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A Call for More Comprehensive Alcohol Education

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LETTER FROM THE PROFESSOR

Preparation, not luck.

Dear Class of 2022,

What a journey this has been! Significant upheavals in world events occurred during your four years at Kenyon College. A global pandemic, mass protests and political uncertainty in the United States, a European war in the twenty-first century that recapitulates the worst nation-state behaviors of the twentieth century. And as you leave college, these events continue to unfold and you are called upon to participate in the world and do your part in shaping the yet to be determined outcomes. As is often the case, many people will wish you well as you transition from college to your post-college life, and you will probably hear the phrase “good luck” quite often. Those who wish you good luck are doing so with the best of intentions, but luck, by definition, emphasizes random chance and minimizes intentional action. And although we cannot deny that some random chance plays a role in all of our lives, we know that to achieve the outcomes for which we strive, we must engage in intentional behaviors and sustained effort. This is how we prepare to meet challenges. To be prepared is to tilt the outcomes in life in favor of the intentional and away from random chance. You wanted your future success to depend less on luck and more on preparation and so you have spent the last four years engaged in sustained, intentional actions in preparing for your future. The paths you have chosen to follow after Kenyon varies, but what cannot be denied is your preparation to walk those paths. That preparation made graduate school possible; it made medical school possible; it made law school possible; preparation made you successful in your job search; preparation gave you the mental clarity to know that you need to take a break between college and your next adventure; and it gave you the confidence to act on that realization. You understood that preparation is more than the acquisition of knowledge in your specific discipline; that true preparation for global citizenship requires a broad, liberal education. And so even as you became experts in neuroscience, you remained or became artists and athletes, and participated in a variety of activities both on and off campus that speaks to that broader engagement. This magazine is a tangible testament to your expertise in neuroscience as well as your ability to communicate complex ideas to anyone interested in hearing those ideas. We, your faculty, were honored to be part of your journey of preparation. Our role was to pushed you to grow and excel; you responded by growing and excelling. You are successful. We too wish you good luck as you leave us; it is our way acknowledging that random chance plays a role in all of our lives. But we know that your success is not due to chance; it is the outcome of focused and sustained effort. It came from persistence; a willingness to try harder, work longer, take the smarter approach. You are successful because you have prepared to be successful. And so, we have no doubt that you will meet and overcome the challenges of the future. Whatever path(s) you take, we are confident that you will represent yourselves, the Neuroscience Department, and Kenyon College with grace and distinction. We wish you well.

Sincerely,

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A Racing Mind
How Time Perception Impacts Athletic Endurance
By Sierra Smith
Take out a stopwatch, hit “start”, and immediately close your eyes. Without counting, open your eyes once exactly 20 seconds have passed. What does the watch say? How accurate was your timing? Try this again, this time, for 60 seconds. Were you closer or further away from being correct? How accurate do you think you’d be if you tried this for an hour — 24 hours, even? While this exercise may feel bizarre, there are many ways we replicate this process of internally measuring time throughout the day. From determining exactly how much time is necessary to wash our hands, to anticipating when the red light our car is stopped at will turn green, our ability to conceptualize time guides many of our actions. Can you also think of instances when losing track of time isn’t necessarily a bad thing? Watching the clock during a 3 hour college lecture, or even a 30 minute jog, has a unique capacity for wearing someone out. While it is easy enough to train yourself to ignore the clock on the wall during a lengthy activity, what would happen if you were also able to ignore your internal clock? There is one woman who potentially holds the answer to this question: Diane Van Deren.

The Ultrarunner

Diane Van Deren, a 61 year-old from Omaha, Nebraska, began her professional athletic career as a tennis player. However, in 2006 at 46 years-old, Diane was the runner-up to Lance Armstrong for outdoor person of the year for ultramarathon running (a race exceeding 26 miles and 385 yards). WNYC studios reporter Mark Philpips highlighted how Diane did not compete in her first ultramarathon until the age of 42, when she entered a 50-mile ultramarathon on a whim, and subsequently won (1). Testing her luck, she entered a second ultramarathon (a 100-mile race through the Bighorn Mountains in Wyoming), and managed to place. Diane was just getting started. A non-exhaustive list of her running victories includes: the Alfred Packer 50 mile race, second place. The Bear 100-miler, first place. The Tahoe Rim 100-mile race, first place. First in “Dances with the Dirt,” a 50-mile race in Hell, Michigan. First place in the “24 hours in Frisco” trial run. Upping the ante by adding the challenge of extreme cold to these races, she won first place in the Canadian Death Race, a 78-miler in Edmonton, Canada (1). One of her craziest accomplishments, however, was when she became the first woman to complete the Yukon Arctic Ultra 300 race — a race where she ran 430 miles in -48 degree weather in the Yukon territory while dragging a 50-pound sled behind her. The race lasted about 10 days, with Diane averaging 1 hour of sleep per night, and trekking onward with frozen shoes. What makes someone wake up one day at 42 years old and become an elite endurance athlete? In Diane’s case, it involved literally losing her mind — to be precise, the removal of a kiwi-sized portion of her brain (1).

While Diane had always been an athlete, (playing professional tennis, winning a marathon, and competing in other athletic competitions) it was not until she had a brain surgery to remove a portion of her temporal lobe as a treatment for epilepsy that she became an ultra-runner. To first provide some background on Diane’s condition: at 28-years old she experienced her first seizure. In an interview with WNYC studios, Diane describes feeling a peculiar sensation, blacking out while in the car with her mother, and waking up in the hospital (1). This “peculiar sensation”, which many epileptics describe feeling before a seizure,
is known as a “premonition” or “aura”, and can serve as a warning sign for the onset of a seizure. The sensation can differ from person to person, but has been described by some as a rising feeling in the stomach — similar to that experienced when riding a roller coaster. For Diane (who began to regularly experience seizures after this initial incident), the seizure premonition was also accompanied by the urge to run. Every time Diane would experience a seizure premonition, she would throw on running shoes, and dash onto the trails in the woods behind her home in Colorado (1). Though this habit frightened her family, it was surprisingly successful at preventing seizure onset. Running potentially “reset” her brain activity to normal levels, and prevented the electrical activity from becoming erratic (which occurs during a seizure) (1, 2).

Diane continued this seizure-preventing strategy, but eventually the time from seizure premonition to the occurrence of the seizure became too short for her to take off running. The seizures became increasingly disruptive to her life at this point, and Diane worried about her ability to care for her 3 children, and perform simple tasks such as safely bathing and driving. After exhausting other potential treatment methods such as special diets and medication, Diane’s doctors proposed a more aggressive procedure: lobectomy.

How to Lose Your Mind

A lobectomy is a procedure involving the targeted removal of a small portion of the brain. To conduct a lobectomy procedure (1, 2) in epileptic patients, doctors use an EEG determine if there is a discrete region of the brain where a patient’s epileptic seizures are originating (1, 2). This device measures the electrical activity of different brain regions by pasting dozens of electrodes to the head of the patient. While the patient is hooked up to an EEG, doctors measure the activity in different regions of their brain when they experience a seizure. If there is erratic electrical activity in a specific brain region during the patient’s seizure, this portion of their brain can potentially be removed to prevent further seizing. While removing a segment of the brain comes with its own risk, for people like Diane with persistent seizures disrupting their daily activities, a lobectomy has the potential to restore some normalcy to their lives. At 37-years old, Diane entered the
hospital to have dozens of EEG electrodes glued to her head, and await the arrival of a seizure for the EEG to record. Doctors cheered at the success of the procedure: a discrete seizure-initiating region of her brain was found. Diane underwent surgery to remove this section of her brain, and never experienced a seizure again (1, 2).

The chunk of brain removed from Diane was pretty significant; a human brain is roughly the size of two clenched fists, and the piece of brain removed from Diane was about the size of a kiwi (3). The damaged brain segment was on the right side of her head in a region known as the temporal lobe, and included a portion of a sea-horse shaped structure known as the hippocampus. The hippocampus is a structure with a variety of functions, including imagining the past and future, learning, memory, spatial navigation, and the temporal organization of memories (which may allow us to register the passing of time) (4, 5, 6). What about the removal of this brain region caused Diane’s seizure to stop, and her ultra-running career to begin? Some theorize that by removing part of Diane’s hippocampus, doctors disrupted her “internal clock” and inadvertently enhanced her endurance (1).

During an interview with WNYC radio reporter Mark Phillips, when asked to describe how she conceptualizes time while she runs by, Diane simply replied, “I stay in the moment.” Diane described her thought processes during a grueling endurance race, emphasizing her focus on the rhythm of her strides rather than the passage of time (1). This ability to “stay in the moment” is potentially a result of her brain processing individual moments of the race, but due to the missing portion of her hippocampus, being unable to stitch these moments into a coherent timeline. If this is the phenomenon Diane is experiencing, it would prevent her from recognizing how much time has elapsed. A lack of time recognition could be the
key to understanding the mental processes behind endurance — if you do not know how long you have been running, and therefore cannot determine how tired you think you should be, this could delay feelings of exhaustion. In a much simpler example, think of the exercise from the beginning of this paper. If every second you had your eyes closed felt like the first second, do you think it would be easier to keep your eyes closed for longer?

Feeding Fatigue

When you consider the feeling of exhaustion, there are two distinct forms that come to mind: physical exhaustion, and mental exhaustion. While physical exhaustion can be easier to identify through sore muscles and achy joints, mental exhaustion can be slightly harder to define. However, it’s likely we’ve all experienced mental exhaustion in some form or another; picture how you feel taking your last exam during finals week, or how ready you are to leave a very long, boring meeting. If mental exhaustion has a profound ability to affect our motivation to continue a task, for someone on the 30th mile of an ultramarathon race, a combination of their level of physical exhaustion (how willing/able their body is to continue), and mental exhaustion (how willing/able their mind is to continue) could shape their ability to run onward. If we consider the development of mental exhaustion in a similar vein to the development of physical exhaustion, we can think of it as operating in a “feedback loop” system.

Many systems in our body operate in a “feedback loop”, where the output of the system has the ability to alter future outputs from this same system. Feedback loops have the potential to be either positive or negative (which does not refer to the connotation of the effects of these loops). Outputs from a positive feedback loop induce the system to produce even more outputs, while outputs from a negative feedback loop inhibit the production of future outputs. While this concept may seem abstract, it is how our body automatically regulates many functions; feedback loops are why we naturally feel more awake during the day than at night, why our heart rate doesn’t forever remain elevated after exercise, and why we can maintain a steady body temperature.

Picture this: you wake up early, and decide to start your day with a long run. Your plan is to run for about an hour. The weather is nice, and you’re feeling well-rested, so you start at a fast pace. The first 10 minutes of your run feel great — your legs feel strong, your breathing is even — and you feel like you could run forever. You begin to slow your pace around 20 minutes into the run, and each
footfall on the running path feels a little harder. By 30 minutes the muscles in your thighs and calves are beginning to feel sore. Over the course of the rest of your run, your muscles grow increasingly sore, and when you finally stop running after an hour, you’re ready to sit and rest. How can you start the run feeling so energetic and strong, but feel so sore and tired by the end? Throughout exercising, your muscles need a source of energy, which is supplied to them in the form of the molecule “ATP”. During the early stages of exercise, your body easily supplies your muscles with ATP; there are high levels of oxygen in your muscles, which react with glucose stores to create ATP. However, as exercise continues, your body needs to produce more ATP, but oxygen levels in your body have dropped. Your body can no longer directly react glucose with oxygen to create ATP, so glucose is converted to a molecule called “lactic acid”, and the process of this conversion sets off a chain of events that eventually results in the production of more ATP. However, there’s a catch. When lactic acid is formed during energy generation in prolonged exercise, this molecule accumulates in your muscles and causes them to feel pain and fatigue. This is where physical exhaustion becomes a feedback loop; as ATP (energy) input into your muscles increases, lactic acid will eventually increase, inhibiting your muscles from continuing to work and stopping the production of more lactic acid. To decrease the rate at which this physical fatigue advances, athletic training over time can increase oxygen availability in muscles to reduce the type of ATP generation that produces lactic acid as a byproduct.

As oxygen levels in muscles decrease during exercise, a new method of energy production is used that increases lactic acid levels. Rising lactic acid levels eventually cause muscle fatigue and physical exhaustion. Original image by Sierra Smith. Created in BioRender.

If we now turn our attention back to the development of mental exhaustion, how could this too operate in the feedback loop? When you think of instances in which you feel mentally exhausted, you’ll usually notice a common denominator: time. A boring five minute meeting is more tolerable than a boring five hour meeting.

When the Clock Stops

Considering mental exhaustion as a feedback loop of its own, it’s important now to consider, like any feedback loop, what the inputs and outputs are. If we consider time as an input in this system, mental exhaustion (involving decreased motivation, decreased motor output from the body) could be the output. Even something as intangible as...
time can reasonably be an input into a functional system due to the hippocampus (the structure that Diane lost), which allows us to register and remember time passage. If we think of the hippocampus as “consuming,” or “taking in” time as an input, how does mental exhaustion manifest as an output? A recent study performed functional brain imaging on people given tasks that induce mental exhaustion, which allowed them to examine the participants’ brain activity during these tasks (10). The authors found that with increasing duration of mentally exhausting tasks, there was a decrease in the activation of the motor cortex of the brain (among many other structures) (10). The motor cortex allows us to execute movements, and forms connections with the hippocampus (11). This suggests that as time is “input” into the hippocampus, the hippocampus could be sending signals to decrease the activity of the motor cortex and cause the feelings and impulses we associate with mental exhaustion. This correlates mental exhaustion with decreased physical ability, and could explain the feeling of “I’ve been doing homework for 4 hours, and I now feel physically incapable of writing the answer to another question.”

What happens then, if your body cannot intake time into this feedback loop — if your internal clock essentially “stops?” A method through which the perception of time could be disrupted is through changes to the hippocampus. The hippocampus helps us determine the amount of time that has elapsed while performing a task. It is often credited with (at least in part) regulating our perception of time due to its ability to store memories in sequential order. This is where we turn our attention back to Diane Van Deren.

### Time Warp

Time loosely exists in Diane’s universe ever since she lost a portion of her hippocampus. To Diane, hour 8 of a run feels like minute 8, and in interviews, she describes never knowing how long she’s been running during an ultramarathon (1). If Diane is unable to receive the input of time into her hippocampus, this could reduce, or even eliminate her ability to feel mental exhaustion. In an endurance event like an ultramarathon, this is wildly beneficial. Given that Diane has always been a high-level athlete (even prior to her brain surgery), she likely has so much physical training that she experiences less physical exhaustion during a long run than the average person. Similar to other ultramarathon runners, Diane’s endurance training limits the amount of lactic acid that accumulates in her muscles and slows her down. On top of this, if she does not have the barrier of mental exhaustion to deter her from completing a time-intensive activity, she now has the ultimate combination of features to elevate her ability to run long distances. This could uncover the mystery of Diane’s superhuman running ability.

While Diane’s running ability seems to be enhanced by her lack of hippocampus, this severely contradicts findings from studies of other ultramarathoners. There are challenges in studying what exactly makes an elite athlete an elite athlete (it is hard to discern what is
an innate ability vs what has been acquired through years of training). However, numerous studies have attempted to find neurological commonalities between elite athletes that could potentially explain their distinction. Over the past several years, research groups have examined brain morphology differences (differences in the sizes of certain brain regions) between marathon runners and healthy, non-runners (12). These studies have found that the hippocampi of the ultramarathon runners have a greater volume — which can indicate an increase in neurons (and potentially use) of this portion of the brain (12). Additionally, in a study of a type of mouse bred to have higher running capacity than a standard mouse, scientists also found greater activation of the hippocampus of the high running capacity mice while they were running compared to normal mice (13). Numerous other studies demonstrate a correlation between endurance aerobic exercise and an increase in neuron growth in the hippocampus, positively associating the hippocampus with endurance activities (14). However, this makes Diane Van Deren’s case even more puzzling — how can the hippocampus be a prominent feature in the brains of endurance athletes if one of the most competitive endurance athletes is missing it?

When asked in an interview if she believed her hippocampal loss gives her a leg up in ultra-running, Diane replied that she doesn’t believe having a brain...
injury gives her an edge on her competitors(1). While it is easy to hear about all of her athletic accomplishments and focus on how hippocampal loss could increase Diane’s running capacity, Diane is forced to confront the other consequences of missing a region of her brain. Given how intricately involved the hippocampus is with memory, Diane reports struggling with remembering the names of people she has met, or remembering to pick her children up from school. Maps appear like gibberish to her, as her brain can no longer interpret spatial directions and information correctly. Looking even at how her brain surgery has negatively impacted her running, Diane talks in interviews about getting horribly lost during dangerous ultra-marathons (1). She laughs, saying that her competitors know better than to follow her on trails now (1). In the Yukon 300 race (the 430-mile race she finished in the Yukon territory), Diane describes getting lost for over an hour in the frozen tundra. She found strategies to combat this issue, such as bringing pink ribbons to drop along her path during a race so she can retrace her steps in case she gets lost, but this impedes her running, and daily life (1). While hippocampal removal could have greatly increased Diane’s mental endurance, the effects are not purely beneficial. Diane has simply learned to work around her injury.

What’s on your mind?

Stories like Diane van Deren’s offer a better understanding of the intricacies of the brain, and cause us to reflect on how we view extreme endurance or athletic ability. It raises the question of whether we are emphasizing the correct strategies when training endurance athletes. You can easily call to mind what is associated with athletic training — fast-paced running workouts, weight lifting, etc., all of which have an emphasis on increasing physical fitness, and ultimately physical endurance. Less emphasis is explicitly placed, however, on how to increase mental endurance. If Diane van Deren’s incredible athletic ability is the result of a combination of superior physical AND mental endurance, this makes the argument that increasing mental endurance should be focused on just as much as physical endurance when training for competition. Disclaimer: this is not advocating in any way for anyone to have their hippocampus carved out of their brain to improve their athletic performance. However, if people could learn strategies that disrupt their ability to perceive time during long activities, this could be beneficial for athletes and non-athletes alike! Whether you’re running 50 miles, or simply trying to remain attentive throughout a long conference call, developing strategies to make yourself neglect the passage of time could improve your ability to persist through monotonous daily activities.
References:

How the Bacteria in Your Gut May Calm the Butterflies in Your Stomach

By Hailey Naiper
This weekend I attended a wedding. On the morning of the ceremony I ate breakfast with the bride and some of her family members. She was so nervous that all she could stomach was a piece of toast and a few nibbles of bacon. To help calm her down, we decided to go around the table listing other stressful things she’d done that went well. She’d performed in multiple musical theater productions, she’d made presentations to critical audiences of powerful people, she’d taken many difficult tests, she was even once dragged across a lake by a runaway capsized sailboat. Comforted by the reminder that she had succeeded before, she finished her breakfast. A few hours later she walked down the aisle, and she looked beautiful, despite her fears that she’d trip and fall over or appear disheveled.

Whether or not you’ve gone through the nerve-wracking process of planning a wedding, you’ve probably experienced a similarly stressful event in your life. Perhaps you were in the spelling bee as a child, or you climbed up a tall tree to rescue a cat. Maybe you’ve had to complete a project on a tight deadline or you’ve experienced meeting a significant other’s family. Recently, we’ve all been experiencing sustained levels of high stress, apart from these isolated stressful incidents. In the past two years, stress has become increasingly present in day-to-day life, be it from the COVID-19 pandemic, increased racially-targeted violence, economic hardship, or growing political partisanship. Last year, the American Psychological Association deemed stress in America a “national mental health crisis”. In a survey conducted in August 2020, 67% of adult respondents said they had experienced increased stress during the course of the pandemic (1). Increased stress seems to be impacting younger generations more. From 2018 to 2020, Gen Z adults (born between 1995 and 2001) have consistently reported higher average levels of stress than the average stress levels reported by adults as a whole (1). This concerning fact indicates a possible upward trend in stress overall as we move into the future, suggesting that stress is a health concern that will necessitate increasing attention in coming years. Furthermore, long term stress, such as that Gen Z adults appear to be facing, can result in more severe mental health issues such as depression and anxiety, which can negatively affect them for the rest of their lives. Indeed, Gen Z adults also report higher rates of stress than the general adult population. This worrying trend means that stress and anxiety will likely become a more significant problem among the general population, and this doesn’t show signs of slowing.

Anxiety vs. Stress: What’s the Difference?

Although they are related, stress and anxiety are two distinct phenomena. While stress is your body’s response to a present threat, anxiety is a response to a threat that isn’t actually there. For example: if you see a tiger in the woods, your heart rate will increase and you will experience the “fight or flight” response associated with stress. Prolonged stress oftentimes leads to anxiety, particularly after the threat ceases to be an active danger. If you’ve been in a jungle filled with tigers for many years, you may still have anxiety about tiger attacks if you move to New York City.

According to the Anxiety and Depression Association of America, anxiety affects about 40 million adults in America alone each year. That’s 18.1% of the adult US population (2). Anxiety can develop as a result of many interacting factors including genetics, life events, and brain chemistry.

In the body, anxiety and stress are most closely linked to the hypothalamic-pituitary-adrenal axis, or the HPA axis. The HPA axis is a communication system between the hypothalamus (a region of the brain that is involved in integrating body information and producing broad responses), the pituitary gland (a small structure that kind of looks like a pea sitting on the bottom of the brain, which is involved in hormone secretion), and the adrenal glands (small organs located on top of the kidneys that also produce hormones) (3). The HPA-axis is in charge of assessing threats and producing hormones like cortisol, the primary stress hormone, which speeds up your heart rate and prepares that “fight or flight” response (3, 4).
Stress Specifics

A system called the HPA axis controls the stress response, also known as the fight or flight response. When you experience a stressful situation, a part of your brain called the hypothalamus secretes a hormone called CRH. CRH causes a gland in your brain, the anterior pituitary gland, to secrete another hormone called ACTH. ACTH then travels through your blood and prompts the adrenal gland to secrete cortisol, which produces the effects we associate with stress.

The Gut-Brain Axis and the Gut Microbiota

Long term, or chronic, stress signaling from the HPA-axis can have many negative effects throughout your body, including increased risk of heart disease, memory impairments, depression, and gastrointestinal distress…. yes, you read that right, stress in your brain can affect your gut (3, 4, 5)! Recent studies have shown that the brain and gut communicate with each other via a pathway known as the gut-brain axis (6–8). Chronic stress signaling from your brain can lead to imbalances in the bacteria in your gut, as well as increased inflammation and dysfunction of gut tissues, which can promote gastrointestinal diseases like irritable bowel syndrome (5).

Gut-brain communication is a two way street though, so your gut is also able to signal to your brain (9). Many hormones and neurotransmitters that are used in your body are produced in your gut. Tryptophan, for example, is an essential amino acid that we use to make proteins and neurotransmitters. Our bodies, however, are unable to produce tryptophan, so we can only get it from foods that we eat. Eggs, cheese, and nuts, for example, are all foods that contain high levels of tryptophan (7). After we consume these foods, they are broken down by enzymes in our stomachs and filtered into the small intestine. Many microorganisms reside within the small intestine, making up what is known as the gut microbiota. The microbiota aids in the digestion of proteins like those in eggs, cheese, and nuts, producing tryptophan.
The Gut-Brain Axis and the Gut Microbiota

Gut-produced tryptophan is then either shuttled into the bloodstream or used to make other molecules, such as melatonin and serotonin. Serotonin is an important neurotransmitter involved in mood, sleep, and eating. Low levels of serotonin are closely connected to anxiety, and drugs that increase the amount of available serotonin in the brain, such as selective serotonin reuptake inhibitors (SSRIs), are frequently used to treat anxiety (7). Cells and bacteria within the gut make up to 95% of your body’s serotonin, but since serotonin is unable to cross the blood-brain barrier, the brain has to produce its own supply using tryptophan transported in the blood (9). The brain is therefore dependent on gut supplies of tryptophan which it needs to generate serotonin. If you were to stop eating tryptophan-containing foods, for example, your brain would no longer be able to produce any serotonin, which would certainly be very harmful to your mental health.

The Relaxing Journey of Dietary Fiber

Let’s follow another nutrient to get a better understanding of how the gut can influence stress in the brain specifically. We’ll begin the journey with a snack: hummus with carrots and whole grain pita bread. Each of these foods contains dietary fiber, which is another important nutrient we can only get from the things we eat. Dietary fiber is plant material that can’t be digested by human stomach enzymes. You may have heard that fiber is important for regulating bowel movements, that’s because it increases the size and weight of stool, but also softens stool so it’s able to move smoothly through the large intestine. Dietary fiber is important for more than just poop though! It also lowers blood sugar and cholesterol, and helps prevent/combat stroke, heart disease, diabetes, and obesity (11).

Since dietary fiber can’t be digested in the stomach, it continues along through the small intestine with the other non-digestible foods and some waste products. The next stop of the journey is the large intestine. Like the small intestine, the large intestine is home to many different types of bacteria that feed on the pieces of food we’re unable to digest. Some of these bacteria break down dietary fiber, producing short chain fatty acids, which are relatively small molecules with many very important functions. Although we still don’t understand everything they do, studies have shown that short chain fatty acids decrease inflammation, mediate brain development, and have the potential to alleviate the symptoms of many illnesses, from depression to Alzheimer’s to Parkinson’s disease (8, 12, 13).

From the gut, many short chain fatty acids diffuse into the bloodstream where they have

From Peanuts to Serotonin

After you eat peanuts, the protein is extracted by enzymes in your stomach. This protein is then converted to tryptophan by bacteria in your small intestine. The tryptophan travels to your brain, where enzymes make it into serotonin.
broad effects on many organs throughout the body (8). In the nervous system, short chain fatty acids have been shown to decrease stress signaling in the HPA axis (14). These discoveries are still very new, and it’s unclear how SCFAs are able to lower stress signaling. The authors of one study suggested that short chain fatty acids might activate receptors in the nervous system that send signals to decrease HPA axis activity (14). Recent studies have also demonstrated that increasing short chain fatty acids levels (which can be accomplished by eating more dietary fiber-rich foods) can decrease levels of the stress-related hormone, corticosterone (14). They can also reduce some of the other effects of chronic stress, including heart disease (16).

Depression in the Gut

Depression is a mental health disorder that may result from a combination of gut bacteria imbalances, short chain fatty acid deficits, and prior experiences with chronic stress. Depression is characterized by feelings of hopelessness and lack of motivation. You likely know someone who suffers from depression. About 21.0 million people experienced a major depressive episode in 2020, as reported by a survey of the US population conducted by the National Institute of Mental Health in 2020 (15).

A prominent physiological feature of depression is a higher level of full-body inflammation than non-depressed individuals. Some scientists speculate that this inflammation may at least in part, be driven by the gut. Imbalances in gut bacteria in depression tend to favor inflammatory pathways. At the same time, gut dysregulation can lead to a ‘leaky’ gut wall, where the cells that line your intestines become less tightly regulated, letting some molecules that would normally remain in the gut sneak into the body. Cytokines are immune system molecules that tend to increase inflammation. The combination of increased inflammatory signaling and increased gut ‘leakiness’ means that cytokines can infiltrate the rest of the body, increasing general levels of inflammation, particularly in the brain (8, 13).

A high-fiber diet offers a possible treatment in this situation as well. Short chain fatty acids are known to be beneficial for targeting some of the effects of depression on the brain, again in ways we don’t yet fully understand. They also seem to decrease the ‘leakiness’ of the gut, keeping cytokines and other gut-molecules from reaching other parts of the body (8, 13). Short chain fatty acids may even act to decrease the production of cytokines, limiting inflammation at the source (8, 13).

The American Health Crisis

Maintaining a healthy level of fiber in your diet is possibly an important tool for combating stress, anxiety, and depression, but adults in America still fail to consume even half of the recommended amount of dietary fiber per day. Adult women should eat about 25 grams of dietary fiber per day, while adult men should eat 3 grams (15). To put that into perspective, you’d be getting about 36 grams of dietary fiber if you ate whole grain toast with peanut butter for breakfast, veggie chili for lunch, a granola bar for a snack, and a burrito bowl with spinach and brown rice for dinner.

When we think of eating healthy, we tend to associate it with physical strength and well-
being. Similarly, when we think of sugary, high fat foods, we link them to negative impacts of cholesterol and diabetes. While it’s true that these are also impacts of poor dietary health, it’s becoming clear that the modern western diet is detrimental to our brains as well as our hearts, bridging the gap between mental and physical health.

Over the past century, food in the United States had experienced a precipitous decline in fiber content while simultaneously becoming exceedingly sugary. At least partly due to this dramatic decrease in general nutritional value, America has seen increases in obesity, diabetes, and heart disease, coupled with a hidden depression, stress and anxiety epidemic. It has taken the onset of multiple traumatic stressors including social isolation during pandemic lockdowns, a polarizing presidential election, and increased racially and politically motivated violence, for the impacts of our poor health practices to be realized. The American Psychological Association is missing the full picture when they refer to America’s “mental health crisis”. Separating mental health into its own bucket (as something that is not treatable in the same ways one might combat high blood pressure) is simplistic and dangerously impacts the ways we assign blame when discussing mental health, as well as the tools that we use to fix it.

As our cultural understanding of mental health stands currently, the blame for mental health disorders is placed on the person experiencing them, instead of the culture that has worked to foster poor mental health practices. Shifting our consideration of mental health towards the way we view physical health will give people experiencing mental health difficulties agency for treatment, while simultaneously shifting the burden of responsibility off of them. That said, it’s important to remember that, just as some physical diseases are genetic and therefore cannot always be cured with simple methods like changing diet, mental health illness is often complicated and driven by more nuanced factors than diet and exercise alone, although both are contributors to overall health.

The Mediterranean Diet Fix

With this caveat in mind, the Mediterranean diet may present a solution to the health crisis brought on by the Western diet. In order to follow the Mediterranean diet, consider adding these tips to your meal planning:

**Eat Frequently:** fruits, vegetables, legumes, whole grains, nuts, and seafood

**Eat in Moderation:** poultry, eggs, and dairy products

**Eat Rarely:** red meat, candy, soda, processed foods, and added sugars

Focusing on consumption of fruits, vegetables, and legumes as opposed to red meat and processed sugar, the Mediterranean diet provides a framework for increased dietary fiber intake relative to the Western diet. The constant availability and relatively low cost of vegetables and beans furthermore makes the Mediterranean diet easy to integrate into your lifestyle. High in fiber and nutrients that support gut microbiome health, the Mediterranean diet therefore also supports brain health. It is furthermore low in refined sugars and saturated fats, decreasing risk of diabetes and heart disease. Example meals include:

**Chickpea pasta with sweet potatoes, cauliflower, olive oil, and garlic**

Preheat the oven to 425 degrees Fahrenheit. Cube the sweet potatoes and cut or break the cauliflower into small pieces. Toss the veggies with olive oil and roast until tender. Meanwhile, cook the pasta and sweet potatoes are cooking, then combine with a few tablespoons of olive oil and salt. When the pasta and veggies are finished cooking, toss the veggies with the pasta and add the garlic/olive oil mixture. Finally, add salt and pepper to taste. Serve hot.

“Pasta with Chickpeas” by Pug Grill. Flickr.
Caprese sandwich on whole wheat bread

Cover one side of one slice of whole wheat bread with a thin spread of pesto or pesto mayonnaise. Layer sliced tomato, arugula, mozzarella cheese on top of the bread and close with another slice of whole wheat bread. Grill on the stove or panini press. Serve hot.

Salmon with brown rice and asparagus

Cook rice according to package directions. Preheat the oven to 450 degrees Fahrenheit. Season the salmon with salt and pepper. Roast until cooked, approximately 12-15 minutes. Coat the bottom of a frying pan and warm it on the stove. Prep the asparagus by snapping the ends off. Toss in salt, pepper, rosemary, and olive oil. Saute until soft. Serve hot.

All recipes developed by Hailey Napier.
Making simple changes, like incorporating more plant-based foods in your diet can potentially have positive effects on your health, even if you don’t make a full conversion to a Mediterranean diet or similar meal planning structure. Changing just a small part of your diet has the potential to dramatically improve the balance of bacteria in your gut, resulting in broad health impacts, including increased serotonin production and decreased stress signaling. These alterations can do more than just make you feel happy, they can also help you to maintain regular sleep patterns, strong memory, low cholesterol, low blood pressure, and can lower your chances of developing obesity or diabetes. All of these factors likely work together to lower your body’s overall stress, and improve your general quality of life.

As life returns to a version of normal, it’s important to remember that the effects of the COVID-19 pandemic on the collective mental health of our world will continue to impact us going forward. The chronic stress we have all experienced over the past two years has changed us in ways that will continue to affect our mental and physical health for the rest of our lives. In coming years we may see higher rates of depression and anxiety, and we need to pay attention to these mental health difficulties. We have learned to be particularly cautious about spreading disease to others, we sanitize our hands and take days off work if we get sick with the flu, and it’s important to remember to be kind and understanding of mental health in the same way, both towards others and ourselves. Many people have developed tools to maintain mental health during the pandemic. Some of these include regular outdoor exercise, new hobbies, therapy, meditation, or cooking healthy meals. It’s important to continue integrating these tools after we return to a more normal life in order to continue caring for ourselves in the aftermath of a chronically stressful event.

If you or a loved one are experiencing stress, anxiety, or depression, seek professional help. The National Suicide Prevention Hotline is 800-273-8255 if you find yourself in immediate distress.

“Brain for everybody” by Ars Electronica. 2013. Flickr.
References

A Controversial New Hope
Exploring recent advancements in Alzheimer's disease treatment

By Lauren Limbach
The Aduhelm Controversy

Most people would probably acknowledge that they’ve made a mistake at work from time to time. This is what happened to Joe, a successful industrial researcher, who one day noticed that he had made a calculation error while at work. But this wasn’t an isolated incident, these types of calculation errors kept happening with increasing frequency. Eventually the repeated mistakes forced him to step away from a job in which he used to thrive. This trend continued for several years, causing him to bounce from job to job, before he was eventually fired and became unemployed. But the changes that Joe experienced weren’t limited to mistakes at work. Joe began having difficulty navigating places he had been many times before, and eventually he lost the ability to perform many basic tasks such as maintaining personal hygiene [1]. Based on these symptoms, you may not be surprised to learn that Joe was eventually diagnosed with Alzheimer’s disease (AD). However what may be surprising is Joe’s age: he was diagnosed with AD at the age of 37 [1].

Alzheimer’s disease (AD) is a neurodegenerative disease characterized by drastic deteriorations in a patient’s cognition, memory and overall function — all of which were observed in Joe’s case [2]. AD also imposes large financial and emotional burdens on families and caregivers, and often necessitates entry into a nursing home [3]. The vast majority of AD diagnoses are made in elderly individuals, while a smaller number of cases like Joe’s are diagnosed early in life [2]. Over 6 million Americans are currently living with AD, yet AD is not often a topic of daily conversation despite the widespread and devastating effects imposed by the disease [3].

However, in the summer of 2021, AD was frequently featured in media headlines because of the US Food and Drug Association’s (FDA) decision to approve Aduhelm: an innovative new drug designed to treat AD. Despite being the first AD drug approved in twenty years, the media coverage of Aduhelm’s approval was largely negative. Confusion over the drug’s efficacy and the basis for the FDA’s decision overshadowed what could have been a victory for everyone involved in the fight against AD. Shortly following the approval of Aduhelm, stories detailing the departure of several members of the FDA’s advisory board began circulating in the news. These individuals cited their disagreement with Aduhelm’s approval as the motivating factor behind their departure from the FDA, stirring public intrigue as to whether or not the FDA’s decision was a sound one [4]. After the board members’ departure, the acting FDA commissioner initiated an external investigation into the proceedings that led to Aduhelm’s approval [5]. The acting commissioner stated that the primary motivation for launching the investigation was to reestablish public confidence in the FDA approval process [5]. However, launching the external investigation fueled the fire of public speculation that something was amiss in regards to Aduhelm’s approval. What followed over the next several weeks was an onslaught of attention-grabbing headlines such as:

“How Aduhelm, an unproven Alzheimer’s drug, got approved”
- New York Times

“FDA Approved Biogen Alzheimer’s Drug Despite Some Staff Concerns”
- Wall Street Journal

Overall, the media coverage of Aduhelm painted the drug as an uninspiring advancement in AD treatment, and a potential misstep by the FDA. Many articles questioned the efficacy of Aduhelm [6], [7], and others highlighted the high price tag associated with the drug [8], [9]. Some characterized the rollout of the drug as unsuccessful and cited numerous reputable hospitals and insurance companies who were choosing not to prescribe or cover Aduhelm [10], [11].

Additionally, in October of 2021 the biotechnology company Eli Lilly filed for FDA approval of their new Alzheimer’s drug, Donanemab, which is mechanistically quite similar to the controversial Aduhelm drug [12], [13], [14]. This raises the question of whether or not the FDA will grant approval to an AD drug similar to Aduhelm after the backlash that resulted from their original approval. The Aduhelm controversy and recent developments with Donanemab highlight the importance of investigating the biological basis of AD, as well as how these treatments fit into our current understanding of AD.
Are amyloid-β proteins the underlying cause of AD?

For the last several decades, the most commonly accepted explanation for AD has been the amyloid-β hypothesis: AD symptoms arise due to aggregations of amyloid-β proteins in the brain [15]. According to the biological definition of AD, the buildup of amyloid-β proteins is a necessary precursor for an individual to be diagnosed with AD [16]. Amyloid-β proteins are derived from the breakdown of the amyloid precursor protein (APP): a protein that is found in neurons and that plays an unknown role in their growth and survival [17]. APP is normally broken down by an enzyme called the α-secretase (Figure 1), [17]. The breakdown of APP by α-secretase produces benign byproducts that do not contribute to AD pathology [17]. However APP can also be broken down by two different enzymes, β-secretase and γ-secretase, which yield slightly different products than those produced by the normal pathway (Figure 1), [2]. Among those products are amyloid-β proteins [2]. The physical properties of these amyloid-β proteins make it easy for them to combine into clumps, referred to as insoluble plaques or fibrils [17]. Amyloid-β plaques are arguably the most prominent feature of AD pathology, and are thought to underlie the cognitive and behavioral abnormalities associated with AD [2]. Research has suggested that the balance between the two pathways for breaking down APP is different in AD patients compared to non-AD patients, leading to increased production of amyloid-β in AD patients [2].

If there is so much evidence that amyloid-β is the underlying cause of AD, then why have the collective efforts of researchers around the globe not resulted in an amyloid-β-clearing treatment capable of curing AD? And why are there studies circulating saying that the severity of amyloid-β plaque buildup isn’t even predictive of the severity of AD symptoms [2]? There are several viable theories for why this is the case. Some scientists think that the initial presence of amyloid-β proteins, rather than the quantitative buildup of amyloid-β over time, triggers a chain of events that leads to the clinical symptoms of AD [2]. In this scenario the quantitative extent of amyloid-β buildup would not predict symptom severity because the symptoms would not result from amyloid-β aggrega-

![Figure 1. Possible pathways for APP breakdown. Original image by Lauren Limbach. Created in BioRender.](image-url)
tion, but would instead result from mere amyloid-β presence [2]. Should this theory be true, amyloid-β-clearing drugs would likely prove ineffective in alleviating the symptoms of AD once the initial presence of amyloid-β triggered the ensuing downstream effects [2]. A second theory suggests that only a subset of amyloid-β proteins are AD-causing agents, and that the clinical symptoms of AD are associated with the quantity of these particular amyloid-β subtypes, as opposed to amyloid-β aggregation as a whole [2]. If this is the case, amyloid-β-based treatments for AD would only be effective if they target the specific disease-causing subtypes of amyloid-β [2].

In fact, recent developments in AD research support the hypothesis that not all amyloid-β buildup plays an equal role in AD pathology. Most AD pharmaceutical trials target insoluble amyloid-β: clusters of amyloid-β oligomers that form a plaque or fiber [18]. However another form of amyloid-β, soluble amyloid-β oligomers, may be wreaking the most havoc in the brains of AD patients [18], (Figure 2). Soluble amyloid-β oligomers are smaller and more mobile than amyloid-β plaques, and appear to be more toxic than insoluble amyloid-β oligomers [2].

If this is the case, the many unsuccessful attempts to treat AD by dissolving amyloid-β plaques may be due to the fact that the soluble amyloid-β oligomers are to blame for AD symptoms [18].

So what do scientists think are the effects of soluble oligomers and how do they lead to the devastating clinical symptoms of AD? They are perhaps implicated in the ability to form memories. Memory formation is a complex process, and its loss is perhaps the most commonly recognized symptom of AD. Memory formation relies on a complex molecular process called long-term potentiation in which the connections between certain neurons in the brain are strengthened over time [19]. Soluble amyloid-β oligomers are capable of altering the proteins on the exterior of neurons, which can prevent long-term potentiation from taking place (Figure 3), [19]. The hindrance of long-term potentiation in AD patients by soluble amyloid-β oligomers would provide a powerful explanation for the memory loss and cognitive deficits experienced by AD patients. Furthermore, overall cognitive functioning is dependent
on timely and accurate communication between neurons. This occurs via the release of small biological containers called synaptic vesicles that contain messenger molecules called neurotransmitters [19]. Soluble amyloid-β oligomers have been demonstrated to interact with many of the proteins involved in synaptic vesicle generation and release, providing a potential pathway through which amyloid-β oligomers may interfere with neuronal communication and as a result, cognitive functioning (Figure 3), [19].

**Neuroinflammation in AD**

Recently there has been an increased focus on the link between amyloid-β aggregation and neuroinflammation, as well as what role this relationship plays in AD pathology. Neuroinflammation occurs when the brain’s immune system is activated in response to a threatening stimulus such as a foreign pathogen [17]. Neuroinflammation is mediated by microglia: a group of cells within the central nervous system (CNS) that are responsible for defending the brain and spinal cord from exterior threats [17]. Microglia are essential for maintaining stability within the CNS, and as such, microglial and neural immune dysfunction have been speculated to play a role in AD [17].

Microglia are responsible for clearing amyloid-β following its secretion from neurons [17]. It is important for amyloid-β to be broken down soon after its release because its molecular makeup makes it easy for it to assemble into oligomers and plaques [17]. The delicate balance of amyloid-β secretion and removal can be upset and result in amyloid-β accumulation if neurons increase their production of amyloid-β to the point where the microglia can’t keep up [17].

When microglia detect a threat in the environment, they enter a distinct activated state and release molecules called proinflammatory cytokines that promote inflammation and other immune responses [17]. Microglia contain receptors capable of identifying amyloid-β in their environment, meaning that microglia become chronically activated following amyloid-β accumulation [17]. This chronic activation causes microglia to release copious amounts of the proinflammatory cytokines TNF-α and IL-1β, which have been found in higher levels in the brains of AD patients [17]. While microglial activation and proinflammatory cytokine release may be helpful following exposure to an isolated pathogen, the long-term continuation of these responses is damaging to the brain [17]. Elevated TNF-α and IL-1β levels have been associated with declining cognitive abilities, suggesting a direct role for neuroinflammation in a hallmark characteristic of AD clinical pathology [17]. Neuroinflammation may also increase the severity of AD pathology in patients because there is a positive feedback loop between neuroinflammation and amyloid-β production: neuroinflammation activates the enzymes that generate amyloid-β, increasing its accumulation in the brain over time [17]. However, the precise role that neuroinflammation plays in AD pathology remains unclear, making it a promising area of future research — particularly as the search continues for effective treatments for AD.
Current treatments for AD

The Alzheimer’s Association website breaks down the currently available pharmaceutical treatments for AD into two broad categories: “Drugs that may change disease progression” and “Drugs that treat symptoms” [20]. Aduhelm is the only drug that is acknowledged to potentially possess the ability to change disease progression of AD. The other drugs may be effective at addressing the symptoms of AD, but have no effect on the eventual advancement of the disease. These symptom-oriented drugs fall into four classes: cholinesterase inhibitors, glutamate regulators, cholinesterase inhibitor + glutamate regulator combinations and orexin receptor antagonists [20]. The drugs in each category mitigate AD symptoms by targeting neurotransmitter systems that are disrupted in the brains of AD patients. Therefore, these drugs attempt to remedy the downstream effects of amyloid-β aggregation, rather than directly addressing amyloid-β aggregation itself.

Cholinesterase inhibitors, one class of symptom-oriented AD drugs, prevent the breakdown of the neurotransmitter acetylcholine [21]. The acetylcholinergic system is integral to memory formation, and AD-associated memory loss likely partially results from decreased acetylcholine production due amyloid-β aggregation [22]. Furthermore, decreased acetylcholine activity may increase the formation of amyloid-β plaques [22]. Cholinesterase inhibitors that increase acetylcholine activity therefore not only address the shortage of acetylcholine that results from amyloid-β formation, but may slow the pace of amyloid-β accumulation by elevating acetylcholine activity. Clinical trials have demonstrated that cholinesterase inhibitors are capable of improving the cognitive abilities and overall functioning levels of AD patients, albeit to a limited extent [22], [21].

In addition to the acetylcholine system, another neurotransmitter system associated with AD pathology is the glutamate system. Amyloid-β affects glutamate activity in an opposite manner than it does acetylcholine. By blocking the reuptake of glutamate molecules back into neurons, amyloid-β aggregation leads to an excess of glutamate that continually activates neuronal glutamate receptors (Figure 3) [19]. Overactivation of glutamate receptors can lead to changes in gene expression that impact cell functioning and survival [19]. Glutamate regulating drugs designed to treat AD block neuronal glutamate receptors, thus preventing the buildup of glutamate from overactivating glutamate receptors [23]. Similar to cholinesterase inhibitors, glutamate regulators are capable of improving cognitive and global functioning levels to a limited extent in AD patients [23]. Glutamate regulators are often prescribed in addition to cholinesterase inhibitors [23]. Simultaneous treatment with both classes of drugs may improve outcomes by addressing the separate effects of amyloid-β aggregation on two different neurotransmitter systems.

The other drug category listed on the Alzheimer’s Association website consists of orexin antagonists. Orexin is a neurotransmitter responsible for keeping individuals awake and alert [24]. Its role in AD is support-
ed by the fact that patients with moderate to severe AD exhibit increased orexin levels compared to patients with mild AD [24]. Furthermore, AD patients often exhibit abnormal sleep/wake cycles, including insomnia: the primary AD symptom that orexin antagonists are designed to treat [24]. Orexin dysregulation and amyloid-β aggregation also appear to be connected. Blocking orexin activity reduces amyloid-β levels, suggesting that orexin influences amyloid-β dynamics, although the precise nature of this relationship remains unknown [24].

The current treatment options available to AD patients attempt to address the symptoms of AD through a variety of pharmaceutical methods targeting different neurotransmitter networks. While these treatments may have positive impacts on the patient’s cognitive and functional abilities, or delay the patient’s entry into a nursing home, they do not address the underlying causes of AD, and therefore do not represent a cure. The only drug that currently targets the underlying biology of AD is Aduhelm. However, even the Alzheimer’s Association website states that Aduhelm “may change disease progression,” indicating that a lot of uncertainty remains regarding its efficacy. So how exactly does Aduhelm work? And in what ways is it different from the current treatments available to AD patients?

Aduhelm and Donanemab

Instead of addressing the adverse effects of amyloid-β aggregation, Aduhelm and Donanemab target amyloid-β aggregation itself. Both Aduhelm and Donanemab belong to a class of pharmaceuticals known as monoclonal antibodies [12], [14]. Antibodies are generated naturally by our immune system and are used to identify and destroy potentially harmful pathogens [25]. In recent decades, antibody production has been harnessed by the biotechnology industry to produce therapeutic monoclonal antibodies. Biotechnology companies can design and produce antibodies that target biological threats of interest. The antibodies are then administered to patients to prompt the immune system to mount an attack against the pathogen of interest. In addition to their use in AD treatments, monoclonal antibodies can be used to treat a host of other disorders from asthma to leukemia, and have recently demonstrated potential for treating COVID-19 [25], [26]. Currently therapeutic antibody treatments are one of the largest areas of biomedical research and account for 50% of biomedical sales revenue [27].

Aduhelm and Donanemab both attempt to treat the underlying biological cause of AD by using monoclonal antibodies to target and breakdown amyloid-β plaques in AD patients [12], [14]. The main difference between the two drugs is that Aduhelm targets the entire amyloid-β sequence in humans, while Donanemab recognizes a specific region of the amyloid-β protein [12], [14]. Because of their slightly different targets, Aduhelm and Donanemab have differing abilities to bind soluble and insoluble amyloid-β. Aduhelm is capable of binding soluble amyloid-β oligomers and insoluble amyloid-β plaques, whereas Donanemab’s more targeted sequence means that it only binds to insoluble amyloid-β plaques [12], [28].

A phase 1 clinical trial found some evidence that Aduhelm reduces amyloid-β aggregation and slows the clinical progression of AD [12]. However, it is important to note that assessing the clinical symptoms of AD was not the primary focus of this study, and therefore these findings remain promising but inconclusive [12]. Following administration of Aduhelm, greater numbers of microglia were identified in close proximity to amyloid-β plaques, suggesting that Aduhelm may induce microglial phagocytic activity to facilitate amyloid-β clearance [12]. Similarly, a phase 2 clinical trial identified cognitive and functional benefits to Donanemab treatment in AD patients, as well as increased amyloid-β clearance [14]. These initial results suggest an incredibly promising future for amyloid-β monoclonal antibody treatments — so why is there such controversy surrounding the FDA approval process?
The Future of AD Research and Treatments

The FDA granted approval of Aduhelm via the accelerated approval pathway [29]. This pathway does not represent permanent approval, nor does it mean that the FDA views Aduhelm as a definitive cure for AD. What it does mean is that the FDA believes it has strong evidence that Aduhelm successfully targets an underlying, physiological cause of AD: in this case, amyloid-β plaques [29]. Because there are no other viable treatments targeting the underlying cause of AD, the FDA is allowing patients to start taking Aduhelm based only on its success in clearing amyloid-β [29]. What remains to be seen is whether or not this is the case, and if Aduhelm’s efficacy for treating the clinical symptoms of AD remains unproven, the FDA may revoke its approval. The accelerated approval pathway through which Aduhelm was approved rests on a basic assumption: ameliorating the underlying source of a disease will alleviate the associated clinical symptoms as well. It is a relatively valid assumption, although its accuracy likely varies based on how many factors are involved in the etiology of any given disease. AD is an extremely complex disease whose underpinnings remain incompletely understood after years of research. While this article has focused on the complexities associated with amyloid-β aggregation and neuroinflammation, there are other biological factors associated with AD including neurofibrillary tangles and loss of synaptic connections, not to mention the roles of genetics, environmental conditions, comorbidities, gender, nutrition, physical activity and so much more [30].

So will the clearance of amyloid-β plaques facilitated by Aduhelm reduce the clinical symptoms of AD? The short answer is maybe. Despite the extremely tangled web of contributing factors, amyloid-β does seem to play a large role in AD, and clearance of amyloid-β plaques may prove effective at alleviating the clinical symptoms of the disease. However, as previously discussed, amyloid-β plaques may be of secondary importance compared to soluble amyloid-β oligomers when it comes to AD onset and progression [18], [2]. It therefore remains to be seen whether or not the clearance of amyloid-β plaques will prove sufficient for alleviating the cognitive and functional symptoms of AD. If so, treatments such as Aduhelm and Donanemab would represent a major step forward in addressing one of the most pressing biomedical issues of our time.
References


Your Mind’s Eye: Metaphor or Reality?

An Exploration of the Varieties of Visual Imagery

By Alia Korot
If you are told to close your eyes and picture an apple, what do you see? Do you actually see an apple? What color is it? How detailed is it? Can you taste it? Smell it? Hear the crunch when you take a bite? Most people can easily answer these questions, and being told to picture something in their mind’s eye makes perfect sense. However, if you’re like me, you don’t see anything when asked these questions. I know what an apple looks, tastes, and smells like, but I do not relive any of those sensations when told to picture something. For me, the mind’s eye has always been a metaphor, and I only recently realized that my experience differs from the majority of people. Like myself, many people are not even aware of their lack of imagery, or that it is abnormal until well into young adulthood. We rarely describe the details of our mental experience to others, and instead assume that others think and imagine in the same way we do. With phrases like “picture this” and “your mind’s eye” so widespread in our everyday language, it is assumed that we all interpret their meaning in the same way. However, this is not the case, and recognizing this can help us try to understand the variety of ways that people think, imagine, and experience the world around them.

Early Studies of Aphantasia

The first recorded study of variations in visual imagery was conducted by Sir Francis Galton, a notable 19th century scientist, in 1880, who recognized that some individuals seemed to lack the power to visualize. However, this phenomenon has been mostly ignored since then, and the term to describe it was only coined in 2015 (1). This distinct experience has now been labeled aphantasia, which is defined as the absence of voluntary mental imagery. Based on what we know so far, aphantasia seems to be found in about 1-4% of people, but this number will likely change as awareness of the phenomenon grows (2).

The study that first defined aphantasia was conducted by a researcher named Rebecca Keogh and her colleagues (2). They used a survey called the Vividness of Visual Imagery Questionnaire (VVIQ), which describes a variety of situations and asks how clearly you can visualize them on a scale from seeing nothing to seeing something as detailed as real vision (this survey is available to the public online). The researchers gave this survey to a group of people who had self-reported a lifelong lack of visual imagery. Interestingly, around half the participants reported a dearth of all types of imagery, but the majority still reported experiencing involuntary imagery, such as “flashes” while awake and dreaming (1). Personally, I don’t experience any type of sensory imagery in my mind, whether that be visual, auditory, or olfactory. While I believe I do dream visually, I rarely (if ever) remember those dreams.

While this study provided the first cohesive report of aphantasia, many people are not even aware of their lack of imagery, or that it is abnormal until well into young adulthood. We rarely describe the details of our mental experience to others, and instead assume that others think and imagine in the same way we do. With phrases like “picture this” and “your mind’s eye” so widespread in our everyday language, it is assumed that we all interpret their meaning in the same way. However, this is not the case, and recognizing this can help us try to understand the variety of ways that people think, imagine, and experience the world around them.
tasia as a defined variation in neuropsychological function, it still relied on self-reports and observational rather than experimental methods. This original reliance on self-reports created some controversy in the scientific community over whether anyone actually lacked the ability to visualize, or if they simply had poor metacognition—meaning they were unaware of their own visualization. However, various other experiments have supported that individuals with aphantasia do indeed lack imagery capabilities. A test called the binocular rivalry imagery experiment is one empirical way to measure the strength of visual imagery. Participants are told to visualize one of two simple images, then are very briefly presented with those two images in a binocular rivalry display (one image displayed to each eye, for less than a second), then asked which image they saw. Individuals with aphantasia had significantly lower priming scores, meaning they were less likely to preferentially identify the image they had been previously told to visualize (3). These results suggest a much lower vividness and influence of visual imagery, and thus support the presence of aphantasia.

Another empirical way to measure visual imagery is through physiological responses. The pupillary light reflex is a normal response in vision where your pupils constrict when you are seeing something bright. Interestingly, this reflex also occurs with mental visual imagery—when imagining a bright image, your pupils will constrict. However, when individuals with aphantasia are told to imagine images of differing brightness, there is no change in their pupils (2). The normal pupillary light reflex provides some insight on the process of visual imagery itself; namely, that it seems to function through similar pathways to normal visual perception. However, there remain many questions about how exactly imagery is formed in the brain.

Understanding Mental Imagery Using Brain Imaging Techniques

Now that we know there are differences in how well people can visualize, let’s try to understand exactly what visual imagery is, and how it works. Visual imagery is used by most people in many of their day-to-day cognitive processes, such as memory, planning, spatial navigation, and reading comprehension. Visual imagery can be voluntary, as in many of the prior processes, or involuntary, such as hallucinations and intrusive images in disorders like schizophrenia and PTSD. This widespread relevance of visual imagery, as well as increasing aware-

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Binocular rivalry experiment. Wilbertz G, van Slooten J and Sterzer P, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons
ness of the variations in the ability to visualize, has led to recent increased investigation into the neuroscience behind mental imagery. Historically, it has been difficult to study the neural basis of cognitive processes like mental imagery, but the growth of functional brain imaging has created new methods that allow us to begin to see what is happening in our brains when we are told to visualize something.

The most important tool that is used in this process is functional magnetic resonance imaging, or fMRI. This technique is safe, noninvasive, and allows scientists and doctors to successfully map and measure brain activity. Magnetic resonance (MR) is the emission or absorption of electromagnetic radiation by an atom in response to a magnetic field. Conducting fMRI on humans involves exposing them to a magnetic field, and measuring MR signals from their brain. Changes in MR signal are indirectly related to changes in blood flow, which reflect changes in neural activity. Thus, when a part of the brain is more active, there is more oxygenated blood flow to this region, so it produces a greater MR signal which can then be mapped and imaged with fMRI (4). With this technology, researchers are able to ask patients to perform certain cognitive tasks and can observe the resulting neural activity. This enables us to understand which parts of the brain are used for different types of thinking and tasks.

Through this use of brain imaging, scientists have further clarified which areas of the brain are involved in voluntary visual imagery. It seems to involve activation of a widespread network in the brain including areas in the prefrontal and visual cortices, similar to those activated in normal visual perception. In vision, visual information enters the brain from the eyes, is relayed to the visual cortex in the occipital lobe, and then enters multiple streams of processing and areas of higher-order functioning (that control thinking, planning, and voluntary behavior). Visual imagery, on the other hand, seems to involve a variety of processes that start at the higher-order areas of the brain, and move down to visual areas. These include decision making, attentional allocation, language processing, and accessing long-term memory—all of which eventually lead to a quasi-visual experience (2). Thus, visual perception and visual imagery seem to utilize similar brain regions, but the flow of activation occurs somewhat in a reverse order, as a more “bottom-up” process for perception versus a “top-down” process for mental imagery. Meaning you consider something in order to perceive it rather than perceiving something, and then considering it.

Amazingly, some detailed brain imaging studies have made it possible to identify what someone is imagining based solely on the pattern of brain activity in their visual cortex! The level of activity measured in the visual cortex also seems to correlate with how vivid someone reports their imagery to be (2). These discoveries highlight how accurately researchers have been able to pinpoint the roles of specific brain regions in visual imagery, though much remains to be discovered.

Now, with a good understanding of the neural activity involved in visual imagery, the next question is how functional brain imaging can help explain the differences in the ability to visualize found in aphantasia. The use of resting state fMRI (in this case, when the brain is not attempting to conjure an image) has been able to successfully elucidate some of the differences in connectivity of brain regions between those with normal imagery, those with hyperphantasia (ultra-vivid imagery), and those with aphantasia. Hyperphantasic individuals show stronger connections between the visual-occipital network and several prefrontal regions compared to those with aphantasia, whereas the aphantasic group shows various other areas of stronger connectivity. Interestingly, these differences in connectivity are similar to those
previously found in relation to different types of autobiographical memory. People with an episodic (and thus more visual) style of memory show stronger resting state connectivity between important memory regions of the brain and visual areas, while those with a more factual style of memory show greater connectivity between those memory regions and prefrontal regions (5). These findings suggest that there are intrinsic differences in brain connectivity underlying variations in the ability to visualize. There are also differences in brain activity, as hyperphantasic individuals show more activation in certain brain areas when asked to visualize something, in comparison to those with aphantasia (5).

While there have only been a few brain imaging studies on aphantasia so far, the findings have led to some hypotheses about what causes a lack of imagery. One suggested neural mechanism is reduced connectivity between cognitive control systems and the visual areas of the brain. This hypothesis is supported by the fact that many aphantasics still experience visual dreams, an experience in which the imagery is involuntary, suggesting the disconnect is in the voluntary generation of imagery and not the imagery itself (5). This is further supported by individuals with aphantasia not having any difficulty with visual perception; they are simply unable to voluntarily create mental images.

Further Defining Aphantasia

While there is much more to discover about the neural underpinnings of visual imagery and aphantasia, it is also important to further define this phenomenon and its variations. Is it a disorder, a defined and discrete condition? Or just a variation of the human experience, as one extreme end of a continuous spectrum of visual imagery? There is not yet a scientific consensus on this question, and perhaps the answer does not really matter for our understanding of the phenomenon. Definitions will always change, and we can work to understand aphantasia regardless of its classification. There have been reports and previous studies of individuals losing their ability to visualize after injury or disease (known as acquired or neurogenic aphantasia), but individuals with congenital aphantasia (which present at birth), like myself, do not recall ever having the ability to form mental images.

Since congenital aphantasia is present from birth, we must consider the role of genetics in this phenomenon. First degree relatives seem to share aphantasia much more often than would be expected by chance, suggesting heritability which suggests a potential genetic component (2). Around 20% of people with aphantasia are confident they have other family members affected, while nearly 50% are simply unsure (7). Many people simply are not aware of or do not discuss their
differences in mental imagery, suggesting that the occurrence of shared aphantasia among relatives could be significantly higher than currently reported. This certainly implies a genetic contribution towards aphantasia, and potentially a strong one, but much more research is required to clarify the strength and details of these genetics.

Another remaining question is whether aphantasia has multiple subtypes, given that people differ on which types of sensory imagery they lack. Some aphantasics lack only visual mental imagery, while others lack all forms of imagery, including auditory, gustatory, and olfactory. Some researchers have suggested a separate name, dysikonesia, for impaired or absent imagery across multiple senses, while reserving aphantasia for the sole lack of visual imagery (6). It remains to be seen whether this term will be more widely adopted, or if aphantasia will simply be generalized to all forms of impaired sensory imagery.

Aphantasia’s Impact on Other Cognitive Processes

For those without aphantasia, mental imagery plays a strong role in a variety of cognitive processes. This raises the question of how aphantasia affects other abilities such as memory. The answer seems to be that there are differences in recall and memory, but it depends on the type of memory. Those with aphantasia have equal ability to successfully complete declarative memory tests or even visual working memory tasks (involving using visual information to complete a task). To complete these tasks with no impairments in capacity or accuracy means that aphantasics must rely on different strategies, such as semantic, meaning-based labels and verbal cues rather than visual representations to process visual information (10). These strategies are likely developed throughout life, and perhaps are not developed by those who rely upon mental images. This suggests that visual imagery and working memory are two separate processes, and mental imagery is simply one possible tool that can be used for interpreting and using visual information.

There are some memory tasks that do demonstrate differences between those with and without aphantasia. For example, in one study researchers presented images of real-world scenes to individuals with aphantasia and control participants without aphantasia, and then asked them to draw the scenes from memory. Aphantasic individuals remembered fewer objects, drew with less color, and relied more on symbolic and verbal representations by labeling more objects with words. In contrast, their spatial accuracy in placing objects from the scene was the same as controls (8). These results support the idea that there are separate memory systems for object versus spatial information, and spatial recall is unimpaired in those with aphantasia. Additionally, despite the aphantasic individuals in this study struggling to illustrate a scene from memory, aphantasia certainly does not preclude artistry. There are many self-identified aphantasic visual artists that seem to use strategies that are slightly different from other artists (2).

Autobiographical memory, the memory of your own past, is another area of potential difference. Normally, many people experience their memories of the past through intense, vivid, and movie-like imagery. However, those with aphantasia do not experience their memories in this way. This lack of movie-like imagery seems to translate to diminished autobiographical memory. People with aphantasia report a significantly lower ability to recall specific life events and have very little ability to produce sensory details while remembering events (9). This difference in the ability to remember details of your own past is perhaps the biggest impact of aphantasia, and certainly seems to be a source of distress for many who are aware of it. However, as with other forms of memory, it seems possible for those with aphantasia to learn to rely on other strategies and develop ways to supplement their own memories. If you cannot visualize and relive your life events through imagery in your mind, you thankfully have the ever-present technology of photos and videos to supplement your own memories. Thus, the consequences of aphantasia certainly do not seem too dire and can be overcome with the breadth of other strategies the human imagination is capable of.

For most people, visual imagination is a central part of their lives and seems an intrinsic part of their cognitive experience. As I have discussed my aphantasia with friends and family, I am often met with the reaction that they cannot imagine a mind without imagery. They cannot comprehend how I think and remember and experience the world. Many authors and philosophers over the years have discussed how our vision of our lives, our ability to imagine, and our ability to represent things in their absence is crucial to our human experience—and perhaps what sets us apart as humans. However, these abilities do not rely solely on visual imagery. It was only in the last few years, when I began discussing my cognitive experience with others, that I
discovered that I lack this internal experience that most people rely on. I have certainly never felt that I was missing some necessary part of cognition, and there are many methods of internal representation besides the visual or sensory.

Aristotle once wrote that “the soul never thinks without a phantasm,” and he was (and is) far from alone in the assumption that illusory representations and mental imagery are intrinsic to human thought. However, it seems Aristotle was in fact incorrect. He fell into the trap that befalls so many and assumed that his own internal experience resembles all others. Let us not underestimate the many incredible multi-representational abilities of the brain or forget the representational powers of language. Visual imagery is simply one tool in the toolbox of the human brain and lacking it does not prevent the human cognitive experience. I feel I can speak for all those with aphantasia when I say that lacking the ability to visualize does not preclude any complexity of thought or feeling. In this case, I will confidently counter Aristotle and say that my soul certainly does think without a phantasm.

References

I Feel Your Pain, Do You Feel Mine?

By Lucy Friedberg
The experience of emotion and pain stem from our interactions with our environment, peers, and selves, capturing the essence of the complete human experience. Our ability to verbally communicate our “feelings” aids in fostering close bonds with each other. The action of feeling holds a double meaning. On one hand, you can physically touch something, experiencing a tactile sensation. While on the other hand, you can also inwardly ‘feel’ intangible sentiments like emotion, encapsulating our introspective experience. Without being able to communicate either physical or internal feelings, our relationships to each other would be completely different and unsustainable. Throughout time, our frontal lobes have evolved to reflect the developing complex social structures and higher cognitive functioning required to uphold it [1]. Expressing an emotion enacts both meanings of “feeling.” A physical stimulus triggers a cascading effect in the brain to produce the conscious thought that you feel “sad.” This sequence inherently suggests that there is an overlap in the emotion and pain signaling networks of our brain [2].

What is Emotion?

Movies, pictures, conversations, and almost every interaction we have with our environment elicit an “emotion.” Emotion is applicable to almost every individual. Our emotional schema develops throughout our entire lives, teaching us how to respond to certain situations [2,3]. In a technical sense, emotions are central brain states that create a cause-and-effect interaction with other brain structures stemming from stimuli and behaviors. These brain states arise from neurochemical interactions such as the release of neurotransmitters. Neurotransmitters serve as chemical messengers between neurons, the brain’s foundation for transmitting sensory input from the external world. Electrical signals travel between neurons along the axon and trigger the release of the neurotransmitter. One commonly known neurotransmitter is dopamine, which plays a crucial role in the modulation of emotion [4,5].

When defining emotion, rather than thinking about neural connections or the release of neurotransmitters, people utilize adjectives such as happy, sad, or mad. Emotions are states of being produced by activation of certain areas in the brain such as the amygdala or thalamus. A common misconception is that one brain area corresponds to one emotion. Instead, the brain is a complex network with communications between different structures. These structures ultimately distribute signals to the rest of our body to produce behavior. The behavior or actions produced is what people think of when imagining emotion. The amygdala isn’t where “fear” is located, but rather, it is involved in the evaluation of emotional importance of a stimulus, and is especially active in response to fear [6].

Earlier theories state that the basic emotion and dimensional models are two separate measures of emotion. The discrete emotion perspective states that we have a propensity for certain emotions such as happiness, anger, and disgust [7]. These exist as categorical, basic, and specific emotions. The dimensional perspective suggests that emotions exist along a range of dimensions based on valence (positive vs. negative) and arousal (activated vs. deactivated) [7]. The dimensional spectrum of emotional experience is determined by where valence and arousal land within the range. Building on the theory of an emotional spectrum, recent models of emotions state that emotions are learned from previous experiences [7]. This suggests that emotions are derived from the ability to recall and apply conceptual knowledge to a situation and produce the appropriate behavior (or emotion) [7]. These models are important to understand because they establish the basis of our emotional experience. They also begin to distinguish between states of being, and feeling, and provide theories for their origin.

Where do we Feel Emotion?

Attempting to decipher emotions has been a prevalent study across philosophical and scientific disciplines throughout all of history. Since the late 19th century, there have been several different theories as to how the brain produces emotional states that ultimately influenced the modern idea of the limbic system [8]. Dr. William James and Dr. Carl Lange answered the question of “After seeing a bear in the woods, does our heart race because we are afraid? Or are we afraid because our heart is racing?” by stating that we are afraid due to the physiological act of our hearts racing [8]. The James-Lange Feedback Theory requires a prior set of changes in the body to produce emotion [8]. What these changes are determine the following experience of emotion [2,8].

In the 1920s, Dr. Walter B. Cannon and Phillip Bard disagreed with James-Lange. They claimed that because humans experience such a wide variety of specific emotions, physiological responses for a single emotion are indistinguishable [8]. For example,
a multitude of scenarios can cause a person’s skin to flush, such as sexual arousal, anger, and embarrassment. In addition, Cannon and Bard pointed to the fact that you can encounter emotion prior to any associated physiological change [8]. Instead, Cannon and Bard suggested that in the brain, the thalamus directs information to the cortex for the generation of feelings (the emotional experience), and to the hypothalamus for the generation of a bodily response (expression of behavior resulting from the emotional experience) [2].

A decade later, Dr. James Papez proposed the Papez Circuit. This circuit defined emotional processing as occurring in the medial walls of the forebrain. Specifically, the structures directly connected to the hypothalamus [2,31]. Building on this theory, Dr. Paul Maclean’s developed the concept of the Limbic System. From 1940-1970, the control of emotional behavior was thought to require recognition of a significant stimulus triggering subsequent activation of a specific emotional response [9]. Maclean believed it was the hippocampus that identified significant stimuli [2]. After 1970, the ‘modern’ limbic system was established [9]. Here, the amygdala is cited as the key proponent of the limbic system. The amygdala determines what a stimulus is, and whether something needs to be done about it. While not exclusive to fear processing, the amygdala plays a significant role in influencing approach or avoidance behavior in response to a frightening or threatening stimulus [9].

Another part directly linked to the limbic system is the insula [34]. The insula filters all bodily information and integrates it to form a representation of the state of our body to our consciousness [34]. Alongside the insula during the active experience of feelings is the anterior cingulate cortex (ACC). These two brain areas function to project the experience of maternal and romantic love, anger, fear, sadness, happiness, disgust, and trust [1,2,21].

Why do we Experience Physical Pain?

Have you ever placed your hand on a hot surface and swiftly pulled it back? Evolutionarily, being able to perceive pain is critical to human survival. Fight or flight is a common adaptation that is referred to when understanding instinct and fitness. It is what tells us to remove our hand from a hot surface or to defend our territory. Being able to distinguish these signals is the job of the central nervous system and pain receptors called nociceptors. Nociception is the process of detecting, experi-
encing and encoding harmful or very unpleasant stimuli [11]. The three types of stimuli nociceptors are activated by are temperature (thermal), mechanical (stretch/strain) and chemical (inflammatory) [11].

What Hurts?

Physical pain is typically described as a part of the body feeling discomfort. This can range from slight to extreme discomfort. The direct pain matrix is made up of the cingulate, insular, and certain somatosensory areas. The anterior cingulate cortex, parts of the prefrontal cortex, and insula have rich nociceptive and motor receptor regions [32]. The interconnected nature of these brain areas allow output of ACC pain to influence immediate behavioral reactions [32]. So, if you put your hand on something hot, the nociceptors signal that there is nociceptive pain, or acute tissue pain, signaling the brain to remove your hand from the hot surface to prevent further injury. The involvement of the secondary somatosensory cortex and posterior insula processes are crucial to experiencing physical pain [6,11]. The ability to process tactile stimuli is essential in understanding our relationship to the physical world.

Don’t Get Your Wires Crossed

When people say as a figure of speech, “love hurts” or you have your “feelings hurt”, they actually mean it. After examining both emotional and pain processing, recent research supports the idea that the two networks are not separate [13]. While everyone experiences emotional pain, it can be harder to articulate since it seems more abstract than physical pain. With physical pain, you can usually point to a spot on the body and where and why it hurts. With emotional pain, if you say your body aches because you’re sad, people may sympathize, but do not understand the extent that your physiological state changes in response to being sad.

If you have ever grabbed your knee when seeing a basketball player fall hard on their own knee, you are not alone. The anterior cingulate cortex (ACC), parts of the prefrontal cortex, and insula are regions of the brain that signal physical pain, but they are also responsible for behaviors stemming from our emotions as well [13]. Part of the foundation of this research is the finding that the anterior insula (Aln) is activated not only when experiencing displeasing stimuli that active nociceptors, but also when viewing someone else experiencing a displeasing stimuli (or even making a displeased face) [13,26]. The cingulate and insular regions are activated when viewing someone in pain, supporting the evidence of emotional pain activating the same brain regions as physical pain. Particularly, researchers have been able to link the nociception areas and neural recruitment to insular and cingulate regions, supporting the theory of the same regions for two types of pain [10,12,13,26].

Most people relate to the common physical pain of scraping your knee or stubbing your toe. Remembering your own painful experience may elicit a twinge of pain. Empathy is the ability to share and understand another’s feelings. Being empathetic, for example, requires recalling how you felt at a time when you scraped your knee and relating to a person in an appropriate emotional way to comfort them. One study linked the common painkiller Acetaminophen (Tylenol) to a reduction in empathy [14]. As mentioned earlier, the ACC is activated when an individual is experiencing distress or when viewing someone else in distress. The reduction of ability to feel pain and consequently the ability to empathize indicates a certain degree of overlap between areas in the brain that express physical and emotional pain. Tylenol reduced both personal distress when experiencing social pain.
(exclusion), but also when viewing others in distress [14].

Emotional Pain

Being empathetic is crucial to our social relationships because it allows us to connect to, and understand what other people are expressing on a deeper level. It helps us understand both the negative and positive affects [15]. Negative affects include emotional or psychological pain. Psychological pain is defined as an unpleasant feeling resulting from a negative experience that is caused by an inability or deficiency of the self [12,16]. This feeling is persistent, but unsustainable. The need to love, to be loved, and connect with others are core psychological needs that if not met can lead to feeling unhappy or dissatisfied [12,16]. This feeling is persistent, but unsustainable. The need to love, to be loved, and connect with others are core psychological needs that if not met can lead to feeling unhappy or dissatisfied [12,16]. Across several experiments assessing psychological pain, the ACC proved to be the most active [10,12]. This extends the ACCs involvement to the experience of sadness, while the insular functions to a greater degree for both negative affect and physical pain [10,12].

Examining Our Social Selves

Being able to perceive social exclusion historically meant a higher chance of survival since in early times, those in groups were more likely to live longer [17]. Feeling emotional and physical pain similarly could be a function of evolution, given that an emotional or social threat (being alone) could result in a physical one (dying). When examining our social selves, the development of self-esteem is frequently fixated on, especially in adolescent aged individuals. Self-esteem is feeling good or bad about oneself which subsequently affects our emotional state. It is an internal gauge of social inclusion or exclusion in relation to others [17,18].

A theory developed by Leary et al. (1995) draws parallels between social happiness and self-esteem. Sociometer theory indicates that self-esteem fluctuates, and is influenced by social experiences. Those who are socially rejected or deemed an outcast have lower self-esteem than those who perceive themselves as included or well-liked. This theory involves our “self” in a social context, providing a psychological framework for our outward behaviors. In a study done on social exclusion, researchers found that regardless of whether a person knew the other people, they exhibited distress at being excluded from a game [27]. Since a sense of belonging is at the forefront of satisfying our penchant for inclusion, studying social exclusion in the context of pain provides an objective perspective.

Theories such as sociometer theory and attachment style provide social implications for the connectivity of our brain structures. In a study done looking at which brain areas are active during social exclusion, researchers found the ACC to be more active during exclusion than inclusion. This activation parallels studies done looking at physical pain [27]. Understanding attachment is important in the context of social pain because it provides an emotional structure that forms a foundation for baseline social interactions. For example, it cues sensitivity to exclusion which may correlate to the activity or reactivity of the ACC [10,12,13,22].

Brain areas such as the insular regions, medial prefrontal cortex, and anterior cingulate cortex that have been identified as being activated by emotional pain such as social exclusion. In the context of empathy and experiencing pain, their activation provides support that these areas are also activated by physical pain [12,13,21,26]. These studies have greater implications for biopsychological interventions and general unification of understanding individual experiences. It also deepens our understanding of empathy, which is fundamental to our social relationships and subsequently, well-being [15,27,28].

**Autism Spectrum Disorder**

Autism spectrum disorder (ASD) presents several emotional and sensory processing variances including both hypo and hypersensitivity to certain stimuli. Studying the emotional and physical pain processing in participants with ASD presents the opportunity to examine divergent neurological functions. This would allow for the development of a more comprehensive understanding of the individual experience of pain [15]. Difficulty with perception and processing the emotions of others is commonly observed in ASD. However, whether this difficulty arises from a general struggle to relate to emotional states, or from struggling to perceive affective expressions is not fully understood. A recent study used pain evaluation in the self and others to link emotional and sensory perception in individuals with ASD. The goal was to distinguish whether these individuals have difficulty recognizing other emotional states due to discrepancies in relating to emotional experience (own or other) or if it is specific to the perception of others [15,19]. They found that participants with ASD demonstrated no difference in evaluating intensity of their own pain to participants without ASD. However, they also found that participants with ASD exhibited more difficulty estimating the pain intensity of others, specifically when evaluating pain level based on facial expressions. These results contrast earlier findings of neurotypical brains showing activation in insular and ACC regions when viewing photographs of people in pain. To support this, the researchers recorded a difference in neural activation between ASD participants identifying pain based on context rather than bodily expressions. Those with ASD had reduced neural activation in response to higher social complexity [19].

Not only did individuals with ASD demonstrate decreased neural activation in response to...
pain identification of others (reduced empathic ability), they also had weaker brain activation in the anterior insula and anterior cingulate cortex. This provides strong evidence for the role of insular and cingulate cortices in pain-related empathy, or the overlapping of emotional and physical pain processing [12,20,21,26]. Through outlining how both neurodivergent and neurotypical individuals experience pain, interpret social stimuli, and process affect, a clear relationship between the signaling of physical and emotional pain develops.

PTSD/Chronic Pain

Being able to understand emotional processing has great implications for fields studying post-traumatic stress disorder (PTSD) and chronic pain. Both PTSD and chronic pain emanate from a biological, psychological, and social field. Chronic pain and PTSD are extremely prevalent across the US and affect people’s day-to-day lives. An incongruence between emotional processing and the experience of physical pain can lead to chronic pain or even PTSD. Chronic pain is the presence or sensation of physical pain in the absence of a clear source of pain over an extended period [33].

People experiencing PTSD often display intense negative emotional reactions, higher reactivity to certain stimuli that may trigger the traumatic experience, avoidance of that stimuli, and chronic overstimulation [24]. Generally, PTSD is classified as an anxiety disorder, and chronic pain is often comorbid with PTSD. Using brain imaging, researchers have been able to establish a relationship between PTSD and increased blood flow in the insular region [23,24]. There is a distinction in pain perception between people with PTSD and those who experience isolated trauma. Those who do not display PTSD symptoms following a traumatic event tend to have higher pain perception than those with PTSD. Mickleborough et al. (2014), associated this with the changes to signaling between the cortical and subcortical structures in the two different groups.

A common self-preservation response to trauma is dissociation. This entails both psychological and physiological responses. People often report feeling “emotionally numb” to most stimuli. Research shows that there are neurological changes that occur that can account for someone dissociating. In the same study done by Mickleborough et al. (2014), they associated induced dissociative states with more activation in the insula, and a simultaneous reduced sensitivity to pain. The occurrence of dissociation can account for the increased pain threshold in those experiencing PTSD compared to those without PTSD symptoms [23,24].

At rest, the brain demonstrates spatially and temporally distributed or synchronous blood-oxygen level-dependent (BOLD) variation [25]. In the brain of chronic pain patients, there is constant processing of “background” pain signaling. Spontaneous pain stemming from the background pain conflicts with both conscious and subconscious processes [25]. This occurrence contributes to fundamental neural plasticity in response to chronic pain. The existence of background pain is attributed to episodic memory resulting in a constant recall of the original pain or injury. The persistent recall resulting in the background pain is evident by examining structural changes to certain pain areas in the brain such as insula, ACC, and Thalamus regions [1,25]. PTSD emotional responses and correlating them to structural changes in the brain draws a stronger connection between the experience and process-
ing of emotional and physical pain. Chronic perceived pain conditions are often correlated with response activation in the thalamus. Thalamic activation is connected to the time since onset of the chronic pain, with differing responses short-term to long-term [29]. Hyper-perfusion occurs in short-term pain, and hypoperfusion in long-term chronic pain, demonstrating adaptive changes during the development of chronic pain [29]. Operant theory of chronic pain is the idea that there are two distinct aspects of pain, sensory and behavioral. Sensory aspects of pain are essentially unobservable while behavioral aspects are observable and measurable. These are categorized under pain behaviors which are subject to the influences of learning and experience. Under this theory, pain can be reinforced via negative and positive reinforcement causing the occurrence of pain to linger [11,29].

Similar to PTSD symptoms, chronic pain creates neurological changes in the brain that demonstrate and support the interconnected nature between emotional and pain processing [29,30]. Several studies have shown a link between chronic pain and mood disorders such as depression and anxiety leading researchers to claim that psychosocial factors affect pain perception [29]. This model is referred to as the biopsychosocial model of pain. These altered states of somatic awareness and pain catastrophizing indicate changes to the peripheral or central nervous system that are crucial to signaling pain. This model has been extremely influential in shaping new behavioral, psychosocial, and physical interventions to pain management. It allows for researchers and doctors to gain a fuller image of individual differences in the experience of pain. It also highlights the multidimensionality to pain processing, both emotional and physical [29,30].

Understanding why humans feel emotions and pain separately allows for a deeper understanding of how the two sensations are related. People often assume physical pain is the only relevant pain to our survival, but research consistently demonstrates that our social needs and subsequent social pain if these needs are not met can be as painful. Comparative research establishes the brain as an active, interconnected entity with a strong network to produce behavior.
References


High Performing Athletes

Does Cannabis Use Enhance Performance?

By Racine Ross
June 19th, 2021

This was the day that Sha’Carri Richardson’s dream of going to the 2021 Olympics was crushed. Sha’Carri Richardson was predicted to be the big gun in the women’s 100-meter race after winning with a time of 10.86 seconds in the U.S. Olympic Track and Field Trials. A turn of events occurred when Richardson tested positive for cannabis as a result of the psychoactive component, THC. Cannabis use, one of the numerous banned substances under the United States Anti-Doping Agency (USADA), results in a three-month suspension if the athlete can confirm that the substance use did not occur within the competition period and had no relation to their sports performance. Additionally, athletes can reduce their suspension to one month if they complete a substance abuse treatment program with approval from the USADA [1]. Insomuch as the Track and Field Trials took place a mere month before the start of the 2021 Olympics, Richardson had the opportunity taken away from her to represent the USA. Richardson completed the counseling program as a result of her cannabis use in response to cope with the tragic news of her biological mother dying just weeks before the start of the competition [2]. Athletes across the board have been in situations like this, but as laws are changing and research is being conducted, the rules remain the same for cannabis use in athletics. Why is this the case?

Brief History Lesson

Cannabis has been present in this world since 4,000 B.C.E originating in China. Its original use was to treat ailments such as gastrointestinal illnesses, seizures, malaria, and pain associated with childbirth. From that time, it made its way through Asia, the Middle East, and Africa. It did not appear in America until 1545, though, when the Spaniards brought the hemp plant in hopes to make good rope for the ships they were building. Fast forward to the 19th century, cannabis became more popular and used for recreational purposes. Cannabis began being used for numerous illnesses, plus drug companies began constructing cannabis tinctures. Subsequently, the Pure Food and Drug Act of 1906 and the Harrison Narcotic Act of 1914 imposed restrictions on alcohol which indirectly increased recreational use of cannabis. Harry Anslinger, who was the first commissioner of the Federal Narcotic Bureau in 1930, attempted to eliminate cannabis which led to the Marijuana Tax Act of 1937 [3]. This tax act ensured that possession of cannabis would result in legal penalties which increased with the implementation of the Boggs Act of 1951 and the Narcotics Control Act of 1956 [4]. Imposing a tax on cannabis was declared illegal by the Supreme Court in 1969 because imposing a tax on someone who wants to possess an illegal substance is considered a form of self-incrimination. It was not until 1970 though when the Federal
Drug Enforcement Agency (FDEA) specified cannabis as a Schedule 1 drug, making medical and recreational use illegal [5]. As a schedule 1 controlled substance, cannabis has no accepted medicinal use, high abuse potential, concerns for dependence, and a lack of accepted safety for use under medical supervision [4]. Despite this, in 1996 California enacted the Compassionate Use Act, which permits legal access to and use of botanical cannabis for medicinal purposes under physician supervision. This created a ripple effect in that 18 states have legalized cannabis for recreational use, 38 states have legalized cannabis for medical use, and 32 states have decriminalized cannabis and eliminated prohibition for the possession of small amounts [6].

Protect and Serve

The justice system in the United States was created to “protect and serve” its citizens, but it does not do so equally. The “war on drugs”, started by Richard Nixon in 1968, was created to reduce the illegal drug trade in the United States. Following this, our jails, prisons, and courts experienced a monstrous wave of rules and regulations while doing very little to decrease the actual use of drugs in communities. The United States has seen a five-time increase in incarcerations as compared to 1972, but there is no equivalent decrease in drug use. Moreover, discrepancies are found concerning the population that serves in prison versus the rate and prevalence of drug use in the general population. Rates of illicit drug use are quite similar between Blacks and Whites, with some lower numbers seen for Hispanics. Reporting of drug use is commonly found in communities of suburban, middle-class areas across the country. Whites were 5 times more likely to use cannabis than their Black counterparts, but Black men are 13 times more likely to be admitted to prison with similar drug charges to White men and thus make up 60% of the prison population. In some cases, there is a 26 to 27-fold increase with this discrepancy. This is not saying that Black men are more likely to do drugs, just that they are more likely to be arrested and convicted. As a result of these incarcerations, Blacks have more difficulty finding work as bosses are less likely to hire people with previous track records. Additionally, their social networks, relationships, and families have all suffered significantly. As demonstrated, the history of cannabis is not only rooted in a plethora of laws and regulations, but also a severe discrepancy that disadvantages Blacks and Hispanics in an already unequal society [7].

What is Cannabis?

Cannabis is a cannabinoid that contains the psychoactive compound delta-9-tetrahydrocannabinol (THC) and non-psychoactive cannabidiol (CBD). The THC in cannabis primarily acts on the brain through the first cannabinoid receptor (CB1) and the second cannabinoid receptor (CB2). Each of these receptors is a G-protein coupled receptors (GPCRs) which are a large number of receptors that respond to various external stimuli. Activating GPCRs causes the release of an intracellular protein, known as a G protein, which controls the activation of an enzyme within the postsynaptic neuron. This activation then communicates with the second messenger, allowing the receptor channel to open and potentially affect additional processes in other parts of the cell. CB1 receptors have a high concentration in the central nervous system (CNS) and are the most common GPCRs in the CNS. CB2 receptors are primarily found in the tissues of the immune system as well as the heart. In 1964, the structure of the main psychoactive compound, now known as THC, was discovered by Mechoulam and Gaoni [8]. Thus, this discovery allowed
researchers to delve more deeply into the world of cannabis.

The Ins and Outs of THC

There are numerous neurotransmitters involved in the mechanism of action for cannabis. As illustrated in Figure 1, upon inhaling a puff of cannabis containing THC, the CB1 receptors are primarily activated. This activation is dependent on two of the endogenous cannabinoids found in the body which are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The cannabinoids inhibit the Ca²⁺ channels which in turn activate the K⁺ channels, making the cell less likely to release neurotransmitters. As a result, there is an inhibitory effect on the neurotransmitter release of norepinephrine (NE), dopamine (DA), gamma-aminobutyric acid (GABA), acetylcholine (Ach), and glutamate (Glu). CB1 activation has been found to increase DA in the prefrontal cortex (PFC), though, which is responsible for high cognitive functioning, planning, and problem-solving. As can be seen in Figure 2, there is a disinhibition of pyramidal Glu neurons. The normal GABA release onto these pyramidal Glu neurons is now suppressed, allowing Glu to be released onto the ventral tegmental area (VTA) which plays a role in drug addiction, behavioral disorders, cognition, motivation, and locomotor activity. The VTA then projects onto the Nucleus Accumbens which then projects onto the PFC and increases dopamine in that region.

THC vs. CBD

CBD was first isolated from cannabis in 1940 and its structure was later reported in 1963. Unlike THC, the most notable difference for CBD is the fact that it is not a psychoactive compound. In other words, CBD has similar pharmacological effects to THC but does not produce the high that you experience when consuming THC. CBD does not have any impact on the CB1 and CB2 receptors which typically produces the psychoactive aspect, or high. CBD has increased in popularity and is more heavily studied with its possible health benefits for the central nervous system such as assisting with generalized anxiety, obsessive-compulsive disorder, panic disorder, and psychosis [9]. Additionally, CBD has been found to have possible use as an antipsychotic, anti-inflammatory, antiepileptic, as well as for some neuroprotective effects. Furthermore, some applications of CBD for medicinal use have emerged such as in treating pain (chronic and neuropathic), diabetes, cancer, and neurodegenerative diseases such as Huntington’s disease [4].

Pharmacological effects and Time Course

Cannabis is known to have psychotropic effects as well as somatic effects such as analgesia, antinociception (pain-blocking), and orexigenia (appetite stimulant). When taken in low to moderate doses, pleasant side effects can be seen such as euphoria, elation, exhilaration, disinhibition, hyperactivity, and an increase in hunger. Additionally, users have reported subjective effects includ-
ing feeling calm, relaxed, and in a
dream-like state. To boot, cannabis
is known to have anxiolytic effects,
so individuals may use it to aid in
relieving their stress and anxiety
[10]. On the contrary, when taken
in high doses, cannabis can induce
adverse effects such as anxiety,
tachycardia, and hypertension.

Cannabis has multiple
routes of administration but its
most effective and well-known is
smoking. When smoked cannabis
typically has peak plasma con-
centrations attained within 3-10
minutes [11]. Inhalation of canna-
binoids bypasses the first-pass me-
tabolism that usually takes place
when orally ingesting compounds.
First-pass metabolism occurs when
enzymes in the GI tract or liver can
significantly reduce the concen-
tration of a drug that reaches the
bloodstream [3]. Cannabis rapidly
distributes into organs containing
high amounts of blood vessels
and then evening out into less
vascularized tissue. Much of the
THC absorbed is stored in body fat
where it is slowly released
from. Metabolism of THC takes
place by hepatic cytochrome P450
enzymes. In metabolizing THC,
its metabolites 11-hydroxy-THC
(11-OH-THC) and 11-carboxy-THC
(11-COOH-THC) go through the
process of glucuronidation which
is excreted in feces and urine [11].
When identifying THC in urine
samples, the focus lies on identify-
ing its inactive metabolite, 11-car-
boxy-THC. In compliance with the
World Anti-Doping Agency, testing
positive for cannabis is found when
the test detects 11-carboxy-THC
concentrations greater than 15
µg/L [13].

The amount of time it takes
for the plasma levels of THC to
fall to 50%, also known as a drug’s
half-life, varies depending on an
individual’s frequency of usage but
is typically around 20-30 hours.
Heavy users typically have a longer
half-life as a result of the slow
redistribution from fatty tissues.
In light users, who are individuals
that consume cannabis less than
twice per week, a positive urine
sample will occur for 1 to 3 days
after ceasing smoking. In regu-
lar smokers, who are individuals
that consume cannabis several
times per week, a positive urine
sample will occur for 7 to 21 days
after ceasing smoking. In chronic
smokers, who are individuals that
smoke daily for extended peri-
ods, a positive urine sample can
occur for 30 days or longer upon
ceasing smoking. Consequently,
testing positive does not techni-

cally mean that an individual has
recently smoked cannabis. There
is little to no correlation between
the presence of 11-carboxy-THC in
urine samples and the presence of
significant concentrations of THC
in the blood [3].

Do you use it too?

Cannabis is considered to be the
most commonly used federally il-
licit drug in the United States, with
about 18% of Americans using it
in 2019. Adolescent cannabis use
has varied since 1979 from 50%
to an all-time low of 22% and now
hovering around 36%. There also
appears to be a gender difference
among adolescents in which males
have a higher prevalence of daily
use of cannabis as compared to
females. Furthermore, daily use
is higher among Black and His-
panic adolescents as compared
to their White counterparts which
elucidates the racial stereotypes
associated with cannabis use in the
United States. These statistics are
found to be true for both adoles-
cents and adults.

When looking at the young adult
age group, there were significantly higher rates of increased past-year cannabis use as compared to those in the older age groups. Contrary to the adolescent age group, cannabis use declined among men in the adult age group while the use in women remained fairly constant. This decline is consistent with the narrowing of the gender gap in the frequency of heavy drinking and alcohol problems. In addition to the racial and ethnic disparities, an individual’s income also plays a role in cannabis use across the United States. Individuals with the lowest incomes had the highest risk and substantial rates of increase in past-year cannabis use as well as cannabis use disorder. Moreover, men in adult households making less than $50,000 have increased prevalence than women in the same situation.

As it happens, cannabis use among pregnant women is more common than we would like to admit. Past-month cannabis use increased to 62% among pregnant women and 47% among non-pregnant reproductive-age women [5]. Thus, we can see that cannabis use is prevalent across all age groups, genders, ethnicities, socioeconomic backgrounds, and reproductive statuses.

Do athletes use it too?

A recent study conducted in 2019 found that cannabis use runs in second place following alcohol use among athletes. A study conducted in 2011 found that one-third of male and one-quarter of female student-athletes in their NCAA Division 1 school reported using cannabis in the past year but the scientists who conducted this study believe this number may be underrepresented of the actual number since they relied on athletes self-reporting their use. These numbers are slightly lower than we see in students who don’t participate in athletics, but it is also thought to believe that student-athletes underreport their cannabis use [10].

Does Cannabis use show evidence for enhancing performance?

Now that we’ve got the nitty-gritty information out of the way, we can talk about what we came to talk about: does cannabis use show evidence for enhancing performance? Studies upon studies are conducted, indicating how exercise is essential for remaining healthy in life. As cannabis becomes increasingly popular and laws are changing around its use, scientists have begun studying cannabis use and its effects on physical exercise performance. There is a lack of strong evidence showing that there is a relationship between cannabis use and athletic performance. Conversely, there are proven to be adverse effects from short-term and long-term cannabis use. On the short-term side, cannabis use has been found to result in impaired short-term memory, impaired motor coordination, altered judgment, and paranoia or psychosis in high doses. On the long-term side, significantly heavy cannabis use has been found to result in chronic bronchitis and increased risk of chronic psychosis-related health illnesses such as schizophrenia, myocardial infarction stroke, and transient ischemic attack [4]. Moreover, research has found that long-term effects may result in immunosuppression, bronchial irritation and inflammation, and even reducing sperm count and viability in men.

Additionally, a review study conducted in 2018 found that there are results that indicate cannabis use negatively affects an athlete’s performance. Thus, cannabis is considered an ergo-
lytic substance as opposed to an ergogenic one. That is, cannabis is a substance that impairs exercise capacity and athletic performance instead of enhancing it [10]. Although there is no evidence on physical performance enhancement, there is some evidence that may suggest that athletes use cannabis due to the euphoric subjective experience. As mentioned earlier, THC has anxiolytic effects at low doses which is why some athletes may depend on the substance to relieve any anxiety before competitions. Additionally, athletes have reported other psychological improvements such as an increase in relaxation, pleasure, and an improvement in sleep. These factors do not directly affect performance, but there is the chance that they can positively impact an athlete’s mindset, therefore indirectly affecting their performance. One thing to note though is that these psychological factors have all been subjective self-reports. There is no concrete evidence that shows a direct relationship between cannabis use and its influences on the mental state of an athlete concerning the management of their anxiety [10, 12].

Throughout the sporting world, there are no consistent penalties found when testing positive for THC. The NFL and National Basketball Association have clearly defined penalties, but the National Hockey League has minimal penalties for athletes testing positive. Moreover, there is no consistency in an acceptable level of THC. The NCAA will not permit THC levels at a threshold greater than 1.5 µg/l while the World Anti-Doping Agency (WADA) will permit THC levels at a threshold of 15 µg/l. On top of this, the NCAA does not allow cannabis use at any point of the season, while the WADA only bans the substance at the time of competition. With all the aforementioned evidence, my question then is, why does our society continue to view cannabis as an illicit substance with no accepted medical use? Why are there numerous discrepancies between levels of accepted concentrations or times at which cannabis use may be appropriate? As Bob Marley once said concerning cannabis use, “Herb. Herb is a plant. Herb so good for everything. Why, these people who want to do so much good for everyone – who call themselves governments and this and that – why them say you must not use the herb?” [14]
References


1 in 5: Why women are more likely to develop migraines

By Karolina Edlund
Kayla’s Story*

The day Kayla found out she was pregnant, she was on cloud nine. Having grown up with siblings, Kayla had always known she wanted a large family of her own. After getting married last year, she and her husband, Adam, had immediately started trying for a baby. Nine months flew by, and they were soon parents to a beautiful baby girl named Hope. Although exhausting, the first few days with Hope were wonderful. Then, Kayla started feeling sick.

She felt an intense pain on the left side of her head, had tunnel vision and often felt dizzy. She couldn’t stand sunlight, and every time Hope cried, she almost threw up. When Kayla tried to explain her symptoms to Adam, she stumbled over her words. Eventually, Kayla retreated alone to her bedroom, and slept for days.

In time, this wave of symptoms subsided, only to return again several days later. “What’s happening to me?” Kayla cried on the phone to her mom. “I can’t take good care of Hope when I feel like this. I can’t even get out of bed, or I’ll puke.” On the other line, her mom sighed. She explained that she hadn’t wanted to worry her anxiety-prone daughter unnecessarily while she was pregnant, but that she knew the feeling Kayla was describing well. After giving birth to Kayla and her siblings, she too had struggled with severe migraines: “When you feel better for a moment, why don’t you google migraine disorder, my love.”

*Kayla’s story is fictional and was written by the author

Kayla’s story is not uncommon; Kayla and her mother are among the nearly 20% of women who experience migraines [1]. But almost everyone gets headaches throughout their lives, why was Kayla struggling so much? Migraines are different from everyday headaches in several important ways (Figure 1). First, headaches affect many more people than migraines; over 96% of people will experience a headache in their lifetime compared to the 18% of people who experience a migraine. Second, there are over 150 different kinds of headaches, while there are only two kinds of migraines, those with and without aura. Third, the physical symptoms of headaches and migraines are distinct: headache pain is often throbbing and not limited to one area of the head; migraine pain is usually dull and centralized to one side of the head. The final most important difference between headaches and migraines is severity. Headaches are not pleasant by any means, but they do not negatively impact daily life. The slew of physical symptoms characteristic of migraines, such as sensitivity to light and sound, dizziness, vision loss, changes in speech and vomiting, make it difficult for sufferers to perform everyday tasks [2, 3]. In Kayla’s case, she struggled to take care of herself and her baby, Hope.

Now that we know the differences between headaches and migraines, let’s delve into the two types of migraines mentioned above — migraines with aura and without aura. The Mayo Clinic defines migraine with aura, also known as classic migraine, as “a recurring headache that strikes after or at the same time as sensory disturbances called aura. Classic migraines are the most common form of migraines, and these disturbances can include flashes of light, blind spots, and other vision changes or tingling and numbness in your hand or face [4].” Aura is thought to be caused by electrical or chemical waves passing through the cerebral cortex, a part of the brain that contains regions responsible for sensory processing, vision, speech and movement. Kayla cried to her mom about the aura she was experiencing — she had changes in her vision and difficulty speaking during her migraines [5]. It is likely that Kayla experienced these electrical waves passing through her visual cortex, the part of the brain that receives and processes sensory input from the eyes, and her Broca’s area, the region of the brain responsible for speech production. If you’ve never had a migraine before, it may be hard to visualize what aura looks or feels like. Figure 2 provides two examples of visual aura: blind or blurry spots and flashes of light.

Many people who suffer from migraines, also known as migraineurs, learn to tell when a
migraine is coming by the appearance of this aura. The onset of migraines without aura is not marked by the same “warning sign,” although, after onset, the two types of migraines are characterized by the same physical symptoms.

So, what causes people like Kayla and her mom to have migraines? While the etiology of migraines is not entirely understood, researchers have identified three main factors that contribute to the development of a migraine attack: 1) genetics, 2) the environment and 3) hormones (Figure 3). Unfortunately for Kayla, she was at risk of developing migraines in all three of these groups. Her story does, however, serve as a useful tool with which to better understand migraine development.

Genetics

“Genetics” refers to the study of how traits are passed intergenerationally, in a process called heredity. To understand heredity, we first need to understand how Deoxyribonucleic acid (DNA) molecules function in the body. Contained within chromosomes, some sections of DNA are called genes, which are the foundational units of heredity. Genes make proteins, which work to allow our bodies to function. Other sections of DNA are thought to act like on/off switches for nearby genes. Mutations in the genetic sequence can also impact gene expression. What’s most important to understand, is that different genes are responsible for different traits — for example, my neighbor has brown eyes because specific genes in his chromosomal instruction manual were turned on or off. Because he has the genetic instructions for brown eyes, his son, who received half his chromosomes from his father, is likely to have brown eyes too.

You may recall that, like Kayla, Kayla’s mom suffered from migraines. Researchers Russel et al. (1996) found that first-degree relatives of people with migraines with aura are four times as likely to suffer from the same type of migraines themselves. This hereditary pattern in migraine development suggests a genetic component to the disorder. But what specific genes have been linked to migraines?

Recent studies on the genetic etiology of migraine attacks have identified several potential genetic markers of the disorder. Focusing primarily on migraines with aura, researchers discovered an overexpression of a C677T gene mutation in migraineurs with aura [7]. One specific type of migraine with aura that affects a single side of the body — hemiplegic migraines — have been linked to mutations in three more genes that contain the instructions for ion channels and transport proteins: CACNA1A, ATP1A2 and SCN1A.

An ion channel is like a cat door, it allows ions (in this analogy the cat) to move between sides of the bigger door (the cellular membrane). Different cat doors open in different ways — some allow the cat to move back and forth across the larger door, others only allow the cat to cross the door in one direction and still other cat doors can be closed for periods of time to ensure that the cat stays on one
side of the door. Sometimes, a cat (ion) needs a little help getting through the cat door (ion channel) or moving around the house (cell) — transport proteins, in our analogy cat owners, can help carry their cats around the house and coax them through the cat door, although this does take some energy on the owner’s part (Figure 4).

When mutations in the genetic sequences that encode for ion channels and transport proteins occur, as in the case of hemiplegic migraines, neurotransmitters and ions are unable to pass through channels or travel between cells, and cortical depression is likely to ensue. Cortical depression is characterized by a wave of depolarization followed by activity suppression in a region of the brain. This decreased function greatly impacts neural and vascular functioning and, as discussed above, may be the mechanism underlying migraine aura [8].

Through the identification of mutations in these four genes, we see how genetics play an integral role in the development and heritability of migraines with aura. Research done on twins tells us that mutations in these migraine-associated genes have an overall heritability of nearly 50%, so it is likely that Kayla’s mom passed one or all of these mutations down to her daughter, resulting in the two women’s shared struggles with migraines [9].

The Environment

In addition to genetic predisposition, many migraineurs report that environmental factors trigger their attacks. Three of the most common triggers include changes in weather, odor and stress. While the majority of studies on the impact of the environment on migraine development have relied on self-reported data, the consistency of responses across the globe suggests their validity.

Weather has been one of the most extensively studied triggers of migraines and, although the findings have been controver-
sial, 45.5% of migraineurs report their migraines and headaches often occur before changes in barometric pressure followed by rain, bright sunshine, humidity and wind [10]. However, the pathophysiology of migraine is complicated, and the physical reasons for why this environmental factor may trigger a migraine attack require more research. More than 40% of migraineurs report odors as triggers and many people experience sensitivity to smell during a migraine attack. One possible explanation for this osmophobia was put forward by researchers Meggs (1993) and Bernstein (2005), who suggested that chemical sensitivity is propagated by neurogenic inflammation in neurons located on the outer protective layers of the central nervous system [11, 12].

There are also several interesting historical hypotheses to support the evolutionary usefulness of these triggers. Many migraineurs claim to be able to predict the weather based on their symptoms, which may have allowed early humans to better prepare for storms. Sensitivity to odor may also have been an evolutionary advantage, as migraineurs may be better able to identify and warn against environmental toxins [10].

For most migraineurs, stress is a major trigger of migraine attacks. Stress may be thought of as the human response to suboptimal conditions in the surrounding environment. Again, the pathophysiological mechanisms underlying the relationship between stress and migraines are poorly understood, but it has been suggested that stress triggers migraines by inducing biological changes that lower a migraineur’s susceptibility to an attack [13]. Unfortunately, the connection between migraines and stress is cyclical in nature — stress triggers migraines and migraines increase stress.

While Kayla did not track the weather or the odors around her at the beginning of her migraine journey, it is certain that she was under a lot of stress. As a new mother her body was physically healing and she was learning how to take care of a baby for the first time. Lack of sleep has also been strongly linked to increased maternal stress and Kayla, like many new parents, was certainly not getting enough sleep [14]. While some triggers are not within a migraineur’s control, like the weather, other triggers may be avoided or managed through lifestyle changes. At the end of this article, we will see how Kayla learned to track, identify and avoid as many of her triggers as possible, particularly through lifestyle changes she made to reduce her stress.

Hormones

Women, both adolescent and adult, are three times as likely to suffer from migraines as men [14]. Oftentimes, women develop their first migraine after first menstruation, pregnancy or menopause; this pattern suggests the role of female sex hormones in migraine etiology.

Hormones are chemical messages that are released via our bodies’ endocrine system and circulate throughout our blood-
stream. These chemical messages control numerous bodily processes, including growth, appetite and sleep cycles. Sex hormones in particular, however, control processes related to sexual maturation and reproduction. In women, the two main sex hormones are estrogen and progesterone. Largely produced in the ovaries, adrenal glands and fat cells, estrogen helps to regulate a woman’s reproductive cycle and is important for cognitive function and bone health. Progesterone is secreted by a type of endocrine gland found in the ovaries called the corpus luteum; it triggers the thickening of the uterine lining to prepare for the potential of fertilization.

During the female reproductive cycle, hormones fluctuate wildly (Figure 4). Amid the follicular phase of menstruation, estrogen and progesterone levels rise in the female body. If an egg is fertilized, the hormones move to support pregnancy, but if pregnancy is not conceived during ovulation then both hormones dramatically fall, causing a woman to shed her uterine lining through menstruation.

These fluctuations in estrogen levels have been shown to trigger migraine attacks, particularly right before menses when estrogen levels are rapidly decreasing in the body. In accord with these findings, many women on hormonal birth control report migraine attacks during their placebo weeks, when they experience estrogen withdrawal.

Pregnancy is also characterized by widespread hormonal changes. Researchers have observed a worsening of migraine attacks during the first trimester, and many women may experience migraines for the first time during pregnancy. The postpartum time period represents another vulnerable time for women, as the dramatic decrease in estrogen levels following childbirth often leads to intense migraines with aura. But why do hormonal changes seem to lead to migraines? Some professionals suggest that decreased estrogen levels may influence blood vessel contractions in the brain. Others believe that low estrogen increases facial and scalp nerve sensitivity. Still others have pointed to the relationship between estrogen and serotonin, a neurotransmitter important for mood stabilization and nerve cell communication. These scientists also suggest that changes in levels of serotonin in the brain may cause the narrowing of blood vessels which, in turn, cause migraines [17].
Kayla experienced her first migraine with aura after the birth of her daughter, Hope. Her development of the disorder was likely in part due to the rapid decrease of estrogen women experience after giving birth. While hormonal birth control has been known to trigger migraines in some women, in others, particularly postpartum women, it has been used to stabilize levels of estrogen in the body as well as to avoid drops in estrogen by skipping periods. Another class of drugs, called Triptans, have also been used to treat the disorder. Triptans work by behaving like serotonin in the brain to calm down overactive pain nerves and, as we will see shortly, Kayla found a combination of the birth control and Triptan medications helpful in managing her migraines [18].

Kayla’s Solution

Kayla had been dealt a bad hand. She was at high risk of migraines in all three of the etiologic categories associated with migraine development: 1) her family had a history of migraines, 2) as a new mother, she was under an immense amount of stress, which was compounded with a lack of sleep and loud environment, and 3) following the birth of her daughter, she was also experiencing dramatic hormonal changes. What I failed to mention at the beginning of this article, however, was that Kayla was a trained neuroscientist. Having dedicated her life to learning about the brain, Kayla was determined not to let this neurological condition affect her quality of life. Soon after being diagnosed with a migraine disorder, she scoured many of the scientific articles cited above and scheduled countless doctor’s appointments. As her list of migraine resources grew, Kayla and her clinical team developed a plan to avoid and manage her migraines.

Kayla could not change her genetics. Neither could her mother. While Kayla found comfort in knowing that mutations in her C677T, CACNA1A, ATP1A2 and SCN1A genes were likely to blame for her and her mother’s migraines, she worried that Hope would inherit these mutations and thus the disorder, as well. Much of Kayla’s distress at the start of her migraine journey came from the confusion of what was happening to her, so she swore not to make her mother’s mistake. She would be open with her daughter about her struggles with migraines and would explain the heritable nature of the condition to Hope early on. She would make sure her daughter was prepared and supported if she were to
Kayla soon accepted that her environment and emotional stress greatly triggered her migraines. While she could not control the weather, she learned to check the weather app on her phone in order to prepare herself for the possibility of a migraine attack. As strong odors often triggered her attacks, Kayla stopped wearing strong perfumes and always opened a window when she knew she or her husband, Adam, were going to be cooking something smelly. While these lifestyle changes were simple life, managing stress as a young mother is anything but easy. It was in this regard that her husband, Adam, became her biggest supporter — aware that sleep greatly affects maternal stress, he took to comforting Hope throughout the night so that Kayla could get a good night's rest. Kayla began meditating, journaling and seeing a therapist, as well. After hearing that she had struggled with anxiety for much of her life, her therapist suggested she look into starting anti-anxiety medication. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant medication in the United States today, and Kayla read that SSRIs work by increasing available serotonin in the brain. They do this through the inhibition of serotonin reuptake by neurons, allowing serotonin to stay active in the brain at higher levels for longer periods of time. SSRIs are highly effective in treating mood disorders like anxiety and depression [19]. Convinced, Kayla soon began taking an SSRI pill every night before bed and, in combination with her other lifestyle changes, her stress levels soon decreased.

Lastly, while Kayla knew that it was only a matter of time before her hormones returned to what they had been before her pregnancy and the birth of her daughter, she was desperate for instant relief. In order to stabilize her hormones fast, Kayla began taking a combination contraceptive pill, which contained both synthetic estrogen and progesterone. This pill helped to regulate her hormones throughout the month, as well as allowing her to skip her period in order to avoid sudden drops in her estrogen levels. As mentioned above, if she were to feel a migraine coming on, Kayla also found it helpful to take a dose of her Triptan medication in order to quickly stop the migraine from progressing.

Kayla's story is not uncommon. Nearly 20% of women experience migraines throughout their lifetime, a statistic which underscores the importance of increased awareness about the disorder [1]. What sets Kayla apart from the rest is her determination to understand the condition and her willingness to try things to manage and reduce the frequency of her migraine attacks. She learned about the heritable nature of her disorder, and the environmental triggers of her attacks. She also learned the importance of hormones to female health. Kayla's training as a neuroscientist undoubtedly helped her understand her condition, which brings us to the point of this article. It is my hope that this article will serve as a resource for other women struggling with migraines; a reminder that you are not alone. As Kayla learned, there are biological and environmental reasons for the pain you are feeling, and through an exploration of these triggering factors, this article aims to provide clarity about and tools with which to manage this disorder.
References

Short Term Cravings, Long Term Effects

A Call for More Comprehensive Alcohol Education

By Madde Hyland
If you were watching television in the early 2010s, you likely saw commercials of people with breathing stomas and robotic sounding voices on nearly every channel. Many companies and non-profit organizations were hoping to use scare tactics in a desperate attempt to stop the devastating effects of a nationwide nicotine addiction. Other campaigns, mainly targeted at younger generations, focused on having a smoke free country and aimed to have the upcoming generation be the one to end smoking. Anti-smoking ads have been produced and consumed for decades. In fact, Britain’s Health Education Council created a Superman comic in which the superhero fights a new villain: Nick O’Teen (1). In the comic, Superman highlights the dangers of smoking, and encourages children to join the fight against Nick O’Teen by saying no to ever smoking cigarettes. The comic even featured a certificate for children who wished to sign on to fight Nick O’Teen with Superman.

Ads and campaigns like Britain’s Health Education Council Superman comic have become a norm in society because the negative effects of nicotine, tobacco, and cigarettes have become common knowledge to the general public. There are long term effects of smoking cigarettes not only on the person who decides to smoke, but also on those around them. Most people know that secondhand smoke is just as bad for a person as smoking cigarettes themselves, and policies have been put in place to prevent people from unwillingly experiencing secondhand smoke. Additionally, the individual long-term health effects of smoking, such as the development of high blood pressure and lung cancer, can pass on a genetic risk of disease to unborn children.

All of this information allows for consumers to become informed about the risks of smoking before they decide to pick up the addicting habit. Specifically, this information puts a sense of responsibility on both smokers and non-smokers to be mindful of the potentially devastating repercussions of smoking on themselves, those around them, and their future children. Because of all of this well-advertised and well-researched information, smoking is no longer seen as ‘the cool thing to do’. In fact, many people will get disgusted looks from others if they are smoking in a public space. This can even be seen in popular culture, where it is no longer common to see individuals smoking in movies, whereas that was the cultural norm several years ago.

Now imagine yourself in college on a weekend with your friends. You’re getting ready to go out and unwind after a stressful week of classes. What’s the first thing that you do? Your likely move is going to be drinking some alcohol to ‘loosen up’ before going out on the town. From getting drunk at parties, to having a few beers with your coworkers at a bar after work, social drinking is considered an acceptable way to spend time with friends, unwind, and meet new people. In fact, drinking is so ingrained into American societal norms that nearly 30% of young adults 18 and older in the United States reported binge drinking while about 7% reported heavy alcohol use in 2019 (2). While these numbers already seem large, they are very likely to be an underestimate.

According to the United States Department of Health, alcohol consumption is considered binge drinking when a person’s blood alcohol levels reaches 0.08%. A person is thought to have heavy alcohol use if this happens at least five times per month.
Many college students go out to parties, bars, and other social events one or two times per weekend (roughly four times a month) and often become intoxicated beyond the requirements for binge drinking. Additionally, it is unlikely that most people will self-report binge drinking and heavy alcohol use for a multitude of reasons, all of which lead to the same result: underestimates of the true amount of people who frequently drink heavily. This means that almost certainly more than 30% of young adults have indulged in binge drinking. The individual long-term effects of alcohol are well-known: excessive alcohol use can lead to severe health effects such as high blood pressure, heart disease, learning and memory problems, risk of addiction, and mental health problems.

Think back to the anti-tobacco campaigns that were mentioned earlier. Can you name an alcohol ad that is similar to any of those? The answer is likely no. It is currently not normal to talk about alcohol consumption in the way that we now talk about cigarettes, nicotine, and tobacco. Other than the occasional ‘Don’t Drink and Drive’ commercial or billboard as the holiday season approaches, there are very rarely discussions about the consequences of drinking alcohol in today’s society. We know the long-term effects of heavy alcohol consumption, so what is the major difference between alcohol and tobacco that allows for drinking to be socially acceptable while smoking is not? The answer is likely that the general public believes that they can partake in these activities without affecting others. As long as people are not drinking and driving, many people view drinking as a relatively harmless activity. To compare this to smoking, the general public understands – and has received an abundance of media teaching them – that anyone who smokes can negatively affect those around them, as well as risk the health of their unborn children. However, people seem to believe that when it comes to drinking, everyone is seemingly off the hook, making it socially acceptable to drink alcohol as much as they would like. That is, unless you are a pregnant woman.

Fetal Alcohol Spectrum Disorders and the Weight of Drinking for Two

In Ancient Greek and Roman cultures, the risks of drinking during pregnancy were constantly acknowledged. In fact, women were told to not drink on their wedding night in order to avoid birthing children with developmental defects. Although this cautionary tale was passed on through generations, it somehow found its way into the world of mythology. Therefore, many people took it as just that: a myth. The identification of the relationship between alcohol and severe birth defects was widely ignored until the late 20th century. For many years it was believed that low levels of drinking were acceptable during certain stages of pregnancy without causing any harm to the unborn child. However, doctors continued to see babies born with severe birth defects, and began to suspect that alcohol may be involved.
As more scientific research was done on the effects of gestational alcohol consumption, it became apparent that there was no safe amount of alcohol that a woman could drink while pregnant. It appeared that all levels of alcohol consumption could risk leaving a developing fetus with serious health defects. As knowledge of this phenomenon grew, the terms ‘Fetal Alcohol Syndrome’ and ‘Fetal Alcohol Spectrum Disorder’ became buzz words as scientists uncovered all of the potential effects of drinking alcohol during pregnancy (6).

Fetal Alcohol Spectrum Disorders, which may occur when an expecting mother consumes alcohol during pregnancy, result in a multitude of physical, behavioral, and learning problems throughout development, many of which can persist into adulthood (6). Symptoms associated with Fetal Alcohol Spectrum Disorders include the following: low body weight, poor memory, intellectual disability, vision problems, heart problems, shorter than normal height, small head size, and abnormal facial features (6). These symptoms are often striking and devastating to new parents. Because many of these symptoms do not go unnoticed, babies are able to be diagnosed with Fetal Alcohol Spectrum Disorders at birth or in early stages of childhood. The growing prevalence of these disorders after their discovery required some sort of action on behalf of public health officials. The public needed to be informed of the dangers of drinking alcohol during pregnancy. Beginning in 1988, the Surgeon General required that every alcoholic beverage must have the following warning on the outside of the container (7):

“GOVERNMENT WARNING: (1) According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects.”

As people became more aware of the risks of drinking alcohol while pregnant, the pressure was placed on pregnant women to avoid alcohol at all costs. Unborn fetuses live in a mother’s womb and survive using the nutrients that they get from their mother. It seems logical that, since the fetus and mother share blood (and therefore blood alcohol content), this is how the negative effects of alcohol are passed down through generations. Pregnant women were — and still are — advised to break societal norms and stop drinking with their friends or unwinding with a glass of wine at night after a long day at work. This responsibility was placed on them alone to make sure that their children were not negatively impacted by alcohol. However, is it really only up to pregnant women?

Changing the Narrative: Everyone’s Drinking Habits Affect Everyone

For a long time, it seemed unlikely that there were any risks to someone’s future children posed by alcohol outside of gestational alcohol consumption given that moms are the only people who have contact with a fetus before it enters the world. However, this frame of thinking ignores the developmental biology of a growing fetus, specifically where it gets the basic genetic information necessary to create human life. DNA from both the mother and father are passed onto the fetus, and therefore mom and dad both have the ability to pass traits on to their children. This leads to a very pressing question: does alcohol affect our DNA? If so, how?

![Image of pregnant woman and baby with arrows indicating developmental effects]

Drinking while pregnant can cause severe developmental effects for new babies. Original image by Madde Hyland. Created in BioRender.
In the last 20 years, research has been done to investigate these exact questions. When a question is asked about how a certain behavior affects our DNA, the field of epigenetics is often a topic of discussion. Epigenetics involve changes to the DNA that, although they do not affect the genetic code itself, can affect the way the certain genes are expressed throughout the body (8). Epigenetic changes can do several things, including turning genes on and off at points when they would usually not be. This can potentially lead to an imbalance of proteins and hormones that regulate bodily functions and behaviors. Researchers have found that certain behaviors lead to specific epigenetic changes to the DNA. Since epigenetic research seeks to explore how a person’s behavior can impact their genetic makeup, scientists set off to explore the impacts of heavy drinking on the expression of specific genes related to learning and memory, as well as addiction. Mouse models are often used to study epigenetics because epigenetics work similarly in humans and mice. Therefore, researchers used mouse models of binge drinking and chronic alcohol consumption to investigate how this can affect gene expression and epigenetics. Studies have shown that alcohol consumption can actually epigenetically modify a person’s DNA. These changes can result in a multitude of behavioral changes, including making an individual more susceptible to the rewarding effects of alcohol and therefore more likely to develop a dependence or addiction (9). Scientists have also demonstrated that high levels of alcohol consumption in mice, similar to heavy alcohol use in humans, can lead to an increased preference for alcohol, and a decrease in working memory – the capability...
to remember information for small amounts of time (10).

Scientists have used mouse models of alcohol consumption to show that these behavioral changes are linked to the differential regulation of particular genes, and that this differential genetic regulation can be passed down to the next generation of mice (10). One specific study investigated the role of alcohol consumption on working memory in the next generation. This study found that the offspring of mice who were subjected to heavy alcohol consumption had a downregulation in dopamine transporter proteins, which are crucial for memory and the formation of new neurons in the brain. These molecular changes in the brain resulted in a deficit in spatial memory, and the mice whose parents had consumed large amounts of alcohol were unable to remember locations that they had previously visited (11).

A separate study showed that heavy alcohol consumption can lead to the upregulation of the SIRT1 gene, which plays a role in the rewarding effects of alcohol (9, 13). An increase in the rewarding effects of a drug of abuse can result in a higher risk of developing an addiction to the drug. Therefore, the upregulation of the SIRT1 gene is a potentially dangerous result of long term alcohol use. Unfortunately, it has been suggested that the upregulation of this gene may be passed onto future generations, which can increase the risk of offspring developing addiction later in life (13). Studies have demonstrated that some of these epigenetic changes can even persist into a second generation of offspring (13). This means that your alcohol consumption can not only affect you, but your children and grandchildren as well. Put simply, anyone who drinks heavily can pass down negative traits to their future children, and can even increase their susceptibility to addiction.

While these studies uncover the impacts that alcohol consumption can have on your children even prior to conception, it also highlights that both sexes are capable of passing these negative traits on to the next generation (10, 11, 14). These research findings, while grim, may be seen as somewhat of a relief for expecting mothers: the idea that they are the only ones responsible for the health of their unborn children has now been debunked. The responsibility is no longer only on them, but rather on everyone to drink responsibly.

**It’s About Access to Information**

The research papers discussed in this article are often hard to read for an undergraduate science student, let alone someone with little to no scientific background. Many forms of scientific research are inaccessible to the general public due to the heavy use of scientific jargon. This leads to a delay in the spread of new and important information and can often lead to a disconnect between the scientific community and the general public.
and the rest of the world. New commercials, advertisements, campaigns, and warning labels all do one thing: they give the general public access to information that allows them to make an informed decision before partaking in potentially harmful activities. As information about the harmful effects of smoking became public knowledge, less people made the decision to smoke. Once people learned that secondhand smoke could affect other people, policies were enacted to give people the choice to be smoke-free. Now that it is known that heavy alcohol consumption can affect people’s future children, it is likely that the incidence of heavy drinking, along with its negative effects, will decrease if this knowledge is transferred from the scientific community to the rest of the world.

Taking Action: Changes in Policy

It has now been established that heavy alcohol consumption and binge drinking can in fact affect those around you, specifically when thinking about your future children. Now that we know this, what is the next step? We can actually use the lessons learned from cigarette and tobacco prevention strategies and apply similar tactics to heavy drinking. The very first step is to educate the general public about the long-lasting and hereditary effects of drinking to an unhealthy extent. This can be done by commercials that target all generations. A short commercial using a simple splitscreen to demonstrate the difference between the life of a heavy drinker and their family compared to a responsible drinker could prove to be an effective way to portray this information to older audiences. For younger audiences such as school-age children, education on the long-term effects of heavy drinking can be implemented into preexisting “Don’t Drink and Drive” education campaigns. Additionally, a spin-off of the Nick O’Teen character in the Superman comic could spread awareness to yet another audience. The main focus of these proposed campaigns is simple: make the long term negative effects of alcohol public knowledge, just like we’ve done with tobacco.

While educating the general public will be a long and tedious process, there are also immediate changes that can be made to the way that alcohol is advertised and distributed across the country. As mentioned earlier, the only warnings currently displayed on alcohol bottles are ones that warn of gestational alcohol consumption and a warning to not drink and drive. Alcohol companies are not required to warn consumers about the risk of addiction or any other potential effects of alcohol consumption (7).

This has been a very recent point of discussion in the tobacco industry, and in March of 2020 the FDA officially required cigarette companies to add warning labels to their packaging and in their advertisements (15). These new warning labels are required to demonstrate some of the less well-known, but still devastating health risks of smoking cigarettes in vivid detail, including imagery of lung disease, cancer, and even a small child on oxygen. These regulations are set to take effect in October of 2022 (15). These now complex and informative labels on cigarette packs are meant to inform consumers about the dangers of their purchase and the potential choice to smoke cigarettes. Given that alcohol also has widely unknown long-term effects, it is of the utmost importance that the warning labels on alcohol containers also change. The addition of a simple image and text box explaining how alcohol can not only affect the consumer, but also their future children, would help to diminish the risk of alcohol addiction and cognitive defects in future generations. It is important to note that the overall goal of this proposed alcohol education is not to scare people away from drinking. Alcohol consumption is ingrained in our society. People enjoy wine with their meal and cracking open a beer while watching football, and these norms will likely remain for the foreseeable future. Rather, the purpose of more comprehensive alcohol education is to inform the public of the potential long term dangers of misusing alcohol, and to encourage them to think before they drink.
References


Exercise Can Give Us Brain-Boosting Superpowers?

By Selam Habtemariam
With the snap of your fingers, what if it was possible to boost brain power, longevity, and function against the strains of time? What if we could slow the brain’s process of aging? For centuries, questions of maintaining the brain’s youth and boosting its power have been grappled with by scientists and nonscientists alike. Legends of fountains of youth have been an alluring topic of many stories throughout pop culture along with similar myths of immortality. Many superheroes in our favorite movies often have these gifts of immortality, extraordinary physical capabilities, sharp instincts, and high-speed problem-solving abilities. Such fantasies of having these superpowers, of course, do not exist to our knowledge. However, the incorporation of a particular lifestyle change has been found to be responsible for extending life expectancy and brain power: staying physically active. In many ways, exercise may be one of the closest things we have to our very own semi-instant power boost for the brain. It does not sound as enthralling as the subject of many expeditions in search of immortality, or having the power to levitate objects with our mind. However, when incorporated into one’s lifestyle, exercise has tremendous influences on the brain that you may not expect.

Regular exercise is widely known for its physical benefits from maintaining a healthy weight, to supporting our heart health, to heightening endurance, to building strength in muscles and bones (1). Though it is not a muscle, the brain also becomes stronger when exercise is incorporated correctly. In fact, physical activity can help to slow the typical aging processes of the brain, along with boosting brain health and function. Many of these aging processes involve neurodegeneration, processes by which neurons lose function, resulting in the deterioration of memory, motor abilities, cognitive function, and many other capacities (2). It is known that exercise is important for brain health, but what specific pathways does it work through? Research has revealed that numerous neurophysiological and neurochemical pathways are altered with physical activity that produce long-term effects, as described previously with neurodegeneration prevention, but also valuable short-term effects (2). Chances are, you have also experienced some of these short-term effects after completing a long or intense workout.

Picture this: as you wrap up a workout, you reach your last rep of burpees. Your body is aching, and you feel like you can’t finish. Your hands hit the ground and you propel yourself upward with a feeling of fulfillment and elation washing over you. Chances are you feel more exhilarated at the end of the workout than before you began from that boost of adrenaline. This is due to modulation of pathways responsible for elevating your mood.

Together, we will continue to explore new strategies that you can incorporate into your own workout routines to maximize both short term and long-term benefits to your health based on emerging research.

“A happy young woman holding two pink weights” by Nenad Stojkovic. June 6, 2022 on Flickr is licensed under CC BY 2.0.
Acute vs. Long-Term Exercise: What’s the Difference?

Before we get into the details of how exercise can influence the brain long-term, it is valuable to understand the benefits of a single bout of exercise — clinically referred to as acute exercise. We have discussed some brain benefits from short-term exercise, but interestingly, there are more benefits than just mood. How do these acute brain benefits of exercise compare to long-term brain benefits? Many clinical trial studies have been conducted trying to answer this question.

Studies on acute exercise explain that performing approximately a half-hour of aerobic exercise has benefits linked to motor learning, characterized by both the excitation and inhibition of the motor cortex observed with transcranial magnetic stimulation (TMS) measurements (2). These measurements provide evidence of motor learning improvements and the potential for enhanced cortical plasticity, or the brain’s extraordinary ability to form new connections between neurons based on lifestyle choices or experiences (2). Intriguingly, this indicates that simply performing a single round of exercise for a short amount of time does so much more than elevating the heart rate and mood. It sparks the performance and adaption of new motor skills, particularly when there is repetition. Acute exercise also introduces the potential for making more neural connections throughout the brain. It was additionally found that acute exercise performed at a large range of intensities, from low to high, improved the following aspects of executive function for up to two hours: attention, problem solving, decision making, verbal fluency, cognitive flexibility, and even working memory (2). Though one may expect that these brain boosts after physical activity occur from activities performed over a longer amount of time, these effects were seen in as little as thirty minutes of aerobic exercise! This is significant because it illustrates that no matter how little exercise is performed, almost any form of exercise performed for some amount of time is great for brain health. As you may guess, if the brain begins to develop stronger motor skills within the span of thirty minutes, the influences of the same exercise over a longer period must hold even more opportunities for levels of neuronal plasticity, learning, memory, and many other benefits.

Researchers have found that compared to short-term exercise, exercise consistently practiced over a long period of time results in many more enhancements and protective mechanisms being activated in the brain. In fact, the long-term benefits of physical activity on the brain are so vast, they have been incorporated into treatment programs for patients with various mental disorders. For example, a previous clinical study worked with middle-aged patients suffering from stress-related exhaustion with exercise incorporated into their treatment. Patients were given physical activity recommendations with comprehensive instructions as a part of a multifaceted treatment program for 18 months. It was found that though all of the patients experienced some level of improvement from burnout, depression, and anxiety, strong and mild compliers to physical activity

Neuroplasticity by CogniFit.com, illustrating neural networks before stimulation (1), after two weeks of stimulation (2), and after two months of brain stimulation (3).
recommendations reported significantly less burnout compared to non-compliers at the end of the 18-month period (3). This study revealed that long-term exercise helps with treating chronic stress and improving mental health, and can be incorporated into current treatment plans. Compliance with these recommendations is important in maximizing enhancement of brain health. Now that we have looked at long term brain benefits of physical activity in middle-aged people, let’s consider these effects on young adults.

Another study with young adult women, ages eighteen to twenty-five years, with moderate levels of depression were also enrolled in an exercise program. The program lasted eight weeks in which researchers found that when students performed aerobic exercises with 60-65% maximum heart rate, levels of depression were reported to significantly decrease over the course of the eight-week period (4). Of course, it would be too ambitious to assume from these results that curing depression through sport or other forms of physical activity are possible. After all, crucial sessions of psychotherapy, compliance to particular prescription medications, self-soothing techniques, and many other forms of treatment suggested by doctors for depression may be necessary to see substantial improvements in mood. But what other neural circuits do incorporations of regular aerobic exercise work through? If you guessed that long-term aerobic exercise improves brain function in more long-lasting ways than mood and stress deficits, you are absolutely right.

Incorporation of long-term exercise into your lifestyle can reduce the risks of developing detrimental effects of aging on the brain, or neurodegeneration (2, 5). Neurodegeneration is a process that occurs in many cognitive diseases such as Alzheimer’s, Parkinson’s, and Huntington’s disease. How does the brain assemble such a strong protection against these deadly brain diseases? The brain does this through heightening brain plasticity and neurogenesis, or the generation of new neurons in the brain (2, 5). Brain plasticity, or neuroplasticity, is responsible for the brain’s extraordinary ability to adapt from experience through growth and reorganization of neural networks. As long-term exercise is performed, neurogenesis facilitates the brain’s powerful ability to adapt through the generation and integration of new neurons. As you go for your next routine jog, think of how transformative exercise can be in strengthening these neural connections and protecting you not only from cardiovascular disease, but also many neurodegenerative and behavioral disorders!
Aerobic vs. Mindful Exercise: What’s the Difference?

Have you ever tried running up a steep hill as fast as you could without stopping? Each step hiking upward to the top seems to make your steps and chest feel heavier, and you begin to pant heavily. Maybe you have been late to class or work. With the elevator taking too long, you grudgingly decide to take the stairs to class as fast as you can, feeling your heart rate increase and gasping for air when you finally get there. Or maybe you remember jumping rope with your friends when you were younger. Swinging the rope as fast as you could, you may have tried to see who could jump rope fastest or for the longest amount of time. What do all of these periods of physical activity have in common? Commonly known as “cardio,” these are all forms of aerobic exercise. Aerobic exercise is characterized by physical activity that produces increased heart rate and increases the body’s use of oxygen. Oftentimes, these are exercises of high intensity, though there are some lower impact aerobic exercises such as walking. However, benefits exist for both moderate and high intensity aerobic exercise. Moderate-intensity aerobic exercise is particularly helpful in improving executive functions, such as working memory. High-intensity exercises, on the other hand, boost information processing (2). Each of these benefits may be something you would like to keep in mind as you think of what aerobic exercises you would like to get into. We now know that intensity matters, but all we have discussed are heart pumping exercises. Let’s slow our pace and investigate another exercise.

Stretch your arms up, take a deep breath in, and slowly pull your arms down by your sides, breathing out. When done with the correct intention and focus, you should be engaging muscles up through the torso with the rising and falling of your breath with this stretch. In fact, you have performed the first step of a new range of brain-boosting exercises: mindful exercises. You may be wondering how these soothing exercises may compare to aerobic exercise. Scientists have made these comparisons in participants of two mindful, low exertion exercises, Feldenkrais, and yoga. These exercises were compared to a computer class that served as a control, and two aerobic classes: an aerobic dance class, and a swimming class (8). Yoga, Feldenkrais, and swimming were all found to improve subjective well-being, anxiety, and general mood (8). On the other hand, participants’ mood did not improve in the control computer class or aerobic dance groups. Interestingly, it was suggested that swimming has
components of both mindful and aerobic exercise. The rapid, rhythmic, and repetitive nature of the movements in conjunction with controlled breathing awareness may produce particularly heightened benefits in decreasing anxiety and improving general mood (8). This suggests that finding an exercise routine that incorporates both mindful and aerobic qualities can maximize the benefits of physical activity on brain health.

Is there such a thing as too much exercise?

We have explored the vastness of benefits that exercise has on the brain along with the diverse modes of exercise that have been studied to maximize these benefits. Taking all of this into consideration, is there a limit to how much we should exercise to reap these benefits? More importantly, how does excessive exercise influence brain functionality? As you may have guessed, too much of anything often leads to more harm than good for the body.

In many of our favorite athletes, we likely have seen the influence of over-training on the physical body. Some of the injuries that result may cause physical burnout, temporary inability to compete, end careers completely, or may even cause life-threatening complications. Unfortunately, overtraining or excessive exercise may cause the brain to burnout as well. For this reason, it is vital to understand the limitations of how much physical activity we should incorporate in our daily lives. We have previously discussed the necessity of compliance with suggested physical activities given by medical providers, and studies have also explored the negative influences of overexertion of the body on the brain (3). Studies have shown that excessive training, particularly through aerobic exercises, causes cognitive fatigue, reduced activity in the prefrontal cortex, and increased impulsive behaviors (9). Cognitive control is required for goal setting behavior. Goal setting behavior helps prevent impulsive behavior, such as not stopping physical exertion of the body when it hurts. These results may seemingly conflict with our general findings on aerobic exercise benefits, but they actually describe how the cognitive effects of burnout can persist if not attended to. For this reason, it is important to be mindful of what should and should not be incorporated into your exercise routines.

Figure 2. Aerobic, mindful, and combination exercises to boost brain health. Created by Selam Habtemariam. Image created with Biorender by Selam Habtemariam.
Tips for Creating your Brain-boosting Exercise Routine

Many people likely have a new year’s resolution of staying active to improve their health. We have explored the specifics of the influence of exercise, so now is a good time to get up, do some stretches, and start warming up before we secure a solid routine! Nevertheless, it can be really intimidating to know where to begin. With time constraints of classes, work schedules, and an even longer list of commitments, it can also be difficult to set a routine that works effectively for one’s individual needs. The main objective is to incorporate exercise into a long-term plan to improve brain function more effectively. It likely will take some time to explore what modes and levels of exercise work best for you.

While these may all be healthy ways to boost brain health, always consult your doctor before preparing lifestyle changes. If other health complications may get in the way of remaining physically active, this is particularly important. Moreover, here are some suggested tips before you make your own routine:

Suggested Tips:

1. Oftentimes, exercises that improve heart health aid in brain health as well.

2. Practicing exercises regularly is crucial to reaping benefits in brain health, longevity of cognitive function, and production of long term changes in brain plasticity.

3. Know the limits of both what your brain and body can handle.

4. Try and craft an exercise routine that incorporates all the benefits of exercise. This likely will mean you may want to try out a mix of aerobic exercise, mindful exercise, high-intensity exercise, moderate intensity exercise, etc. We have discussed that swimming is a mode of exercise that thoughtfully engages in many of these aspects, making it a great option for enhancing your brain health.

5. Know what your brain needs. This will likely mean you will want to work with a professional and do your research before you dive in.

“Exercise is really for the brain, not the body. It affects mood, vitality, alertness, and feelings of wellbeing. Exercise is the single best thing you can do for your brain in terms of mood, memory, and learning.”

John Joseph Ratey, M.D., clinical professor of Psychiatry at Harvard Medical School.

As you engage your body in some healthy physical exercise, think of all these lasting benefits and hopefully they will motivate you to fulfill your goal of elevating the power of your brain.
References


In 500 Feet, Turn Right Onto Memory Lane

How Our Brains Create Maps of Our Memories

By Sofia Alonso
We as humans have an incredibly refined understanding of the physical world. Remembering in detail specific landmarks and spaces in our everyday lives comes with very little effort. Evolutionarily speaking, this innate ability was crucial in ensuring our survival during a time where maps had yet to make their debut. It isn’t surprising that our strongest memories are significantly linked to the spatial information associated with its consolidation. Giving physical context to our memories can help to lock them in and improve our ability to retrieve those memories when necessary.

An ancient form of this technique is used by the well-known fictional detective Sherlock Holmes in the form of a “memory palace,” also known as the method of loci. According to myth, the invention of this technique is said to have come from the Greek poet Simonides of Ceos who invented it after attending a banquet that ended terribly. Simonides is said to have stepped outside during this banquet. Upon arriving outside, the banquet hall collapsed in his absence. Simonides was able to identify his fellow banqueters, despite their bodies being crushed and disfigured. He did so by putting a name to each body in relation to where they had been sitting before the hall collapsed. The technique was further adopted by the Greeks and Romans, such as the orator Cicero. During a time where writing was an expensive luxury few had, he would utilize a memory palace to help memorize his speeches (1).

This memory strategy is a mnemonic device that helps to memorize information by positioning a visual cue or item at a specific point along an imaginary journey of your choice. Typically, this journey must be at a familiar location with a well-known route. This could be your house, high school, or a familiar stretch of road whose layout you know how to navigate like the back of your hand. To satisfy the conditions of a memory palace, you would have to create a mental journey through your chosen geographical entity composed of numerous discrete loci. If you are imagining your home, these loci could be your bedroom, staircase, kitchen, backyard, and many other locations specific to your house. To then embed information into your memory palace for later recall, one is advised to travel through the mental journey and commit imagery of the information you would like to memorize to any locus of your choice. When the time comes that you wish to retrieve the information, all you must do is walk through your memory palace and come upon the loci associated with each piece of information, activating it into your memory. Let’s try it out! Here’s
Let’s Go Back in Time!

Henry Molaison, also known as Patient H.M., was a 27-year-old epileptic patient in 1953 when he experienced severe memory impairment following an experimental brain procedure. Surgeons removed a thumb-sized piece of tissue from each side of Molaison’s hippocampal formation and surrounding medial temporal lobe areas of his brain in hopes that it would help relieve the severe seizures he had been suffering for 10 years. Although the seizures subsided following the surgery, Molaison experienced severe memory loss and was not able to form new memories, leaving him with permanent amnesia. This tragic event for Molaison became a significant turning point for the field of neuroscience, letting us know that each cortical region of the brain may be associated with a specific mental function such as learning or memory. Memory was now considered separate from other cognitive functions of the brain and was specifically attributed to the medial temporal lobe, which includes the hippocampus, amygdala, and parahippocampal regions. Research inspired by Patient H.M. focused on replicating similar memory impairments in laboratory animals which led the animals to display memory deficits as well. It was also established that the hippocampus played an important role in declarative memories — memories of facts and events that can be consciously recalled or “declared” in humans (2). Researchers were still left wondering what underlying neuronal mechanisms are involved in storing information as memories.

The term cognitive map — a mental image that provides the layout, or map, of a space — came about when American psychologist Edward Tolman tested the concept of latent learning. At the time it was widely accepted in the field of behaviorism that learning only took place when the individual was conditioned to a specific stimulus or reinforcement. Tolman tested three groups of food-deprived rats and observed their ability to transverse a maze all the way to its end. One group had food rewards at the end of the maze, the second group had none, and the third group had no food for the first ten days, but on the 11th day, food was placed at the maze’s exit. Interestingly, after the 11th day when rats in the third group found the food at the end of the maze, subsequent maze trials immediately showed that the same rats were able to quickly and efficiently find their way out of the maze, similar to the rats who were always fed. Tolman’s experiment showed that the rats developed a cognitive map and learned the layout of the maze despite the lack of any reinforcement, disproving accepted theories of learning at the time (3).

Palace Cells

Some things remained unclear following Tolman’s discovery. O’Keefe and Lynn Nadel tested and proved their belief that a population of neurons exists in the hippocampus that holds the ability to encode the position of the mammal within its spatial environment. These neurons were given the name place cells. Recordings of these place cells in the hippocampus of rats showed that when

"John O’Keefe" by NTNU, Faculty of Natural Sciences is licensed under CC by 2.0. Flickr.
the rats would enter a particular location in their environment (cage) place cells specifically associated with that location would fire (4). If we take for example yourself navigating through your kitchen, some place cells will become activated as you hover your hand over your collection of holiday-themed mugs trying to find your favorite mug. Other place cells will fire as you try to navigate your kitchen through the dark attempting to find the refrigerator door handle. Place cells are responsible for our sense of place. Once you have explored your environment and place cells have anchored themselves to particular places, they accumulate and create a mental map of the space. These cells are subject to change, remapping to different landmarks as the location of the subject changes and so does the environment (4). When you walk from your kitchen upstairs to your room, it may be that the place cells that were once firing when you approached your kitchen cabinets are now firing when you come upon your bed.

They discovered that the hippocampus not only has an important role in declarative memory but is also primarily involved in spatial interpretation and navigation. Given that both memory and space appeared to function within the same brain region, researchers were challenged to account for both and better understand how they work together. A linkage between space and memory became apparent in some early studies of place cells where they were able to express past experiences in mice. It was discovered that place cells are not just markers of an animal’s instantaneous location, but they also represent locations in the environment that the animal experiences in the past, present, and future. Mice placed through maze tasks showed place cells that fired when the animals went the wrong direction, or when they made errors trying to navigate out of the arena, showing that these neurons have stored information of these spaces into memory (5). In a separate study, similar place-cell activity in rats persisted through multiple “morphed” environments, exhibiting the brain’s ability to reanimate previous representations of the external world that seem to be retrieved from memories (6).

Place cell firing sequences that were activated during spatial behavioral tasks in mice were found to “replay” or “reactivate” during sleep episodes, showing that these sequences were also saved into memory (7).

**Grid Cells**

Given the flexible nature of place cells, researchers were not sure whether they were entirely responsible for the spatial blueprint we use to fabricate how we perceive and experience our surroundings. These uncertainties eventually led to the discovery of grid cells by the wife and husband duo, scientists May-Britt Moser and Edvard Moser, and their students at the Norwegian University of Science and Technology. These types of neurons are located in the entorhinal cortex — the hippocampus’ very talkative, next-door neighbor. The entorhinal cortex is a flood gate for information leaving and entering the hippocampus. Grid cells are specialized cells of the brain that, unlike place cells, do not represent specific locations, rather they internally create a coordinate system that allows us to

![](image_url)
navigate our external world. They do not require sensory information from the environment, such as sounds, textures, and visuals, to form this spatial framework. Each grid cell will fire at various locations that are at a consistent distance from each other, forming a grid-like hexagonal pattern across the space (8). An easy way to picture this is if you position yourself in a small room and imagine the floor is made up of large, hexagon-shaped tiles. Now imagine dividing each one of those hexagons into six equilateral triangles and assigning a specific color to each. A unique grid cell will fire every time you step on a certain colored triangle. Let’s say you move to the corner of the room and step on a red tile, grid cell #1 will fire. Then you move to another red triangle at the other corner of the room and grid cell #1 fires again. Finally, you move to a green triangle in the middle of the room and grid cell #2 fires up. These grids can overlap and can have various orientations or different hexagonal sizes. When you take them all into consideration, they all add up in a way that maps out the exact spatial structure of our world. Specific locations in your home, whether that be the corner of your hallway that you must turn to enter your room or that one creaky step in your staircase, are represented by a special sequence of grid cells.

Your brain will understand where your body is positioned in relation to space when multiple grid cells that overlap at a specific location are firing at once, almost like when your GPS tells you your exact location relative to a map. Together place cells and grid cells work somewhat like Google Maps. Place cells establish the presence of landmarks and important locations in your cognitive map. Grid cells are responsible for the coordinate system, fragmenting your environment into latitudinal and longitudinal points that track direction and distance.

It is believed that the grid code which underlies how grid cells communicate structural information of space to your brain, could also be responsible for representing other types of information. There is reason to speculate that grid cells can also represent the structure of conceptual knowledge and abstract thought. Mapping not only our physical world but our internal world as well. It has been hypothesized that we humans can process conceptual information in the same manner that we approach navigating space. It was speculated that the hexagonally symmetric grid-code produced by grid cells during spatial navigation may also be activated during the storage of conceptual knowledge. Timothy Behrens and his team of researchers at the University of Oxford tested this hypothesis by having human subjects navigate two-dimensional knowledge. Subjects were instructed to watch a video where the black outline of a bird continuously morphed as the leg and neck lengths were shortened and elongated. They found in their data the presence of a hexagonal grid code that changed and varied as if the subjects were navigating their way through a “two-dimensional conceptual bird space”

"Grid cell firing pattern." Action potentials are shown in black superimposed on movement path shown in gray. Adapted from Stensola et al. (2012). Nature, licensed under CC by 2.5.
— the two dimensions being the bird’s neck length and leg length. Their results suggest that this code is used in both the navigation of physical space as well as non-spatial conceptual information (9). As of recently, many neuroscientists have sought to propose the idea that the hippocampal-entorhinal region provides a universal geometric code that maps out all types of knowledge — experiences, memories, and ideas — within cognitive spaces in the brain.

Memories Are Not Forever

Most memories are not permanent as you may have come to realize yourself. Many of the things we have learned or studied in school do not stick with us forever. Although we have spent a significant amount of effort attempting to store this information long-term, it is impossible to remember everything we have experienced. According to Ebbinghaus’s forgetting curve, most of our memories of learned knowledge will tend to fade over time, unless this knowledge is attended to with repetitive review across a long period of time (10). Despite the effort it might take to store most information into long-term memory, some meaningful memories can be permanently retained. Considering this observation, Kentros and his colleagues investigated the long-term stability of place cell firing fields when paired with attentional demands to specific spatial cues. Mice were trained in a cylindrical arena to locate a goal location while their hippocampal place cells were being recorded. Other mice were allowed to freely roam through the arena with no specific goal location or task to complete. They found that place cell stability, which is when the same place cell can maintain a consistent firing field across multiple exposures to the same environment, is strongest when the mouse was encouraged to pay attention to spatial cues to complete the task at hand. Essentially pointing to the notion that when spatial cues are attributed to memories, whether that be facts or experiences, the retention of the information is strongest and most consistent (11).

Therefore, you may have noticed that most of your episodic memories are the easiest to recall. Episodic memories are those of autobiographical events that we have experienced. These types of memories allow us to “re-experience” the events as if we were actors in a mini movie playing in our heads. They can be engraved in our minds as they are strongly characterized by multiple cues such as location, time, and sensations. Take, for example, a significant event in your life whether that be the death of a loved one or the day you won a grand prize from a contest you decided to randomly enter. If you try to re-experience this moment it would probably not be difficult to see all the details that made up your environment the day you received the news.

The strong association between memory and spatial cues can be attributed to place-cell activity in the hippocampus. The possibility that spatial characteristics of our episodic memories are encoded by our place cells was tested on patients awaiting surgery for their epilepsy. The subjects had electrodes placed in their medial temporal lobes while they were asked to navigate a virtual town and deliver items to one of

![Figure 3. Grid cells will record and track the mouse’s location through an overlapping hexagonal coordinate system. Left image: Singul
ar grid cells firing at locations A, B, and C as the mouse moves through its environment. Right image: Multiple, overlapping grid cells firing along the red dotted path depicting mouse’s movement. Image created with Biorender.com by Sofia Alonso.](image-url)
the stores. The recordings showed that place cells, once active at the locations where each item was delivered, were also activated when the subjects were asked to recall each item. The findings suggest that when attempting to recall an event, place cell activity during this recall will bring into consciousness the spatial context that the event or item took place in (12). Similar to how a memory palace associates imaginary spatial cues that give spatial context with objects or facts. Time is also a crucial element of information regarding experiences and events in our lives that are stored as episodic memory. A study led by Kraus and a team of researchers discovered that grid cell activity in rats running on a treadmill was able to track not only spatial features but temporal features as well. Their findings supported the notion that a common circuitry is present between the computation of spatial mappings in our brain as well as the temporal organization of episodic memories (15).

Now What?

How can we utilize the grid code and use it to answer some of the problems and questions that come up in our everyday lives? Researchers are looking into how the grid code can be applied to social relationships and hierarchies. There is a spatial component to our perception of the social world around us. When we consider social status and hierarchies, sometimes we group certain individuals as having a "higher" or "lower" social standing. A study conducted in 2015 observed the social brain by tracking its hippocampal activity in response to changes in social relationships. The participants were asked to play a computer game where they navigated a virtual world in which they interacted with cartoon characters and worked to increase their social status by finding a new home and job. They were able to find that the hippocampus of the participants navigated the social space of the game in two dimensions, that being affiliation and power (14). Researchers are hoping to utilize the concept of encoding social information into a social cognitive map to examine social deficits present in clinical disorders like autism spectrum disorder (15).

Additionally, studying place and grid cells in these new contexts has propelled researchers to study their connection to diseases associated with age. A paper published by Stangl and his colleagues looked into the progressive loss of navigational abilities that come about with old age. They hypothesized that since the entorhinal cortex is predisposed to neurodegeneration during aging and Alzheimer’s disease, grid cell functioning should be significantly reduced in these individuals causing navigational decline. They were able to find exactly that. The older subjects were less successful in keeping track of their position when attempting to navigate a course with curved paths while their vision was impaired. The researchers believe that taking into consideration grid code stability could be a potential early measure...
for Alzheimer’s and other neurodegenerative disorders. Since the spatial grid code system also provides a neuronal basis for non-spatial domains such as conceptual knowledge and memories, broadening our understanding of how this system may be destabilized in the brain could help us to comprehend how our memories and other cognitive domains are affected with time (16).

Coding the Future

Researchers within this specialized field are just beginning to expand on the concept of place and grid cells in a variety of different ways. They speculate that there is a slew of intricacies that may link memory and spatial navigation within our brains, inspiring research that approaches this potential unity from different directions. Many theories and claims on this notion remain unexplored, with some claims being more striking than others. A team of researchers led by Jeff Hawkins are looking to expand our understanding of the grid code beyond memory and the hippocampal-entorhinal region of the brain. They hypothesized that grid-cell-like neurons are present throughout the entirety of the neocortex rather than at just one localized area. Similar to how grid cells in the hippocampal-entorhinal complex can process and store spatial information, the neocortex also utilizes such cells to learn the structure of objects that one touches or looks at, as well as to learn higher-level cognitive tasks. According to Hawkins, if you were to hold a pen in your hand, each sensor patch of your skin, like sections of your hand’s palm or your fingertips, will be associated with grid cells in your neocortex that will process each patch’s location relative to the pen. Your neocortex will add up all the information generated by each sensor patch and create an expansive internal map of the object’s features, helping your brain recognize that the object you are holding is a pen (17). The “neocortex” model has been met with controversy as some researchers believe grid cells may not be present in other areas of the brain beyond the hippocampus and entorhinal cortex. If this model were to be proven true, it could pave the way for the incorporation of a universal grid-code system into the world of artificial intelligence.

And so we ask: Can this universal grid framework help create machines that better mirror the human brain and its abstract qualities? Neuroscientists at University College London and AI researchers at DeepMind may have just launched us in the right direction. Using a deep learning AI technique inspired by brain structures, they were able to train a rat-like computer simulation to keep track of its position as it navigated a virtual maze. Surprisingly, the simulation program created activity fields of hexagonal patterns similar to the hexagonal grid code generated by grid cells in mammals. The simulation was then able to utilize the grid code to learn and navigate its way through the maze. It almost seems impossible to imagine what more we could discover about how we store and navigate knowledge and memories with the help of AI and a universal grid-code. The possibilities seem endless!

Now that you know more about the memory palace and the neuroscience behind this technique, let’s put it to the test! Go back to the memory palace you created and retrace the route you took when placing the ten items on our list. Grab a sheet of paper and jot down the items you see in your route and in the order you come across them. See if you can match your list with the one I provided above. Feel free to continue expanding your memory palace. I’ll leave it up to you and your imagination to “map” out your memories however you see fit!
References


Are You Depressed?

Or are you just on birth control…

By Olive Cowan
Sixty-five percent of women of reproductive age in the United States take birth control pills. It is likely therefore, that if you are an American woman reading this article, you have used some form of birth control in your lifetime. Societal standards have deemed women responsible for carrying the burden of birth control. However, the first clinical trials for birth control were actually conducted on men; they consisted of two injections of two different hormones and were found to be 96% effective. However, the trials were terminated when men reported side effects such as acne and mood swings (2). Researchers replaced women as the subjects because it seemed easier to block the release of one egg a month as opposed to millions of sperm. In the U.S., hormonal contraceptives such as IUD or combination pills are most commonly used for women—because who wouldn’t opt for 99% efficacy?

Across cultures, the implications of birth control vary immensely. Many religions advocate against birth control or abortion because they believe one should not alter the innately biological processes of reproduction. In underdeveloped countries, it can even be difficult to gain access to birth control. Additionally, birth control can be viewed negatively because of its association with sex, and subsequently female pleasure (another taboo topic in many societies). However, hormonal contraceptives are not just used to prevent pregnancy; many women are prescribed birth control to treat common reproductive disorders that affect the ovaries such as polycystic ovarian syndrome (PCOS) and endometriosis. When I was 16, I was diagnosed with PCOS and prescribed birth control as a medication to treat it. I was relieved to know that there was a medication that could help, but overwhelmed by the list of side effects associated with taking birth control.

If you have used hormonal contraceptives before, you have probably experienced a moment of shock when you learn all the possible side effects and risks. Even though they tend to be rare, side effects range from common/minor effects such as changes in bleeding, headaches, weight fluctuation, facial acne, nausea or cramping, to serious/rare side effects such as blood clots, ovarian cancer, or vaginal infections. They are rare, and if caught early they can be treated. The important factor is knowing side effects are a possibility so that if you experience them, you can recognize them and tell your doctor. Another side effect listed under the rare section is depression/mood changes. However 2.2 out of 100 women who are taking hormonal birth control developed depression compared to 1.7 out of 100 women who did not use hormonal birth control (29). Indicating that if you are taking hormonal birth control, you are potentially at a higher risk for developing depression or other mood disorders. Additionally, this number is likely underestimated because many individuals do not report their mood changes as a side effect of birth control, instead they view them as independent issues. After I started birth control, I was one of the unlucky few who experienced these mood related side effects. For a while, I too believed they were independent, but now I’m not so sure. A few months ago I stumbled upon an article titled “Can hormonal birth control trigger depression?”, and what I learned was shocking. If you have ever experienced something similar, or relate to what I have already said, I suggest you continue reading. Before we begin, a solid understanding of menstruation, hormones and birth control is necessary to understand the implications of the aforementioned article.

What is Menstruation?

Menstruation begins when a woman goes through puberty. Her hormone levels fluctuate and she becomes fertile. The menstrual cycle has a few stages, first, menstruation where the uterus releases its inner tissue lining through a “period”. In the Follicular phase, the uterine lining begins to build
Mood
Birth control can offer relief for cyclical mood symptoms in some women, others find it amplifies anxiety and depression. For some women, birth control can accompany new onset of mood symptoms and may increase the risk of suicide.

Hair
Some women experience hair loss on their head when starting birth control and others may find decrease growth of unwanted hair.

Thyroid
The pill depletes nutrients the thyroid requires to produce hormones and increases thyroid binding globulin, a protein that prevents thyroid hormone from being used by the body.

Breast
Breasts may become tender and enlarged after beginning birth control. Birth control may also improve cyclical breast changes.

Liver
The pill specifically alters the liver on a structural and genetic level. There is an increased risk of both benign liver tumors and liver cancer.

Gallbladder
Women with a history of gallstones on birth control may experience faster stone formation.

Blood Pressure
Birth control can lead to elevated blood pressure. Be sure to have your blood pressure checked regularly to screen for this.

Weight Changes
For some women, birth control can cause fluctuations in weight, weight gain and weight loss.

Pregnancy Prevention
Some forms of hormonal birth control are up to 99% effective with perfect use.

Period Relief
Birth control can help reduce heavy periods and cramps in some women.

Diabetes Risk
Current use of the pill has been shown to lead to insulin resistance and blood sugar dysregulation. In postmenopausal women who have ever used the pill there is an increased risk of developing diabetes.

Blood Clots
There is an increased risk of developing a blood clot while on birth control. If you’re a smoker, have a genetic predisposition, have heart or liver disease, have migraines with an aura or are overweight you may be at increased risk. According to the CDC, being over age 35 is also considered a risk factor.

Brain
Birth control alters brain structure, function, mood, selection, and can increase the production of neurotoxins in the brain.

Migraines & Headaches
While birth control can provide hormonal headache relief, migraines and headaches can start or become worse while on birth control.

Skin
Estrogen and progesterin can resolve acne for some women, in others it can get worse.

Stress
Women on birth control have been found to have disruption in their HPA axis and an altered stress response.

Cancer
Birth control can reduce the risk of some cancers like ovarian, uterine, and colorectal cancers. It has been shown to increase the risk of brain, liver, and breast cancer.

Heart Attack
Certain pill formulations can increase the risk of a cardiovascular event. In women with pre-existing conditions, this risk may be higher.

Gut
Birth control increases intestinal hyperpermeability (leaky gut), disruption of the microbiome, allows for overgrowth of yeast, and is associated with an increased risk in developing autoimmune disease of the gut in people with a genetic predisposition.

Nutrient Deficiencies
The pill is specifically shown in multiple studies to cause deficiencies in many vitamins, minerals and antioxidants.

Vaginal Infections
Increase in yeast infections can occur for some women using birth control.

Libido
Women on birth control often report low or absent libido. Birth control can also lead to vaginal dryness and pain with sex.

Bone Health
Hormonal birth control may impair bone density in teenage women and may not have the “bone protecting” effect once thought.

Autoimmune Disease
Hormonal birth control is associated with an increased risk of developing crohn’s disease, multiple sclerosis, lupus, interstitial cystitis and ulcerative colitis.
Hormones and Birth Control

Hormones are responsible for regulating a number of different biological processes mostly within the endocrine system (a network of glands that dictate the functioning of cells and organs). The endocrine system is made up of regions of the brain (hypothalamus, pineal and pituitary gland), thyroid/parathyroid gland, adrenal gland, pancreas, ovaries, and/or testes (20). This system is responsible for essential biological processes such as homeostasis, metabolism, physical/mental growth, energy, fear, and reproduction. The endocrine system interacts with the HPA axis (hypothalamic-pituitary-adrenal axis), a network of communication and feedback within the hypothalamus, pituitary gland and adrenal gland that dictates our body’s stress response. The pituitary and pineal glands release stress hormones called cortisol, which signal to the hypothalamus and other brain regions to go into fight or flight mode. Hormone fluctuations can have effects throughout the whole body because hormones interact with many different physiological processes. You might be wondering what this has to do with periods and birth control; birth control manipulates this pathway by altering levels of the female sex hormone (estrogen) to interrupt the menstrual cycle.

Estrogen has three major endogenous forms: estriol, estradiol and estrone (17). $\beta$-estradiol is the most abundant form of estrogen produced naturally in the body (3). Scientists spent years researching these hormones in order to generate synthetic versions that act in a similar manner. The primary goals for using synthetic hormones were hormone therapy and hormonal contraceptives. Supplemental synthetic estrogens increase estrogen levels which can stop periods, and prevent ovulation. Increased estrogen levels signal via the endocrine system to the brain and the ovaries that the body is pregnant (even though it isn’t actually). When the body thinks it is pregnant, it does not ovulate (release eggs) and therefore cannot become pregnant. Hormonal contraceptives can be administered in several ways. Some work through a daily pill which releases hormones into the bloodstream. Hormones can also be administered through an intrauterine device (IUD). This is placed in the uterus and slowly releases small doses of hormones over time to the localized area. These hormones do not interact with the brain or the bloodstream, however similar changes still occur in the uterus. The hormones in the IUD cause the tissue lining of the uterus to become thinner which results in lighter/less frequent periods. The IUD prevents pregnancy by triggering swelling and mucus generation in the uterus so that it is inhospitable to sperm (34). These hormonal contraceptives are composed of synthetic hormones such as ethinylestradiol (the most commonly used hormone in oral contraceptives) or levonorgestrel (a synthetic hormone similar to progesterone used in an IUD) (10, 34).

Treating Other Disorders

Hormone therapy is often used to treat disorders that impact the endocrine system. These
disorders impact processes such as reproduction, growth/development, mood, and hormone regulation. Endometriosis is an endocrine disorder that affects the growth/development of the uterus by overproducing endometrial/uterine tissues that begin to grow on the outside of other organs. When the uterine lining is shed during a period, it can cause small lacerations on other organs which can be very painful and lead to infertility (19). Polycystic ovarian syndrome (PCOS) is another endocrine disorder that affects the uterus. It is caused by the overproduction of androgens (a male sex hormone found in low concentrations in women) that leads to cysts (small fluid filled sacs) on the ovaries. The hormone imbalance can prevent some women from menstruating. Menstruating with PCOS can be very painful and also poses health risks by increasing your risk of having a cyst burst (19). Hormonal birth control as a form of treatment has a positive impact on the severity of both PCOS and endometriosis symptoms. Supplementation of synthetic progesterone and/or estrogen decreases menstruation by thinning the uterine lining which makes periods less painful and decreases the risk for lesions or burst cysts (36). Medications used to treat endocrine disorders such as hormonal contraceptives have widespread effects due to the diffuse nature of the endocrine system.

The Emotional Side of Things

While the physiological side effects of birth control have been widely studied, the emoti-
specific estrogen receptors used by synthetic and natural forms of estrogen. Estrogen receptors are nuclear receptors, a special kind of receptor that is able to interact with DNA and regulate gene transcription. Transcription impacts a wide range of biological processes such as reproductive organ development, bone density, and brain functioning (27). Alterations in brain functioning due to transcriptional changes is a potential route in which depressive symptoms can emerge. Fluctuations in estrogen levels caused by the menstrual cycle have been shown to cause structural changes in the brain such as decreased overall volume, in addition to decreased volume in specific regions associated with depression/mood such as the hippocampus, amygdala, temporal and parietal regions (24).

Another possible mechanism by which estrogen can impact mood is through estrogen receptors abundance in areas of the brain responsible for serotonin regulation and usage. Serotonin is a neurotransmitter associated with mood regulation. When serotonin levels are low, individuals experience symptoms of anxiety or depression. It is not clear how serotonin levels get depleted, but scientists have speculated that early life stressors, persistent trauma, or lack of gut microbiota can all impact serotonin levels (13, 38).

You May be Moody Or It Could be Your Birth Control

Women are often ridiculed for being moody or asked “are you on your period?” when they are irritable. This is a normal response to hormone fluctuation and should not be criticized by others. The drastic changes in hormones during the menstrual cycle can cause moodiness or irritability which can be worsened by life changes or new stressors. Supplemental hormones in birth control can often intensify these effects and in some cases lead to different mood disorders. When doctors prescribe birth control, they rarely go into detail about the potential severity of mood effects.

The statistics on prevalence of mood related side effects and hormonal birth control are shocking. 47% of women who began taking birth control terminated their use within the first six months due to adverse effects. These women tend to switch forms of birth control or discontinue use permanently (26). Due to the
recent evidence supporting an association between mood disorders and use of hormonal birth control, scientists have begun researching ways in which this could occur. The route is not completely clear, however based on the information discussed above, there are a few mechanisms by which these mood changes are possible. Estrogen may interact directly with the endocrine system and produce effects in areas of the body such as the brain and reproductive organs. It is possible that the supplemental synthetic hormones disrupt proper cognitive functioning and lead to mood changes. Another possible mechanism is through gene transcription caused by the estrogen receptors. Scientists do not know which genes the hormones turn on or off. It’s possible based on the fact that estrogen receptors are highly concentrated in regions of the brain that produce serotonin, that the synthetic hormones turn off genes that produce serotonin, and decrease serotonin levels.

**Back to The Article That Started it All**

Now that you understand the background information about hormones, birth control, and their effects on mood, we can begin to explore why this is applicable to you and a large portion of the population. After reading “Can hormonal birth control trigger depression?” I googled some key words and the results of my search were astounding. I knew that moodiness or irritability were among the other potential side effects on the generous list. However, I was unaware of how direct the correlation between depression and hormonal birth control is.

A study tracking women taking birth control found that 47% of women taking an oral contraceptive discontinued it, and 14% changed to a different type of pill within the first 6 months of starting (26). One of the leading causes of these changes was their awareness of worsening mental/emotional wellbeing. Various experiments have shown that women taking hormonal birth control pills experience higher scores of depressed mood, mood swings, and fatigue than individuals receiving a placebo treatment (14).

Even when the hormone release is localized to the uterus, such as an IUD, women have reported experiencing depressed mood or anxiety. A population study in females with an IUD detected a decrease in psychological well being, an increase in anxiety...
about health, and an increase in alcohol dependence (32). This particular study ran statistical analyses to determine if the contraceptives, or a different variable, were contributing to the issue. The correlational analysis determined that the use of hormonal contraceptives was contributing most heavily to the psychological effects. Another population study done in Denmark revealed that adolescents with IUD’s were more likely to subsequently be prescribed antidepressants than adolescents who did not take birth control (28). These women were 50% more likely to be diagnosed with depression within six months of starting birth control than individuals who were not taking any hormonal contraceptives. These same researchers did another study, using a similar sample, but this time looking at women with IUD’s risk of attempted or completed suicide. Shockingly, they found that these women, about 21 years old with no previous psychiatric diagnosis, antidepressant use or hormonal contraceptive use before the age of 15, were two times more likely to attempt suicide than those who did not use hormonal contraceptives during these years [28]. Unfortunately, the risk of completed suicide was even higher; women using hormonal contraceptives were three times more likely to commit suicide.

Remember the HPA axis? It’s responsible for our stress response. Patients with depression have been shown to have a blunting effect, in which patients have a diminished stress response and impaired stress recovery (5). A diminished response indicates an inability to cope and deal with stress, one of the principal contributors to mental disorders. This blunting effect commonly found in disorders such as anxiety and depression is also seen in women on the birth control pill.

Necessary Societal Changes

These statistics are disturbing and indicate that significant changes need to be made in regards to the way in which women are informed about mood effects and the use of hormonal birth control in general. Mood effects are not usually discussed in detail as a side effect of birth control use. In order to decrease the prevalence of mood effects, doctors need to inform women taking birth control of the increased risk for mood effects. This way, they can look out for them and make the association between mood changes and birth control rather than viewing them as independent issues. Potential interventions could be changing dosages or forms of birth control to decrease the mood effects. Some individuals may be more sensitive to oral contraceptives because they are absorbed into the bloodstream, but not as sensitive to an IUD which releases hormones to a localized region of the uterus. Determining which method is safest for you is imperative to your emotional wellbeing.

The Bright Side

While these statistics are grim and you are probably feeling like getting your IUD taken out or stopping your birth control, that isn’t the first step and there are other options. While there is a
risk for developing depression or mood disorders, not all women do. Some women benefit greatly from hormone therapies. Women using hormones to treat endometriosis or PCOS experience significant reductions in pain and dangerous physical impacts. Additionally, some studies show that hormone therapies can actually have positive impacts on mood for women with severe premenstrual syndrome (PMS) or post menopause (7).

If you are worried that your birth control may be contributing to a depressed or anxious mood, you can talk to your doctor to discuss maybe switching the concentration of your hormones, or changing to a different form of birth control. These small changes can make a big difference. Factors such as personal/familial past medical history of mental illness or mood related side effects from hormonal contraceptives can have a significant impact on your sensitivity to synthetic hormones (15, 12). In addition, the use of progesterone only pills or multiphasic pills (hormone dose increases over the course of your cycle rather than remaining constant) can increase your likelihood of the development of negative mood effects (31). Lastly, starting birth control at a young age increases your risk; the less developed your mind is, the more likely you are to experience these mood related side effects (28). Therefore, it may be best to consider starting hormonal birth control as late as possible.

In light of these concerns for women’s mental health, scientists have gone back to the lab in search of non-hormonal birth control options. The FDA has approved a number of different products, however none are as effective as their hormonal counterparts. One of the most promising new options is a non hormonal gel used before sex called Phexxi. It works by altering the vaginal pH to be inhospitable to sperm. This birth control was shown to be 93% effective in clinical trials, making it relatively competitive with other forms of hormonal birth control.

This birth control is now on the market, but it requires a prescription from a doctor to ensure it is a safe option for you. However, this is made easy with telehealth appointments on phexxi.com. Some doctors recommend progesterin-only birth controls to alleviate the emotional side effects; however, literature has shown similar negative emotional effects with these pills (31). The overall trend is ambiguous and requires more research to make any conclusions.

Additionally, researchers are working hard to generate an effective birth control pill for men. One drug called “11 βmethylnortestosterone dodecyl carbonate” has moved into phase one of its clinical trial (28). It works by suppressing testosterone and another male sex hormone essential for sperm production. It is unclear if these will be viable options, but if they are safe and effective, this medication may prevent many women from suffering mood related side effects. Regardless of the scientific limitations, there are societal stigmas surrounding men and infertility which makes implementing male birth control difficult. Reproduction is biological and innate; any deficiencies in this domain are frowned upon. There needs to be both societal and scientific growth in order for change to occur and the norms of birth control to shift.
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Consciousness

Our most basic state is more complicated than you think!

By Alyssa Dowling
Rude Awakenings

In 1998, Carol Weiher awoke to the sound of disco music—and, if that wasn’t bad enough, the next thing she heard was “cut deeper, pull harder.” Carol was having her right eye surgically removed and the muscle relaxants she was administered prevented her from alerting anyone that she was still conscious and in pain (1).

“I was doing a combination of praying and pleading and cursing and screaming and trying anything I could do but I knew that nothing was working,” said Weiher. Weiher is one of a relatively small group of people who have experienced anesthesia awareness, a phenomenon in which anesthesia does not render the patient properly unconscious. In the worst scenarios, the patient wakes to tremendous pain without any means of communicating; they must simply bear the physical and psychological consequences of this deeply traumatic experience.

Still, though one or two people out of every thousand who go under anesthesia experience some degree of awareness during their procedure, only an unlucky few can feel pain (1).

Experiences like Carol’s highlight our tenuous understanding of consciousness and the dangers of not researching the subject further. Through the study of comas, anesthesia, and artificial intelligence, scientists and philosophers alike have realized that our ability to understand and scientifically define consciousness is crucial. Even so, a precise scientific definition of consciousness is extremely difficult to establish, in part because we use the word in so many ways. We are conscious, but we can lose consciousness while sleeping, under anesthesia, or from a brain injury. I can also say that I am conscious of something to indicate that I am aware of it, a definition that has little to do with consciousness in reference to the self.

Consciousness is a problem so nebulous that it is often difficult to know what questions to ask or if science will even be able to provide greater insight. It is a subject that some think is an illusion and others consider the essential question of neuroscience. Some believe it is irreducible, while others want to study it at the molecular level. Still, to productively discuss consciousness, we must have a generally agreed-upon definition. Though the scientifically accepted definition of consciousness will change over time, it is possible to combine several popular definitions to make the concept more accessible. Broadly, consciousness refers to the ability to experience one’s existence rather than simply recording and responding to it as a computer program might. Consciousness consists of inner, qualitative, subjective states and processes of sentience or awareness (2). Though a robot may detect the world around it, it is not conscious because this requires a qualitative feeling along with those inputs in conjunction with communication, thought, and reflection (2). Consciousness can be divided into two functional components: wakefulness and awareness. While wakefulness refers to arousal, awareness refers to how we process the content of our consciousness. Put simply, wakefulness is required to perceive a tree or experience happiness, but demonstrating wakefulness does not guarantee awareness—both are necessary for consciousness (3).

The History of the Study of Consciousness

In the seventeenth century, after the Renaissance, the Greek concept of a “theory” was combined with systematic observation and experimentation (2). However, at this same time, conflict between science and the Church raged, and scientists and philosophers adjusted their teachings to protect themselves and their field of study. To separate science away from the church and thus protect it, Descartes argued that reality has a strict and abiding cleavage between the mental and the
physical, a designation that was long accepted. Given this reasoning, Descartes was able to create a separation between religion and science of sorts, with a degree of success. At the time, this was a decent compromise—the church had uncontested domain over the mind and soul, and scientists were relatively free to study the material world. Although this distinction was useful at the time, it has persisted much longer than its utility. Consequently, for reasons ranging from ease to convention, science has been considered a strictly objective, third-person endeavor. This leaves scientists little agency to provide insight on first-person subjective experiences—especially not one as abstract as consciousness. After all, to study consciousness is to examine our very conception of the human soul.

This history meant that it wasn’t until the 1990s that neuroscientists began to regard consciousness as a legitimate area of study in the natural sciences. The Merriam-Webster dictionary defines neuroscience as “a branch (such as neurophysiology) of the life sciences that deals with the anatomy, physiology, biochemistry, or molecular biology of nerves and nervous tissue and especially with their relation to behavior and learning.” Simply put, it is the study of the brain. It is thus puzzling that we do not study a fundamental function of the brain—consciousness. Studying the brain without studying how the brain causes and sustains conscious states is like studying the lungs without studying how they allow us to breathe. Though consciousness admittedly involves more philosophical, spiritual, and ethical considerations and is certainly more complex than breathing, the logic stands. Further, the study of consciousness should be driven by many of the same medical considerations that would drive the study of any other major physiological process. Even if neuroscience will never be able to fully explain consciousness, and I suspect its study will provide useful insights into comas, anesthesia, and perhaps our very personhood.

The Neuroanatomical Basis of Consciousness

The study of the neuroanatomical basis of consciousness is still in its nascent stages. There are many different theories, but it is important to understand some of them and how they are derived to understand the ways in which neuroscientists are making progress in their study of consciousness. The traditional viewpoint is that consciousness essentially arises from interacting neurons in the midline of the brain, the cerebral cortex (associated with attention, awareness, etc.), and the reticular activation system (regulating alertness and wakefulness) (4). At the same time, contemporary research suggests that consciousness originates in the frontal region of the brain, while others maintain that it comes from the hindbrain. In studying the material basis of consciousness, researchers must address the external sensory network and the internal self-conscious network, making consciousness a uniquely complex function. There may be many theories of consciousness simply because so many parts of the brain are involved.

One way that neuroscientists attempt to simplify the physical study of consciousness is through the study of neural correlates of consciousness (NCC). Because these “signatures of consciousness” are not necessarily causal, they are much easier to study and identify (if slightly less illuminating). Stanislas Dehaene, a neuroscientist at Collège de France, has identified four “signatures of consciousness (5).” Of those, the P3 wave in the dorsolateral cortex (behind the top of your forehead) correlates most reliably with normal conscious states (5). Physicians have successfully used measurements of these “signatures of consciousness” in coma patients to predict which individuals are most likely to regain consciousness. Neuroscience jargon aside, our understanding of neural
correlates of consciousness is proving to be an essential part of developing more accurate prognoses for individuals in unconscious states.

Curious Case of the Claustrum—A Promising NCC

The claustrum is a thin sheet of neurons attached to the bottom of the neocortex in the middle of the brain (6). Relatively little is known about the function of the claustrum, but we do know it provides functional links between the frontal cortices and the association cortices in the brain. These linkages suggest that the claustrum plays a role in how perceptual information interacts with the arousal (alertness) system, and thus is involved in the generation of consciousness. In 2014, Koubeissi et al., in the pursuit of a cure for epilepsy, implanted electrodes deep in a woman’s brain in an attempt to record signals from different brain regions during seizures (7). When an electrode next to the claustrum was stimulated, the woman lost consciousness. When the stimulus stopped, she immediately regained consciousness without recollection of the incident. Other wider-scale studies have found that the degree of claustrum damage affects the duration of consciousness loss, suggesting that the claustrum plays a role in the restoration of consciousness, but not maintenance (3). One study looked at Vietnam veterans with traumatic brain injuries that were limited to one brain region, and impacted the claustrum. Researchers defined traumatic brain injuries as injuries that caused at least 24 hours of loss of consciousness. They found that damage to the claustrum was moderately correlated with the duration of consciousness loss following brain damage. The study of the claustrum as a neural correlate of consciousness demonstrates major issues with the study of NCCs in general. For one, the structure is thin and in close proximity to a variety of other brain structures, making it challenging to study using neuroimaging (3). Additionally, though scientists like Crick and Koch proposed that the claustrum plays a crucial role in consciousness due to its structure and connectivity, more recent research does not support this same hypothesis. Instead, results suggest that several neural networks combine to generate and maintain consciousness, although some, such as the claustrum, may be more involved than others (3).

Theories of Consciousness

While research of the neurobiological basis of consciousness expands this field of study, a more holistic approach is to perhaps examine the experience of consciousness. Instead of trying to reduce consciousness into biological parts, theories of consciousness attempt to give a more systemic explanation. The first, the global workspace theory of consciousness (GW), was proposed in 1998 (14). This idea is essentially that a single brain region is incapable of generating consciousness. Instead, consciousness requires the coordination of many different parts of the cerebrum—an idea that encourages researchers to explore the brain as a whole (8). Interestingly, this theory (along with some related ones) posits that computers will one day gain consciousness. Critics of this theory say that it fails to explore what consciousness is and instead only provides a vague call.
to consider the entire brain in the production of consciousness.

The integrated information theory, on the other hand, conjectures that consciousness is simply “the capacity of a system to integrate information,” and provides a mathematical framework for evaluating the magnitude and quality of consciousness (9). This theory, while helpful for measuring consciousness on a clinical level, provides conditions that are necessary, but not sufficient on their own to produce consciousness.

More metaphysical theories of consciousness exist, with two being the most prominent. Some think that consciousness is a fundamental building block of the universe in the way that physicists think of space and time and mass (13). According to this theory, there are fundamental laws that govern these building blocks, but they cannot be understood and explained in more basic terms. Others still think that consciousness could be universal and that every system can possess some degree of consciousness. This idea is called panpsychism and suggests that everything, from a human to a photon, has some element of subjective feeling, some primordial precursor to consciousness as a human experience. This idea does not assert that everything is intelligent or thinking, but rather that everything has some aspect of “universal” conception of consciousness. While this idea is somewhat incomprehensible in Western, monotheistic culture, it is seen as a more intuitive explanation in cultures that see the human mind as continuous with the rest of nature.

The idea that consciousness is both fundamental and universal has been taken up by a neuroscientist by the name of Giulio Tononi, who has rigorously developed the idea via mathematical theory (13, 9). This mathematical theory is centered around the idea of phi, which is a measure of the amount of information integrated in the system, and thought to be related to consciousness. Therefore, the human brain, with its large degree of information integration, has the highest degree of consciousness. Everything else, down to a microbe, has a non-zero degree of consciousness. In the science of consciousness, this is one of the leading theories, and it has the potential via ethical and social implications to transform how we relate to nature. On the other hand, this theory could apply to non-organic systems like computers, which, according to the pan-psychic view, have the capacity to be completely conscious. This is a view that many neuroscientists, philosophers, and religious leaders would take major issue with. On the topic of computers especially, leading neuroscientists have taken the stance that consciousness has much more to do with our nature as living and breathing organisms than with pure intelligence, and thus would reject Tononi’s hypothesis (12). It perhaps follows that the “pan-psychic” view would need to only apply to living things, at least for the time being, to properly mesh with other neuroscientific conceptions of consciousness.
Philosophy of Consciousness and the Limits of Consciousness

There is tension between neurological and philosophical theories and conceptions of consciousness. Although to be human we must have a brain in relative working order, some philosophers believe that there is confusion between the necessary and sufficient conditions for consciousness. Thus, when thinking about neuroscience, it is important to not lose sight of that fundamental mind-brain problem. Most neuroscientists do not think that the mind is the brain, but some neuroscientists seem to get lost in chemical and anatomical explanations of consciousness and risk losing sight of the forest in their study of the trees. There is a legitimate fear that an overly reductionist approach to consciousness will lead to purely chemical explanations of behavior. For instance, there is a quoted instance in which Patricia Churchland, a so-called neuro-philosopher, came home after a difficult day at work as told her husband, “Paul, don’t speak to me, my serotonin levels have hit bottom, my brain is awash in glucocorticoids, my blood vessels are full of adrenaline, and if it weren’t for my endogenous opiates I’d have driven the car into a tree on the way home. My dopamine levels need lifting. Pour me a Chardonnay, and I’ll be down in a minute (10).” It is hard to say how seriously these sorts of sentiments are taken, but at the very least I think it is easy to understand how such statements would alarm those who take a more holistic approach to human consciousness and behavior. Further, such explanations do not yet provide a particularly convincing explanation for consciousness, and cannot be taken entirely seriously.

Covert Consciousness

Severe brain injuries often lead to a loss of consciousness for weeks or even longer. In such unresponsive states, it is difficult to determine to what degree the patient is aware or conscious. Fifty years ago, these patients probably would not have survived their injury, but as life support technology has improved and such patients can be sustained for longer periods, doctors and neuroscientists have identified a newfound demand for more robust techniques for determining the degree of a patient’s consciousness. Many patients who are unable to give muscular or behavioral indications of consciousness have been shown, through brain imaging, to have some degree of covert consciousness (11). These findings have many clinical applications and can be used to give more
accurate treatments and diagnoses to unconscious patients. This can also contribute to more accurate prognoses—that is, brain imaging that discovers some degree of covert consciousness can help provide more accurate predictions as to whether or not a patient will regain consciousness. Patients who exhibit some degree of subjective experience as discovered by brain imaging are substantially more likely to recover from their injuries.

When we discuss impairments of consciousness, it is essential to distinguish between the different states that are possible and the spectrum on which they exist. Although there are ideal types, each unconscious state is different from the next, and a person’s level of consciousness exists at different degrees of several different axes. The coma is the most referenced impairment of consciousness and can basically be understood as a very deep sleep that you cannot awake from. In the “ideal type” of coma there is little to no movement, the eyes are closed, and the patient has little to no awareness or processing of their surroundings. The opposite of a coma is understood to be full consciousness in which you have total awareness, normal processing, and physical ability to respond to the environment. Still, there are types of consciousness impairments that fall into other categories, such as the vegetative state, during which a person can open their eyes and there is some level of alertness, but they do not exhibit full consciousness. An individual in a vegetative state is sort of a physical shell of a person in that they lack consciousness, but display some movement and the theoretical ability to use their body (if their brain could utilize that ability) (11). Opposite from a vegetative state is a person who is “locked-in.” These patients are fully conscious but have limited to no ability to express their consciousness, often due to an injury to the pons, a part of the brain which plays a large role in transmitting and receiving motor information. This is a condition in which it is particularly vital to discover covert consciousness since it is distinctly inhumane to mistake a fully conscious (though immobile) person for someone in a vegetative state. Consider, for example, instances in which fully conscious patients overheard family members saying that it would be better if they were dead, or adult individuals who were stuck in front of a TV playing Barney for several months (7). Indeed, when locked-in patients recover or find ways to communicate, they generally have suffered trauma from having been treated as an object during the time in which their degree of consciousness was misunderstood. At the very least, discussions of covert consciousness should include the vital importance of what physicians have been taught for decades)—medical professionals and family alike must treat seemingly unconscious individuals as if they can understand and respond to everything that is said and done around them.

Considering that there is no direct test for consciousness, the study of covert consciousness is intimately connected to the technologies which detect it (11). While behavioral and muscular indications of consciousness are undeniably central to our understanding of the concept, brain imaging has demonstrated how limiting and unsatisfactory such markers are. Functional MRI scans have drastically changed the quality of life for seemingly unconscious patients and have helped identify a need for further therapeutic strategies. Still, these scans always require transporting the patients, which can be costly and dangerous. The scan itself is expensive and logistically difficult since there must be physicians,
nurses, and respiratory technologists present to safely perform an MRI on a patient who may be on some degree of life support (11). Additionally, consciousness generally fluctuates during recovery, and so a patient that starts out unconscious may become increasingly conscious without any behavioral change. However, repeated MRI scans may not be logistically or financially possible. Luckily, many new promising technologies are being researched that could be used more consistently. One major study used EEGs and found that around 15% of patients in an “unconscious” state demonstrated some degree of covert consciousness. Other studies have put the number at closer to 30, or even 40 percent (11).

Conclusions

Pinning down a definition of consciousness demonstrates how nebulous the concept can be. At the same time, however, the clinical advantages of better understanding consciousness are evident. Providing more suitable treatment plans and prognoses for unconscious patients, preventing anesthesia awareness, and finding a more connected way of thinking about our place in the world are all reasons the study of consciousness is essential. While there is certainly some validity to complaints of the inscrutable nature of consciousness, it is not an area of neuroscience that we can afford to ignore because it is too complicated or because of the possibility that we might never understand it. All we need to know is that the journey toward a better understanding of consciousness will improve clinical outcomes, our understanding of ourselves, and perhaps even our understanding of our place in the world.
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