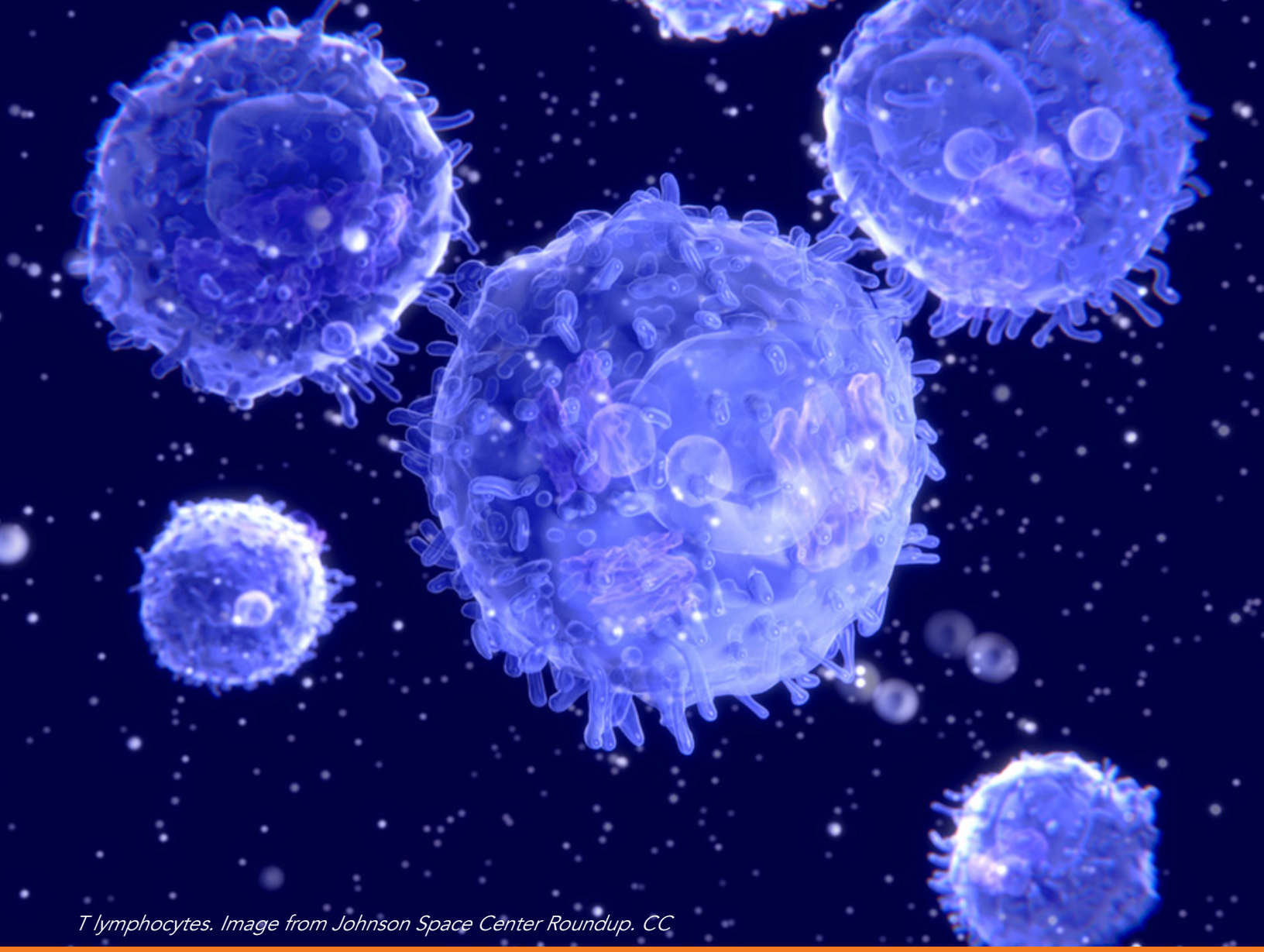

T lymphocytes. Image from Johnson Space Center Roundup. CC

Honey, are these my kids?

My hands?

My organs?

My cells?

By Anoohya Muppirala

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

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

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

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

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

Immunological Memory:

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

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

Multiple-Sclerosis is not MOG-nificent

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

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

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

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

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

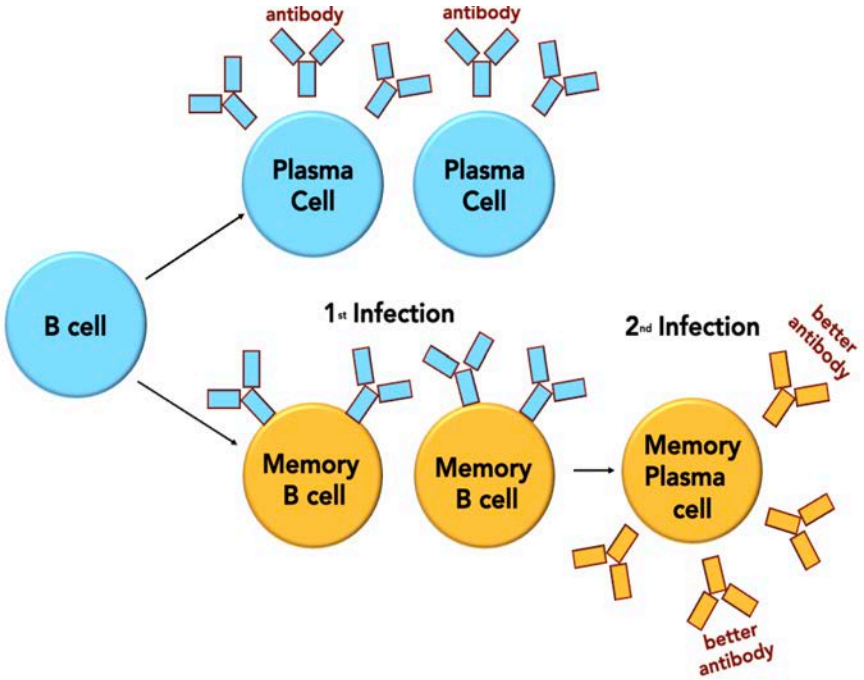

*Fig. 2: Process of B cell response during primary and recurrent infection. After first infection, B cells become **plasma cells** that secrete antibodies (Y shaped proteins) to target the infectious pathogen. At the same time, **memory B cells** that remember the pathogen are being created and rest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

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

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

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

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

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

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

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

**Patient names changed to protect identity*

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

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

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

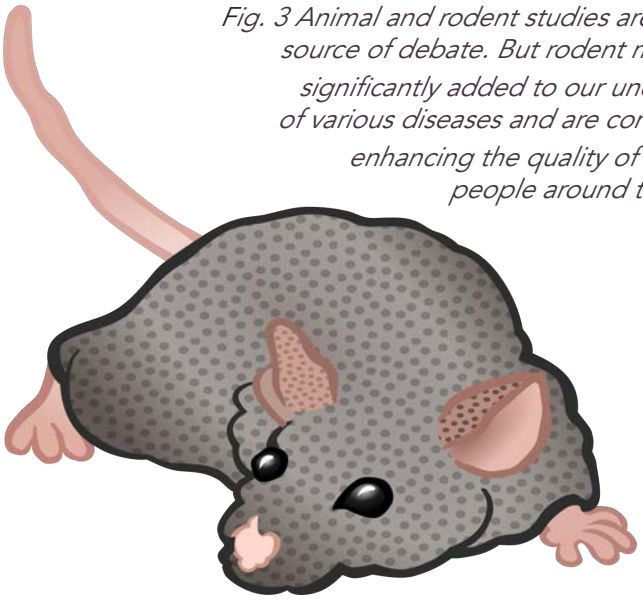

Fig. 3 Animal and rodent studies are a constant source of debate. But rodent models have significantly added to our understanding of various diseases and are contributing to enhancing the quality of life of many people around the world[9].

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

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

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

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

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

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

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

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

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

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

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

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

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

*character name of anecdote

Let's Get Natural

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

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

Berries on pxhere

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

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

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

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

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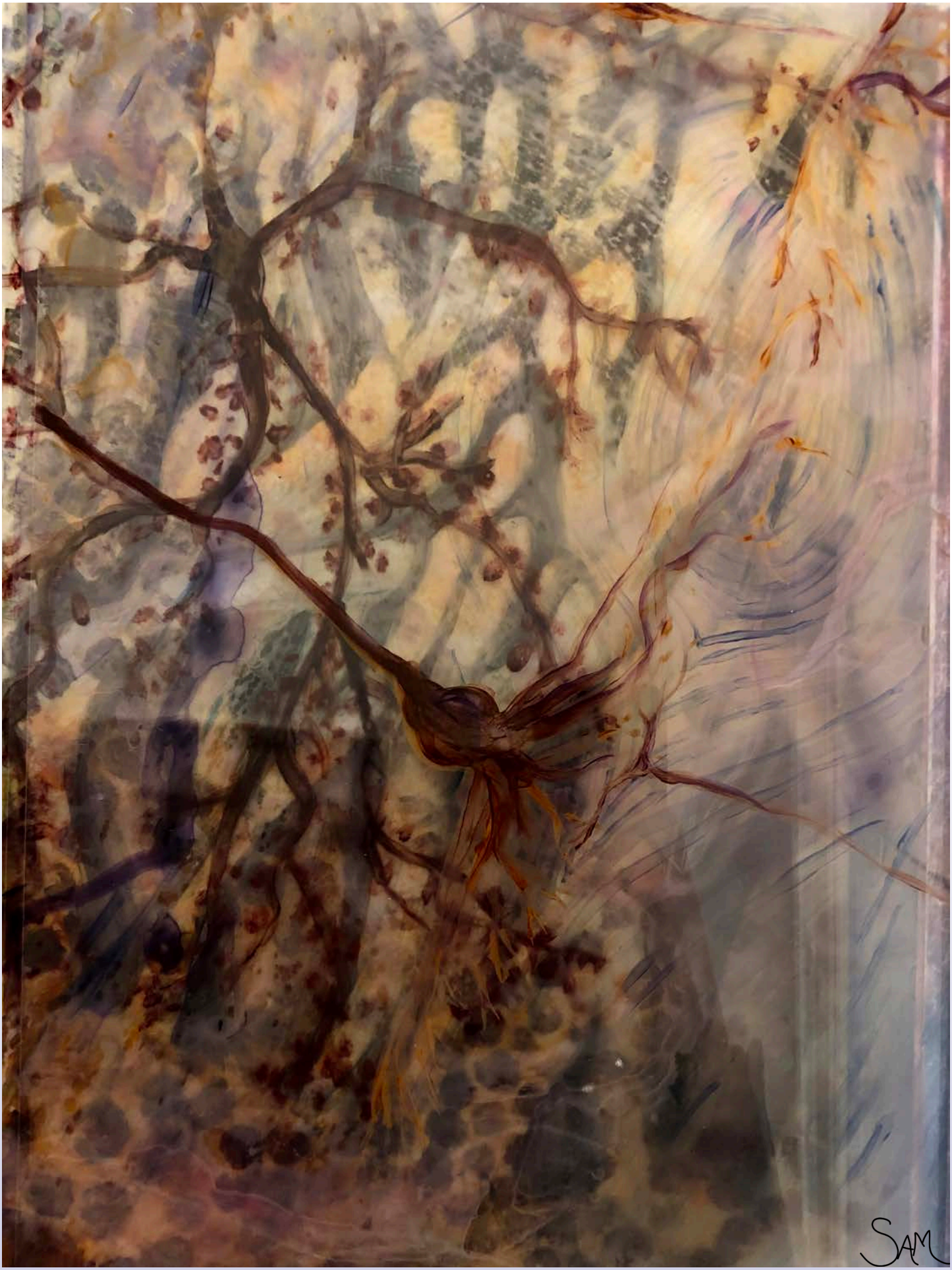

Retinal Ganglion Cell. Page from Images Formed in Darkness by Samantha Montoya