Taking a Peek at Our Brains:
Zombies, Mutants and Grandmothers

Thank you for that introduction. I work with many amazing colleagues who are gifted, inspiring teachers, and so it was a true surprise and honor to have been asked to give the Karofsky Encore Lecture this year.

Let me start with a brief story.

I am a total romantic about old houses. 15 years ago, my husband and I bought an old, federal-style house built in 1828 that needed significant work. Though we make a great team on many fronts, our combined skill set would not make us good candidates for an HGTV fixer-upper-type show.

A few years ago, with the help of my parents (who are here actually—hi mom, hi dad!), we were sprucing up a small interior bathroom just off our living room, painting the walls a cheery orange.

We also wanted to move the light switch from outside the door to inside the bathroom. My job was to drill a hole so we could move the wires. I carefully chose the proper height and location and started to drill.

When I broke through the wall, I bent down to look through the hole, obviously expecting to see my cheery new bathroom. I was shocked to see something entirely different. I was looking at an outdoor scene. I saw sunshine streaming down, a green tree, some purple flowers, and the white siding of a house. I stood up; I think I might have actually rubbed my eyes, and I peeped through the hole again. Sure enough, there it was again.

--pause--

For longer than any adult should probably admit, ….. I considered the possibility that I had discovered a portal to an alternate universe. As I turned over this momentous possibility in my mind. I was, very briefly, filled with a feeling of awe, of endless possibilities. I was overcome with a wild, intense, child-like wonder. I had goosebumps.

Stepping back and slightly to the side, while I dug around inside my head for Occam's razor, I looked up and out my living room window. What I saw was sunshine streaming down, a green tree, some purple flowers, and the white siding of a house. …. Obviously, I had missed the bathroom entirely, broken through into the living room and was staring, through this hole, out my living room window and into my yard.

What can we learn from this anecdote? Well, "measure twice, cut once" for starters!

I share this anecdote because it both captures the feeling I get when I learn new, amazing Neuroscience, and it is a decent metaphor for scientific research. When doing science, you design a hypothesis, carefully plan your experiment, then take the plunge—you drill that hole! When you finally peer at your results, often they are exactly what you predicted. Sometimes, the results are bewildering! Every once and a while, they are downright thrilling.

Perhaps the perspective-shifting experience of working on Neuroscience was why I was just a tad willing to consider the possibility that I had discovered an alternate universe. The feeling I had in that moment is the feeling I get when I learn something new about the brain—the wonder, the awe, the pondering of exciting new possibilities.

My students and I have experienced this type of moment a couple of times in my lab. I study how nerve cells recover from injury, and I focus on the auditory system of crickets, which remains particularly flexible and "plastic" into adulthood. Some of our experimental results have been expected. Others are interesting and manageable surprises. In other experiments we've completed, we have gotten results so far outside the range of our expectations that we don't even really know what we are looking at. Are these results a mistake? Just junk? Was my experimental aim off? Or, am I glimpsing something real and interesting that I don't yet know enough about to be able to interpret?

In my own research and teaching, I continually get to explore new worlds in the Neuroscience universe. As I planned this talk, I figured that I needed no more than 6 hours to give you a proper tour. My request for an extended speaking schedule was denied, (thanks a lot, President Rose), which forced me to make some tough choices. What I'd like to do today is to share 3 of my favorite neuroscience stories. My students will laugh, because I probably say every other day in class, "this is one of my favorite Neuroscience stories…"

Picking just three was an agonizing challenge. Should I talk about theories of language acquisition in babies? Or, what about the effects of recreational drugs on the brain? We could talk about how bats hunt insects at night using echolocation. Or perhaps how honeybees learn to remember a flower location. How about experiments where scientists are using cool new techniques, such as optogenetics and CRISPR/Cas, to tackle problems in incredibly inventive ways.

You can see my dilemma…

In the end, I have chosen three stories that have taught me something new and unexpected. I hope these stories surprise you

and give you new insight into who you are and how you interact with the world.

Act 1: Zombies…

With Halloween just a few days away, I want to start by talking about zombies. Imagine yourself at the Brunswick Farmer's Market on a Tuesday morning. You are out buying your kale and squashes. You don't notice but a fine dust-like substance is raining down on you from the trees above your head. You take your goodies home, go about your business, working, cooking, studying and having fun for a week. A week later, you are at the farmer's market again, when suddenly, in a zombie-like state, you head to the large tree in the middle of the farmer's market. Ignoring the questions from your friends, you walk around the tree to the side facing the Androscoggin river, and you climb 40 feet up. At that exact height, you find a branch, wrap yourself around it, and there you stay…. As you slowly turn into a fungus-spewing zombie!

This is indeed a true story, and it could happen to you--if you happen to be an ant.

Most of us know that ants live in colonies. As part of this colony, individual ants have a role that they faithfully execute—whether an ant is a worker sent to collect food, a soldier who defends the colony, or the queen herself, laying millions of eggs in her 30-year life.

(If I may add an aside, it is with some horror that I include these details. My youngest is an eager amateur myrmecologist, and he has had up to a half a dozen queen ants laying eggs in test tubes in our house. Queen ants live for 30 years??? Those are going to college with you, honey!)

If fungal spores drift down and land on a foraging ant, that ant might become infected. At first, infected ants go about their business quite normally. After about a week, instead of continuing to forage for food, an infected ant will feel compelled to climb up a plant, to a leaf that is just about 25 cm above the ground. This leaf is always on the North/NorthWest side of the plant. She will climb to the underside of the leaf, and she will locate a leaf vein. The zombie ant will then bite down on that vein in what is referred to as a "death grip" because she will grip this leaf vein continually, without moving, until she dies of the fungal infection growing inside her. While the ant doesn't fare so well, the fungus thrives. It turns out that the temperature and humidity 25 cm above the ground on the N/NW side of plants is perfect for incubating the fungus. If scientists move a leaf with a zombie ant lower or higher, the fungus doesn't thrive nearly as well.

As a neuroscientist, what most fascinates me about this story, is how the fungus directs the zombie ant behavior in such a specific way. How does the fungus get the ant to leave the colony, climb up a plant to just a specific height? How does it know south from north? One imagines little fungal cells pulling on levers, consulting dials, and pushing buttons to drive the ant like a robot. But of course, brains don't have levers, dials and buttons, so how does the fungus highjack the nervous system of the ant?

As with many neuroscience stories, this one is still developing, and we don't know the full answer yet. We do know a couple of things. The fungus converts most of the innards of the ant into sugars that it can digest. I say "most" because the muscles that control the jaw of the ant are spared. It is in the best interest of the fungus that the ant stay immobilized on the leaf, so these muscles stay put. Eventually, a stalk grows out of the back of the ant, forms a large fruiting body, which explodes, releasing fungal spores into the air, which fall on the unsuspecting, foraging ants below, thus creating more zombies.

In order to understand how the fungus alters the behavior of the ant, scientists have started to apply new, cutting edge molecular biology techniques to this problem. They can survey the genes expressed by the invading fungal cells as well as in the brain of the infected ant and ask how these differ from normal. Not surprisingly, many of the genes expressed appear to encode proteins or alter the release of chemicals (you can think of these as the dials and switches of the nervous system) that manipulate the functions of neurons within the ant's brains. Some changes to proteins and chemicals are likely to alter neuronal and muscular excitability or are even capable of killing off specific cells in the brains of the ant, which would change the behavior exhibited by the animal.

The zombie ant isn't an isolated example either. The emerald cockroach wasp attacks and stings a cockroach in the brain in such a specific manner that it creates an obedient zombie. The wasp is able to pull on the roach's antenna, walking the cockroach like a dog on a leash, to a den where the roach will remain immobilized and serve as a food source for the wasp's developing larva.

If you ever doubted that you are your brain chemistry, these stories might get you to re-think this a bit.

But insect brains and nervous systems are so simple compared to ours, right? Would it really be possible for humans to be manipulated so strongly by an invading foreign organism? The answer is a pretty clear yes. There are obvious examples where invasion radically changes human behavior.

One of the more gruesome examples is rabies. Humans who get infected by the rabies virus and do not get treatment, exhibit radically abnormal behavior before they die. They become

irrationally fearful, often of water. They hallucinate and often lash out at strangers for no apparent reason.

Another example is Ergotism, which is the long-term effects of exposure to the fungus Ergot. This fungus can infect rye and other grains. When humans ingest Ergot, they present with hallucinations, delusions, and convulsions. This is probably the result of the inappropriate release of serotonin in the brain. Some have even provocatively proposed that this fungal infection was responsible for the madness that engulfed Salem Massachusetts in 1692.

A more subtle example of our brain chemistry being manipulated by a foreign organism comes from investigations of our microbiome. The microbiome is the collection of bacteria that grows on our skin and in our gut. These bacteria are mostly beneficial and actually critical for our continued good health. New evidence suggests that these bacteria in our intestines can alter our anxiety levels, and possibly even influence the gene expression in our brains, thereby altering our behavior in subtle ways.

The zombie ants teach us that the expression of proteins and balance of chemicals in our brains can have profound influences on our behaviors. And, that these characteristics may not be completely in our control, but may be influenced by external invaders.

Act 2: Mutants:

If that example seems a little disturbing, here is another story that isn't so gruesome--the genetic control of brain development. The instruction manual for building your brain is built into your genes and you will pass it along to your children. All of us have a blueprint for a beautiful, complex nervous system, and though it

can be shifted by external events, your developing self knew exactly what to do at every stage.

It is difficult to appreciate the enormity of the challenge of growing a nervous system from scratch, and how such a magnificent and complex structure results.

As Gerald Fishbach, a pre-eminent neuroscientist, has so nicely put it:
"The brain immediately confronts us with its great complexity. The human brain weighs only three to four pounds but contains about 100 billion neurons. Although that extraordinary number is of the same order of magnitude as the number of stars in the Milky Way, it cannot account for the complexity of the brain. The liver probably contains 100 million cells, but 1,000 livers do not add up to a rich inner life."

In the developing human brain, after each nerve cell is born, it must migrate into its proper position, and send out little tendrils to neighborhoods near and far to make connections with the proper partners. These trillions of connections aren't made randomly, but instead in accordance with a plan that is mind-boggling in its complexity.

We could study the development of the brain in a number of different systems, but one of the simplest and most informative is found in the developing fruit fly. Early on the fruit fly brain is essentially a set of roadways that look like a ladder, with the sides of the ladder running parallel to the mid-line of the animal, and with rungs crossing the middle of the animal connecting the sides. Neuronal cells might be born on one side of the midline, but they are supposed to connect with cells in a neighborhood on the other side. They do this by sending a small tendril along their side of the ladder. But at some point, one particular tendril might need to turn onto a rung in order to cross to the other side.

So, today, I can announce the answer to the age-old question: "why did the neuron cross the midline?" 5.850 peer-reviewed scientific articles confirm that the answer is indeed: "To get to the other side!" You heard it here first, folks!

Of course, the most interesting question is not why, but how.

So, if I'm a scientist interested in the question of "how," what is the best way to approach this question? The answer is with mutants. Scientists purposefully but randomly create mutations in the genome of individual flies. They do this by hitting flies with X-rays or a chemical called EMS (ethyl methane sulfanate), which creates a variety of random mistakes in the genetic code. If these genetic mistakes are translated into proteins with mistakes, and the protein in question is important for development, we would see mistakes when we looked at the flies. In this case, if you are interested in the normal development of this ladder, you would screen lots of mutant flies for unusual looking ladders.

It should also be noted that labs often employ small armies of sharp-eyed undergraduates to sit at microscopes and sort through these thousands of flies! Once an unusual pattern is identified, neuroscientists work to identify the mutated gene and protein that gives rise to this pattern. From this, we can infer the normal function of that gene and protein in development.

This approach revealed that the midline was repelling our growing tendrils. We now know that the midline is made up of cells that release a protein called slit. A gradient is produced, with lots of slit right at the midline, and less and less as you move away. The tendrils growing on the side of the ladder can sense the slit—it is almost like they can smell it—they have receptors on the end of their growing tendril that sniff out this substance, and when they sense it, they avoid it, bypassing ladder rung after ladder rung.

So, what is a neuron to do? It is supposed to send its tendril across one particular ladder rung to get to its destination, but it senses this repellent at the midline and can't do it. Also, what if we think about this in the developing brain as a whole? Thousands and thousands of these tendrils are filling in this ladder, many with a specified destination on the other side. If the developing brain were to turn off the repelling slit at the midline, chaos would ensue—all the tendrils might cross or even re-cross the midline at one particular time, however high up the ladder they had grown, instead of at the proper time and place for them to make it to the correct neighborhood on the other side.

Well, the answer is that each particular tendril turns off its slit receptors—just removes them from the growing tip—at just the proper time and place. In essence, it flies blind for a while—at least blind to the slit—and is able to turn onto a ladder rung to get to the other side. Once there, it must turn its slit receptor back on so that it now stays on THAT side of the ladder and doesn't accidentally cross back over the midline, preventing it from arriving at its destination.

This story is oversimplified, obviously—there are likely dozens of cues in and around the ladder that this tendril is paying attention to simultaneously, but this slit story, in isolation, gives you a good picture of how we think the developing system coordinates the growth of its thousands or, in a human brain, its hundreds of millions of neurons.

Once again, you might be thinking, "interesting, but this is in a fruit fly—big deal!" Well, it turns out that the protein slit as well as the receptor for slit are both found in us humans as well. There is even a known disorder that is a result of a mutation in one of these proteins. "Horizontal Gaze Palsy with Progressive Scoliosis" is caused by a mutation in the human version of the slit receptor. In

this disorder, the growing tendrils in the brain can't sense the slit because they don't have a functional receptor, and they get a bit lost as they grow. One of the main results of this is a disrupted visual system.

Slit itself has another known function in humans, which is to suppress the growth of tumors. When the slit protein is mutated or lost completely, people have an increased risk for some particular types of cancer.

There are a couple of broad lessons we can pull from this vignette, beyond the super-cool neuronal development piece. First, basic research is incredibly important. The story I told you about the developing fruit fly brain taught us something about an unusual human disorder and some types of cancer, though the people who did this research weren't researching cancer or any other human disorder. The knowledge accumulated about these proteins as a result of basic research over nearly two decades helped the relevant health research in humans go that much more quickly. It is nearly impossible to predict how and when basic research will be directly useful to humans, but it happens routinely.

For students asking fundamental questions about how various biological systems work, and there were beautiful examples of this on the posters this afternoon, the importance of basic research should be an inspiration. Others will build their work on yours, and who knows, you might even discover some important key that will be used years from now to unlock a human disorder.

The other lesson I like to pull from this story is about barriers. The slit barrier is a very real barrier, and very important. If you genetically alter it—mutate it in a fruit fly—you create a big mess—an interesting and informative mess for the scientist—but certainly a mess for this particular organism. So, this barrier is a positive and important and necessary thing---until it isn't. Each

cell that must cross needs to make the decision to simply ignore the barrier for a bit, pretend it is not there, even though the barrier itself hasn't changed one bit.

I like thinking about barriers in this way. They can be important, helpful, and useful, but there might be a time—at just the right time and place, that barriers just need to be ignored and vaulted right over as if they weren't even there.

Act 3: Grandmothers

In this last story, I'll turn our attention to the human brain. Many neuroscientists think that the human brain is where it is AT!

For example:

Nobel laureate Stanley Pruisner has said:
"Neuroscience is by far the most exciting branch of science because the brain is the most fascinating object in the universe."

Others have referred to the human brain as "the organ of destiny" or an "enchanted loom."

This is all quite lofty, but I think my personal favorite comes from Richard Gregory, who is known as one of the founders of Cognitive Psychology, and who said
"One of the difficulties in understanding the brain is that it is like nothing so much as a lump of porridge."

So, how does one investigate this 3 lb "lump of porridge?" And more philosophically, is it even possible for us to use our brains to understand our brains?

Emerson Pugh, a computer scientist who spent most of his career at IBM, put this conundrum this way:

"If the human brain were so simple that we could understand it, we would be so simple that we couldn't."

Nevertheless, many scientists are trying to use their brains to study our brains. They do this in many different ways, but the example I'd like to talk about today starts with a simple question:

How do you recognize your grandmother?

Many years ago, as scientists were beginning to think about this specific problem, they proposed what has become known as the "Grandmother Cell Theory." The basic idea here is that all the information about your grandmother is stored in a neuronal circuit that is shaped like a pyramid. At the bottom are many cells that store bits and pieces of information about your grandmother. Perhaps the color of her hair or eyes, or what her voice sounds like. The theory proposes that these neurons then converge by sending their information to new cells, and this results in the creation of more and more sophisticated neurons that start to put all the parts of your grandmother together, until, at the top of this pyramid, is a master cell of sorts, or more plausibly a relatively small network of cells, that is responsible for the perception and recognition of your grandmother as a whole.

On the one hand, this idea makes a lot of sense, since we know that there *are* neurons like those at the bottom of the hypothetical pyramid, which encode pieces and parts of stimuli. But, there are some obvious problems with this theory as well. Can you really represent something complex like your Grandmother with one cell or even a sparse network of cells? What would happen if a few cells at the top of the pyramid died? Would you lose the ability to recognize your grandmother, but be able to recognize everyone else?

The idea of the Grandmother Cell was proposed in the 1960's, and since that time, people have found cells in the human brain that do recognize faces, but they respond to ALL faces, not just the face of one individual. The Grandmother Cell theory was used mainly as a strawman in theoretical arguments until just over 10 years ago, when neuroscientists found something incredible. Surgeons and scientists were "listening in" on the activity of individual cells in one particular patient's brain as she looked at pictures or did other activities. These scientists found what for all intents and purposes appeared to be a "Grandmother cell," though it didn't respond to pictures of that patient's grandmother, instead, it responded to pictures of…….Jennifer Anniston.

Let me back up and explain why they were spying on this patient's brain. The patient in this case had severe epilepsy. In some rare individuals, after finding that drugs won't help to control the seizures, the patient can opt to have surgery to remove the diseased portion of their brains. An important part of the planning for this surgery includes mapping the patient's brain, identifying the diseased area as well as regions critical for speech or motor control. To do this mapping, the surgeons can implant tiny electrodes, each less thick than a human hair, and listen in on neuronal chatter as patients go about their business. Many patients also volunteer to be involved in some experiments during this pre-operative phase, so they spend some time in front of a computer looking at pictures, watching movies, or listening to music while scientists record the activity of a bunch of cells in their brains.

In the process of showing one particular patient lots of images—of tools, animals, faces and places, they were having trouble finding anything that the cells they were recording from were interested in. And then, Jennifer Anniston's face popped up on the screen, and one of the brain cells they were recording from responded like crazy. The scientists presented the faces of several other people, famous and not, but got no response. In fact, this cell responded to

something like 12 different pictures of Jennifer Anniston, from different angles, wearing different colored outfits, and in different locations.

It turns out, this wasn't a fluke thing. In other patients, the doctors found cells responsive to Halle Berry, Bill Clinton, Oprah Winfrey, Julia Roberts, Kobe Bryant, and even Luke Skywalker. And, it wasn't just the faces that these cells responded to. For example, the Halle Berry cell they found responded to Halle Barry in a cat woman suit, images of Halle Berry in various movies she has been in, and even to the words "HALLE BERRY." In another patient, the Luke Skywalker cell responded to the spoken name, Luke Skywalker, and also to a picture of Yoda. Obviously if the patient had never seen or heard of these movie stars, presumably their representations would not be lurking in their brains. But, what was this individual cell doing responding to a single person or concept? Is there a single Jennifer Anniston cell?

More fundamentally, is this a so-called "Grandmother Cell?"

The answer is probably a bit "yes" and a bit "no." For sure there is not a single Grandmother cell, but a small network of cells encoding a concept is likely. Modeling studies have predicted that a network of about 15-20,000 cells could be sufficient to encode the concept of Jennifer Anniston.

The scientists who discovered the Jennifer Anniston cell have newer experiments that they think tell us more about how memories are formed. In the same patients that they find, say a Jennifer Anniston cell, they can show that patient a picture of Jennifer Anniston at the White House. After only a single viewing of that picture, the Jennifer Anniston cell will now respond to a picture of the White House too, effectively adding to its concept of Ms. Anniston. The theory is that both concepts, Jennifer and the White House, are encoded by pre-existing networks. The visual

presentation of a connection causes the brain to make a new association that essentially links two existing concept networks together.

So, while these experiments are on small numbers of cells in an even smaller numbers of people, it is changing how we think about the ways in which our brains encode information.

Families, parents, and relatives, even though your kids may be far away, rest assured—you are represented in a neuronal circuit within that student's head. You are a constellation within the universe of their minds.

Thank you, families, for helping to shape the growing minds of the students here at Bowdoin. You have enriched their lives; be assured that their selves and indeed their brains are a physical manifestation of your love and care.

And students, you carry all the important people from your life in the circuits of your head. It is true that beloved family members might be represented on par with your favorite singer or movie star, but they are all in there, and you take them with you wherever you may travel.

Thank you, Bowdoin students, for being such a joy to teach, and a hearty congratulations on the honors received today. I thank you especially for the classroom light bulb moments that feed my soul.

I hope that these stories have given you a glimpse into the world of Neuroscience that I love so much. My wish for you is that you will find the academic subject that makes you feel as if you've discovered an exhilarating new universe—that here at Bowdoin, you will find that portal to a new, exciting intellectual world—whether it be, music, literature, history, or science. May you get goosebumps as the features of this universe reveal themselves to

you. This new knowledge might even help you understand yourself and your world a little better every day.

Thank you…