# brainSTEM

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Dear readers,

It is with great pride that we present for your enjoyment the second issue of brainSTEM, Western Washington University's premier, student-lead Behavioral Neuroscience magazine.

Within, you will find a superb selection of neuroscience topics that are of personal and professional interest to the authors or otherwise topical. Scientific literacy is not easily cultivated and many individuals are daunted by the prospect of sifting through a peer-reviewed journal article. As such, our goal was to present a more easily digestible reading experience while still capturing our fascination for these topics.

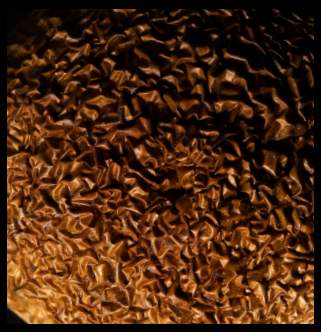
This year has been marked by consistent grief and adversity, with ongoing protests in response to the Coronavirus pandemic and in wake of George Floyd's murder. This magazine notwithstanding, our collaborative writing process had to adapt to fit the state regulations surrounding COVID-19. Nevertheless, creating and authoring this magazine was a pleasure, and we hope you find these topics as interesting as we do.

Lastly, we would like to acknowledge and kindly thank Kelly Jantzen and Andrea Swanson whose help and supervision has been integral to the creation of this magazine.

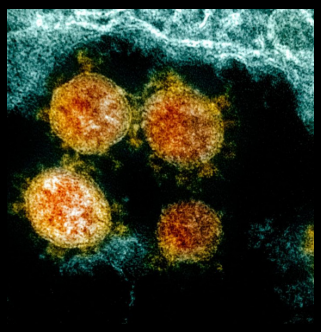
Sincerely,
The brainSTEM creators and authors

# CONTENTS

WHAT'S INSIDE THIS ISSUE

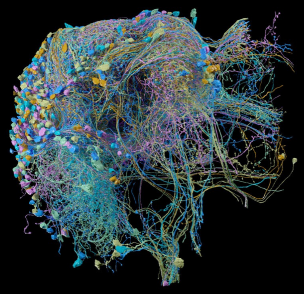






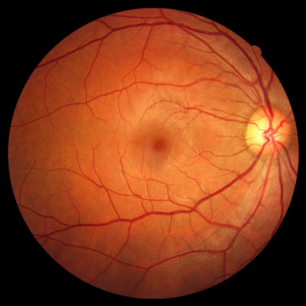
















Psilocybe cubensis

# Drug Policy and Limitations in Neuroscience

By Finn McGuinness

Among the many negative consequences of the War on Drugs, the limitations imposed upon biological and neuroscience research by prohibition are often overlooked and underappreciated. Herein, the social, economic, and regulatory obstacles that drug researchers face will be discussed.

To be more precise, drug scheduling conventions in the United States have presented neuroscientists with a Catch-22, for which there is no easy solution: simply put, U.S. drug policy defines Schedule I drugs as having no accepted medical use, while impeding efforts to determine whether that is really the case. Furthermore, there is currently no sensible method of rescheduling controlled substances after thorough scientific inquiry has demonstrated that there is a clinical use for said drug, and that it is safer than many substances that are not ranked as severely.

It is evident that many controversial drugs, such as cannabis, psilocybin mushrooms, and MDMA, have potential for the treatment of numerous disorders and underlying conditions, but the stigma and regulations that predominate today greatly hinder any efforts to study these fascinating chemicals.

Likewise, no drug is without its potential risks, but it is incredibly difficult to study the developmental consequences of cannabis use, for instance, when governmental oversight makes it time-consuming, costly, and potentially injurious to one's career to conduct that research.

American drug policy has routinely been criticized by editors at Scientific American

as being “outdated,” claiming that it “thwarts legitimate research [1].” Additionally, editors at Nature have called to prioritize cannabis research, which has been echoed throughout the neuroscience community [1]. In the case of cannabis, and indeed all controlled drugs, we know very little in comparison to what insights and innovations could emerge through studying these substances.

In the United States, the first barrier that any drug researcher must overcome is the time-consuming process of gaining approval from the US Food and Drug Administration (FDA) to receive a federal Drug Enforcement Administration (DEA) license [2].

Another principal reason illegal drug research is so inaccessible in the United States is that it is prohibitively expensive, for preclinical and clinical experiments alike.

Animal model research is crucial for answering basic questions about a drug’s toxicity and mechanism of action, but is limited by the high cost of drugs. MDMA, for instance, can cost over $400 per 50mg, or over $7000 for a single-dose zebrafish experiment [2]. For clinical trials, because humans require much larger doses than laboratory animals, the costs are exorbitant.

Additionally, a considerable deterrent for drug research is the risk it poses to one’s reputation. Researchers, institutions, review boards, and funding agencies are all potentially concerned what effect endorsing research of controversial substances might have on their reputations.

As such, obtaining funding for these types of experiments is a difficult process. In most instances, specialty organizations such as the Beckley Foundation or the Multidisciplinary Association for Psychedelic Studies (MAPS) are able to provide small grants for psychedelic research, but funding for Schedule I drug research is otherwise practically nonexistent [2].

The National Institute on Drug Abuse (NIDA), the National Institute of Health (NIH)’s main funding agency for drug research, is only interested in studying drug related harms, rather than possible therapeutic benefits. In the words of NIDA’s director Nora Volkow:

**"It is not NIDA’s mission to study the medical use of marijuana... [1]”**

In my opinion, this exemplifies how classifying drugs as Schedule I creates a negative bias, making research surrounding it seem “less clinically relevant [2].”

Researchers have suggested several solutions to the current legal obstacles surrounding drug research, such as placing all controlled drugs that are routinely used in basic research into a separate category. Likewise, removing hallucinogenic drugs from Schedule I has been suggested frequently [2]. Nevertheless, federal drug policies are exceptionally difficult to reform for a number of reasons soon to be discussed.

In most countries, the legal status of psychoactive substances originates from three United Nations treaties:

- The 1961 Single Convention on Narcotic Drugs,
- The 1971 Convention on Psychotropic Substances, and
- The 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances [3].

Signatories of these treaties are to "prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them [3]."

That being said, different countries apply their own internal drug policies, and the ranking of certain drugs can differ somewhat among them. For instance, in the United States, the legislation that serves as our implementation of the Single Convention on Narcotic Drugs is known as the Controlled Substances Act (CSA).

The CSA created five schedules for the classification of psychoactive substances and is enforced by the DEA. When determining scheduling, the DEA considers a substance's potential for bodily harm, harm to society, potential for addiction, and medical efficacy. According to the DEA, Schedule I drugs, the most severely ranked substances, such as heroin, LSD, cannabis, and MDMA, have no accepted medical use and high potential for abuse [4].

However, the DEA administration are not scientists nor are they experts on the relative risk of drugs. In a 2012 congressional committee hearing on the DEA's oversight, acting DEA administrator at the time, Michele Leonhart, made that perfectly clear. Here is a transcript of a conversation between her and Rep. Jared Polis:

**POLIS**: Is crack worse for a person than marijuana?
**LEONHART**: I believe all the illegal drug —
**POLIS**: Is methamphetamine worse for somebody's health than marijuana?
**LEONHART**: I don't think any illegal drug —
**POLIS**: Is heroin worse for someone's health than marijuana?
**LEONHART**: Again, all the drugs —
**POLIS**: I mean, either yes, no, or I don't know. I mean, if you don't know, you can look this up. You should know this as the chief administrator for the Drug Enforcement Agency. I'm asking you a very straightforward question. Is heroin worse for someone's health than marijuana?
**LEONHART**: All the illegal drugs are bad.
**POLIS**: Does this mean you don't know?
**LEONHART**: Heroin causes an addiction that causes many problems that's very hard to kick.
**POLIS**: Does that mean that the health impact is worse than marijuana, is that what you're telling me?
**LEONHART**: I think that you are asking a subjective question.

**POLIS**: No. It is objective. Just looking at the science. This is your expertise. I am a lay person, but I have read some of the studies and [am] aware of it. I am just asking you as an expert in the subject area, is heroin worse for someone's health than marijuana?
**LEONHART**: I am answering as a police officer and as a DEA agent that these drugs are illegal,
because they are dangerous, because they are addictive, because they do hurt a person's health.
. . .
**POLIS**: Well, again, this is a health-based question, and I know you obviously have a law enforcement background, but I am sure you are also familiar, given your position with the science of the matter, and I am asking, you know, again, clearly, your agency has established abuse of prescription drugs as the top priority. Is that, therefore, an indication that prescription drugs are more addictive than marijuana?
**LEONHART**: All illegal drugs are addictive [5].

It is unsurprising that an individual whose entire career is focused on eradicating drug use rather than promoting it would lack any nuance when discussing the relative risks of psychoactive substances.

What's more, much of the reasoning behind the current legal status of drugs is lacking in scientific considerations. Rather, they are historical artifacts. Case in point, in the early 1970s, President Nixon convened a group of experts to determine what threat cannabis posed to the status quo.

The Shafer Commission, originally known as the National Commission on Marihuana and Drug Abuse, deemed cannabis a non-issue and recommended that it be decriminalized, largely comparing its effects on society to that of alcohol [5]. Against all reason, however, the Nixon administration opposed these suggestions. Nixon was deaf to the voice of reason, even saying:

**"As you know, there is a Commission that is supposed to make recommendations to me about this subject, and in this instance, however, I have such strong views that I will express them. I am against legalizing marijuana. Even if the Commission does recommend that it be legalized, I will not follow that recommendation [5]."**

Many politicians are no longer so dogmatic when it comes to drug policy, but there is still considerable political resistance towards scientists interested in researching drugs, specifically the potential beneficial effects of some drugs. For instance, Professor David Nutt, a former chief drug adviser for the UK government, was fired from his position when he claimed alcohol to be more dangerous than MDMA or LSD [6].

A major obstacle that we face in reforming our drug laws is that our policies are dictated by United Nations treaties. Thus, any substance that is Schedule I under the 1971 convention could not be moved to Schedule II (which would greatly improve access to research), because it would require a majority approval from United Nations Member States. Unfortunately, these treaties have been resistant to change [3].

Federal and State agencies understandably have concerns about the regulation of potentially harmful drugs. As such, the War on Drugs aims to eradicate drug related harm by criminalizing the production, distribution, and consumption of psychoactive substances. After all, it serves to reason that if there were no drugs, there would be no drug-related harm.

In spite of this naive misconception, the Drug Enforcement Agency is almost comically inefficient at obstructing international drug trade. For instance, according to the White House's Office of National Drug Control Policy, the total annual value of all of the drugs sold in the United States was estimated to be as much as $64 billion [7]. If you consider the fact that, in 2005, the DEA apprehended $1.9 billion in drug proceeds, they have a rate of efficiency of less than 1% [8].

Even more surprising, the DEA is often credited by clandestine chemists as being one of the largest and most detailed providers of information regarding the illegal synthesis of psychoactive drugs. Hobart Huson, under the pseudonym Strike, developed an online forum known as The Hive and authored several books on the underground synthesis of a variety of illicit substances. Along with owning a chemical supply company known as Science Alliance, Huson is recognized as being hugely influential in the proliferation of the information and precursors necessary for undertaking clandestine drug synthesis.

Interestingly, Huson regards Terry Dal Cason, a former forensic chemist for the Bureau of Narcotics and Dangerous Drugs (the predecessor to the DEA), as the "godfather of clandestine MDMA manufacturing [9]." Dal Cason is allied towards the efforts of drug war through and through, but his detailed descriptions of thwarted clandestine chemistry operations have been instrumental to the endless proliferation of copycats. Not unlike battling a Hydra, every time an illegal drug operation is put down, several new ones spring up elsewhere.

Considering that humans have been altering their consciousness with psychoactive substances since at least the Neolithic period, it's not surprising that little can be done to hinder the production, sale, and consumption of drugs [10]. Drugs are so popular recreationally that their rate of consumption is relatively unaffected by the price. In economics, this is known as "price inelasticity [11]." As a result, a supply-side drug war is futile in reducing drug use and drug related harm, because suppliers will always find a way to traffic their products, and consumers will always want drugs.

Ultimately, there is no point in perpetuating a War on Drugs that does more harm than good. Drug abuse is a public health issue, not a moral or criminal one.

Imprisoning drug users can be far more deleterious to an individual's health than drug use. Many books could be written on the racist history of the War on Drugs, and is beyond the scope of this article. Whether or not drug policies were explicitly created to be racist is up to interpretation, but it is inarguable that people of color are disproportionately affected by the War on Drugs, despite having similar consumption rates as Caucasians [12].

Why shouldn't people be allowed to alter their consciousness with drugs that are less harmful than something such as alcohol? As long as someone is not a danger to others, I believe everyone is born with the inalienable right to alter their consciousness as they see fit. Especially in the case of psychedelics, which are shown to be among the safest drugs to users and society, decriminalization needs to be seriously considered [13]. Routinely, individuals rate their psychedelic experience as being among the most important, insightful and life-changing events in their lives. Why should anyone be disallowed from that enjoyment [14]?

In neuroscience, the concept of cognitive liberty, the freedom of an individual to control their own consciousness, is of growing concern due to the rise of invasive technological advancements. Increasingly, the ability to monitor and influence human cognition technologically and pharmacologically is approaching a level that borders on unethical.

The term cognitive liberty was coined by neuroethicist Dr. Wrye Sententia and legal theorist Richard Glen Boire [15]. Sententia and Boire delineate two key principles of cognitive liberty:

1. As long as their behavior does not endanger others, individuals should not be compelled against their will to use technologies that directly interact with the brain or be forced to take certain psychoactive drugs.
2. As long as they do not subsequently engage in behavior that harms others, individuals should not be prohibited from, or criminalized for, using new mind-enhancing drugs and technologies [15].

Decades earlier, Timothy Leary anticipated Sententia and Boire's principles with his own take on cognitive liberty in his "Two Commandments for the Molecular Age:"

1. Thou shalt not alter the consciousness of thy fellow man.
2. Thou shalt not prevent thy fellow man from altering his own consciousness [16].

Even still, psychedelic drugs could lead to the maturation of society, as well individual scientific discoveries. Karry Mullis, the inventor of the polymerase chain reaction (PCR), a technique which is fundamental to nearly all disciplines of biological science, claimed that without LSD, he wouldn't have been creative enough to have invented PCR [17]. Many people are surprised to know that drug use amongst scientists and academics is not uncommon, but for obvious reasons individuals choose not to disclose that information.

Dr. Carl Hart has recently written a book titled Drug Use for Grown-Ups: Chasing Liberty in the Land of Fear. In it, he bravely depicts his own recreational drug use, which as a responsible and informed adult poses no threat to him or society. Academics have a responsibility to be honest about their drug use, as many people only associate drug use with the stereotypical unsuccessful ne'er-do-well. The truth is, many successful scientists use drugs. Francis Crick, for instance, a Nobel Prize laureate and one of the discoverers of the helical structure of DNA, used LSD later in his life [18].

Neuroscientists have a crucial role to play in ending the War on Drugs. Neuroscience research is absolutely necessary to developing sensible drug policy, but there are currently obstacles in place that limit the ability of scientists to inform change. Stringent drug regulations make drug research exorbitantly expensive, socially injurious, and time-consuming. Drug policy reform should be of interest to everyone, but neuroscientists should be especially vocal in their opposition to the War on Drugs.

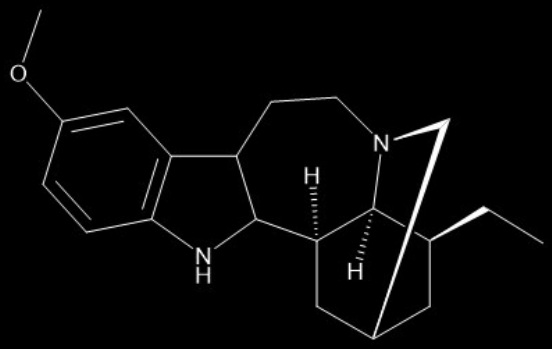
Potentially dangerous drugs should be regulated to some degree, but not to the point that researchers cannot study them. Conversely, drugs that pose little harm to individuals and society should not be regulated so harshly. The most effective method of reducing drug-related harm in our communities is through honest, science-based drug education. In the sagely words of Alexander Shulgin: “Be informed, then choose [19].”

Because this topic is so complex, here are some additional resources to learn more about the history of drug use and prohibition, as well as drug-related neuroscience:

- PiHKAL: A Chemical Love Story
  by Alexander and Ann Shulgin
- Chasing the Scream: The First and Last Days of the War on Drugs
  by Johann Hari
- The Drug Science Podcast
  hosted by David Nutt
- Hamilton's Pharmacopeia
  Viceland docuseries created by Hamilton Morris

If you are passionate about drug science and ending the War on Drugs, please consider joining Western Washington University's chapter of Students for Sensible Drug Policy.

# Illicit Drugs with Potential for Healing




Ibogaine - Schedule I

Ibogaine is a non-classical psychedelic naturally produced by the African shrub Tabernanthe iboga which interacts with a variety of receptor targets.

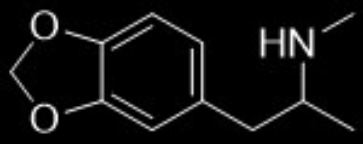
There is limited clinical research on ibogaine's effects, but what little there is, in addition to striking anecdotal evidence and a large body of animal model research, indicates that ibogaine is effective at treating addiction by reducing drug cravings [20].

Even more fascinating, ibogaine has been shown to alleviate the withdrawal symptoms of opioid dependence. This is potentially revolutionary for psychiatry, as withdrawal symptoms are difficult to treat and one of the main reasons for relapse.


Psilocybin - Schedule I

Psilocybin is a prodrug naturally produced by nearly 200 species of fungi [21]. When ingested, psilocybin is metabolically converted into psilocin, which produces the psychedelic experience characteristic of psilocybin-containing mushrooms.

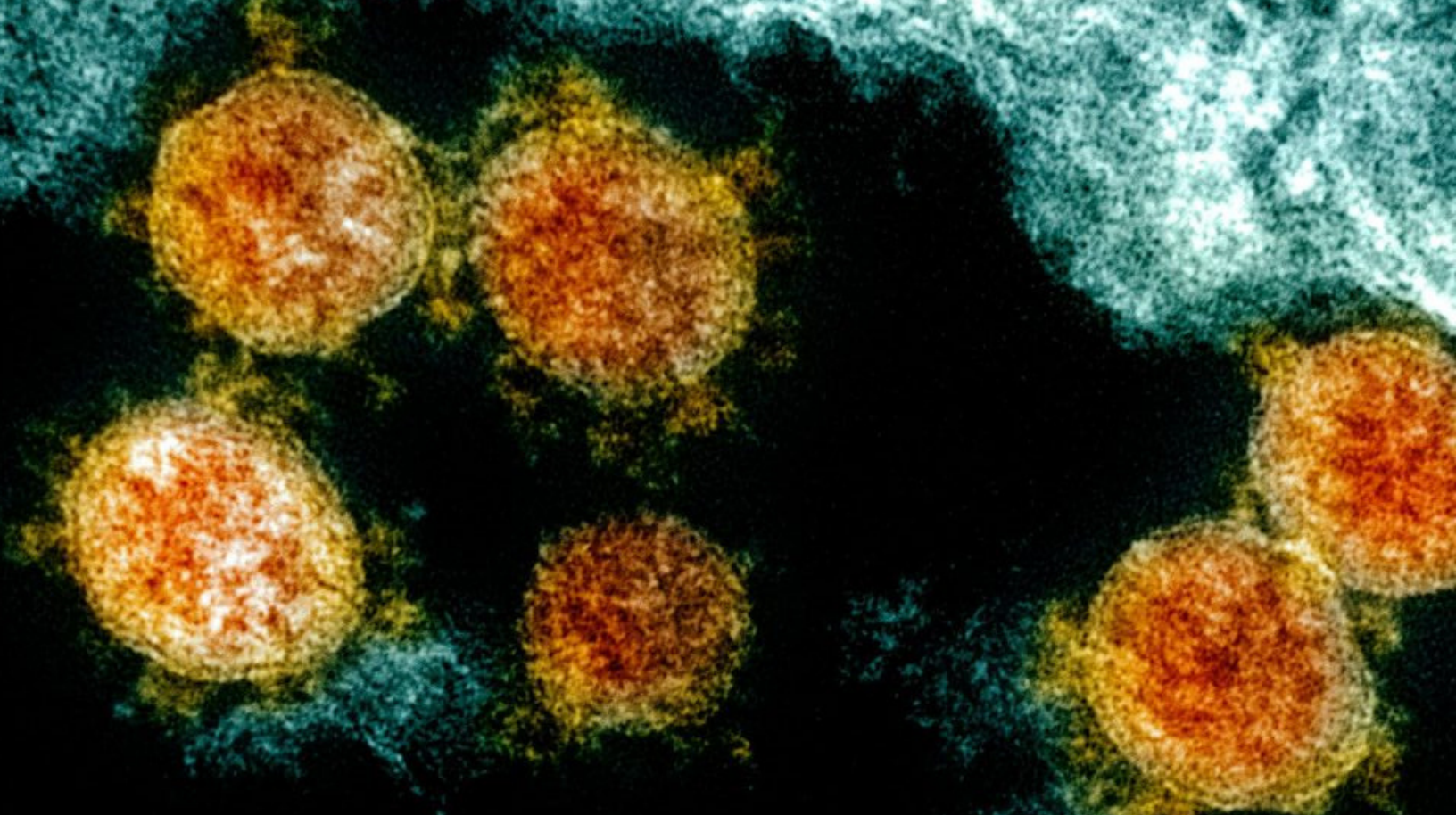
Psilocybin has been shown to be at least as effect as escitalopram, an SSRI, at treating depression [22]. Additionally, in 2019 the FDA granted Breakthrough Therapy Designation for psilocybin therapy in the treatment of major depressive disorder [23].




MDMA - Schedule I

Commonly known as ecstasy or molly, MDMA acts primarily by increasing serotonin, norepinephrine, and dopamine in the brain.

Although mainly used recreationally, phase 3 clinical research for the treatment of PTSD with MDMA-assisted psychotherapy is currently underway. This is the final phase of research before the FDA will decide if MDMA should be approved as a legal prescription for PTSD [24].



# Neuropsychiatric Outcomes of COVID-19 Survivors

By Finn McGuinness

Since the beginning of the coronavirus outbreak, more than 170 million cases of COVID-19 have been recorded and nearly 3.7 million people have died due to complications of their infection [1]. Thankfully, however, more than two billion people worldwide have received the COVID-19 vaccine and regulations are beginning to lessen [1].

In spite of a growing sense of skeptical optimism, recent observations suggest that individuals who were infected with and subsequently recovered from COVID-19 could be at a higher risk of developing a neurological disorder or psychiatric illness.

Indeed, a large-scale analysis of an electronic health records network (consisting of 236,379 patients) determined that the likelihood of receiving a diagnosis for a neuropsychiatric illness in the six months following recovery from COVID-19 increased significantly, estimated at 33.62%.2

Overall, they found that most diagnostic categories were more common in COVID-19 patients than in individuals who were diagnosed with influenza or another respiratory tract infection [2].

The diagnoses that were most common included mood disorders, psychotic disorders, neurodegenerative diseases, and — most frequently observed — cerebrovascular events, such as ischaemic strokes and intracranial hemorrhages [2].

Additionally, the severity of the infection was found to be correlated with the likelihood of developing a neurological

or psychiatric disease, where patients who were hospitalized in an intensive therapy unit were markedly more at risk than those who were hospitalized only for a short time and (even more so) when compared to individuals who did not require hospitalization [3].

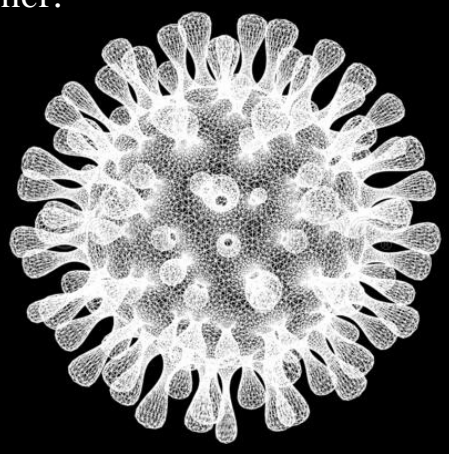
What causes this vulnerability to developing a psychiatric illness requires further investigation but several preliminary theories have been put forth. Firstly, it is possible that the COVID-19 virus is able to cross the blood-brain barrier (BBB), a membranous border that selectively regulates which molecules circulating in our blood can enter the brain.

Some researchers propose that the symptoms associated with COVID-19 could be directly caused by the virus invading the central nervous system and targeting specific brain regions, such as those responsible for controlling respiration. Still, whether or not SARS-COV-2 can penetrate the BBB cannot be concluded with any certainty currently [3].

Coronaviruses derive their name from the image they make when viewed underneath an electron microscope, which resembles a solar corona, the million-kilometer-long streams of plasma that surrounds our sun and other stars. This resemblance is due to the spiky proteins that cover the surface of coronaviruses.

In support of the theory that COVID-19 symptoms may be caused by direct actions in the central nervous system (CNS), researchers at the University of Washington demonstrated that the SARS-COV-2 spike protein (S1) readily crosses the BBB of male mice when injected intravenously [4]. Therefore, it is possible that, even if the SARS-COV-2 virus cannot enter the brain, the transportation of the S1 spike protein into the CNS could be responsible for causing some of COVID-19's symptoms.

The researchers did not notice any significant differences in the permeability of the BBB between their in vivo rodent model and an in vitro human assay [4]. Despite these interesting findings, it must be noted that the S1 spike protein is usually attached to SARS-COV-2 as a trimer — a protein consisting of three covalently bonded subunits; in this experiment, a single subunit of the S1 protein was used, a monomer.



Nonetheless, these findings should be of significant interest to researchers and physicians.

Another possible explanation for how COVID-19 might increase the risk of developing a neuropsychiatric disorder is COVID-19's observed propensity to increase blood coagulation. One study found individuals with depressive, bipolar, or schizophrenic disorders to be almost three times more likely to develop a venous thromboembolism, (VTE) which is associated with hypercoagulation [5].

Medication, lifestyle choices, and environmental factors all contribute to this increased risk, though biological dysfunction caused by an underlying disorder is thought to contribute as well.

Therefore, it is possible that the increased risk of receiving a psychiatric diagnosis in the six months following recovery from COVID-19 could be partially caused by a state of hypercoagulation. The increased risk of a cerebrovascular event seems to be explained especially well by this hypothesis.

Patients with severe COVID-19 have also been observed to exhibit cytokine storms, a dysregulated immune reaction that causes excessive release of pro-inflammatory molecules known as cytokines [3].

Cytokine-induced damage of epithelial cells allows tumor necrosis factor (TNF)-α to readily cross the BBB, activating microglia and astrocytes, which leads to phagocytosis of damaged cells and the release of inflammatory mediators like glutamate [6,7,8]. Excitotoxicity caused by an increased concentration of glutamate leads to neuronal loss, which could result in neurotransmitter- and region-specific neuropsychiatric symptoms [3].

It is likely that inflammation and hypercoagulation both contribute to the development of neuropsychiatric symptoms following recovery from COVID-19. Based on the evidence, dysregulated immune responses caused by SARS-COV-2 seem to weaken endothelial cells and vasculature, which in tandem with a state of hypercoagulation increases the risk of cerebrovascular events and micro-hypoxic/ischemic injuries.

In essence, the neuropsychiatric symptoms associated with post COVID-19 recovery could be due to so-called microstrokes, the expression of which is dependent on which brain region is affected [3].

# LEARNING AND MEMORY STORAGE:

## Epigenetics vs. Synapses

By Hannah Milford

What would life look like if we weren't constantly adapting to our environment? If we couldn't learn from mistakes or form new habits there most likely wouldn't be a human race. Learning and adapting to environmental changes is an essential function. Consolidation of these memories is also essential. You can think of learning and memory as a series of biological processes. Persistent changes in neurotransmitter flow, ion channels, and synaptic connectivity are called brain plasticity. These persistent changes alter neuron (cells that comprise our brain) sensitivity and excitability.

Forming associations in our environment, thus creating a plasticity event can happen quite readily. But, it has been debated by many researchers if long-lasting changes are stored in the synapses or cell body. Those changes are called long-term potentiation (LTP) and long-term depression (LTD).

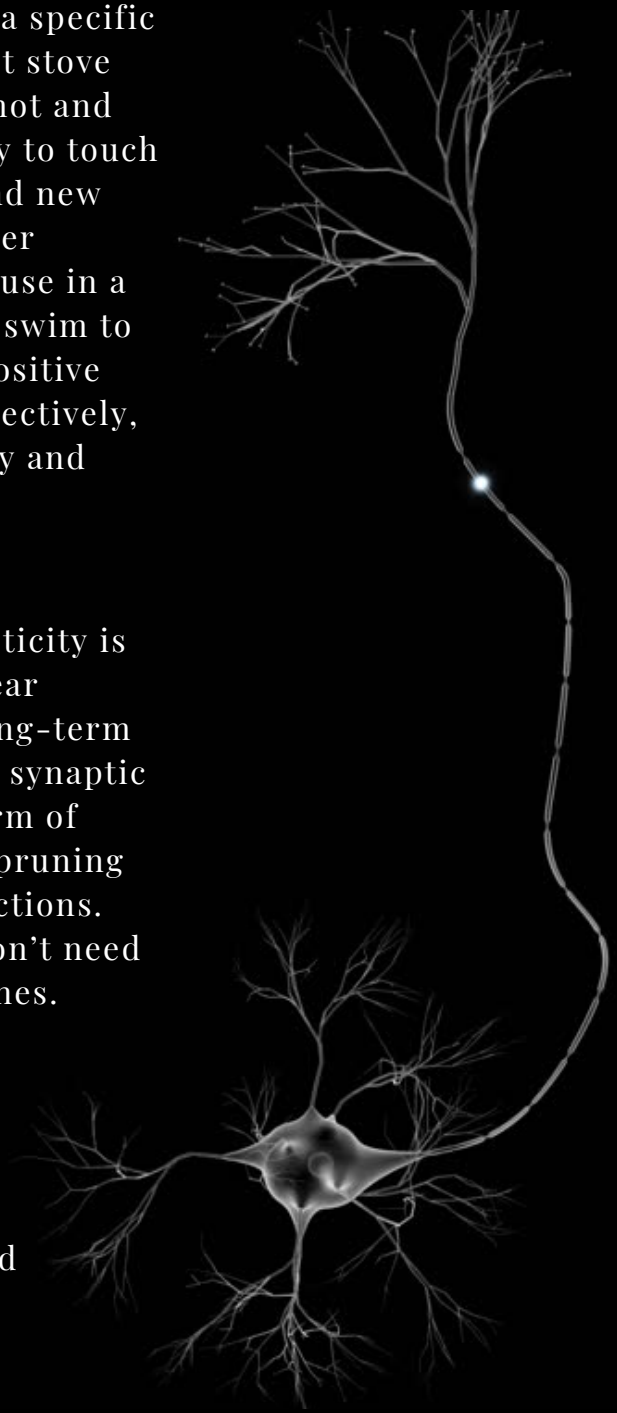
Early theories by Donald Hebb and Ramon y Cajal, who first proposed synaptic adaptation during learning, coined the phrase "cells that fire together wire together" [1]. Meaning, a neural pathway that is stimulated consistently will become stronger, and the unused pathways will be pruned. So, an event that takes place more than once reinforces neuronal connectivity. Opposing this theory, Camilio Golgi proposed a nuclear model of learning, where information stored was in a continuous cellular network.

There has been extensive discussion over the century of whose

theory is correct. How is memory maintained and where is it stored? The following is a brief overview to give you the inside scoop.

## Cellular Changes lead to Changes in Neuronal Response

A cell that has increased connections to other neurons or increased sensitivity to a stimulus, is more likely to have a response. In other words, increased sensitivity will make the response to a stimulus greater. This results from high or frequent stimulation at a specific synapse. For example, if a child touches a hot stove and burns their hand, that association with hot and stove is strengthened. They will be less likely to touch the stove again because they have learned and new connections in the brain have formed. Another example in a mouse model: if you place a mouse in a pool of opaque water with a platform, it will swim to the platform quicker with each repetition. Positive and negative associations, LTP and LTD respectively, are the results of changing neuron sensitivity and excitability.



## How is memory maintained?

Memory stored in our DNA and synaptic plasticity is ever-changing based upon experience. Nuclear memory is hypothesized to be the form of long-term memory, like LTP and LTD [2]. Alternatively, synaptic plasticity is thought to be the short-term form of memory. One mechanism of maintenance is pruning unused dendrites to strengthen other connections. Which is essentially weeding out those we don't need in order to strengthen the most important ones.

## Synaptic Regulation

When an event happens, catastrophic, miniscule, or anything in between, the connectivity between individual neurons in our brains is changed. This is due to high and low stimulation. Changes in connectivity of neurons include alteration of receptors (AMPA and NMDA receptors) that lie on

dendrites, which act to regulate synapses. Synaptic plasticity is thought to act as short-term memory storage.

## Nuclear Regulation

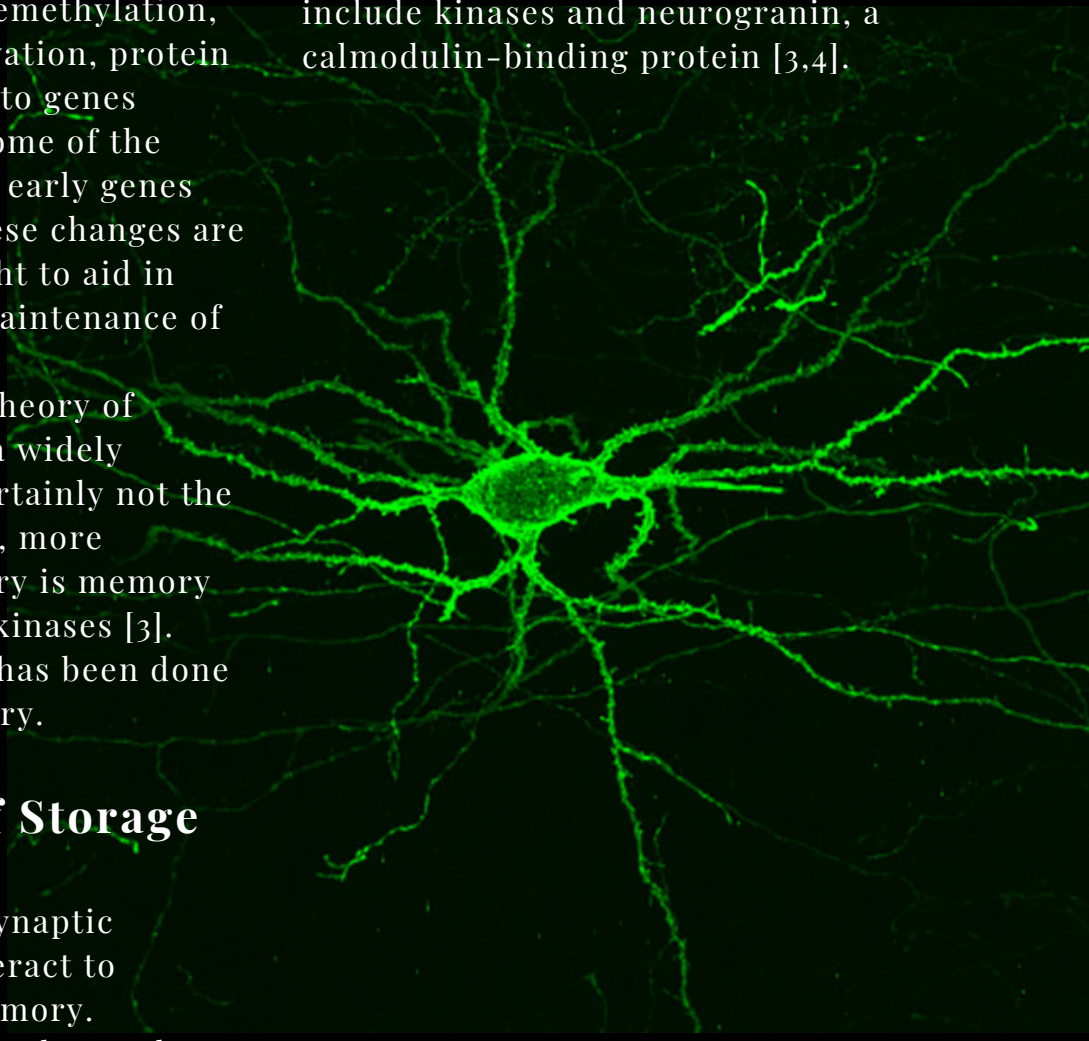
It has previously been hypothesized that synapses are the sole site of information storage in the brain. However, as research progressed, scientists now hypothesize that the cell body also plays a role in memory storage.

As previously discussed, an event triggers neuronal stimulation. This triggers a cascade signal to the nucleus. This signal leads to nuclear events like DNA methylation, DNA demethylation, transcription factor activation, protein synthesis, all which lead to genes becoming transcribed. Some of the genes include immediate early genes and late onset genes. These changes are long-term and are thought to aid in long-term storage and maintenance of memory.

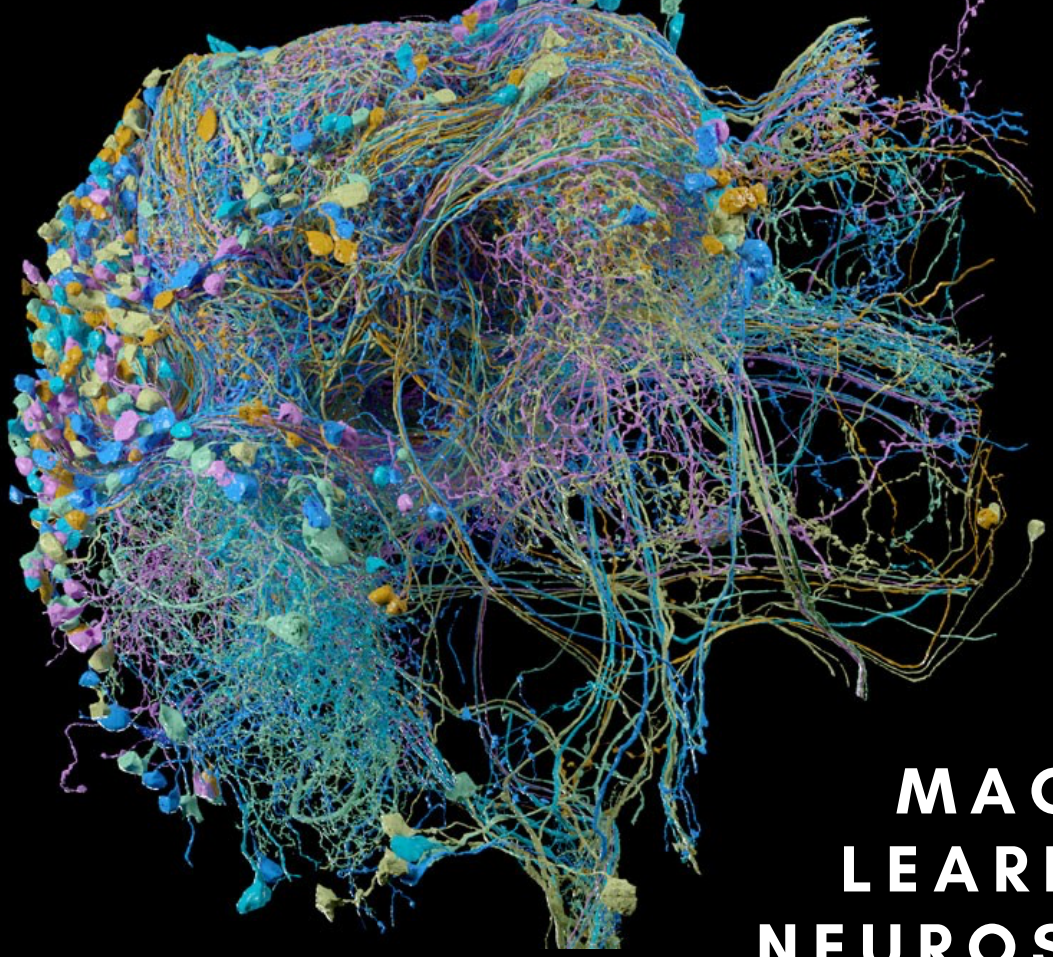
The nuclear regulation theory of learning and memory is a widely supported theory, but certainly not the final engram [1]. Another, more recently, supported theory is memory storage and transfer via kinases [3]. However, little research has been done to fully support this theory.

## A Combination of Storage Methods

Nuclear regulation and synaptic plasticity most likely interact to produce learning and memory. They "complement" each other and different memory could be stored via different mechanisms in the brain. One possibility of complementing each other is a continuous process of synaptic plasticity triggering nuclear events within the nuclei [1]. This is a popular theory among many scientists, however, it has not been 100% confirmed that nuclear regulation and synaptic plasticity act to complement each other. What scientists can confirm is that both synaptic plasticity and nuclear memory are necessary for memory storage and maintenance. But as with many scientific endeavors, more research is needed and other possible storage mechanisms are still being discovered. Some other storage mechanisms may include kinases and neurogranin, a calmodulin-binding protein [3,4].



Imaging of fluorescent voltage indicator showing voltage of single mouse neuron upon stimulation [5].



# MACHINE LEARNING & NEUROSCIENCE

**By Hannah Milford**

The above picture depicts neural circuity mapped through a process called machine learning. It shows the largest connectome at the synaptic-level ever reconstructed [1]. This is only a thin slice of a fly brain, or *Drosophila*, including 25,000 neurons, about 250 micrometers of tissue. For a sense of scale, the human brain has 86 billion neurons.

Machine learning, under the umbrella term of artificial intelligence, is a process by which a computer is programmed to make predictions about future data based off patterns from an original data set [2]. Machine learning integrates techniques from statistics, applied mathematics, and computer science. For neuroscience, it is used in a few different ways: understanding complex experiments, brain-machine interfaces, and modeling through neural networks.

In a complex neuroscientific experiment, a massive amount of data is usually received, which can be very complex to interpret. For example, if you record neuronal activity of 100 neurons over a period of time, it is not possible to interpret that much data efficiently. So, you can use machine learning techniques to simply describe the activity of the neurons. This is called dimension reduction. Brain-machine interface is essentially when electrodes are implanted into neurons to record/stimulate neural activity. Machine learning is used in this case to interpret brain activity and learn a model of the activity through some mathematical function. The model created can be used to further study the brain activity. Finally, machine learning is used to model artificial networks, or simplified models of neurons. This helps researchers understand how networked systems function.

To learn more about machine learning in neuroscience, I spoke with Dr. Kameron Decker Harris Ph.D., an assistant professor in the Computer Science department at Western Washington University. His research interests include computational neuroscience, networks, graph theory, and applied mathematics. Currently, he works on a variety of projects including developing computational techniques to reconstruct the mesoscale wiring in mouse brains, using a model of the brainstem to generate a breathing rhythm to study effects of opioids on breathing, and finally, how connections in artificial neural networks enable networks to learn functions.

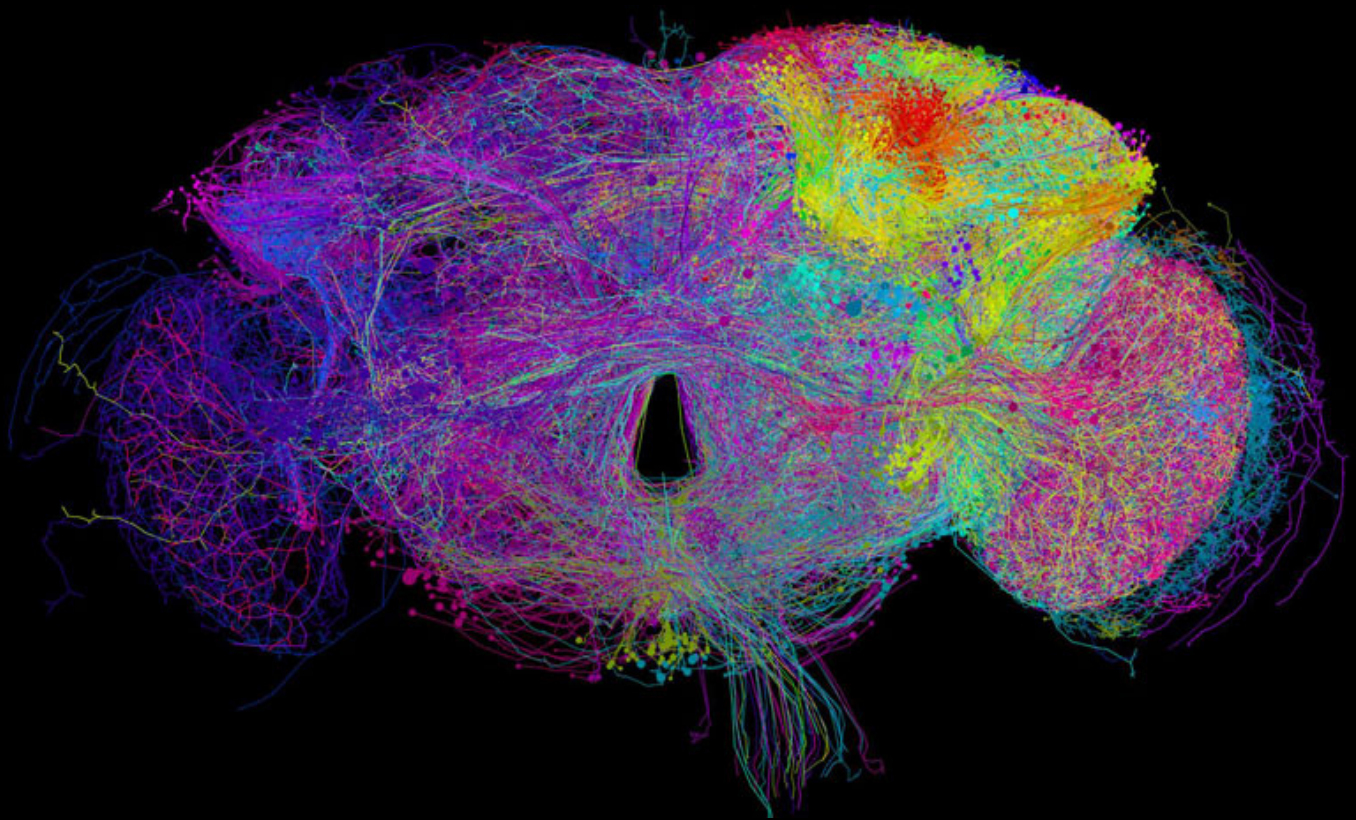
I found his research in measuring neural pathways and connectivity the most interesting. Within this topic, he used machine learning to look at viral tracing methods to measure neural connectivity at a 100 micron, or mesoscale. For reference, viral tracing methods are essentially the same methods used in some COVID-19 vaccines, which employ a genetically modified adenovirus. Efforts in other labs aim to tackle an even smaller scale: connectivity within a nanometer. Dr. Decker Harris described how this scale could potentially identify single synapses through electron microscopy, though there is still a lot of work to be done.

Machine learning is a process that has been involved in computational neuroscience research for a while. In fact, research around artificial neural networks has actually been around since the 1940s. Machine learning has seen a massive increase in popularity and importance due to the rise in computational power and availblity of computers. The main cause for the new popularity is really the accesibility of the computational power. Recently, efforts to use machine learning to develop brain-machine interfaces has created a promising outcome. Technology has advanced to the point where brain-machine interfaces could be implanted into people's brains, who have cognitive or physical limitations, so they can use their brain to control a machine to speak or move [3].

But as researchers piece more of the connectivity puzzle together, unexpected complexities have unraveled. For example, it took 50 full-time employees a year to produce mapping of the 25,000 neurons, 20 million connections, in the *Drosophila* brain shown in the beginning of the article [4]. Furthermore, a team at the Allen Institute for Brain Science captured imaging of one cubic millimeter of mouse brain in 6 months, not including mapping. This took 2 petabytes of data, or 2 million gigabytes. So, you can imagine how complex it would be to map a human brain, capable of far more that a model animal. Time and data storage seem to be two main limiting factors in developing brain-machine interfaces and modeling through artificial neural networks.

**"Machines are learning to be smarter by studying the wiring of machines that are fundamentally smarter — biological machines." - Jeff Lichtman**

In current neuroscience research, machine learning is highly regarded. It seems like it can solve many research barriers, such data analysis. However, Dr. Decker Harris describes the interest, “mostly due to perceived big successes in machine learning, which may or may not be exaggerated. So, computational neuroscientists have been part of this trend of wanting to use machine learning to analyze experiments and also as models for the brain.” The excitement around machine learning in neuroscience makes sense: it gives the advantage of quick data analysis and the ability to predict future trends. However, a lot of work remains. The excitement may be premature, and as new territory is charted within machine learning, I’m sure many surprises and complexities await.



The most complete brain mapping to date of a Fruit Fly ( (*Drosophila melanogaster*) brain showing all 100,000 neurons [5].

# "The Dress" and Color Perception

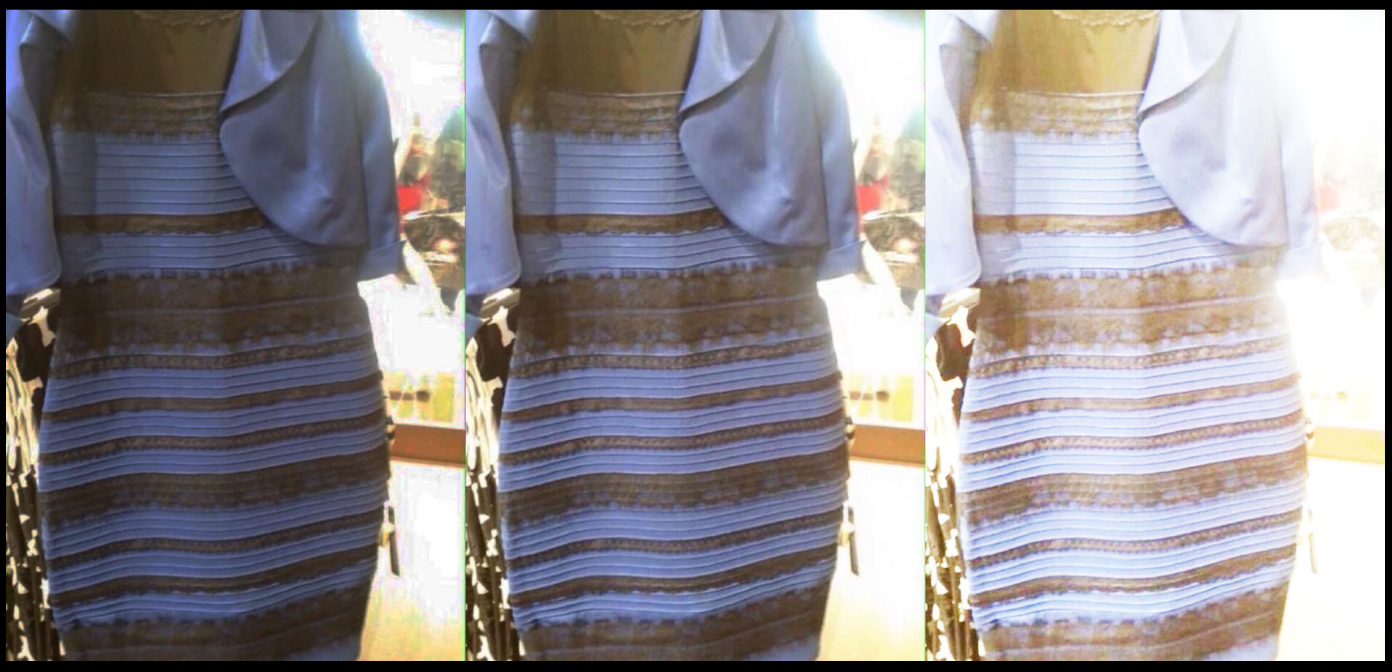
By Trinity Wilson

For the average person, color perception is integral to interacting with their surroundings. It serves in identifying the difference between a raspberry and a blackberry, whether you should stop or go at a stop light, determining what team your favorite football player is on. Yet, despite its active role in our lives, the mechanisms of color perception and the neuroscientific explanations for how the brain perceives color are incomplete and require further inquiry. Every day new discoveries are made, unearthing the mysterious and complex ways we process color and how various stimuli effect color perception. Discoveries regarding the mechanisms of color perception often arise from studying visual stimuli that cause observers to have percepts outside the ordinary. For example, color vision optical illusions can lead people to believe two identical objects are different colors simply by changing the background or orientation of the image. The most intrigue comes from illusions where people perceive the same image in different ways. They open a door into the natural variation in color perception, highlighting that people perceive color in unique ways. One such illusion took the internet by storm. Known as “The Dress,” this illusion went viral in 2015 because of the varying interpretations as to the color of the image, some claiming it was white and gold while others were adamant it was blue and black. While there is still conflict about what individual differences in the brain leads to varying percepts, The Dress gives scientists an incredible opportunity to gain insight into color perception [1,2,3].

# The Dress illusion is an example where color constancy mechanisms fail.

An essential aspect of understanding the intrigues of The Dress illusion involves understanding the concept of color constancy. An object doesn't have color as a property: the color we perceive is related to the object's reflectance and the surrounding illuminant [1,4]. Changes in lighting conditions can change the overall wavelengths of light that reaches our eyes. Nonetheless, we perceive the color of an object as remaining constant. This is because our visual system is continuously color correcting. By discounting the illuminant, whether that be a shadow or a bright light shining on the object, we maintain color constancy of the object [5,6]. This means that the subjective color a person perceives will remain relatively constant under different illuminance conditions. For example, a strawberry will still look red in dim lighting or in bright lighting. The Dress illusion is an example where color constancy mechanisms fail. People perceive The Dress in different ways because their visual system is making different assumptions about the illumination in the photo. Subtracting one illuminant causes the dress to appear blue and black, whereas subtracting the other causes it to appear white and gold.

The colors of the individual pixels of The Dress image fall remarkably close to an area in color space known as the Daylight Locus [4]. This spectrum of light is composed of short, "cool" wavelengths in the morning and longer, "warm" wavelengths in the evening [7]. The Daylight Locus is important for determining illuminance cues, since this is the illuminance we are exposed to most often in our day to day lives. The Dress image has an ambiguous illuminant. This means the observer must assume the illuminant, whether it is "cool" or "warm."



A cool illuminant represents bluer wavelengths of light. Therefore, people who perceive The Dress as white/gold tend to assume the illuminant is more blue than yellow. Recall, that color constancy involves subtracting the wavelengths of the illuminant from the wavelengths of the object, so a bluer illuminant will make the object appear more yellow. On the other hand, observers that assume a more yellow illuminant tend to see The Dress as blue/black. Because the colors in the image are very close to the Daylight Locus, they strongly affect slight changes in how the visual system perceives the overall illuminant.

## Is it possible to predict whether an observer will assume a yellow or blue illuminant?

So what determines how individuals perceive the illuminant in The Dress illusion? It turns out experience and context may play an important role. Based on a large scale study performed by Wallisch in 2017, it is possible to predict whether an observer will assume a yellow or blue illuminant based on whether they are morning people (larks) or night people (owls). Larks have more exposure to shorter, blue wavelengths of light characteristic of the morning. Owls are more exposed to the longer wavelengths of light of the evening as well as artificial, incandescent light, which also has long, yellower, wavelengths. Therefore, most morning people assume a bluer illuminant, seeing The Dress as white/gold. Owls tend to assume a yellower illuminant and thus are more likely to perceive The Dress as blue/black.

Assumed illuminant color is not the only predicator of perception of The Dress. Assumptions about the position of the illuminant are also important [8]. For example, if you assume the illumination is coming from behind The Dress, you will interpret The Dress as being in a shadow. Shadows primarily represent shorter, blue wavelengths, so when you assume The Dress is in shadow, color constancy mechanisms discount the shadow, making The Dress appear white/gold. In contrast, assuming the illuminant is coming from in front of The Dress indicates The Dress is in full light, causing The Dress to appear blue/black.

The ambiguity regarding the illuminant is related to properties of the photo. First, there is a high degree of photorealism [3]. This convinces observers that what they are perceiving in the photo are the true properties of The Dress, which is why people remain steadfast in their interpretation, even upon learning that others perceive it differently. Second, the image has several different color temperatures, relating to the white balance of the photo [1]. White balance relates to the color temperature of the photo and how the color temperatures range from cool to warm. Cameras have a difficult time adjusting the white balance automatically when there are multiple color temperatures illuminating the scene, for example from natural light (cool) and incandescent light (warm) [9].

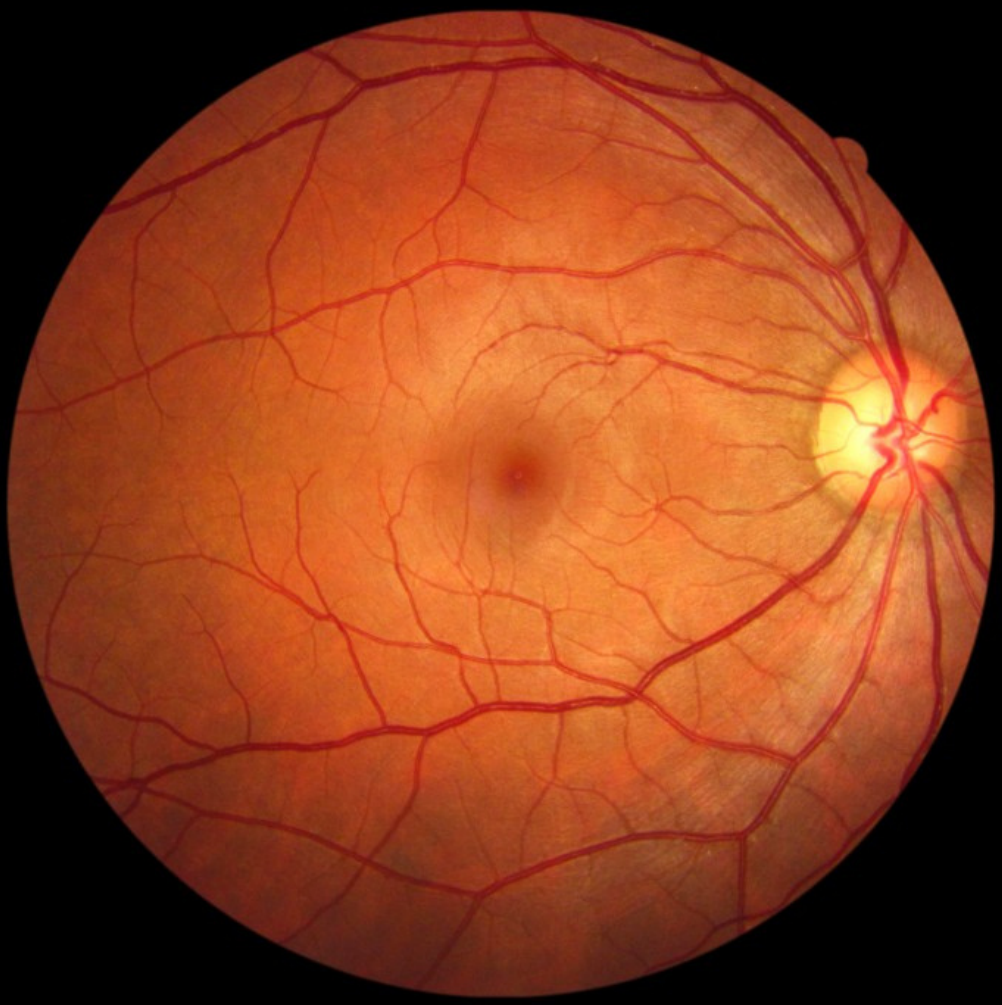
The Dress image contains multiple color temperatures, causing the illumination to be ambiguous.

A study performed in 2017 by Hugrass and colleagues modulate observer's perception of The Dress by employing apparent lightening and darkening illusions to the image. They did this by modifying the white balance of the original dress image to disambiguate white/gold and blue/black images. By brightening the image, the illuminant colors shifted to cooler, blue wavelengths of light, meaning that regardless of how an observer perceives the original image, they would see The Dress as white/gold. Dimming the image created the opposite effect, shifting the illuminant colors to warmer, yellow wavelengths of light, creating a disambiguated blue/black image.

There are a rare few who can switch their perception of The Dress from white/gold to blue/black and back again. These people are known as switchers. Likely, the reason they are able to switch their perception is because the lighting conditions of The Dress are very close to their perceptual boundary of perceiving the illuminant as more blue or more yellow. In these rare cases the perception switches depending on which illuminant is perceived.

**The Dress illusion has aided immensely in the deeper understanding of how humans perceive color.**

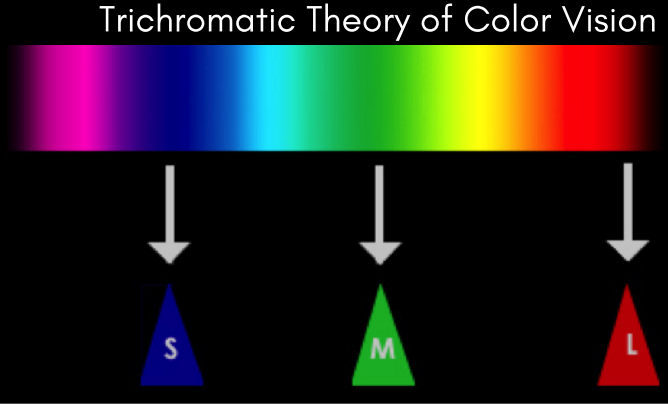
There is currently no consensus on the neuroscientific reasons behind the varying percepts of The Dress and research is still ongoing. Despite this, The Dress illusion has aided immensely in the deeper understanding of how humans perceive color. It also has brought color vision science into the minds of people other than color vision scientists, allowing for increasing accessibility to the intrigues of color vision. As time passes, more will become known about the neuroscience of color vision. Further understanding will be wrought regarding our understanding of The Dress. Until then, we will continue to question how and why our brains process color and continue to enjoy the beauty of color and all it does for interacting with our environment.



# How Our Brains Process Color

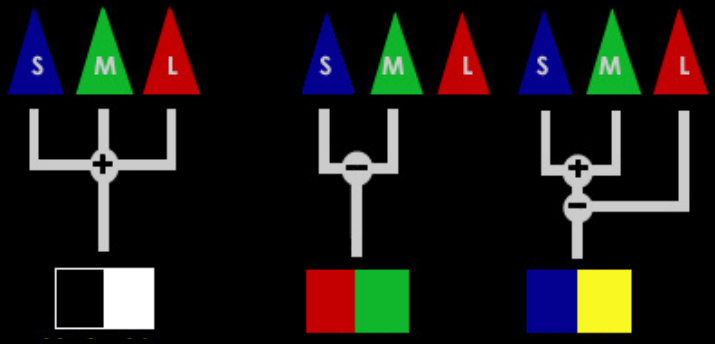
By Trinity Wilson

When we refer to color, we are referring to the small, visible spectrum of light, each of which has a different wavelength. In the visible light spectrum, blue has the shortest, highest energy wavelength and red has the longest, lowest energy wavelength [1]. All other colors reside between these two. There are two types of photoreceptors in the retina; rods and cones. Rods are achromatic, meaning they receive information not relating to color, including variations in illuminance and brightness. Cones, of which there are three sub-types, are important for color vision and detail. Short (S) cones are the most sensitive to blue wavelengths, medium (M) cones are sensitive to green, and Long (L) cones are most sensitive to red wavelengths [1]. There is overlap in the wavelengths of light each cone can absorb. Sensitivity to a certain color doesn't mean an S cone can't absorb some green wavelengths of light. It simply means that each cone is most sensitive to specific wavelengths. According to the Young-Helmholtz trichromatic theory of color vision, this overlap of absorption between different photoreceptors allows for all colors in the visible light spectrum to be created by combining red, green, and blue [2].



Color perception requires input from at least two different types of cones. Once the information from the rods and cones enters the brain, color perception is controlled by three receptor complexes; red-green complex, blue-yellow complex, and black-white complex [3]. Known as the opponent process theory of color vision, these complexes act in an antagonistic manner, where excitation of one component of a complex leads to inhibition of the other component [3].

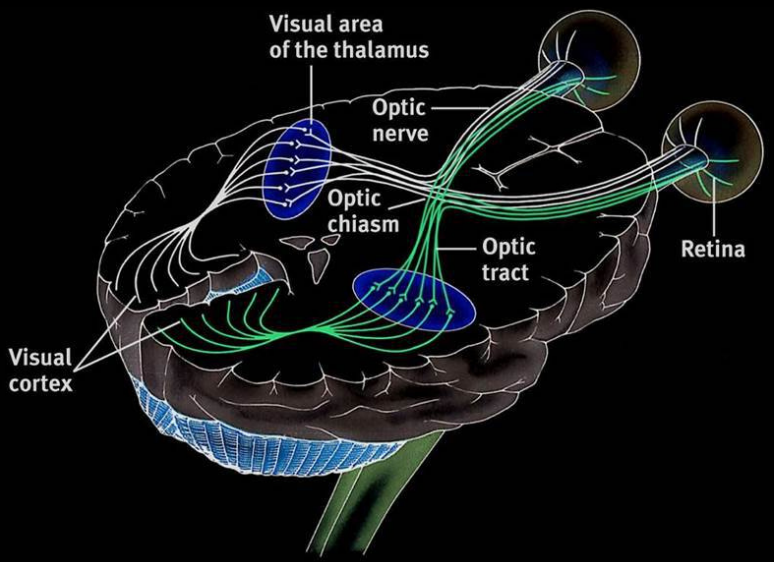
Opponent Process Theory of Color Vision




This is the reason you would never describe a color as greenish-red or yellowish-blue. The brain can only detect one of those colors at a time because the colors oppose each other [3,4]. The black-white complex is achromatic and is necessary for detecting the luminance of a scene and is closely linked to rods in the retina, which are important for detecting luminance and brightness [4]. An implication of this is the presence of negative after-images, for example, with the lilac chaser illusion. This illusion consists of 12 blurred lilac dots arranged in a circle. Each dot will disappear briefly, going all around the circle. When you look at the image, you will see a green after image in the blank space after staring at a small cross in the middle of the circle [1].

This opponent processing occurs in the visual cortex, a small, quarter sized section of the occipital lobe located on the rear of the brain [4,5]. The process for this color information to eventually reach the visual cortex starts with excitation of photoreceptors (rods and cones) in the retina [2]. From the retina, information enters the brain via the optic nerve, travels to the lateral geniculate nucleus (labeled visual area of the thalamus in the figure below), then via the optic radiation to the visual cortex for further processing [5]. In terms of color processing, the lateral geniculate nucleus and the small part of the visual cortex dedicated to color contain two major classes of ganglion cells, which are extremely important in the whole process. Magnocellular (M) with large cell layers are important for the black-white complex. Parvocellular (P) with small cell layers are necessary for color processing. P cells are important for processing red/green color differences, blue/yellow differences, and light intensity [4,5].

General Color Vsion Pathway



# NEURALINK:

## Revolutionary or Reinventing the Wheel?

By Alexandra Jean Gilsrud

In March of 2017 Elon Musk, a business magnate known primarily as the CEO of Tesla Motors and SpaceX, announced his newest foray into the STEM fields. The multibillionaire proudly made public the founding of a new company, dubbed Neuralink, that would focus on advancing the field of brain-computer interface (BCI).

The endeavor to create a safe, accurate, and efficient link between human thought and external hardware has been an ongoing battle since the invention of electroencephalography (EEG) and subsequent recording of human brain activity in 1924. In the near century since, our ability to detect and interpret the electrical activity responsible for human life and experience has greatly improved. Despite these improvements, the BCI medically available is still extremely limited in both ability and availability. Most products are limited to carrying out simple-seeming motor commands and are provided to patients with paralysis, in particular patients of locked-in syndrome or late-stage Parkinson's Disease [1].

Undeterred by the limits currently facing the field of BCI, Musk issued ambitious claims about his new company in a launch live stream on July 16th, 2019. Musk implied that there were two ultimate goals to the development of the Neuralink device. The first and most immediate goal would be to remedy neurological diseases and disorders, both congenital and

trauma induced. The second more lofty goal would be to facilitate symbiosis between humans and artificial intelligence (AI). While explaining these lofty goals to his audience, Musk qualified his claims by stating that Neuralink would take a very long time to reach its full potential, however he did not give an estimate of how long [2].

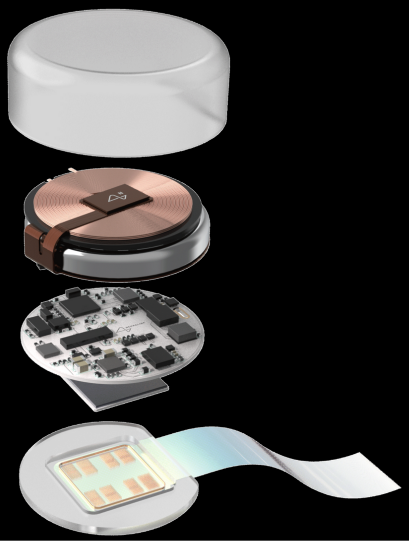
To understand to what degree these goals are attainable, one must first understand the current state of BCI technology. The current gold standard of brain computer interface is the microelectrode array. The use of a microelectrode array involves the implantation of a large number of electrodes in living brain tissue. As neurons propagate action potentials, the changes in electrical charge surrounding the cells are detected by electrodes. The changes in charge are transmitted to connected processing hardware that filters the input from multitudes of electrodes and translates the electrical activity into a decipherable recording [1]. Implanted electrodes are typically only nanometers thick as the small size allows the implants to avoid damaging vasculature within the brain. However, current BCI is restricted to cortical tissue due to the difficulties in avoiding deeper vasculature during implantation and restrictions in electrode materials.


**"It's kind of like Fitbit in your skull with tiny wires."**
**-Elon Musk**

The most widely used microelectrode array technology comes from Blackrock Microsystems, a company known primary for the Utah Array. With the devices available from Blackrock Microsystems a human patient may have 128 stiff electrodes in grid formation implanted up to 1.5mm deep, connected to the NeuroPlex E headstage, which is no larger than a quarter. The head stage is not wireless and must be connected to the Neuroport processor to function [3]. However, Blackrock Microsystems does have wireless headstages available for animal research, these have yet to be approved for human use by the FDA, but it's not far-fetched to believe wireless products from Blackrock will become available for human patients within the next decade. The human-available technology of Blackrock Microsystems certainly has a long wait before becoming anything more than a partial treatment for extreme cases, but the company's products have helped recover sensation and motor function for many patients.

With such advanced BCI already available, the purpose of Neuralink as a company comes into question. On August 28th, 2020 Neuralink streamed a live update in which Musk presented the current prototype for the "link", a chip intended for implantation in the human skull with 1000 electrodes. He announced during his introduction that the Neuralink mission statement was now to "Solve important brain and spine problems with a seamlessly implanted device". Musk went on to say that the goal was to make a single device

that is both affordable and generalizable, in listing examples of brain and spine problems to be solved, the CEO named many common but disparate conditions, ranging from depression and addiction to blindness and paralysis. Musk claimed the current prototype could serve as a diagnostic tool for heart attacks and could play music. However, the CEO did not substantiate these claims by explaining how the device could accomplish these tasks. Musk went on to claim that implantation of this device would be possible within an hour without use of general anesthetic [4]. On stage with Musk was the surgical robot used for experimental implantation of the "link". A white paper from August 2. 2019 provides more insight into the innovations being developed at Neuralink. The most pivotal development of Neuralink is arguably the development of the aforementioned surgical robot. Neuralink is capable of implanting up to 3,072 electrodes on 96 individual threads up 6mm deep. These impressively large values are due in part to the power of the links processor, and largely due to the flexibility of the polymer threads. Neuralink is not the first to implant flexible electrodes, but the placement of said electrodes in the past has been difficult. The surgical robot developed by Neuralink allows for extremely precise implantation without damage to vasculature, allowing for a great



number of threads to be implanted with relatively low risk of inflammation and therefore side-effects. The robot operates like a microscopic sewing machine, specialty lights mounted to the machine allow a camera to confirm thread placement, and though the machine can be fully automated, manual controls for a surgeon to adjust placement are also optional [5].

Despite the impressive advancement in BCI materials developed by Neuralink, their microelectrode arrays are still confined to cortical layers of the brain and are not comprehensive enough to treat complex neurological issues such as schizophrenia. Animal trials have been successful, but the company has yet to announce any experimental outcomes that haven't been similarly achieved by investigators using arrays from Blackrock Microsystems. So far demonstrations have included real-time readings of brain activity in pigs and a monkey capable of playing pong via the link alone [2,6]. The advancements of Neuralink have been exciting, in fact, the FDA has classified Neuralink as a Breakthrough Device in recognition of the company's accomplishments. That being said, despite Musk's far-flung dreams, humanities symbiosis with artificial intelligence seems to be a long way off, if it's on the horizon at all.

# The Development of Synthetic Flavor

By Alexandra Jean Gilsrud

The concept of taste simulation is not a new one, many children have watched on in envy as characters like Willy Wonka conjure chocolate bars or other sweets from a tv in some distant fantasy world. Fortunately, it appears humanity is progressing steadily towards the ability to simulate taste. Augmented food devices are not necessarily new, knowledge that electrical current could induce flavor sensation has been in literature for decades. However, some scientists have considerably upped the ante with electric straws, spoons, glasses, bowls, chopsticks, and most impressively, the Norimaki Synthesizer.

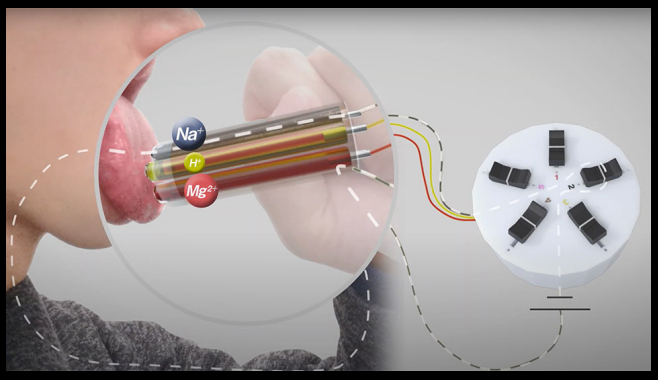
## Why would researchers invest so much time and money into the simulation of taste?

The motivation that first comes to mind for researching taste simulation may be entertainment purposes, and though this is a small motivator, taste simulation could also be of great value for those requiring dietary restrictions. A device that can digitally reproduce salty or sweet foods could assist patients in maintaining necessary diets and could improve quality of life for patients incapable of eating certain foods. An ability to synthetically reproduce taste could be culturally significant as well, allowing for archival of food in a way never thought possible before.

To understand how taste simulators reproduce the sensation of flavor, a basic understanding of the tongue is necessary. The tongue is a sensory organ containing five types of chemoreceptors, producing five flavors: bitter, sweet, umami, salty, and sour. Each type of receptor responds to the presence of a different molecule, texture and heat can also affect perception of flavor and the information from the mouth is integrated with visual cues and smells to create a complex experience [1].

Some cutlery and dishes have recently been

designed with LED lights and electrodes to produce different taste experiences. Two such prototypes are the Spoon+ and the Bottle+. Both have settings that vary in current, polarity, and frequency of electrical current to elicit sour, salty, or bitter. The LED lights on the devices change the user's perception of what sweet, salty, or bitter food or drink is being emulated [2]. For a more comprehensive taste experience, a gustatory augmentation device called the Norimaki Synthesizer has recently been developed. The cylindrical device has a handle plated in copper to act as an electrode, and the tip contains five electrolyte-containing gels that complete a full circuit when touched to a user's tongue. The five gels vary by the type of electrolyte contained within. Glutamic sodium targets Umami receptors, citric acid targets sour receptors, magnesium chloride corresponds to bitter receptors, sodium chloride is present for salt receptors, and glycine targets sweet receptors.


When no electrical current is applied a user experiences all five flavors, when electrical current is applied, cations move away from the tongue, eliminating that taste. In this way the Norimaki Synthesizer can create any combination of the five basic flavors continuously for at least 30 minutes without the presence of real food, and only a slightly metallic accompanying flavor [3].

As impressive as the above-mentioned devices are, they lack the rich experience of flavor achieved by real food. They don't replicate smell and are only beginning to integrate visual input. These deficits aside, with proper funding and a decade more of research, maybe we'll have our own "Wonkavision" someday.

# Citations

**Drug Policy and Limitations in Neuroscience**


1 Andreae, M. H., Rhodes, E., Bourgoise, T., Carter, G. M., White, R. S., Indyk, D., Sacks, H., & Rhodes, R. (2016). An Ethical Exploration of Barriers to Research on Controlled Drugs. *The American journal of bioethics : AJOB, 16*(4),36–47. https://doi.org/10.1080/15265161.2016.1145282

2 Stewart, A. M., & Kalueff, A. V. (2013). Controlled substances and innovation of biomedicine: a preclinical perspective. Nature reviews. *Neuroscience, 14*(12), 877. https://doi.org/10.1038/nrn3530-c1

3 Nutt, D. J., King, L. A., & Nichols, D. E. (2013). Effects of Schedule I drug laws on neuroscience research and treatment innovation. Nature reviews. *Neuroscience, 14*(8), 577–585. https://doi.org/10.1038/nrn3530

4 Federal Drug Enforcement Agency. (2021, June 16). *Drug Scheduling.* https://www.dea.gov/drug-information/drug-scheduling

5 Burrus, T. The Systematic Prohibition of U.S. Drug Science. Cato institute. https://www.cato.org/sites/cato.org/files/2020-02/burrus-sciencetocracy-2019.pdf

6 Cressey, D. Nutt dismissal in Britain highlights diverging drug views. *Nature Medicine, 15*(12), 1337. https://www.nature.com/articles/nm1209-1337.pdf?origin=ppub

7 Office of National Drug Control Policy. (2000, December) *What America's Users Spend on Illegal Drugs 1988 - 1998.* https://web.archive.org/web/20070312034207/http://www.whitehousedrugpolicy.gov/publications/drugfact/american_users_spend/index.html

8 Federal Drug Enforcement Agency. (2005, December 28). *Drug Enforcement Administration Highlights Year's Accomplishments*. https://web.archive.org/web/20060627001334/http://www.dea.gov/pubs/pressrel/pr122805.html

9 Morris, H. (Host). (2020, May 31). An interview with DEA chemist Terry Dal Cason. [Audio podcast episode]. In *Hamilton Morris's Patreon.* Patreon. https://www.patreon.com/posts/podcast-4-with-37745739

10 Samorini, G. (2019). The oldest archeological data evidencing the relationship of Homo sapiens with psychoactive plants: A worldwide overview. *Journal of psychedelic studies, 3*(2), 63-80. https://akjournals.com/configurable/content/journals$002f2054$002f3$002f2$002farticle-p63.xml?t:ac=journals%24002f2054%24002f3%24002f2%24002farticle-p63.xml

11 Powell, B. *The economics behind the U.S. government's unwinnable war on drugs*. The Library of Economics and Liberty. https://www.econlib.org/library/Columns/y2013/Powelldrugs.html

12 NORML. (2021). Racial Disparity in Marijuana Arrests. https://norml.org/marijuana/fact-sheets/racial-disparity-in-marijuana-arrests/

13 Nutt, D. J., King, L. A., Phillips, L. D., & Independent Scientific Committee on Drugs (2010). Drug harms in the UK: a multicriteria decision analysis. Lancet (London, England), 376(9752), 1558–1565. https://doi.org/10.1016/S0140-6736(10)61462-6

14 Griffiths, R., Richards, W., Johnson, M., McCann, U., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of psychopharmacology (Oxford, England), 22*(6), 621–632. https://doi.org/10.1177/0269881108094300

15 Sententia W. (2004). Neuroethical considerations: cognitive liberty and converging technologies for improving human cognition. *Annals of the New York Academy of Sciences, 1013*, 221–228. https://doi.org/10.1196/annals.1305.014

16 Leary, T. (1968). *The politics of ecstasy*. Ronin Publishing.

17 Wudan, Y. (2020, December 9). *The Nobel Prize-winning, LSD dropping, yet problematic scientist who invented PCR*. Elemental. https://elemental.medium.com/the-nobel-prize-winning-lsd-dropping-yet-problematic-scientist-who-invented-pcr-26b6678ccd46

18 Roberts, A. (2015, May 14). *Francis Crick, DNA & LSD*. Reality Sandwich. https://realitysandwich.com/francis-crick-dna-lsd/

19 Shulgin, Alexander & Shulgin, Ann. (1991). *PiHKAL: A Chemical Love Story.* Transform Press.

20 Glick, S. D., & Maisonneuve, I. S. (1998). Mechanisms of antiaddictive actions of ibogaine. Annals of the New York Academy of Sciences, 844, 214–226.

21 J.W. (2001, December 3) *A list of the (186) known Psilocybin Mushrooms*. The Vaults of Erowid. Erowid. https://www.erowid.org/plants/mushrooms/mushrooms_info12.shtml

22 Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. The New England journal of medicine, 384(15), 1402–1411. https://doi.org/10.1056/NEJMoa2032994

23 Businesswire. (2019, November 22). *FDA grants Breakthrough therapy designation to Usona Institute's psilocybin program for major depressive disorder.* https://www.businesswire.com/news/home/20191122005452/en/FDA-grants-Breakthrough-Therapy-Designation-Usona-Institutes

24Multidisciplinary Association for psychedelic studies. (2017, July 28) A Phase 3 Program of MDMA-Assisted Therapy for the treatment of severe posttraumatic stress disorder. https://maps.org/research/mdma/ptsd/phase3

**Neuropsychiatric Outcomes of COVID-19 Surviviors**

1 Johns Hopkins University of Medicine . (2021, June, 5). Covid-19 Map. Coronavirus Resource Center. https://coronavirus.jhu.edu/map.html

2 Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). 6-month neurological and psychiatric outcomes in 236379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The lancet. Psychiatry, 8*(5), 416–427. https://doi.org/10.1016/S2215-0366(21)00084-5

3 Boldrini, M., Canoll, P. D., & Klein, R. S. (2021). How COVID-19 Affects the Brain. *JAMA psychiatry, 78*(6), 682–683. https://doi.org/10.1001/jamapsychiatry.2021.0500

4 Rhea, E. M., Logsdon, A. F., Hansen, K. M., Williams, L. M., Reed, M. J., Baumann, K. K., Holden, S. J., Raber, J., Banks, W. A., & Erickson, M. A. (2021). The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice. *Nature neuroscience, 24*(3), 368–378. https://doi.org/10.1038/s41593-020-00771-8

5 Lin, C. E., Chung, C. H., Chen, L. F., & Chien, W. C. (2019). Increased risk for venous thromboembolism among patients with concurrent depressive, bipolar, and schizophrenic disorders. *General hospital psychiatry, 61*, 34–40. https://doi.org/10.1016/j.genhosppsych.2019.10.003

6 Daniels, B. P., Holman, D. W., Cruz-Orengo, L., Jujjavarapu, H., Durrant, D. M., & Klein, R. S. (2014). Viral pathogen-associated molecular patterns regulate blood-brain barrier integrity via competing innate cytokine signals. *mBio, 5*(5), e01476-14. https://doi.org/10.1128/mBio.01476-14

7 Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W. S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., Stevens, B., … Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature, 541*(7638), 481–487. https://doi.org/10.1038/nature21029

8 Vasek, M. J., Garber, C., Dorsey, D., Durrant, D. M., Bollman, B., Soung, A., Yu, J., Perez-Torres, C., Frouin, A., Wilton, D. K., Funk, K., DeMasters, B. K., Jiang, X., Bowen, J. R., Mennerick, S., Robinson, J. K., Garbow, J. R., Tyler, K. L., Suthar, M. S., Schmidt, R. E., … Klein, R. S. (2016). A complement-microglial axis drives synapse loss during virus-induced memory impairment. *Nature, 534*(7608), 538–543. https://doi.org/10.1038/nature18283

**Learning and Memory Storage: Epigenetics vs. Synapses**

1 Abraham, W., C., Jones, O., D., & Glanzman, D.L. (2019) Is plasticity of synapses the mechanism of long-term memory storage? npj Science of Learning 4. doi: 10.1038/s41539-019-0048-y

2 Abraham, W. C., Robins, A. (2005) Memory retention—the synaptic stability versus plasticity dilemma. Trends Neurosci 28(2), 73–78. doi: 10.1016/j.tins.2004.12.003

3 Bernabo, M., Haubrich, J., Gamache, K., & Nader, K. (2021). Memory destabilization and reconsolidation dynamically regulate the PKMζ maintenance mechanism. Journal of Neuroscience 41(22), 4880-4888. doi: 10.1523/JNEUROSCI.2093-20.2021

4 Hwang, H., Szucs, M. J., Ding, L. J., Allen, A., Ren, X., Haensgen, H., ... & Xu, W. (2021). Neurogranin,
encoded by the schizophrenia risk gene NRGN, bidirectionally modulates synaptic plasticity via calmodulin-dependent regulation of the neuronal phosphoproteome. Biological Psychiatry, 89(3), 256-269. (https://doi.org/10.1016/j.biopsych.2020.07.014)

5 Piatkevich, K.D., Jung, E.E., Straub, C., Linghu, C., Park, D., Suk, H., ... & Boyden, E. S. (2018) A robotic multidimensional directed evolution approach applied to fluorescent voltage reporters. Nat Chem Biol 14(4), 352–360. doi: 10.1038/s41589-018-0004-9

**Machine Learning & Neuroscience**

1 Landhuis, E. (2020). Probing fine-scale connections in the brain. Nature 586, 631-633. doi: https://doi.org/10.1038/d41586-020-02947-5

2 Vu, M. T., Adalı, T., Ba, D., Buzsáki, G., Carlson, D., Heller, K., ... & Dzirasa, K. (2018). A shared vision
for machine learning in neuroscience. The Journal of Neuroscience 38(7), 1601-1607. doi: 10.1523/JNEUROSCI.0508-17.2018

3 Mahmood, M., Mzurikwao, D., Kim, Y., Lee, Y., Mishra, S., Herbert, R., ... & Yeo, W. (2019) Fully portable and wireless universal brain–machine interfaces enabled by flexible scalp electronics and deep learning algorithm. Nature Machine Intelligence 1, 412-422. doi: 10.1038/s42256-019-0091-7.

4 Xu, C. S., Januszewski, M., Lu, Z., Takemura, S., Hayworth, K J., Huang, G., ... &Plaza, S. M. (2020). A
connectome of the adult Drosophila central brain.
https://www.biorxiv.org/content/10.1101/2020.01.21.911859v1.article-info

5 Zheng, Z., Lauritzen, J. S., Perlman, E., Robinson, C. G., Nichols, M., Milkie, D., ... & Bock, D.D. (2018)
A complete electron microscopy volume of the brain of adult drosophila melanogaster. Cell 174(3), 730-743.e22. doi: 10.1016/j.cell.2018.06.019

**The Dress and Color Perception**

1 Hugrass, L., Slavikova, J., Horvat, M., Musawi, A. A., & Crewther, D. (2017). Temporal brightness illusion changes color perception of "the dress." Journal of Vision, 17(5):6, 1–7, doi:10.1167/17.5.6.

2 Schlaffke, L., Golisch, A., Haag, L. M., Lenz, M., Heba, S., Lissek, S., Schmidt-Wilcke, T., Eysel, E. T., & Tegenthoff, M. (2015). The brain's dress code: How The Dress allows to decode the neuronal pathway of an optical illusion. Cortex, 73, 271–275. https://doi.org/10.1016/j.cortex.2015.08.017.

3 Witzel, C., Racey, C., & O'Regan, J. K. (2017). The most reasonable explanation of ''the dress'': Implicit assumptions about illumination. Journal of Vision, 17(2):1, 1–19, doi:10.1167/17.2.1.

4 Gegenfurtner, K. R., Bloj, M., & Toscani, M. (2015). The many colours of ''the dress.'' Current Biology,
25(13), R543–R544. doi:10.1016/j.cub.2015.04.043.

5 D'Zmura, M., & Lennie, P. (1986). Mechanisms of color constancy. Journal of the Optical Society of America A, 3(10), 1662–1672.

6 Wallisch, P. (2017). Illumination assumptions account for individual differences in the perceptual interpretation of a profoundly ambiguous stimulus in the color domain: "The dress." Journal of Vision, 17(4):5, 1–14, doi:10.1167/17.4.5.

7 Panorgias, A., Kulikowski, J. J., Parry, N. R. A., McKeefry, D. J., & Murray, I. J. (2012). Phases of daylight and the stability of color perception in the near peripheral human retina. Journal of Vision, 12(3), 1–11, doi:https://doi.org/10.1167/12.3.1

8 Chetverikov, A., & Ivanchei, I. (2016). Seeing ''the dress'' in the right light: Perceived colors and inferred light sources. Perception, 45(8), 910–930, doi:10.1177/0301006616643664

9 White Balance - What is it & Why Does it Matter? Click Love Grow. (2021, May 14). https://clicklovegrow.com/white-balance-what-is-it-why-does-it-matter/#:~:text=White%20balance%20is%20the%20colour%20temperature%20of%20an,balance%20temperatures%20affect%20the%20appearance%20of%20an%20image.

**How Our Brains Process Color**

**1 L**earning, L. (n.d.). Introduction to Psychology. Lumen. https://courses.lumenlearning.com/wmopen-psychology/chapter/outcome-vision/.

2 Cherry, K. (2021, March 14). The Early Theory That Explains How We Perceive Color. Verywell Mind. https://www.verywellmind.com/what-is-the-trichromatic-theory-of-color-vision-2795831.

3 Cherry, K. (2020, January 13). How the Opponent Process Theory Explains How We See Color. Verywell Mind. https://www.verywellmind.com/what-is-the-opponent-process-theory-of-color-vision-2795830.

4 Wikimedia Foundation. (2021, May 22). Opponent process. Wikipedia. https://en.wikipedia.org/wiki/Opponent_process.

5 Wikimedia Foundation. (2021, May 15). Lateral geniculate nucleus. Wikipedia. https://en.wikipedia.org/wiki/Lateral_geniculate_nucleus.

**Neuralink: Revolutionary or Reinventing the Wheel?**

1 Martini, M. L., Oermann, E. K., Opie, N. L., Panov, F., Oxley, T., & Yaeger, K. (2019). Sensor modalities for brain-computer interface technology: A comprehensive literature review, Neurosurgery, 86(2), E108-E117. https://doi.org/10.1093/neuros/nyz286

2 Neuralink. (2019, July 16) Neuralink launch event [Video]. Youtube. https://youtu.be/r-vbh3t7WVI

3 Balckrock Microsystems. Blackrock Microsystems products. https://blackrockmicro.com/products

4 Neuralink. (2020, August 28) Neuralink progress update, summer 2020 [Video]. Youtube. https://youtu.be/DVvmgjBL74w

5 Elon Musk & Neuralink. (2019) An integrated brain-machine interface platform with thousands of channels. Journal of Medical Internet Research, 21(10). https://doi.org/10.1101/703801

6 Neuralink. (2021, April 8) Monkey mindpong picture-in-picture [Video]. Youtube. https://youtu.be/LgJpYOTII8U

**The Development of Synthetic Flavor**

1 Lindemann, B. (1996). Taste reception. Physiological Reviews, 76(3), 719–766. doi:10.1152/physrev.1996.76.3.719

2 Ranasinghe, N., Lee, K.-Y., Suthokumar, G., & Do, E. Y.-L. (2016). Virtual ingredients for food and beverages to create immersive taste experiences. Multimedia Tools and Applications, 75(20), 12291–12309. doi:10.1007/s11042-015-3162-8

3 Miyashita, H. (2020, April 25) Norimaki Synthesizer: Taste display using ion electrophoresis in five gels. CHI Conference on Human Factors in Computing Systems, Honolulu Hawaii, USA. https://doi.org/10.1145/3334480.3382984

# Citations

**Citations of Images By Order of Appearance in Magazine**

**Title Page and Dear Readers**
canva.com

**Drug Policy and Limitations in Neuroscience**
Psilocybe cubensis photos provided by crearte media

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https://news.wbfo.org/post/coronavirus-doesnt-change-quickly-and-thats-good-news-vaccine-makers
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https://www.dreamstime.com/coronavirus-covid-viral-cell-infection-causing-disease-black-background-pneumonia-viruses-h-n-sars-flu-cell-infect-org-image174316200

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https://www.shutterstock.com/video/search/neurotransmission
https://www.shutterstock.com/video/clip-2601764-single-neuron-brain-cell-nerve-growing-impulse
https://www.nature.com/articles/s41589-018-0004-9

**Machine Learning & Neuroscience**
https://www.nature.com/articles/d41586-020-02947-5
https://www.sciencealert.com/scientists-scan-fruit-fly-neurons-for-most-detailed-brain-image-ever

**"The Dress" and Color Perception**
bquIxU.jpg (2560×1600) (wallpapersafari.com)
5DO6KDVA66PSNWA77YATTXEKYI.jpg (1200×737) (nydailynews.com)

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shutterstock_216759742.jpg (1110×740) (nofilmschool.com)
untitled-140601F9D2F353540B7.png (576×396) (classconnection.s3.amazonaws.com)
3+cones+used+in+opponent+process+theory.jpg (432×264) (bp.blogspot.com)
visual_pathway.jpg (788×577) (butterfill.com)

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https://neuralink.com
https://blacckrockmicro.com

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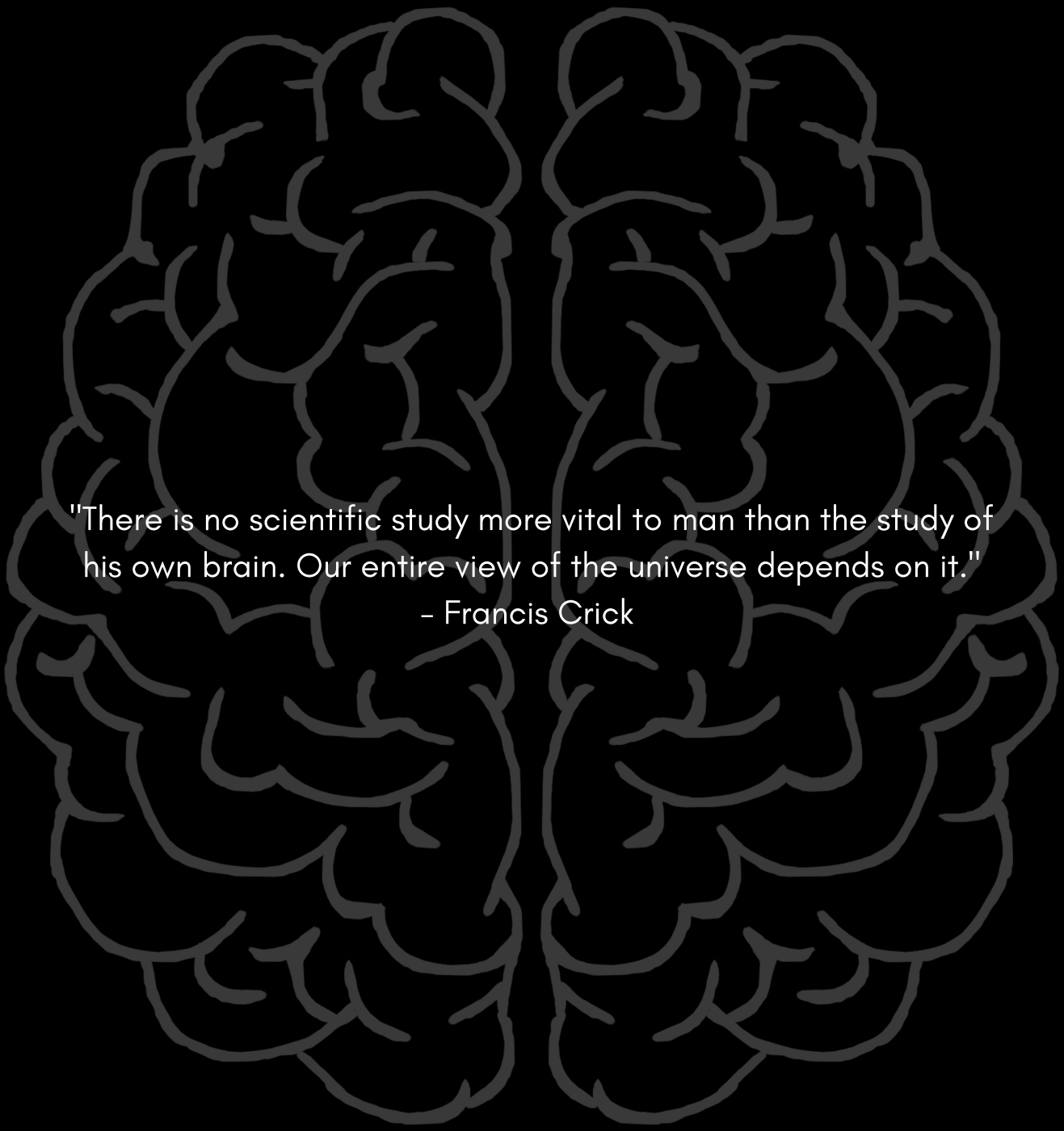
https://cdn.vox-cdn.com/thumbor/hr1R5ma1vvTc3xzsDluE2hKdFJk=/1400x1400/filters:format(jpeg)/cdn.vox-cdn.com/uploads/chorus_asset/file/9152263/the_art_of_flavor_excerpt.jpg
https://media.techeblog.com/images/norimaki-synthesizer-taste-device.jpg



"There is no scientific study more vital to man than the study of his own brain. Our entire view of the universe depends on it."
- Francis Crick