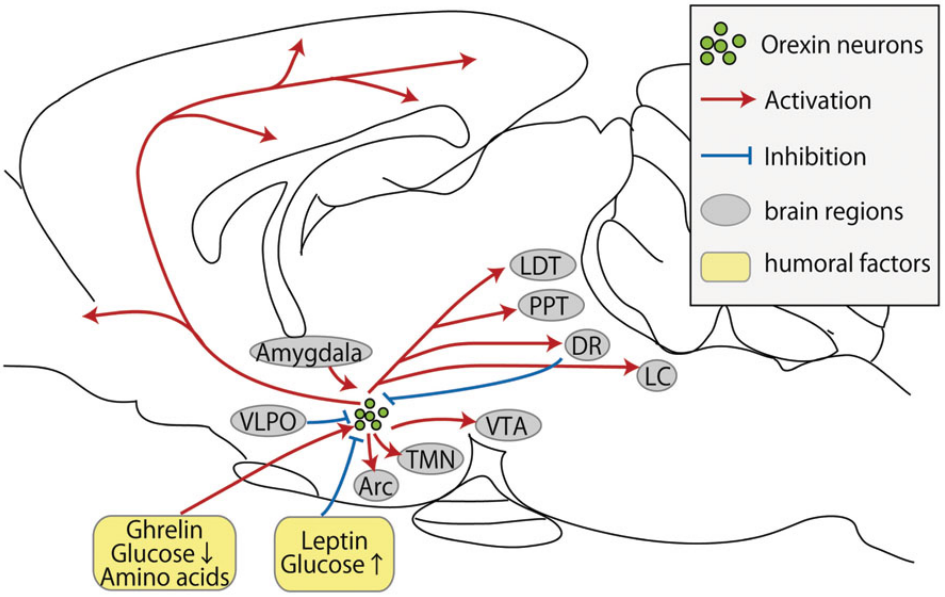
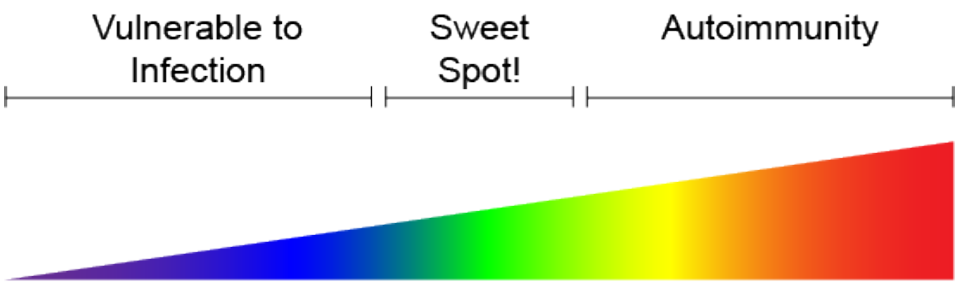


Figure 1: Schematic representation of inputs and outputs of orexin neurons. On CC

What causes narcolepsy?

There are a few hypotheses to what causes this disease. The most popular one is the autoimmune hypothesis[1,2,5]. Many years of research and scientists have backed this up, believing narcolepsy to be an autoimmune disease. But first we will discuss what an autoimmune disease is. An autoimmune di-sease is characterized by an individual's own immune system attacking their body. This occurs when the immune system can no longer tell the difference between the body's own healthy cells and foreign pathogens. What triggers an autoimmune response is not known for certain, but some people may have a genetic predisposition for developing these diseases[1]. Sometimes autoimmune diseases may be triggered by infection, like strep throat. The body's immune system makes T cells and B cells, both being the main lines of defense against foreign invaders. T cells recognize cells infected with the virus and kill them. T cells also help produce B cells, which secrete antibodies that bind to antigens. The antibodies increase the immune response and the body's fight against antigens, which is an infection. Sometimes the immune response can go wrong, and this is what starts an autoimmune disease. The antibodies produced to fight an infection accidentally start binding to healthy cells and mislabeling them as the antigen. The immune system does not realize they are making a mistake and continue to attack healthy cells, which can lead to the immune system itself weakened.

The autoimmune hypothesis of narcolepsy postulates that the disease is caused by the immune system attacking the orexin-producing neurons in the hypothalamus of the brain[1]. Some studies have pointed out the increased incidence of narcolepsy after an upper respiratory infection[6]. Although correlation cannot determine causation, it is thought that the antibodies produced to



Immune Activation by Kevbonam on CC

fight the infection somehow end up attacking the neurons as well. The mechanism by which it occurs is currently unknown[1].

Can narcolepsy be in your genes?

Narcolepsy has also been strongly linked to the human leukocyte antigen gene HLA DQB1*06:02[7,8]. Genetic studies have concluded that over 90% of narcoleptic patients have this gene[8]. But why is this significant or even important? This specific HLA gene is part of a family of genes, also known as the human leukocyte antigen (HLA) complex. The HLA complex helps your immune system in distinguishing between the proteins your own body produces and the proteins produced by pathogens. If this was somehow out of order, our immune system could attack itself or fail to protect the body from infections. The HLA DQB1*06:02 gene is thought to provide the instructions for making the proteins present on the surface of immune cells[8]. This HLA protein produced partners up with another protein to form an antigen-binding complex. This complex binds and displays the foreign antigens to the rest of the cells in the immune system to trigger a response. Many studies have been done to explore the mechanisms of the HLA DQB1*06:02 gene's effect on orexin-producing neurons but too many confounding results keep this uncertain. Although this gene is a key player in narcolepsy development, environmental factors such as prior infections also greatly influence disease onset[6].

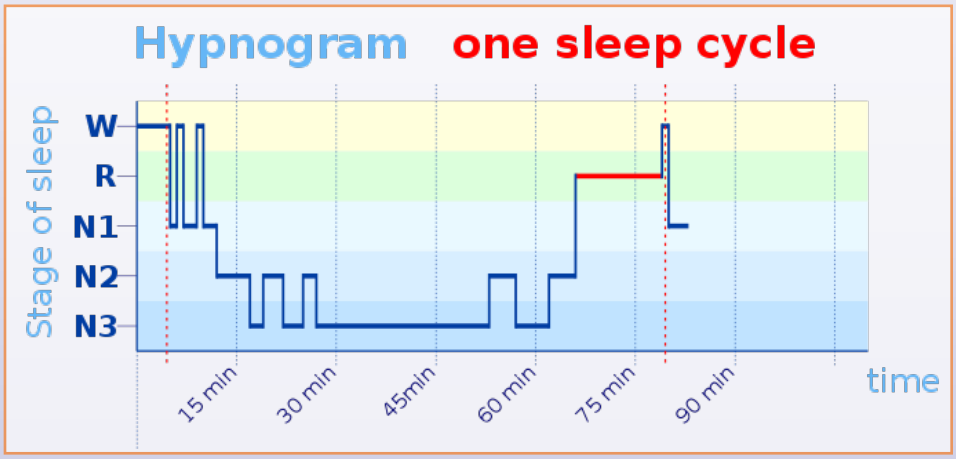
How is Narcolepsy Diagnosed?

Narcolepsy must be diagnosed by a healthcare professional, like a primary care doctor or neurologist. There are two tests that are essential in diagnosis. The first is the polysomnogram and the second is the multiple sleep latency test (MSLT). Having the patient fill out a questionnaire, like the Epworth Sleepiness Scale, is also commonly utilized to examine if the excessive daytime sleepiness criteria is met.

The MLST measures sleep latency. This is defined as the time it takes from the start of a daytime nap to the first sign of sleep[9]. If a person has narcolepsy, it should not take them long to fall asleep, usually less than 5 minutes. In the graph to the left, "SL" in red indicates the sleep latency. This graph would be an example of the MLST recordings of a narcoleptic patient. In a polysomnogram, a variety of other data is collected about the individual's sleep. A polysomnography will record brain waves, heart rate, breathing, eye and leg movements, etc. These recordings will allow the doctors to visual how the individual moves through different stages of sleep and catch any abnormalities in sleep pattern. In a normal sleep cycle, an individual will reach rapid eye movement (REM) sleep about 60 to 90 minutes after they go to bed. For a narcoleptic individual, REM sleep is achieved much faster, in about 15 minutes.

Another test helpful in diagnosing narcolepsy with cataplexy is performing a spinal tap[10]. A needle will be inserted into the patient's spine area to obtain a sample of cerebrospinal fluid. Doctors can look at the cerebrospinal fluid to measure orexin levels in the body[10]. If they are lower than normal, it indicates the loss of orexin-producing neurons and thus narcolepsy..

Narcolepsy can also present symptoms other than excessive sleepiness or cataplexy. Many



Stages of Sleep on Wikimedia Commons

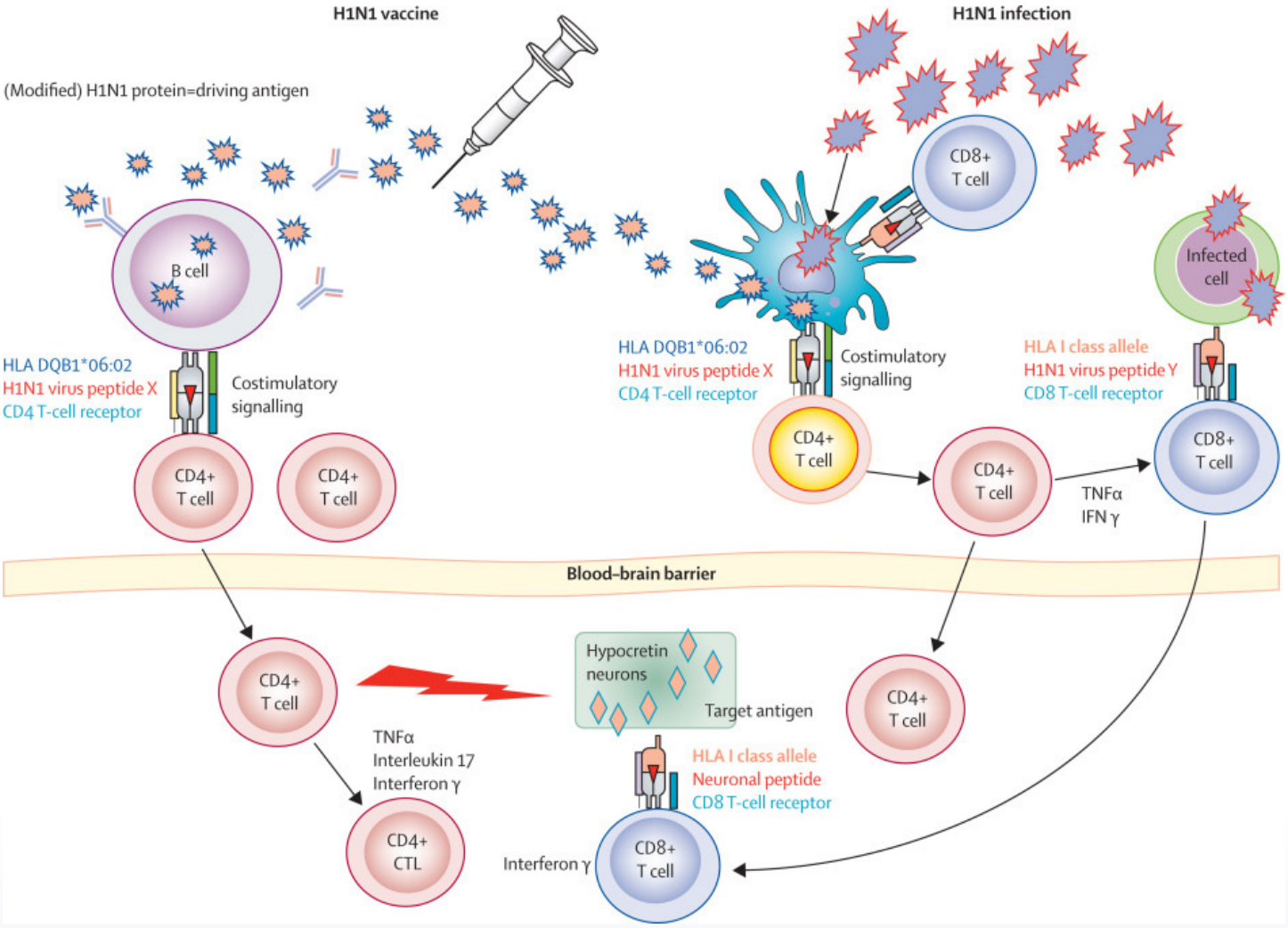


Figure 3. How the H1N1 virus and vaccine cross the blood brain barrier and attack orexin-producing neurons. Image courtesy of Partinen, Markku et al. 2014.

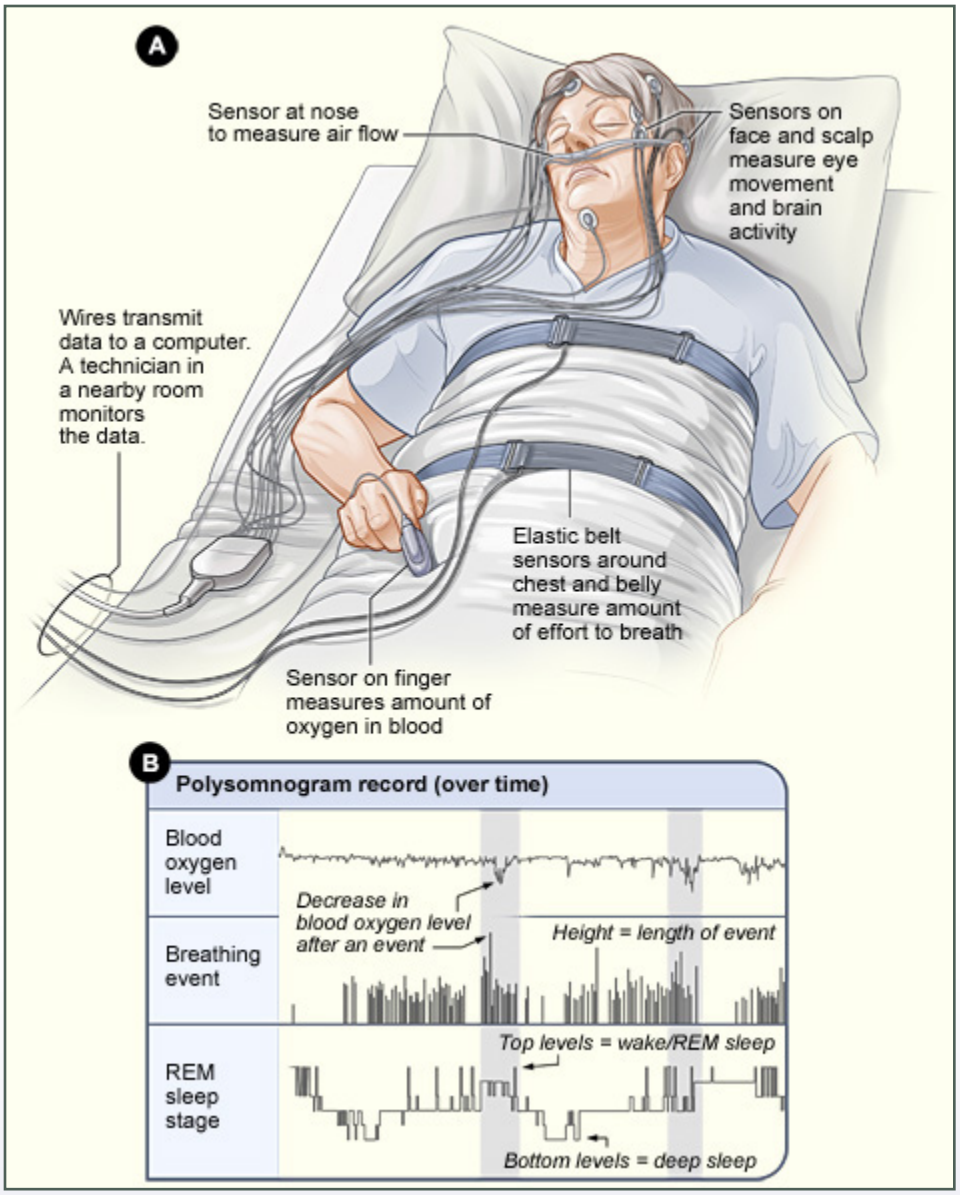
report poor quality of sleep, trouble falling asleep at night, inability to move when falling asleep or waking up, hallucinations, and extreme increase in appetite.

Does the H1N1 vaccine and narcolepsy support the autoimmune hypothesis?

Back in April of 2009, fear spread nationwide. Reports of an outbreak of a new influenza A virus spread throughout the U.S. This new virus, also called H1N1 influenza or "swine flu" spread quickly across the U.S. and other countries. At the time, the H1N1 pandemic caused a lot of panic. It was unlike other viruses seen before, made up of a combination of viral genes not seen in animals or humans previously. Seasonal flu vaccines available for the public did not provide protection against the H1N1 influenza, and an H1N1 specific vaccine was not available until after the peak of the pandemic. The CDC estimated that about 12,500 people in the U.S. died due to the virus.

Later in the year, reports of an increased incidence of childhood narcolepsy after H1N1 vaccination appeared in Finland and Sweden[11,12]. By the beginning of 2010, other countries also began reporting the same thing. It seemed that diagnoses of narcolepsy had increased dramatically in the year following the H1N1 pandemic, with a possible link to a specific H1N1 vaccine: Pandemrix[13].

There were two different kinds of vaccines available for injection: Pandemrix and Arepanrix. Both were very similar to each other but were not produced in the same way. They differed in the method in which the H1N1 antigen was isolated and purified. Pandremix ended up having a higher amount of structurally altered viral protein compared to Arepanrix[13]. The higher amount of the viral protein in Pandemrix may have caused too much of an immune response and thus triggering an attack on orexin-producing neurons. Initially, scientists thought that both



In figure A, the patient lies in a bed with sensors attached to the body. In figure B, the polysomnogram recording shows the blood oxygen level, breathing event, and rapid eye movement (REM) sleep stage over time.
A Polysomnogram on Wikipedia Commons

vaccines were linked to narcolepsy. However, thorough review of vaccination records revealed that Pandemrix was widely distributed and administered across Europe. On the other hand, Arepanrix was used in Canada and South America. This may be why Finland and Sweden saw a dramatic increase in childhood narcolepsy.

What is hypothesized to have happened here is that the vaccine triggered an immune response that was too big[7,14]. The amount of the viral antigen introduced to the host body may have caused the immune system to go into overdrive. One possible idea is that the T cells and B cells were overproduced[14]. Another possible idea is that mutant T cells and B cells are produced and released without the body realizing[14]. These mutant cells can be dysfunctional in that they are programmed to recognize the proteins on healthy cells and attack them instead of invaders. If the immune system does not realize it is producing dysfunctional immune cells and continues to churn them out, we have a big problem. As time passes more and more healthy cells are being destroyed, the immune system rages out of control, and it turns into an autoimmune disease. Since we only saw incidence of narcolepsy with patients that received the Pandemrix vaccine, researchers have come to believe that either of the two possibilities, or even both, occurred. The introduction of the vaccine may have triggered an exceptionally large immune response where lymphocytes were wrongly programmed to attack the orexin-producing neurons.

Reports of Narcolepsy in Finland and Sweden after Vaccination

Many of the people reported to have developed narcolepsy after Pandemrix vaccination were children under 17 years of age. Narcolepsy is a rare occurrence in children, especially under 10 years of age. One of the earliest cases report a 7 year old Finnish boy, complaining of excessive daytime sleepiness by December of 2009. At this point the pandemic was still ongoing and he had received the Pandemrix vaccine. He did not have a history of an upper respiratory infection, allowing doctors to rule that out as a triggering factor. Only a few months later, in February of 2010, the boy was diagnosed with narcolepsy. By August, 14 more diagnoses of narcolepsy were confirmed. They were just like that first boy: young, no history of upper respiratory infection, and receivers of the Pandemrix vaccine. Finland decided to halt the usage of Pandemrix and pulled it out of the market. As Finland began to investigate the link between Pandemrix and the increase in narcolepsy, several similar cases appeared from Sweden and France.

You can see in the year

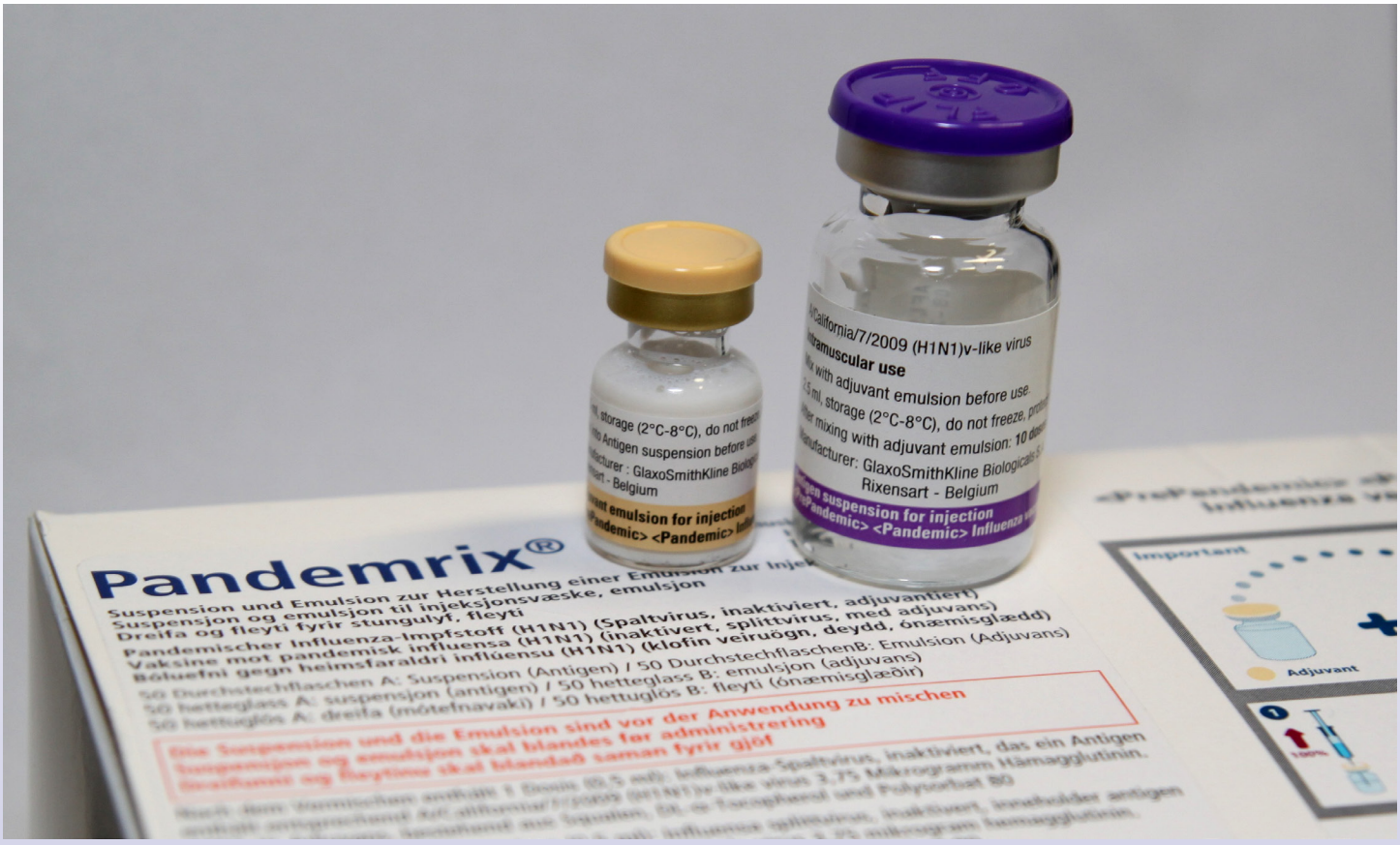
Year	2000-2009	2010
Number of Narcolepsy Diagnoses	335 (~48 per year)	101
Incidence Rate	0.79/100,000	0.79/100,000

Figure 7. Data courtesy of Partinen, Markku, et al. (2012).

after Pandemrix vaccine was administered that both the number of diagnoses and incidence rate spiked. In just 2010 alone, 101 new diagnoses of narcolepsy were made. This is more than twice the average amount from the previous years. Out of the 335 people diagnosed within a 7 year span, only 26 were under 17 years of age. This averages out to almost 4 kids each year. On the other hand, out of the 101 new diagnoses in one year, 54 were younger than 17 years of age.

Conclusion

The abnormal immune response triggered by Pandemrix vaccine seems to play a crucial part in the loss of orexin-producing neurons characteristic of narcolepsy. This event highlights the need for more research on how and why autoimmune diseases occur. Genetic predisposition, family history, physical trauma or injury, ethnic background, medical history, etc. are all factors that differ with each individual and can contribute differently to their immune response. Knowing that even a simple vaccination could initiate an abnormal response, further knowledge is necessary for protecting ourselves when our bodies turn on us.



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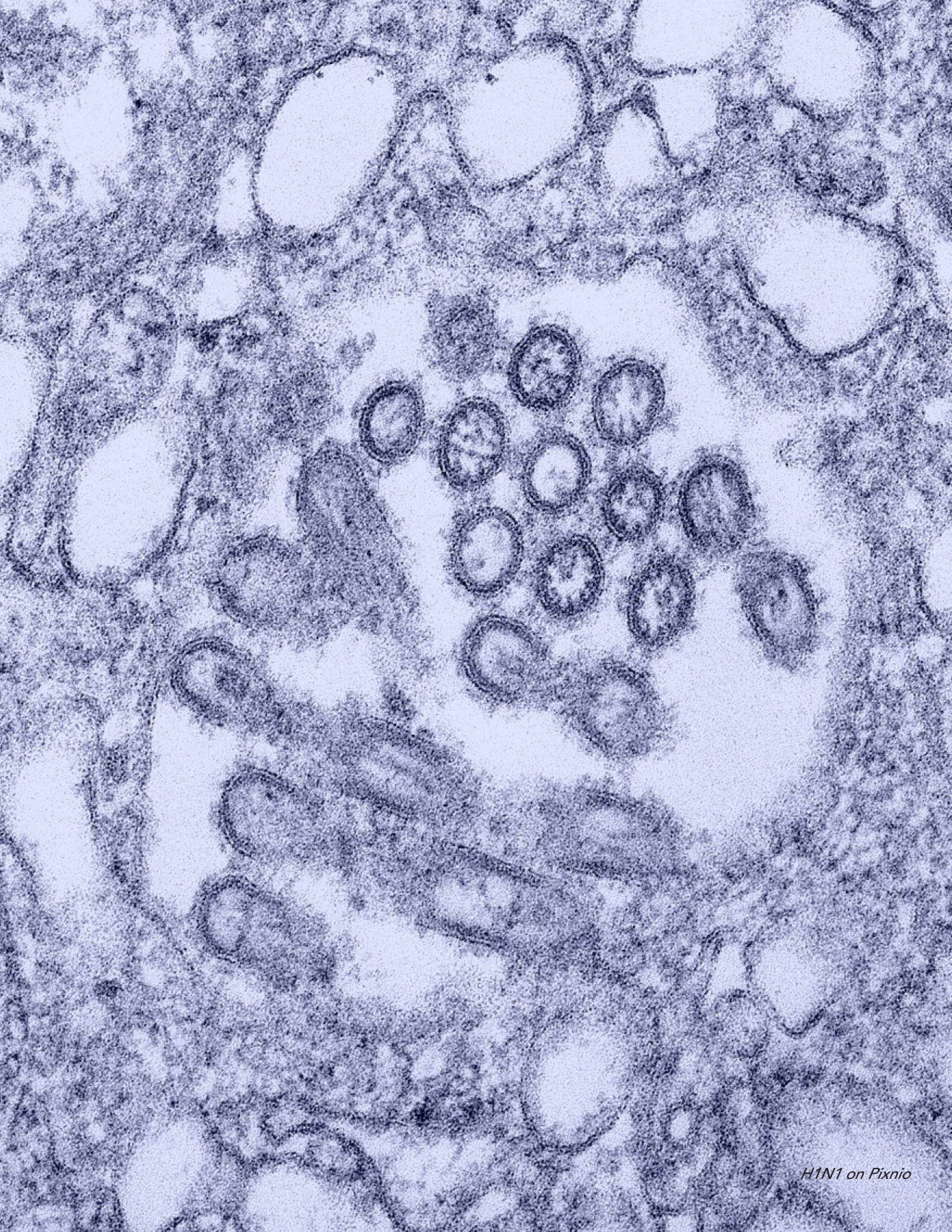
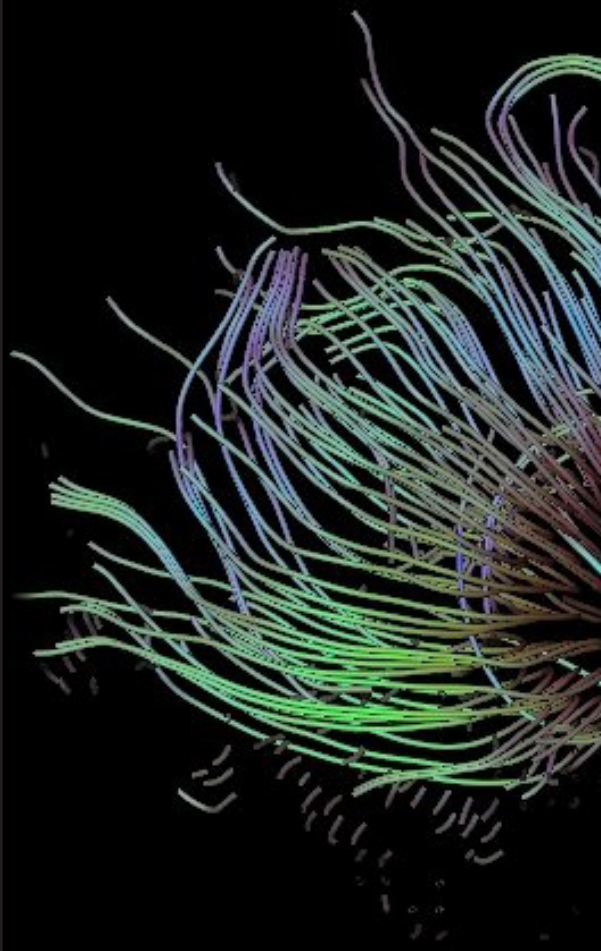
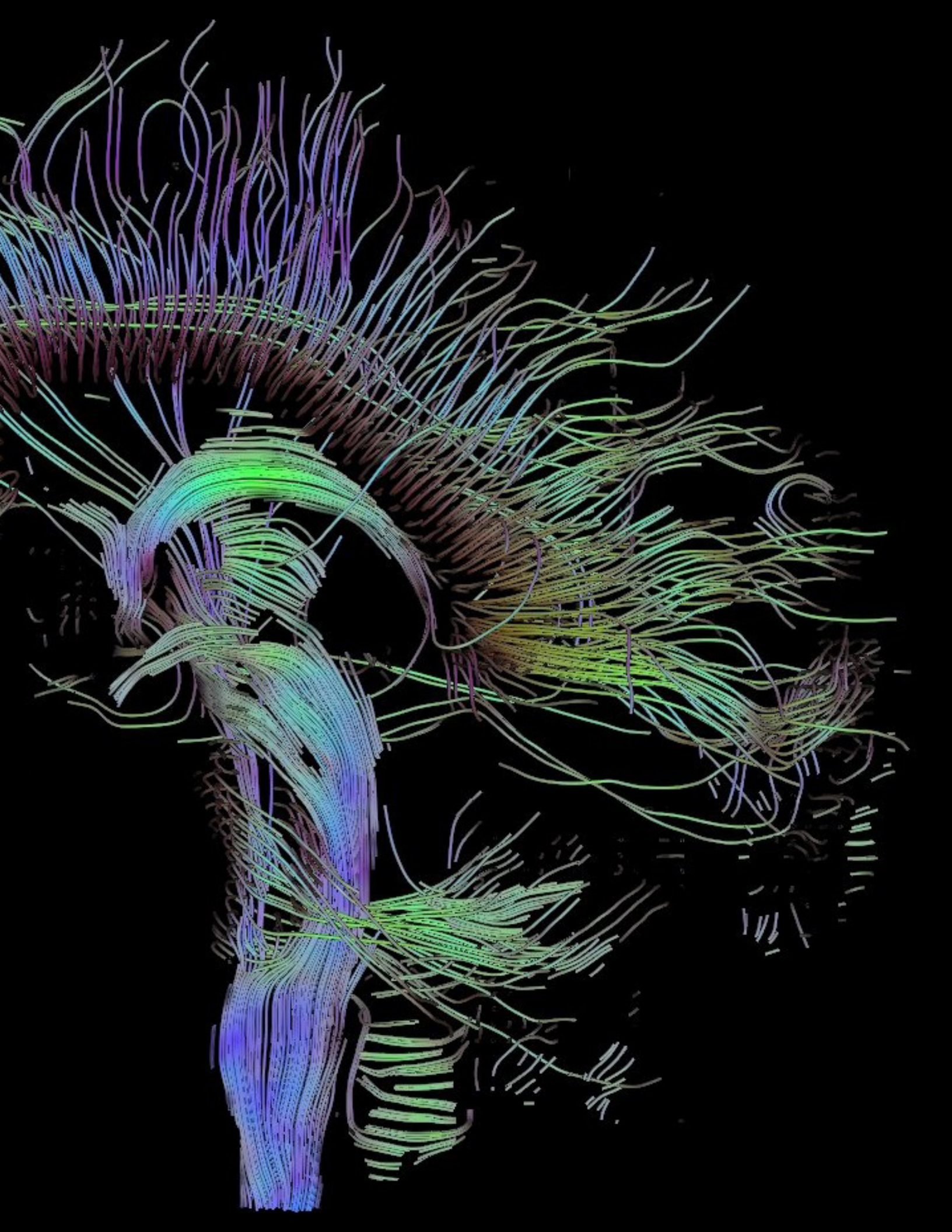

H1N1 on Pixnio



Mapping the Mind

By Natalie Twitchell

Connetome on Wikipedia Commons



C. elegans shown at high magnification (12)

In 1986, at the birth of the information age, the Royal Society devoted a massive three-hundred forty pages of an issue of one of their academic journals to the work Sydney Brenner and his colleagues had done on a relatively unknown microscopic roundworm. This animal, *Caenorhabditis elegans*, would go on to become one of the most significant model organisms in the biological sciences, particularly in neuroscience. However, the full significance of Brenner's study remained unrealized until computers became powerful enough for a new branch of neuroscience, called connectomics, to emerge. Connectomics seeks to diagram the means of communication between brain cells—also called neurons—with the end goal of understanding the precise route through which a sensation becomes a thought, a thought becomes a memory, a memory becomes a rationale, and a rationale becomes an action. The field has grown from these humble origins to profoundly influence our understanding of neural anatomy, hardware design, and even consciousness itself.

Brenner's paper, simply and ambitiously titled *The structure of the nervous system of the nematode Caenorhabditis elegans*, was the culmination of over a decade of study. The paper delivered exactly what its title promised: a full diagram of every one of the *C. elegans*' three-hundred two neurons and how they connect with each other. Although *C. elegans* has a much simpler nervous system compared to other animals,this was a herculean task given the nearly eight thousand unique connections among these cells. A map of neural connections such as this is called a connectome.

Although *C. elegans* is very different from a human being, the systems that drive *C. elegans* motion and neural activity are very similar to a human's. Therefore scientists can glean insight about humans from understanding this worm. For this reason, *C. elegans* is commonly used a model organism—a simpler animal that can be studied to learn the basics of human biology. However, more complicated behavior such as cognition requires a more complicated model—a challenge many teams in the thriving field of connectomics are taking on. Work is being done to diagram the fruit fly brain, as well as parts of the mouse brain. The most ambitious and large scale initiatives, such as the European Union's Human Brain Project and the American National Institute of Health's Human Connectome Project, are working towards whole-brain modeling, which is the ability to describe an entire human brain in terms of individual cells.

From Neuron to Nuance:

Finding Ourselves within the Brain

The search for the mind—what gives us personality and identity beyond biology—has intrigued philosophers and other thinkers long before neuroscience as a field existed. It has eluded humanity's best efforts to characterize it, and many think that it will continue to elude thinkers even after our knowledge of neuroscience is much more complete than it is now. What is known, however, is that complex processes such as movement and behavior can arise from the electrochemical signals, called action potentials, that neurons send to each other.

The moment a sensory stimulus—such as a smell, texture, or ray of light—touches your body, the first action potential in a sequence is triggered. This stimulus causes the neuron to physically change in a way that alters the concentration of chemicals—called ions—inside the neuron. This triggers a change called an action potential, in which the neuron sends an electrical signal down its length. Once the signal has

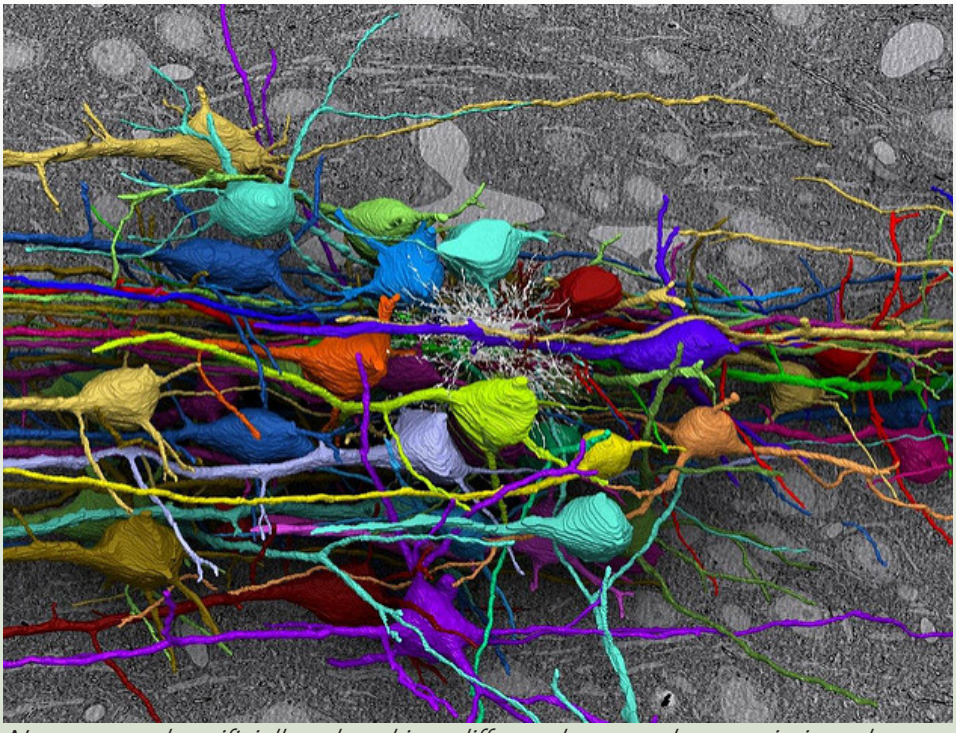
reached the end of the neuron, it is converted into a chemical, called a neurotransmitter, that triggers an action potential in the next neuron. This signal ricochets from one cell cluster to another throughout the brain, causing different functional regions to be activated, translating a biological response to stimuli into a response made up of higher order functions such as actions and emotions.

Although the distance between cells, called the synapse, is microscopic, it perhaps represents the widest gulf between known and unknown in connectomics. This is partially on account of the sheer number of synapses—the human brain has billions of neurons, forming trillions of synaptic connections[1].

However, whereas the number and placement of neurons remains mostly fixed throughout an organism's lifetime, the synapses they form onto each other vary tremendously. Each day, unused synapses decay and previously unconnected neurons reach out to one another as the brain learns and adapts. This means the connectome changes as the organism interacts with its environment. In addition, the brain is similar to every other part of the body in that it has general similarities but granular differences. For example, the vast majority of human beings have eyes that work in a very specific way, but the precise combination shape, color, and capability of that your eyes have is extraordinarily rare. This tremendous amount of variability means that scientists working in connectomics must contend validate their results by working with more than one organism in each study. As a result, each connectomics study contends with terabytes of data (orders of magnitude higher than what a cell phone can hold) to even map a portion of the human brain. The challenges inherent to a dataset this large mean that, in order to find techniques to analyze their data, these neuroscientists work at the frontier of data science and hardware engineering, advancing one field in pursuit of the other.

The convergence of the insights derived from connectomics and the bleeding edge of engineering points to a possibly unsettling location of the mind—within the mechanics of the brain itself. The advent of neuromorphic hardware—hardware based on the mathematical and physical structures of the brain, has provided proof of concept that the remarkable speed and organization of the brain is not mystical, but mathematical. By applying algorithms and theories originally developed by computer scientists to studies of brain function, scientists have made discoveries about the functionality of the brain that push us closer to understanding human thought and how it is constrained the same physical and mathematical laws as other systems that convey information.

In light of these dramatic implications, it is crucial to remember that connectomics is in its infancy. Even the most sophisticated models cannot claim to have described essential human behavior—such as thought, motivation, and identity—in their entirety. Even so, connectomics has provided tools to both doctors and research scientists that allow them to address complex questions in ways that would have been impossible before the advent of the silicon chip.

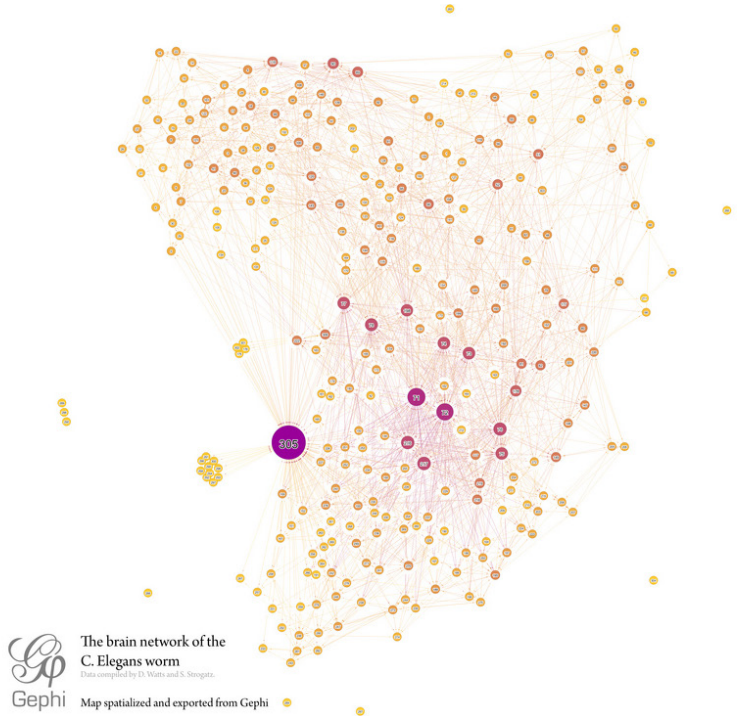


Neurons, each artificially colored in a different hue, send out projetions that meet, forming synapses[13].

A New Page in the Connectome

In order to trust bold claims and results from connectomics, it is important to make sure that the models used accurately reflect what they are meant to. To this end, a group of scientists led by Gang Yan tested the ability of Brenner's original *C. elegans* connectome to make predictions about how the worm moves that transfer from *in silico* (on the computer) to *in vivo* (in a living organism).

In order to do this, they had



A visualization of the connections in the C. elegans connectome. Each neuron is a numbered dot, and each line is a synapse[14].

The results of these calculus equations are called Linear Controllability Predictions. Linear Controllability Predictions made based on the *C. elegans* connectome identified specific neurons that, if damaged, would prevent the movement from occurring. Remarkably, these predictions held in a real *C. elegans*, validating both the *C. elegans* connectome and the use of computer science principles to describe how information is transmitted in the brain[1].

Even so, the *C. elegans* nervous system is not fully mapped. The type of signaling pathway—synaptic connectivity—that Brenner mapped is only one of the many kinds of signaling that the brain uses constantly. In order to develop a richer picture, another group of scientists have studied the signaling networks of peptides (tiny signaling protein-like molecules) and monoamines (the celebrities of neurotransmitter molecules, such as dopamine, norepinephrine, and serotonin).

Recently, Barry Bentley and his lab have attempted to understand how monoamine and peptide signaling connects the same neurons described in the traditional connectome. They described the synaptic connections as 'wired' connections between two neurons, because information travels directly between one to another. Much like a computer chip, groups of cells that are highly interconnected are physically close to each other. They found that monoamine and peptide networks break all of these rules. Unlike in man-made networks, critical groups of one type monoamine—or peptide—signaling cells are not located in the same physical space as these 'hubs' of other types of cells. In addition, the monoamine and peptide emitting cells communicated not with just one neuron at a time, but with a wide range of neurons, allowing their signaling molecules to float through the fluid of the brain over relatively long distances. For this reason, these connections are deemed 'wireless.' A shocking ninety-six percent of monoamine connections—connections which may be implicated in anxiety, addiction, and memory in humans—are not described by the classic connectome[2].

By combining the wired and wireless connectomes, scientists are able to understand C. elegans better than ever before. Even so, our map of the nematode mind is still incomplete. The authors of the study worked with an incomplete definition of what guarantees that a cell will send or receive a certain neurotransmitter, simply because all of the anatomical and biological factors at play are not known. But even a perfect C. elegans connectome would not be able to fully describe and predict what happens in the brain of a human being. For that, it is necessary to look at the nervous system of a more complex organism, an initiative only possible since the advent of high throughput computing systems.

The current front-runner for the second full connectome is the *Drosophila melanogaster*—better known as the fruit fly. When not bringing home ribbons at science fairs or colonizing trash cans, the fruit fly provides valuable data to biological scientists. Because the fruit fly has a short genetic sequence and an even shorter time between generations, abnormal changes in the DNA (called mutations) are easy to study. Some genetic information that causes human illness or underlies necessary biological functions were first discovered in a fruit fly that did not appear or behave normally. The fruit fly's brain, although not as complex as a human being's, possesses 20,809 neurons and 1,044,020 synapses and can learn, emote, and choose. Clearly, these are too many to map by hand as Brenner and his colleagues did. A research group led by Yu-Chi Huang turned to Artificial Intelligence to develop a platform that they are calling

"Flysim" that simulates the entire brain of the fly *in silico*. This project is analogous to Brenner's original C.elegans connectome modeling, only wired connections and not taking into account external stimuli. Although the project has only just begun, it has yielded impressive results. The Flysim team developed an algorithm that combed through a database of pictures of fruit fly neurons in order to reconstruct a three-dimensional model of how they connect in space[3].

Flysim is capable of not only predicting how a pair of neurons will connect and subsequently exchange electrical signals, but synthesizing these million connections into a model of the brain at rest. This task is extremely complex due to the large amount of processing power and amount of information that must be managed. Early simulations have indicated that brain modeled by Flysim would have electrical patterns similar to those seen in actual brains, validating the accuracy of these connections. This is important because conditions such as epilepsy are connected to misregulation in neural electrical patterns[3]. With science this promising so early on, it seems that the fruit fly will continue as a model organism into the information age.

Beyond the Neuron

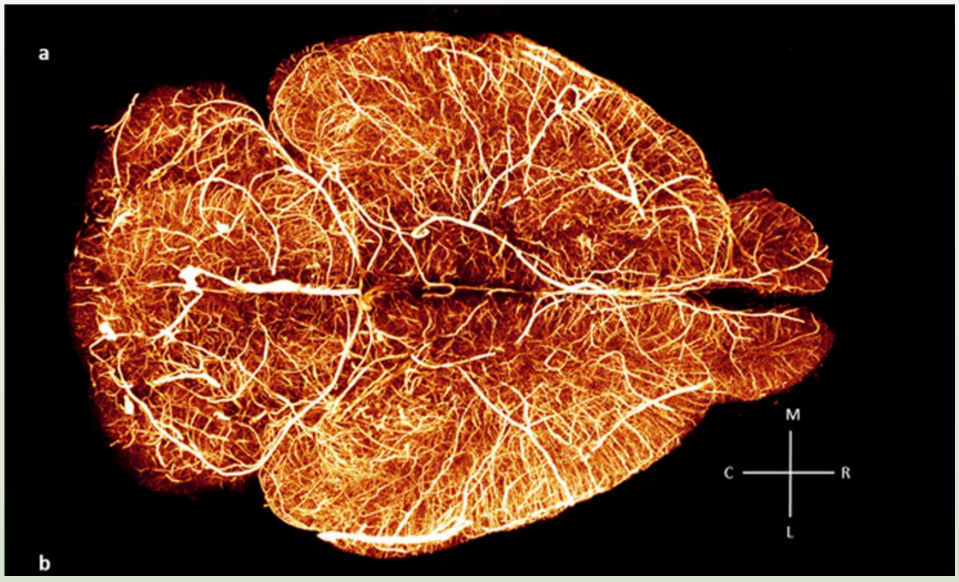
For all their strengths, these models only look at one type of cell in the brain: the neuron. Neurons do not communicate solely among themselves; they act in concert with glial cells - multifunctional nervous system cells that aid in brain function - and other bodily systems such as the immune system, vasculature, and the digestive system. In order for connectomics to understand how the brain works and why it fails, it is not enough to take into account the neuron alone.

For this reason, Antonino Paolo Di Giovanna's lab became interested in connectomics and whole brain modeling have turned their attention to understanding the vasculature of the brain down to the level of capillaries, the tiniest blood vessels, where the interchange of oxygen, nutrients, and waste takes place. Capillaries nourish brain cells and are a potential entry point for viruses, medications, and illicit drugs. In order to build this model, the group had to utilize AI to make predictions about how the vessels traced from disjointed two-dimensional sections of dead cross sections of neural tissue on slides would connect into a whole brain[4].

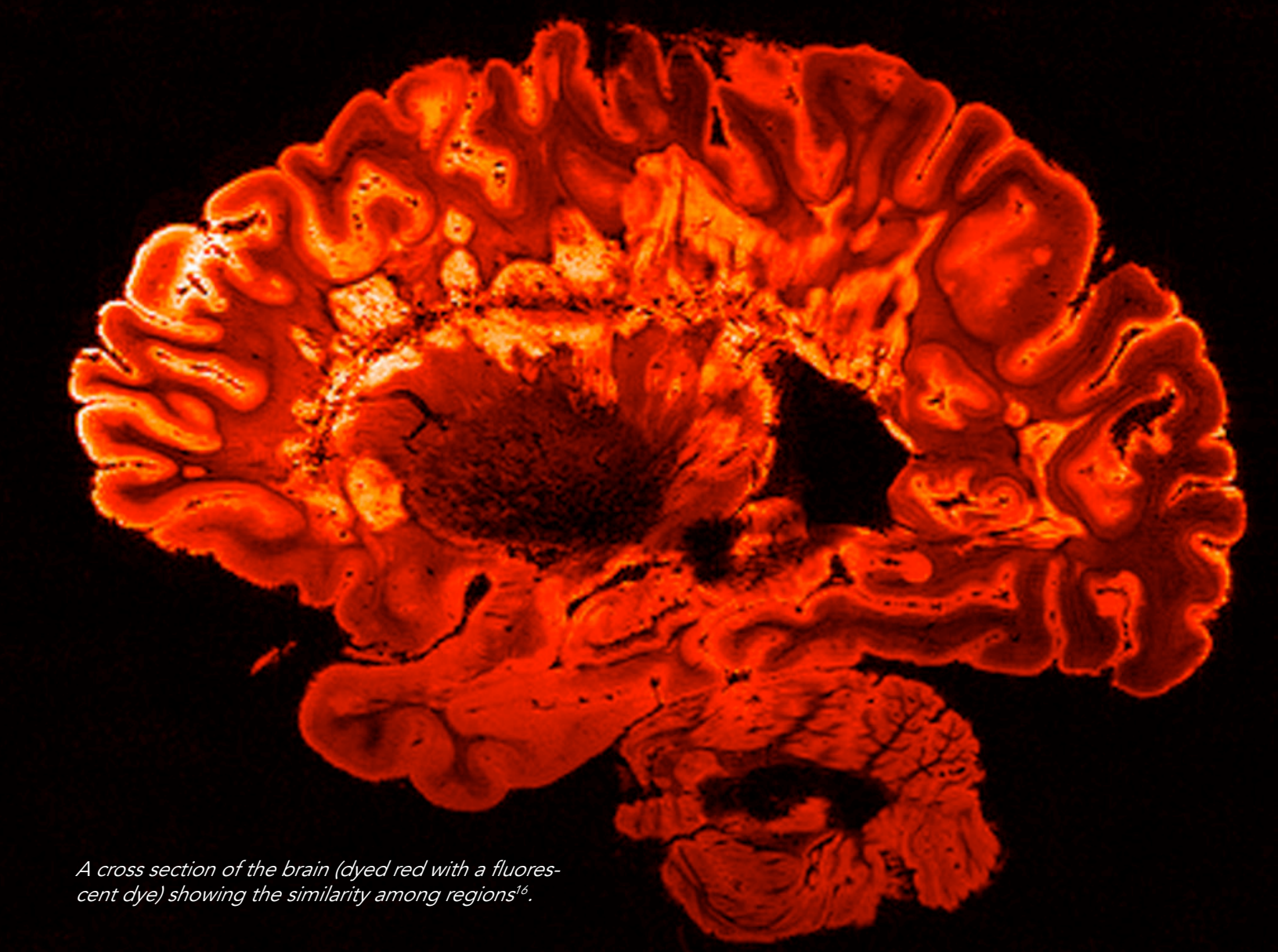
Another recent study by Estibaliz González de San Román and labmates expanded on connectomics by looking at the molecular makeup of the primary visual cortex, an area of the brain that is crucial to our ability to see, that has already been mapped in the traditional ways. This area was of particular interest because the biological mechanism behind image processing remains a mystery and it has a distinct pattern of subareas. San Román's group used a technique called multimodal mass spectrometry, which combines multiple different methods of identifying specific particles and cell types using chemistry. This tool allowed the researchers to identify certain proteins, fats, and metal atoms that were present in specific subareas but not others. Since proteins, fats, and metal atoms are used by cells for signaling and manipulating their environment, this information is a valuable step towards whole brain imaging and may provide insight as to how this mysterious region of the brain processes visual information[5].

Reshaping the Brain

Even the connectome alone has been a boon to neuroscientists who study the anatomy and regional connectivity of the brain. It is well known that certain regions of the brain have a high degree of control over certain functions, and anatomists have worked to map circuits of multiple regions that work in concert to regulate particular tasks, such as monitoring balance, responding to a drug, or recognizing the face of your baby. Still, brain anatomy remains a morass of unsolved questions. Even well characterized regions can be involved in multiple circuits,



Di Giovanna et. al's model of vasculature of the mouse brain[15].



A cross section of the brain (dyed red with a fluorescent dye) showing the similarity among regions[16].

and can be divided into distinct sublayers, such as in the primary visual cortex. These regions are made of neurons that look similar and communicate through a similar set of neurotransmitters, but can have vastly different functions based on what other regions their region is connected to.

Robert Langner and his colleagues used a relatively recent tool called meta-analytics to search for circuits that may be involved in our ability to self-regulate. Meta-analytic studies use large databases of previous studies and use statistics to seek patterns in the results. In his study, the authors looked at studies that postulated networks that might regulate two separate but interconnected systems involved in self-regulation called cognitive action regulation (CAR) and cognitive emotional regulation (CER). They selected studies that had rigorous methods for detecting activation of a brain region and used the field standard coordinate system to describe their measurements of the brain.

Meta-analytics harnesses the power of using measurements from more than one brain. Human beings are incredibly complex—mental and neurological illnesses, genetics, and even life experiences can alter the physiological structure of the brain. By including dozens of studies, each with multiple patients, means that any single study with nonrepresentative volunteers or mistakes in methodology will not entirely skew the results.

Once the dataset was assembled, the group used an algorithm to evaluate their predictions. They identified functional associations and postulated networks. Their finding, that CAR and CER moved through some of the same areas, but are distinct, comes at a time when the field's opinion is divided as to the relationship between the two mechanisms. Although not conclusive, this study represents a solid attempt to use whole-brain modeling to resolve a crucial neuroscience question in a relatively unbiased way[6].

Jianghai Ruan's anatomy lab has also used whole brain modeling to confirm brain structures that were dentified visually over a century

ago. Their first step was to perform coactivation studies, which look at which areas of the brain send and receive signals at the same time. Next, they algorithmically identified the boundaries of two areas that are important to neuroscientists—the supplementary and pre-supplementary motor areas, which, as the names suggest, are involved in preparing the body to move. Algorithms, although influenced by the limitations and biases of their programmers, are ruthlessly consistent, and able to identify patterns that their creators may not have been able to see on their own. Therefore, they can provide insight into trends in physiological data, as in this study, where the algorithm, looked for trends in physiological markers and functional boundaries to confirm the boundary between these two brain regions, which is important to neuroscientists who study motion[7].

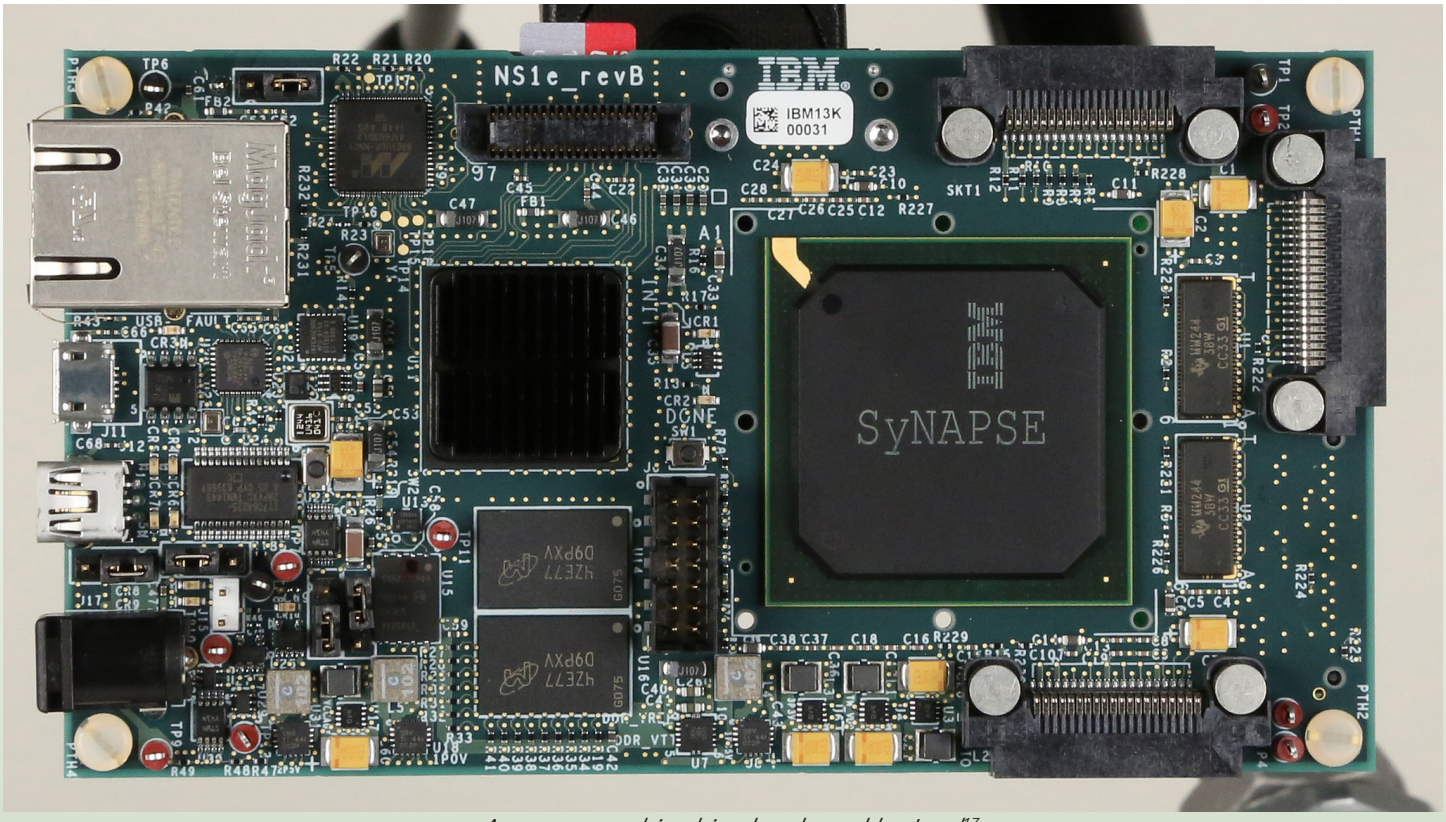
In Silico

Modeling the brain at this level of precision and raises the question of whether complex systems such as the brain can be replicated by mankind. Hardware engineers, inspired by the efficiency of the human brain, have taken results from neuroscience and applied it to their work.

A team of theoretical computer scientists, led by Guillaume Bellec, who are working to make computer processing more efficient was inspired by contrast between complexity of our thoughts and the small space between our ears. Specialized projects such as connectomics require computers much more powerful than the standard laptop, and therefore much more technologically elaborate, will be required, *small*. energy efficient chips will make these projects not only accessible, but in some cases possible.

In order to tackle this problem, the engineers developed an algorithm called DEEP R. DEEP R takes inspiration from the brain's ability to make and delete connections in response to new information. This process, which is called learning when it happens in the brain, was adapted for DEEP R. Instead of just making new connections between pieces of information, and therefore generating more data, like traditional algorithms, DEEP R deletes connections that no longer hold information in order to keep the memory usage of the algorithm low, and therefore the efficiency high. Surprisingly, this leads to the algorithm outperforming its traditional counterparts[8].

Other groups have taken further inspiration from neurobiology. Computer chips have been made that attempt to—and are very close to—direct analogs to neural circuitry both in hardware and software. As our need for computation for grows,



A neuromorphic chip developed by Intel[17].

the sophistication, capacity, and efficiency of these chips, called neuromorphic hardware, will rise to meet it. However, it is important to remember that these chips are not able to think. They are extremely task-specific, and only adaptable to a degree[9].

Defining the Mind

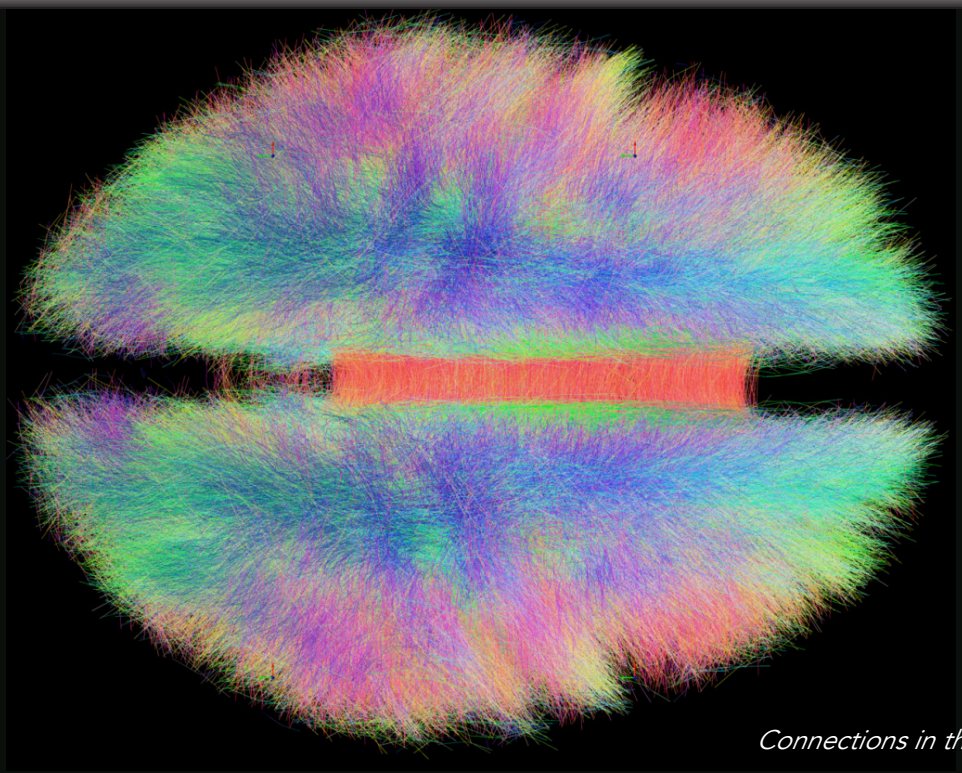
Although the project of the human connectome is not finished, it is already bolstering our ability to treat patients.

A recent study of patients with disorders of consciousness in France illustrated the power of whole-brain mapping in the clinical setting. Even though science has not reached a formal definition of consciousness, specific patterns in brain waves are fairly—but not entirely—reliable markers that doctors can use to identify whether a patient is conscious. Doctors can detect these markers using a noninvasive brain scanning tool called the EEG. Making sense of these markers is as difficult; disorders of consciousness are complex, individual, and poorly understood. As a result not every marker is present in every patient, and there is not a simple test that can be done. The analysis is left to the judgement of a physician.

A group of scientists working with machine learning—a type of Artificial Intelligence—developed a machine learning based algorithm to help doctors identify whether or not a patient is conscious. The algorithm does this by first analyzing previous EEGs and whether or not they came from a conscious person or not, and then applying the patterns from that dataset to the new EEG. The algorithm identified several markers of consciousness that seemed to be more significant than the rest, which on its own is an important piece of information to scientists attempting to understand brainwaves. The most groundbreaking result, however, is that the algorithm was able to better identify the patients' states of consciousness than a trained physician[10].

As connectomics and brain modeling become more saturated in medicine, it will become more important to understand both the power and fragility of this software. Like all scientific innovations, these algorithms are built by human hands, and therefore flawed, slated for improvement, and fallible. It should give us pause that algorithms based on datasets that may be incomplete in ways we do not know how to look for are modeling medical advances. But this is not so different than more traditional science - no individual scientist or clinician has perfect judgement.

Perhaps there is one last lesson to be learned from Brenner's *C. elegans* connectome: that the work he and his colleagues did by painstakingly mapping neurons by hand, although imperfect, incomplete, and unable to be realized fully by the technology of his time, would take part in creating a better future.



Connections in the Human Brain[18].

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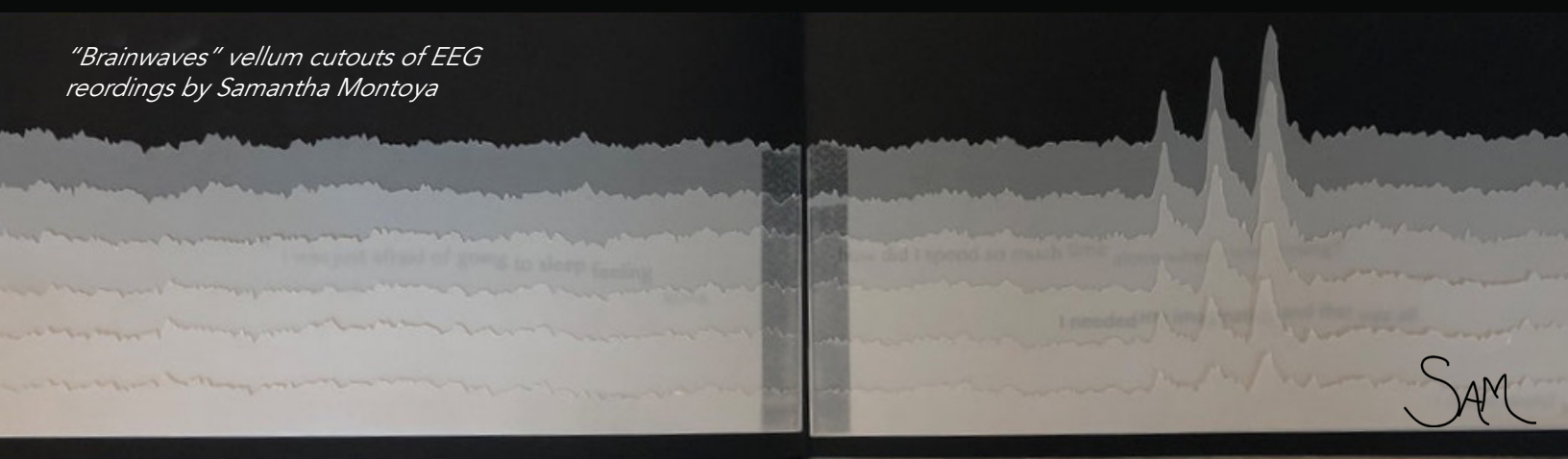

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