

mind

Issue 3: Age | Spring 2020



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Letter From the Editors

Dear Reader,

What you see before you is something much more than a magazine. On these pages, you will see late nights in the library, caffeine-fueled brainstorming sessions, and rousing debates about the relationship between our brains and technology. You will see a team swept up in a global pandemic, putting our campus and the whole world on pause. And most of all, you will see the passion in our writing.

This issue of Mind builds upon the strides made by its predecessors. Issue 2 saw Mind become a shared resource of the Neurotech community, and while it featured a collaboration between UCLA and UC Berkeley, its distribution was confined to print. Issue 3 is fully online, allowing anyone who has an interest in neurotechnology and a working Internet connection to engage with the ideas it presents. This shift was made with our commitment to equity in mind, as well as our desire to facilitate communication, not just education.

Moreover, Mind is no longer confined to the United States. Featuring submissions from Germany to Canada, Issue 3 is a fully global publication.

This iteration of Mind also pushes the content in a new direction. Each Issue of Mind will now have its own theme, voted on by the writing team at Neurotech@Berkeley. This semester, we decided on Age, grappling with everything from memories to education to pop culture.

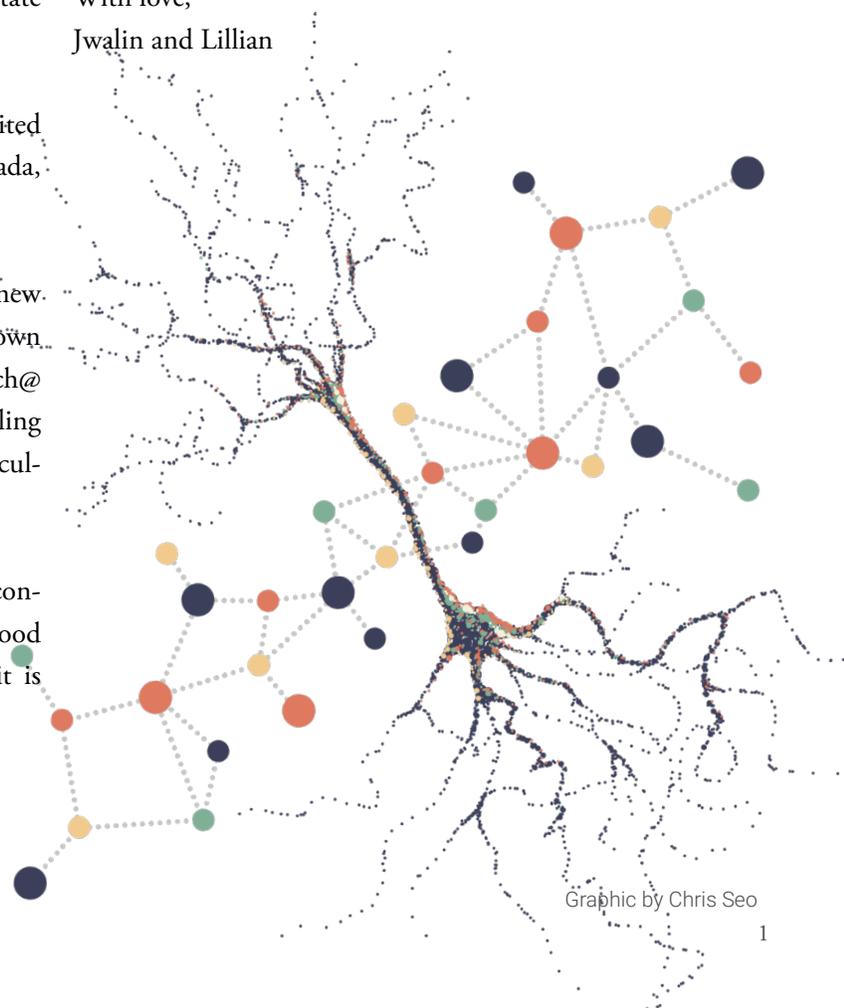
Through this lens, we explore the brain within the context of a human life: from childhood through adulthood and old age. We decided to explore age because it is something that unites us all. We all have childhood

passions, fears about death, and a hesitation to surrender our most precious asset, our mind, to the constant march of technological innovation. Through this issue we hope to give you the tools to look inward and ask yourself the big questions, and then hopefully share your answers with us down the road.

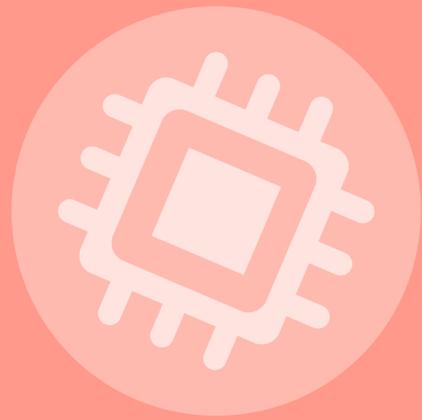
For now, we are extremely grateful to our writing and design team, who have braved the fears of a global pandemic and the logistical terror of remote work to pour themselves into this issue. We are honored to have been able to work with all of you.

Now we present to you Mind, Issue 3: Age. May what is within expand the horizons of your psyche and make you think as much as humanly possible.

With love,
Jwalin and Lillian



Graphic by Chris Seo



YOUTH

"Youth is a dream, a form of chemical madness."

F. Scott Fitzgerald

The Lost Memories Of Infancy

Why Childhood Amnesia Is Weird

By Michael Xiong

If you, like me, are no longer a child (on the outside), you probably don't remember much from anything earlier than preschool. At first, this fact may not seem very surprising. After all, memories fade over time. But there is something special about memories made during those first few years after birth. Teenagers and adults seem to have equally poor memories of their first three years of life, while their memories of the years afterward remain rather stable.¹

This phenomenon, the disappearance of memories from roughly the ages of zero to three, is called childhood or infantile amnesia, and it presents a paradox. Nobody is quite sure whether or not it serves an evolutionary purpose. But to learn why this is such an unusual occurrence, we must first learn about memory.

Typically, we divide memory into two broad categories. One is called declarative, and the other is called nondeclarative. Declarative, or explicit memories are the ones that you can recall at will. They can be episodic—memories detailing events—or semantic—memories detailing concepts and ideas. These are what you use when you take a test or tell a goofy story to your friends. These are also largely the kind of memories wiped out by childhood amnesia.

Nondeclarative, or implicit, memories, on the other hand, do not seem to suffer the same fate¹. These memories are what you might call “skills,” and are most often drawn upon instinctively. You do not need to be focused when you summon these memories. When you walk, you do not need to remember the correct pattern in which to move your limbs, or think about

the tiny adjustments needed to stay in balance—which is actually no small feat (ha) for a biped. The same is true for riding a bicycle, and, if you play the piano, for pounding out the keys to your favorite song. Many of these skills, such as locomotion and language comprehension, were most likely taught to you at a very young age. An age that you can no longer remember. The fact that childhood amnesia applies to declarative memories and not the nondeclarative ones is not fundamentally surprising. It has been known that these two

forms of memory are consolidated differently ever since the study of a patient named Henry Molaison (H.M.), who underwent a surgery removing areas of his hippocampus in 1953². Following the operation, H.M. was unable to form new declarative memories (anterograde amnesia) but was still able to develop motor skills, growing better at tasks that he could not recall performing².

Given this fact, it might be intuitive to wonder if infants suffer from a similar condition. One theory

to explain childhood amnesia is that the hippocampus is not yet well developed enough during infancy to properly form long-term memories. Studies in both humans and animals show that the hippocampus is one of the last regions of the brain to finish development³. In addition, the whole of the cerebral cortex—the folded surface of the brain—also experiences slower development. However, it is not as if infants cannot form declarative memories at all. Three year olds can recall their declarative memories, and up until around the age of 8 or 9, most children still retain declarative memories from their earliest years.

This progression can be measured with the “cue word” testing method, in which a subject is asked to recall their earliest



Graphic by Amy Wang

1 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5473198/>

2 <https://www.brainfacts.org/In-the-Lab/Tools-and-Techniques/2018/The-Curious-Case-of-Patient-HM-082818>

3 <http://learnmem.cshlp.org/content/19/9/423.full.html>

memory in association with a particular word⁴. The veriticity of this memory is confirmed by someone else, most often a parent in this case. At 7 years of age, 60% of children can recall something from before the age of three. At 9 years old, however, only 36% of children were able to remember anything from before three years old³. Another study conducted with the cue word method found that infantile amnesia can be explained, at least in part, by an increasing retention time for memories with age⁵. This means that, although an infant can form declarative memories, these memories are forgotten more quickly than those of an older child. In fact, memory retention time seems to increase linearly with age up to 20 months. This study was also replicated in rats, where memory retention could be measured with their performance in a task in which they had been trained before.⁶

Scientists have investigated other explanations for this disappearance of memory, which are often related to the underdevelopment of the hippocampus. One theory poses that memory retrieval, and not memory formation, is the real culprit behind childhood amnesia. Somehow, memories from before a certain age may not be gone, but rather are stored in a way that cannot be retrieved. This is supported by studies showing that, when a subject is asked to recall a certain event frequently, their memory of it can persist through childhood amnesia. This inability to retrieve memories may be caused by great changes in the hippocampus or cortex due to their development. A 2012 study found that the rapid creation of new neurons in the hippocampus, called neurogenesis, is correlated with a drop in the retention time of memories. In addition, animals that are more fully developed after gestation, such as guinea pigs, appear not to experience infantile amnesia. For comparison, a guinea pig's brain only increases in weight by about 60% following birth, while that of a rat (which does experience infantile amnesia) grows by 600%.

Another, related, theory is that memories formed during toddlerhood lack an “autobiographical” point of view. This can be due to both the lack of a “theory of mind” and a lack of complete language skills. Theory of mind is the ability to be aware of yourself and others. On a basic level, this means recognizing yourself in a mirror, but human capacity for theory of mind goes much deeper, and includes understanding the thoughts and motivations of others. This ability is not com-

plete in young children, and this could mean that the memories formed during this period are not seen as a memory concerning oneself. In addition, language skills may also lead to a lack of autobiographical recollection. Once language skills are completely formed, language becomes central to how the brain thinks and tells stories. Without complete lingual ability, it is possible that a young brain does not store its memories with the same structure of language that is crucial to how an older brain recounts events. These theories however, seem very specific to humans, and would not explain the infantile amnesia observed in other animals, such as rats. Although they may have some merit, it appears likely that biological mechanisms are the forefront cause of childhood amnesia.

Does it Have a Purpose?

Freud was one of the first people to ponder the significance of infantile amnesia. Oddly, Freud believed that this forgetfulness was a coping mechanism for “psychosexual trauma.”⁴ The idea of memory repression, however, has been largely disproven, not to mention the disturbing implications Freud's idea has regarding the experience of most infants.

Gladly, most infants are not exposed to trauma, because, while declarative memories from this time seem to disappear, childhood experiences—such as neglect and trauma—can have lasting effects on how the brain is structured. The first few years, after all, are a “critical period” of brain development, where certain skills—such as language—develop at a rate unseen in adults. Critical periods are defined as “temporal windows of development during which the brain is particularly sensitive and responsive to experience. One proposed explanation for childhood amnesia is that it occurs due to a critical period of development for the hippocampus. In other words, the early struggle of the hippocampus to form long-lasting memories is necessary for its development.

So, as nostalgic as it would be to remember our first words or other early milestones, perhaps forgetting them has been for the best for our brains. For now, however, childhood amnesia is as much of a mystery as the early experiences it has evicted from our minds⁷.

⁴ <https://www.psychologytoday.com/us/blog/media-spotlight/201404/exploring-childhood-amnesia>

⁵ Rovee-Collier C. 1997. Dissociations in infant memory: Rethinking the development of implicit and explicit memory. *Psychol Rev* 104: 467–498.

⁶ Campbell BA, Campbell EH. 1962. Retention and extinction of learned fear in infant and adult rats. *J Comp Physiol Psychol* 55: 1–8.

⁷ <https://psychcentral.com/blog/childhood-amnesia-why-cant-we-remember-the-early-years/>

Learning Disorders and Education Policy

By Josephine Tai

While our ancestors were born with brains that have a natural ability for speaking, Dr. Vera Blau-McCandliss, a cognitive scientist specializing in education research, reveals that reading is “a relatively new and unnatural phenomenon.” That’s why reading is a task that is hard to learn and teach. And for children with the learning disorder dyslexia, this task is even more challenging.

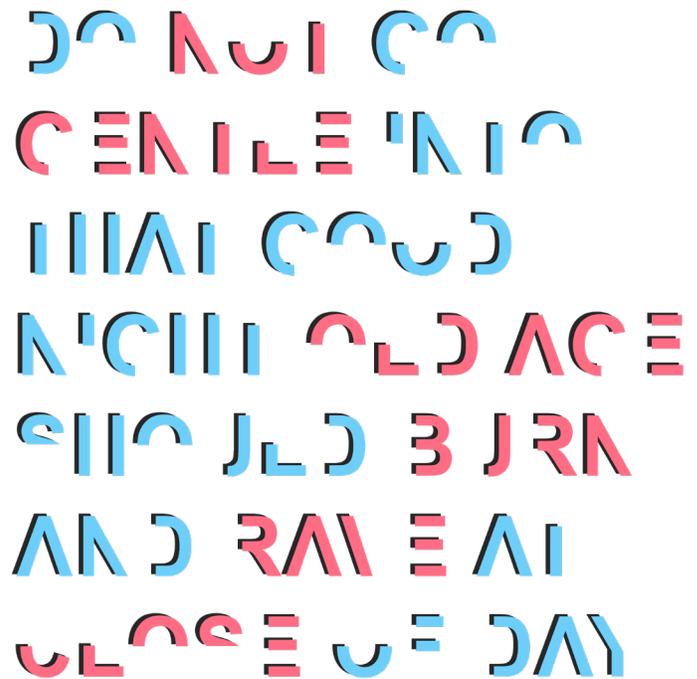
Overview of Learning Disorders

According to a comprehensive 2014 study done by the National Center for Learning Disabilities, an estimated 2.4 million students enrolled in the American public school system have been formally identified with a learning disorder, as defined under the Individuals with Disabilities Education Act. That number represents five percent of the total public school enrollment. But given the problems surrounding the diagnosis of learning disorders, that percentage is likely an underestimate.

Numbers aside, learning disorders significantly impact young children, and the current public school system is struggling to properly support these neurologically diverse learners.

Learning disorders are broadly defined as conditions that are rooted in genetic and/or neurobiological factors that change brain functioning in a way that impacts learning and cognitive processes related to learning. When a child has a learning disorder, they may have difficulty in acquiring or developing written language, oral language, reading, or mathematics.

There are five main types of learning disorders that are commonly recognized: dyscalculia, dysgraphia, dyslexia, oral/written language disorder and non-verbal learning disabilities. These disorders should not be viewed in isolation. In fact, the co-occurrences of these specific learning disabilities are all too often a reality and ADHD, dyspraxia, and executive function disorders are commonly associated with learning disorders.



Graphic by Chris Seo

What is Dyslexia?

The most common learning disorder is dyslexia. While dyslexia is often portrayed as simply reversing the position of letters or words - such as switching b’s and d’s or reading “was” as “saw”, there is a lot more to the story. The Greek root dys- means “bad, ill, difficult” and lexia means “a word.” When put together, dyslexia literally means “difficulty with words.” Broadly, dyslexia is a learning disorder that involves difficulty with reading and language-based processing skills. The formal definition of dyslexia developed after 25 years of research by the International Dyslexia Association is:

“Dyslexia is a specific learning disability that is neurobiological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede growth of vocabulary and background knowledge.”

Neurological Basis of Dyslexia

At the cognitive level, many dyslexic children have difficulty in some aspects of processing speech sounds and their mental representation, called a phonological deficit. Since dyslexic symptoms depend on the consistency of mapping between letters and sounds in alphabets, dyslexia manifests in different ways depending on the child's primary language.

But at the neurological level, dyslexia always impacts areas of the brain that link letters to speech sounds. While there isn't a single location in the brain that serves as the "reading center," most of the brain areas that are involved in language processing and reading are found in the left hemisphere.

More specifically, dyslexia researchers are focusing on two systems in the left hemisphere that are involved in language processing within and between lobes. The first is the parietotemporal system which is used in the conscious act of decoding a word, the act of mapping letters and words into letter sounds and spoken words. In practical terms, this is the area of the brain that is active when we are sounding out words. After some time, our brains get the hang of the decoding process for a word and the visual cortex begins to recognize it by sight. This is where the second system involved in reading becomes important: the occipitotemporal area. As part of the visual processing center of the brain, the occipitotemporal area is critical for fluent reading because we can train this area to visually recognize letters and words, almost automatically.

Imaging of dyslexic brains reveals that both the parietotemporal and the occipitotemporal systems are underactivated; as a result, individuals with dyslexia struggle with understanding how words and letters are related to sound and language.

Structural differences have also been observed in dyslexic brains. The brain is mainly made of gray matter, which is composed of chiefly nerve cells and whose primary function is processing information, and white matter, which is composed of myelin-coated connective fibers and whose primary function is information transfer. Individuals with dyslexia have decreased gray matter density in the left temporal gyrus as well as decreased white matter volume in the left arcuate fasciculus. While having less gray matter in the gyrus could cause language processing problems, having less white matter

in the fasciculus could cause problems with communication and information transfer between the parts of the brain that link letters and speech sounds.

Genetic Basis of Dyslexia

While dyslexia has a substantial genetic component, for years researchers struggled to determine the root cause. However, in 2013, Dr. Jeffrey R. Gruen, professor of pediatrics, genetics, and investigative medicine at Yale conducted a study of the genetic origins of dyslexia that could allow for earlier diagnoses and better interventions. After analyzing data from more than 10,000 children, Gruen and his team identified genetic variants that can predispose children to dyslexia. Some variants of a gene regulator called READ1 are associated with difficulties with reading while other variants are associated with problems in verbal language.

Current Problems with Diagnosis & Treatment

The prerequisite to being able to help treat young children with dyslexia is to be able to identify that there is a developmental problem in the first place. However, there are issues with the way the current education system and society as a whole deals with learning disorders that cause ambiguity in diagnosis and treatment.

While 46 states in the US have passed legislation related to dyslexia, the policies are not uniform. On one hand there are states such as California that are increasing funding allocation for special education services including dyslexia while on the other hand in states like Michigan, dyslexia is just getting its first mention in law. Worse, there is a lack of accountability and funding and widespread confusion about how the policies should be implemented in practice. Ultimately, these issues hurt dyslexic children and leave families to fend for themselves in trying to best support their child's education.

Problems with Diagnosis

While there has been a lot of research into genetic linkages and functional and structural differences of dyslexic brains, there is still a lot of ambiguity how children should be diagnosed with dyslexia.

Over the years, there have been several changes in the model that educators use to define and diagnose dyslexia. Prior to the amendments to the Individuals with Disabilities Act in 2004, it was generally accepted that dyslexia and other reading disabilities should be identified by discrepancies between aptitude determined through IQ tests and achievement. However, the problem with this approach is that studies have shown that poor readers with and without the discrepancy between aptitude and achievement performed similarly on phonological processing skills that are fundamental to reading.

The low achievement model has also been proposed to diagnose dyslexia however there are issues with this model as well. For example, it would be hard for teachers, administrators, and parents to differentiate between a low achieving student and a student who hasn't been given the proper instruction or education.

The high subjectivity of these models make them vulnerable to individual teacher and administration biases and exacerbate the long history of racism, classism, and stratification in the education system. In fact, in the paper "Disproportionality and Learning Disabilities: Parsing Apart Race, Socioeconomic Status, and Language," researchers Dara Shifrer, Chandra Muller, and Rebecca Callahan write that while federal guidelines talk about learning disorder diagnosis through a medical lens, the fact that disproportionate identification of learning disabilities occurs among groups that are already socially disadvantaged suggest that "diagnoses may be operationalized through a social or functional perspective." Some attribute the disproportionality to racism, the rejection of minority cultures by dominant cultures and the cultural biases of achievement assessments while others attribute it to economic factors. In either case, the subjectivity and ambiguity of these methods of diagnosing learning disorders are at the root of the problem because they are what enable these biases to manifest as diagnoses.

The most recent approach to diagnosing dyslexia is called the Response to Intervention or RTI model. RTI is a three-tier approach to the identification and support of students with learning disorders. The first tier involves providing high-quality classroom instruction and periodically screening students to establish an academic and behavioral baseline and to identify students that are struggling. The second tier involves targeted interventions. And the third tier involves individual, intensive

interventions, and comprehensive education. And at any point in time, parents or guardians of the student are able to request a formal evaluation to determine eligibility for special education. RTI is a general guideline that is given to schools to follow.

However, many school districts in the US struggle to properly implement RTI. The challenges come from lack of funding, resistance to change from staff members, and most importantly, lack of training and development for teachers and administrators.

On a broader level, another issue that plays a huge role is the accessibility of diagnostic tests and formal evaluations for learning disorders such as dyslexia. In order to officially diagnose a child with dyslexia, a formal evaluation must be done. However, even if parents and guardians request that the school do some testing, because of how expensive, time-consuming and in-demand these tests are, coupled with the shortage of qualified psychologists in American public schools, schools are often resistant. In cases like this, some parents resort to expensive private testing, an option that many families find to be too great of an economic burden to bear.

Problems with Treatment

The problems do not just stop with the diagnosis. Even after young students identified with a learning disorder are given an Individualized Education Plan (IEP), there are barriers that prevent these children from getting the educational support that they need.

In addition to lacking the knowledge to properly educate neurological diverse students, the reality is that public school teachers are often overworked and undertrained. While teachers get a copy of a student's IEP in the beginning of the school year, these documents are lengthy and teachers may simply lack the training and time to alter their teaching methods.

In the end, these young students with learning challenges are the ones that get tossed aside and lost in a system that unfortunately isn't built to properly support their needs and their education.

Solutions & Moving Forward

With the help of neurotechnology and improvements in education policy, the reality for these young children with learning disorders can be drastically improved moving forward.

Neuroimaging

Researchers and educators can (1) utilize multimodal neuroimaging to diagnose dyslexia and (2) identify neuroimaging markers to predict future academic outcomes and detect children at risk early on. Providing a neurobiological model of diagnosis and evaluation can be helpful in decreasing the subjectivity of current diagnosis models and ultimately, help combat the inequalities in the education system and disproportionality of learning disorder identification amongst socially disadvantaged groups. Moreover, these powerful images can serve as illustrative tools to improve communication of neuroscientific research to educators, policymakers, and the community at large.

Education Policy

In terms of education policy, teachers, administrators, and campus psychologists need to have access to better training, funding, and resources to best help these students and identify their challenges. There also needs to be a paradigm shift in the way teachers approach teaching and education in general. Educators need to recognize the idea that each learner is a unique individual with a unique set of challenges and more wholly value and embrace neurodiversity. Only when educators recognize this will the education system be able to truly support individuals with learning disorders.

The education system is failing its most vulnerable, and it will continue to do so without sweeping changes in the way we approach learning disabilities and neurodiversity. —○

Seb's Favorite Color

Age-Different Reinforcement Learning Strategies

By Malachi Tran, Jwalin Joshi

Math helped me learn Sebastian's favorite color. It was green. The color his favorite cartoon alligator from weekend television--like *green peas and matcha* he'd exclaim! To him, something made sense or it didn't. To him, everything green made sense to be in his world, and it took math to help me be a part of it.

Computer models are a growing approach to understand behavior. Rooted in computer science, neuroscience, and psychology, scientists have created equations and multi-step algorithms as a way of mathematically explaining why humans think and do the things they do. Reinforcement learning is a notable area of machine learning, an area teaching machines to think like us, helping us realize differences between children, adolescents, and adults that we may not have discovered otherwise.

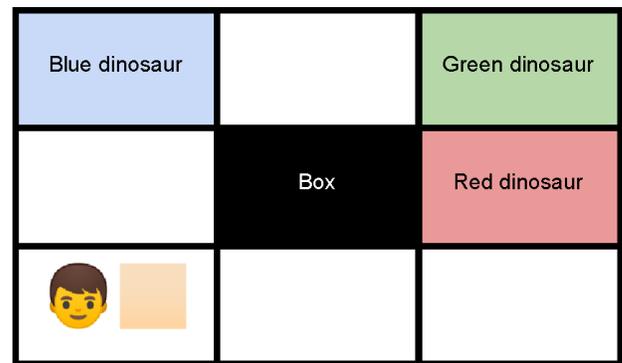
Before Sebastian could walk, he'd stare at the trove of toys around him and crawl to anything with funny textures. One minute he was scrambling to his bumpy legos, and the next he had a couple of scaly dinosaurs in his hands. He'd move back and forth, from spiky plastic soldiers to round cars, circling all around. He was curious about the room and his toys, and I was curious about him.

In psychology, reinforcement learning refers to strengthening or weakening a connection between an action and its result, whether a reward or punishment. In computer science, reinforcement learning is concerned with not just obtaining a reward, but how to obtain the greatest amount of reward possible. This reach for the most (and sometimes the least) out of something is mathematically known as optimization, and in this case, we want to maximize the obtained reward.

I didn't realize Sebastian wasn't actually interested in how the toys felt. He was just paying attention to their colors. And he always sought the green toys. Whether they were dinosaurs or donut-sized rings to stack on top of each other, I loved see-

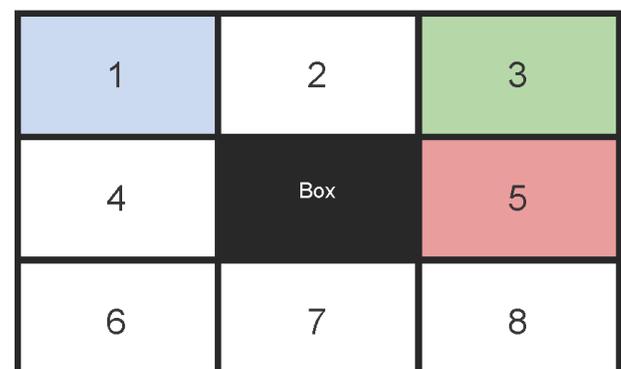
ing how excited he got to finally sit down and enjoy his green things. Sometimes Seb settles for his blue figurines, but cannot stand anything red. I wanted to test my ideas, so one day, I placed different colored dinosaurs -- a blue, a green, and a red -- in different areas of the room. I put a box in the center of the room so Seb wouldn't immediately be able to see what I thought was his favorite color. If every square was a possible area Seb could crawl to, the room would look like this:

Sebastian's Playroom



A typical reinforcement learning model has an agent, a set of actions A , a set of states S , and a set of rewards R . The agent, capable of interacting with the environment, performs a number of different actions in a number of different states, in such a way to maximize the amount of reward obtained at the end. Sebastian is the agent and his playroom is the environment. His movement to each area are actions, and each area is considered a different state. Every dinosaur Seb encounters is a reward, and as a special definition in computer science, a reward is (1) a numerical value and (2) either positive or negative, meaning that a reward can also be undesirable to the agent. Let's label the areas in Sebastian's playroom:

Areas of Sebastian's playroom mapped as states



In an unchanging, or *deterministic environment*, each reward (dinosaur) holds onto its assigned reward value. This means that every time Sebastian encounters one of the dinosaurs, he greets them no better or worse than when he did yesterday, or last week. Knowing what type of environment the agent is in is important because the ability to move to a different area (state) after performing an action a in the agent's current state s , calls upon different mathematical formulas.

In a deterministic environment, the agent uses the *Bellman Equation*:

$$V(s) = \max_a (R(s,a) + \gamma V(s')) \quad (1)$$

where,

- s = a particular state (Seb's playroom)
- a = a particular action (moving between areas)
- s' = the next particular state
- γ = discount factor (how significant Seb considers the value of the next state)
- $R(s,a)$ = reward function
- $V(s)$ = value of a particular state

The Bellman equation assigns a numeric value to each state, indicating how close the agent is to maximizing his reward. In this case, it takes in Seb's position and returns a number that describes how close he is to the green dinosaur. It does this by considering all possible places that Seb can move to and calculates the reward that results from the states that arise from those actions. This form of reinforcement learning is called Q-learning, and it utilizes something called a Q matrix.

A Q matrix is a table that remembers important details about specific areas and actions, and Q-learning works by updating the table as it traverses through states. We mathematically call these important details the quality of the state and the corresponding action.

Before we dive into how the table is updated it's important to define our reward function. The reward function tells us the reward corresponding to a certain state. For example, if we wanted to teach a computer to play chess, we would assign higher rewards to positions that are favorable, and assign an extremely high award to a checkmate. In the case of Seb, let's keep things simple. He gets 10 points for finding the green dinosaur because it is his favorite. He gets 2 points for the blue dinosaur, because it is just okay, and -10 points for the red dinosaur,

because he really doesn't like red. The non dinosaur squares are assigned 0 points.

Okay, now that we know how much each square is worth, we can let Seb go and explore right? Well, not really. Even though we know the value of each current square, we want to be able to take into account the potential future actions that Seb can take given his current state. For example, squares 2 and 8 both have rewards of 0, but square 8 is next to a red dinosaur and square 2 is in between the green and blue dinosaurs.

Seb would much rather be in square 2 than square 8, because the future actions he can take would increase his reward. So now we need a way to mathematically describe this phenomenon, so the algorithm can act on it. We do this through the discount factor.

The discount factor allows the algorithm to explore future rewards, and weighs future considerations appropriately. If we want Seb to not look at future rewards, we set the discount factor to 0. If we want him to weigh future rewards just as much as current rewards, we set it to 1. In practice, most machine learning engineers try to optimize this value to get the best possible behavior, but let's set it to 0.8 for now.

Whew! Now we can finally let the algorithm run, and observe Seb's behavior as the Q Matrix is updated. The states, i.e Seb's current position, are the rows, while the columns are the actions, or potential squares Sebastian can get to from his current position.

It starts out with all 0's, because Sebastian has no information about what is in each of the squares.

Q Matrix
(States S \ Actions A)

	1	2	3	4	5	6	7	8
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0

Then let's say he moves from square 6 to square 4. The algorithm looks ahead one movement, and is able to see that the blue dinosaur is within reach. So we take the value of the current state, 0, and add it to the product of the discount factor, which we decided was 0.8, and the value of the best state achievable. This gives us a value of 1.6, which we then assign to the appropriate spot on the matrix.

Moving from 6 to 4.

$$Q(6,4) = R(6,4) + 0.8 * \text{Max}[Q(4,1), Q(4,6)]$$

$$= 0 + 0.8 * \text{Max}[2, 0] = 1.6$$

	1	2	3	4	5	6	7	8
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	1.6	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0

Then let's move to the blue dinosaur, from square 4 to square 1. The reward at square 1 is 2, but Q-learning also takes into account possible futures. Remember how we said being on square 4 is good because Seb is close to blue dinosaur? Well, the algorithm doesn't remember that we just came from square 4, so it treats square 4 as a possible future state. So we add 2 to the discount factor times the value assigned to square 4, giving us 3.28 on our Q matrix.

Moving from 4 to 1.

	1	2	3	4	5	6	7	8
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	3.28	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	1.6	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0

If we just stopped here, and let Seb move around with just this information, what would he do? Q-Learning assumes that the agent will always seek to maximize the value of its current

state, so Seb would crawl over to the blue dinosaur and just stay there. Since the algorithm hasn't learned anything about the green dinosaur, it assumes that the blue dinosaur is the best outcome. Seb will be content with his blue dinosaur and never learn about the green one.

In order to prevent this, we have to let the algorithm run multiple times, until the Q matrix is complete. Seb must explore his entire environment before he is able to effectively exploit it given the information he has. When the Q matrix is completely populated, we can confidently place Seb at any starting point and assume that he will get to the green dinosaur in an optimal fashion.

Q-learning is a primitive machine learning model. We have to teach the algorithm about all the possible outcomes before it is able to make good decisions. It may serve as a useful model for infants, but as we age our learning becomes more complex. Perhaps one day we will be able to create a mathematical model for human learning, capturing the intricacies of thought and cognition through a set of equations, but until then, we have to watch Seb play with his dinosaurs.



Graphic by Chris Seo

Note: This is a made-up narrative made to explain real ideas. Any references to historical events, real people, or real locales are used fictitiously. Other names, characters, places, and incidents are the product of the author's imagination, and any resemblance to actual events or locales or persons, living or dead, is entirely coincidental.

The Neuropsychology of Tik-Tok:

Breeding Imitation, Repetition, and Attention

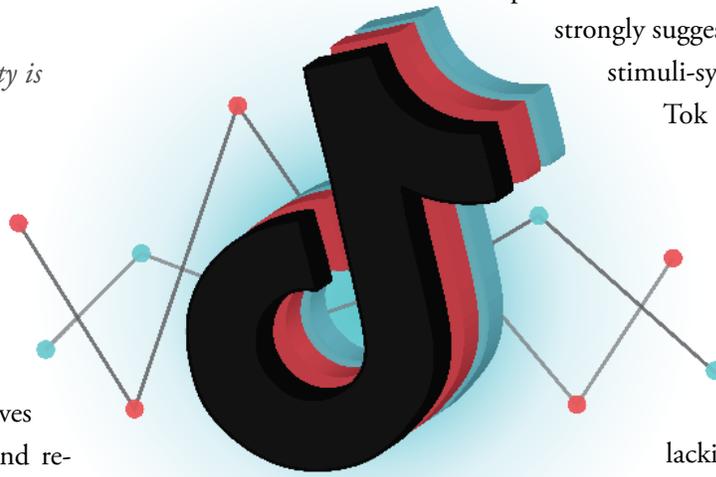
By Kyle Giffin

"In individuals, insanity is rare; but in groups, parties, nations, and epochs, it is the rule."
-Friedrich Nietzsche

Introduction & Thesis

Idiosyncratic dance moves synchronized with catchy and repetitive sound-bites have swept the nation as Tik-Tok's trends & challenges have garnered the app more than 2 billion downloads in less than three years. Owned by the Chinese tech conglomerate ByteDance, Tik-Tok far surpassed Facebook, Instagram, and YouTube as the #1 downloaded app in 2019. The user base, 41% of which is between the ages 16-24, spends an average of 52 daily minutes watching or making content.¹ If ever there was a case study to understand how large groups of people rapidly divert attention to something, this is it. Incessant daily use of a Chinese-tech company's app from a predominantly young crowd raises questions worth investigating. What cognitive mechanisms allow Tik-Tok to generate attention so rapidly from its users? How might primitive neural processes preferentially encode for the highly-repetitive and seemingly brainless content that floods Tik-Tok's 'for you' page?

A critical look at the app's virality and addictive nature raises myriad implications about free-will and the ethics of technological influence. While existing social media networks like Facebook and YouTube undoubtedly employ similar tactics of influence, Tik-Tok differs in that short-sequence videos loop indefinitely and are recommended solely by a machine learning algorithm. Of particular interest is the primary phenomenon that differentiates tik-tok from any other social media: the immensely popular 'dance challenges' which synchronize and



Graphic by Amy Wang

loop audio-visual content of people dancing. An analysis strongly suggests that the repetition, looping, and stimuli-synchrony of these videos give Tik-Tok the ability to influence and guide user behavior, often subconsciously, encouraging imitation on a massive scale. It is of critical importance to society that we understand the behavior of large swaths of people, particularly when their actions seem to be impulsive and lacking agency. As our dear friend Albert Einstein wrote, "when we all think alike, no one thinks very much." While some may claim Tik-Tok

to be a harmless platform for creative expression, a deeper foray into neuroscience and psychology shows that Tik-Tok content encourages imitation and repetitive behaviors through subconscious influence and social pressure.

Neuroscience

Nearly 30 years ago, a research team intended to analyze a monkey's brain as the primate held and grasped various objects.² The researchers were surprised to find similar patterns of neural activity in the fronto-parietal network (FPN) both when the monkey grasped the objects and when the monkey observed a human doing it. This led to the discovery of 'mirror neurons', brain cells which fire both when an animal acts and when the animal observes the same action performed by another. This discovery revolutionized the field of cognitive neuroscience as it implicated the motor cortex in the role of cognitive functioning.³ Since then, hundreds of neuroimaging studies have been conducted on mirror neurons, a large number of which "have shown that the human fronto-parietal mirror neuron system is engaged during action observation and imitation." (Szakacs, 2006) A prominent study in 2006 found that fronto-parietal mirror neurons were also activated by music, implying that "music perception, cognition and emotion

¹ "TikTok Statistics - Everything You Need to Know [April 2020 Update]." Wallaroo Media, 30 Apr. 2020, wallaroomedia.com/blog/social-media/tiktok-statistics/.

² Di Pellegrino, G, et al. "Understanding Motor Events: a Neurophysiological Study." Experimental Brain Research, U.S. National Library of Medicine, 1992.

³ Ferrari, Pier Francesco, and Giacomo Rizzolatti. "Mirror Neuron Research: the Past and the Future." Series B, Biological Sciences, The Royal Society, 28 Apr. 2014.

occur via an experiential (i.e. motor) mechanism.”⁴ This result aligns beautifully with the additional discovery that the same mirror neurons in the FPN are also activated during dance.

Given these findings, it is highly likely that mirror neurons are activated in Tik-Tok users during the viewing and subsequent imitation of whatever dance challenge is trending. First they observe the action, mirror neurons fire, then they replicate it, and the same neurons fire. This illustrates the concept of Hebbian learning: neurons that fire together wire together. Furthermore, the challenges on Tik-Tok integrate not just dances; they synchronize to soundbytes such as “Roxanne” or “Renegade” with highly repetitive characteristics. A study on music-dance synchrony found that “synchronized movements enhance memory and give rise to increased looking times,” suggesting that users would be likely to watch Tik-Toks for longer due to the high level of audio-visual synchrony that’s occurring.⁵ This synchrony, in combination with the desire to learn the dance, may lead to consistent repetition of the video. So what happens cognitively when the same audio-visual stimulus is repeated dozens of times?

Sensory Information Encoding

In music, the catchiest songs are often the most repetitive. Comedian Bo Burnham mocked this aspect of the music industry in his song, “Repeat Stuff” where he likens Justin Bieber to Satan and demonstrates how easy it is to create a catchy song: “you just repeat stuff.” Ironically, this one of Burnham’s most well-known bits, a fact that bluntly illustrates the point he was making. Catchy stuff is recognizable, easy to anticipate, easy to remember, and easy to share. Enter Tik-Tok.

Sounds which recur regularly in our every-day lives are assigned importance by the brain and stored for later, as they often indicate behavioral cues. With this in mind, consider any of the popular trending soundbytes associated with Tik-Tok challenges (“Say So,” “Old Town Road,” “Roxanne,” “Renegade,” etc). Biologically, these segments of sound are stimulating the auditory nerve of the listener in the exact same pattern of amplitudes over and over again, training the brain to encode the sequence for easier recognition and recall in the future.

A fascinating phenomenon called Involuntary Musical Imag-

ery (INMI) occurs when musical sounds or patterns recur in consciousness without the attempt to recall them. Informally dubbed an ‘earworm’, this is the common feeling of having a song or a chorus ‘stuck’ in one’s head. These earworms may be highly relevant to Tik-Tok users, as earworms occur more frequently in individuals who listen to the same music repetitively.⁶ (Fry, 2013) Tik-Tok differs from other media networks in that videos repeat on their own, looping until paused or scrolled away from. This results in increased likelihood that a Tik-Tok user is experiencing INMI due to increased exposure to repetitive auditory sequences.

Researchers aiming to understand INMI found that “if a song begins mentally replaying it is likely to return to awareness over several days,” and that “over time this can become intrusive and unwanted.” These catchy sequences of sound can recur subconsciously, without the individual trying to make them appear, and may even disrupt desired thought processes. Furthermore, it turns out that imagining music and actually listening to music both activate many of the same neural networks.⁷ This means that a Tik-Tok user may find themselves imagining the catchy video that they watched earlier and activating the same neural network, thus reinforcing it, even when they are not on the app.

Other byproducts of this repetition of stimulus include higher rates of memory; musicians such as Bieber, who recently used the word “yummy” sixty-eight times in one song, have clearly used this principle of the mind to their advantage. However, Tik-Tok takes memory reinforcement a step further through something called spaced repetition, wherein memory of a stimulus (i.e. song/dance) is enhanced when that stimulus is presented at spaced-out time intervals. When frequent users are presented with the same song and dance over weeks of viewing, spaced repetition generates in them a longer-term memory of the event.⁸

It is clear both scientifically and intuitively that repetition enhances learning and memory. By integrating looping soundbytes as a fundamental aspect of the platform, Tik-Tok can reap the benefits of increased attention and retention thanks to the mechanisms that drive our sensory information encoding systems. However, beyond the myriad biological phenomena

⁴ Molnar-Szakacs, Istvan, and Katie Overy. “Music and mirror neurons: from motion to ‘e’motion.” *Social cognitive and affective neuroscience* vol. 1,3 (2006): 235-41. doi:10.1093/scan/nsl029

⁵ Woolhouse, Matthew Harold, and Rosemary Lai. “Traces across the body: influence of music-dance synchrony on the observation of dance.” *Frontiers in human neuroscience* vol. 8 965. 3 Dec. 2014,

⁶ Müllensiefen, Daniel, et al. “Individual Differences Predict Patterns in Spontaneous Involuntary Musical Imagery.” *Music Perception: An Interdisciplinary Journal*, vol. 31, no. 4, 2014, pp. 323–338.,

⁷ AR, Zatorre RJ;Halpern. “Mental Concerts: Musical Imagery and Auditory Cortex.” *Neuron*, U.S. National Library of Medicine, pubmed.ncbi.nlm.nih.gov/15996544/?mod=article_inline.

⁸ Karpicke, Jeffrey D., and Althea Bauernschmidt. “Spaced Retrieval: Increased Long-Term Retention Regardless of the Spacing Schedule.” *PsycEXTRA Dataset*, 2010, doi:10.1037/e566842012-024.

that are already working in favor of Tik-Tok, are there additional aspects of the mind which can incentivize prolonged use of the app? How might Tik-Tok invoke compelling principles of group social psychology to systematically drive user behavior on their platform?

Psychology

“These repetitive words and sequences are merely methods of convincing the subconscious mind”

- Claude M. Bristol

Many industry leaders in marketing, media, technology, and entertainment have employed psychological tools to exert subconscious influence on their customer base, increasing the adoption of their products through mentally ‘sticky’ brand exposure tactics. Tik-Tok is no different. In Robert Cialdini’s book “Influence”, the experimental psychologist identifies a variety of persuasion tactics which prove to be effective ways to exert this type of influence. The methods can be used to increase the likelihood of compliance or engagement in a desired behavior, oftentimes without an individual noticing. For example, waiters who leave a chocolate or a mint on their bill tend to earn 23% more in tips than those who do not; this engages the principle of reciprocity, inciting a feeling of subconscious indebtedness in the recipient of the mint.⁹ In addition to reciprocity, the book describes several fundamental tools of behavioral influence. Three of these tools in particular provide an excellent framework through which to explain and understand how Tik-Tok uses challenges to persuade its users: social proof, commitment, and automaticity.

Social proof, defined by Cialdini, is “the tendency [for someone] to see an action as more acceptable when others are doing it.” We look to authorities as well as our peers for which behaviors to adopt. Thus, social media authorities with millions of followers have immense influence on those who look to them for advice. Companies often engage social proof by paying famous people to wear or use their products. While all social media networks prominently rely on this principle, Tik-Tok is unique in that it engages social proof not through the adoption of beliefs or ideas, but learned physical behaviors. The moment top-user Charli D’Amelio releases a new Tik-Tok to her 55 million followers, she is giving social credibility to a

new trend, a challenge that displays flawless execution of bizarre dance moves in synchrony with the catchiest song of the day. When the average Tik-Tok user, often an impressionable teenager, sees how popular Charli is and then taps their own camera icon, uncertainty arises... “What should I film? How should I behave?” This uncertainty increases the likelihood that the user will mimic Charli’s dance, as this is the behavior that is socially proven. Simply put, we look to validate our actions via the behaviors of the crowd, and often conform to social trends even when we find them to be wrong.¹⁰

This fact is compounded by the mechanisms through which Tik-Tok spurts commitment in its users. Consider as a case study a recent Wallstreet Journal article about ‘do-it-yourself’ social-media videos that generate hundreds of millions of views per month. Creators of these popular life-hack videos had developed a “virality checklist” which was based on a simple idea: their best performing content was always that which appeared “simple and easy” to replicate but “still produced an impressive result.”¹¹ These videos resulted in more views and more attempts by viewers to recreate them. On Tik-Tok, a similar phenomenon can be seen in that many viral videos are ones which depict complex dances appearing flawless and easy to accomplish. Upon seeing this, nudged by the apparent ease of learning and the social proof of the phenomenon, the user is more likely to mentally commit to recreating the video. As soon as they set the stage and hit the record button, they have entered a commitment which produces consistency of behavior; the repetition of the dance over and over until the user starts to learn how it works. Time to activate those mirror neurons.

Commitment generates the powerful behavior of consistency. Even if the user finds that the dance has taken much longer to learn than expected, they have already sunk enough time that it would appear foolish and inconsistent to suddenly back out before completion. This type of self-consistency is “vital for organized functioning and health,” however, once a commitment is made, there is a natural tendency for one to behave in “ways that are stubbornly consistent with the [commitment].”¹² If the Tik-Tok user were to suddenly put the phone down and stop attempting to learn the dance, they may face an internal psychological resistance to behaving inconsistently with prior actions. Further resistance may be galvanized by the idea of missing out on a popular social trend. The power of these psy-

9 ‘Sweetening the Till: The Use of Candy to Increase Restaurant Tipping’ by David B. Strohmetz, Bruce Rind Et Al.” Site, scholarship.sha.cornell.edu/articles/130/.

10 Asch, Solomon. “Opinions and Social Pressure.” Scientific American, 1955.

11 Horwitz, Jeff. “Why Life Hack Videos Seem Too Good to Be True. (They Are).” The Wall Street Journal, Dow Jones & Company, 9 Oct. 2019.

12 Cialdini, Robert B. Influence: Science and Practice. Prentice Hall, 2020.

chological forces can result in hours spent looping the same video over and over, each time storing an audio-visual packet of information that activates mirror neurons, increases memory & gaze time, and reinforces a pathway for future recall.

This brings us to the final psychological principle, automaticity. A Harvard paper titled “Automaticity of Action” describes conscious automaticity as the “acquisition of skills that become automatic and unconscious after significant repetition.”¹³ Behavioral automaticity can be generated by the well-established principle of classical conditioning, first pioneered by Ivan Pavlov. The Russian Physiologist and father of behaviorism famously demonstrated that dogs presented with a stimulus (a bell) repeatedly paired with a behavior (eating food) would later induce a response (increased salivation) when the bell was presented alone. This classical conditioning is the basis for many of our behaviors, and is the exact reason why you check your phone upon hearing the text tone or press on the brakes when the light turns yellow. In Tik-Tok terms, the consistent exposure to a stimulus (a catchy song) repeatedly paired with a behavior (synchronized dance) may induce a response (desire to dance) when the stimulus is presented. In users, the result can be an unconscious urge to re-enact Tik-Tok dances upon hearing the associated stimulus.

Brew these three psychological concepts together with a dash of likes, a hint of social collaboration, and the overwhelming allure of potential virality. You’ll have a cup of behavioral compliance; a pipeline of action that turns social proof into commitment, commitment into consistency, consistency into repetition, and repetition to behavioral automaticity. While this framework can be applied to a variety of social media behaviors, Tik-Tok dances are a particularly well-fitted example. For younger populations who are highly vulnerable to social pressure, the psychological forces alone carry an enormous weight. Combine these with the additional mechanisms of sensory and neurological influence and it quickly becomes clear how a person can feel abnormally compelled to replicate what they see on Tik-Tok.

Whether or not one believes malintent on the behalf of the creators of Tik-Tok, there’s no denying that neuropsychological strings are being blatantly pulled to extract attention from its users. The Chinese app’s suddenly vast presence in the digi-

tal economy is due to its ability to rapidly garner attention, a resource so valuable that it drives a \$1.2 trillion advertising industry.¹⁴ This monetization of attention requires that we be extra wary as to how our attention is being spent. Naive is the reader who scoffs at the notion of attentional control and bur-geons an idealistic worldview wherein they are somehow immune to the myriad mental effects discussed in this paper.

This analysis of Tik-Tok is not meant to criticize its users nor to demonize the app as an unusually malevolent player in the media industry. In fact, a well-formed argument could be made to claim that other media platforms are having a larger and more negative impact on the world as a whole. However, Tik-Tok represents an unprecedented phenomenon in that its growth rate and content have no modern analogues. The app’s exponentially-increasing adoption is miraculous when viewed at face value. However, in illuminating the cognitive mechanisms which have facilitated this growth, we can understand more deeply where our global consciousness resides in terms of attention, memory, and stability. Existential questions arise when we ask why we’ve arrived at this point. What happens to human progress when our youth’s attentional capacities have been manipulated by platforms that use neuroscience, psychology, and algorithmic optimization to inspire uncontrollable and compulsive use? I encourage the reader to think critically about the impact that these forces may have on the thoughts and actions of our next generation.

As philosopher Cornel West poignantly remarks, “clever gimmicks of mass distraction yield a cheap soulcraft of addicted and self-medicated narcissists.” These words, while harsh, allude to a general truth: the game we’re currently playing is a dangerous one. We’ve normalized technology that increasingly jeopardizes our ability to make focused, rational decisions, particularly when those decisions don’t immediately benefit ourselves. It would be smart to ask whether the tradeoff is worth it: do we sacrifice some cognitive ability in exchange for the fleeting pleasure we derive? Or are we too distracted to even answer the question? 

13 Happe, Frederick. “Automaticity of Action: Psychology of Automatic Thoughts.” Scholar.harvard.edu, 2001, scholar.harvard.edu/files/dwegner/files/wheatleywegner.pdf.

14 Mutunhire, Ten. “The Advertising Industry Is Now Worth \$1.2 Trillion, Marketing Continues to Grow through Mobile Content, Social Platforms and New Digital Platforms.” Towers of Zeyron, 2 Dec. 2017, 15

“He did not want to be young again -- that time had had particular and transcendent horrors -- but the thought of being any older filled him with panic. He could not imagine finding tranquility of soul in old age; if he could only be allowed to mark time for a while all might yet be well, one might suddenly achieve equilibrium, certainty, serenity. There would still be possibilities. Hopes.”

Penelope Lively

ADULTHOOD

Getting Back Your Lost Brain Cells

How we can use current research efforts in adult neurogenesis to our advantage.

By Iris Lu

Sometimes we feel like our brains have given up on us -- whether it's when you walk into a room and immediately forget what you were going to do, or when there's just that one answer on a test that you can't help but blank out on.

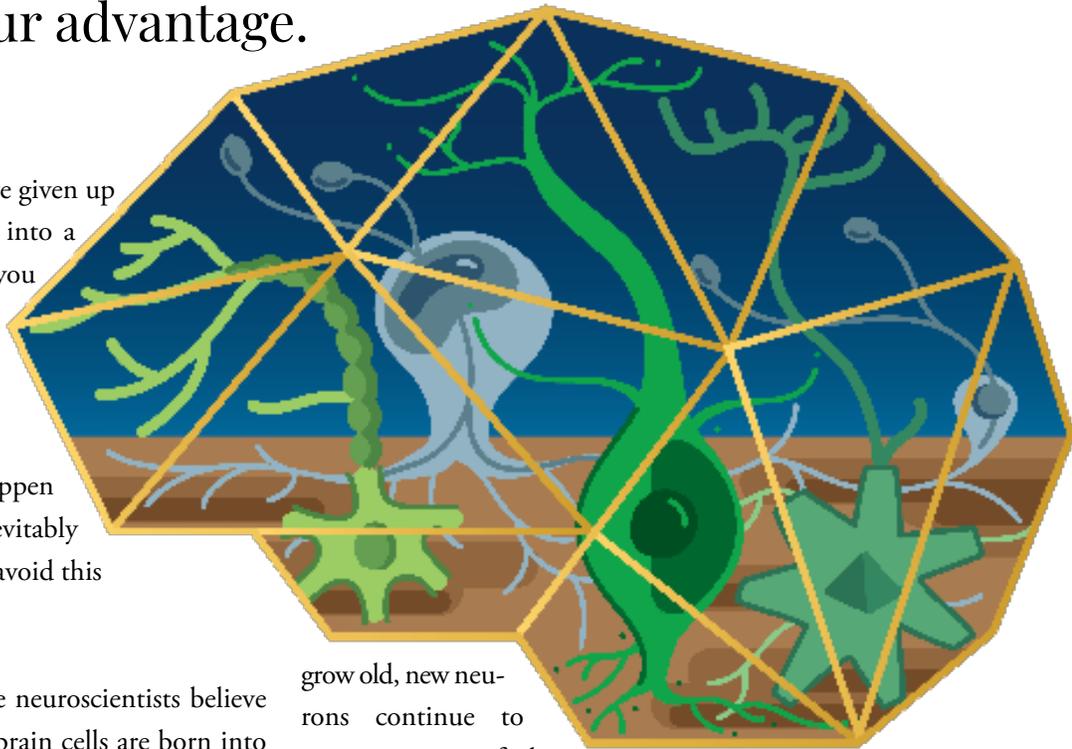
As we age, this feeling only seems to happen more often than not, as the brain inevitably changes and shrinks. But how can we avoid this regression?

Though not a complete reversal, some neuroscientists believe that there exists a process where new brain cells are born into the adult brain. This phenomenon, more commonly known as adult neurogenesis, describes the process of newborn neurons integrating themselves into pre-existing brain circuits even after brain development has ceased.

The possibility of adult neurogenesis in humans is a fairly recent idea -- in fact, the neuroscience community was staunchly opposed to the notion for a long time. In 1913, renowned neurobiologist Santiago Ramon y Cajal reflected this by claiming that "In the adult centres, the nerve paths are something fixed, ended and immutable. Everything may die, and nothing may be regenerated".

Fortunately, this is not the case. The human brain is famous for its ability to adapt and change, with neuroplasticity being what helps our brains develop continuously throughout our lives -- including, but not limited to, the formation of new brain cells.

Years after Cajal's claim against neurogenesis in adults, there still remains considerable doubt on whether or not humans truly continue to generate new brain cells throughout the whole brain after maturity. However, it remains true that even as we



grow old, new neurons continue to grow in areas of the brain most susceptible to our memory, logic, and function. But whether or not it grows in more widespread areas across the brain continues to be a difficult theory to prove.

Graphic by Amy Wang

There remains an overwhelming amount of research showcasing events of new neuron growths in rats, mice, birds, lemurs, and other nonhuman primates¹ -- however, we have yet to see convincing data mirrored for humans as well. But how can we use the knowledge we know of mammalian brains to apply similar concepts to the human brain? What is it about post-natal neurogenesis in other animals, that makes it increasingly possible for it to also occur in humans through the form of adult neurogenesis?

Of Mice and Men

In both rats and human brains, new neurons are primarily generated through the work of neural stem/progenitor cells (NSPCs) which originate from specific areas of the brain.

In rodents, these NSPCs are mostly located in the hippocam-

¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6659986/>

pus, which is responsible for learning and memory, as well as the subventricular zone where NSPCs first grow before migrating to the olfactory bulb. From there on, they are differentiated into olfactory neurons, which are primarily used for smell. However, this case is not the same in human brains -- instead, NSPC generation in the hippocampus continues without migrating to any other area of the brain, remaining stationary, while neurogenesis in the subventricular zone at all is comparatively rare.

This causes most NSPCs generated in the human brain to remain in the hippocampus, and eventually grow into mature, adult neurons. Though the amount of time it takes for each cell to undergo maturation differs from neuron to neuron, it all ends with the new neurons' complete integration with a pre-established functioning neural network.

While the existence of NSPCs in the adult hippocampus alone provides ample insight into the possibility of adult neurogenesis, a new question persists -- for how long?

Compared to humans, rodents and mice have a much shorter lifespan. The average mouse only lives for up to 2 years, while humans can live up to 50 times that amount -- and while a mouse can be deemed to be a mature adult once it reaches three months of age, humans do not become fully developed until the estimated age of 24.

In this case, rodents tend to have an obvious spike in neurogenesis activity during their adult phases of life, but these levels noticeably deteriorate as they get older and older. In contrast, humans are most likely to have the highest levels of neurogenesis during their prenatal development, meaning that levels of neuron development in the human brain considerably drops after ~3 months of age.

Evidently, the levels of neurogenesis differ starkly between mice and men. Though mice have much shorter lifespans, their levels of adult neurogenesis continue to decrease until they are almost nonexistent as they age. But for humans, this level of neurogenesis remains at a constant after its initial decrease, persisting despite our longer lifespan. And so we see adult neurogenesis in humans occurring most commonly in the hippocampal region, with a steady rate of new neuron development that remains consistent as time goes by.

But just like every form of neuroplasticity, the consistency of adult neurogenesis varies greatly from person to person. A large number of factors contribute to the birth of new brain cells, and it's just a matter of finding which one works best for you.

Use it or Lose it

To no surprise, adult neurogenesis levels are tied closely to our lifestyles. Getting a good night's sleep, eating healthy, and exercising are all important activities people are told to lead a healthier, happier lives -- but it's what is in the specificities that make these activities vital to improving neuron development in the adult brain.

One bad night of sleep, for example, does not have a concrete effect on neurogenesis levels in the average person -- but this is very different for those with chronic sleep deprivation, as well as chronic sleep disturbances. Cases where normal sleep times (~8 hours) decreased by 50% over the span of 4 days can cause a sharp drop in cell survival, causing neurogenesis to take a dive as well.

The same can be said when referencing diet -- though it is easy to simply say "eat healthy", the intricacies of what kinds of protein and fibers are most preferable for neuron development is difficult to determine. However, it is certain that high-caloric diets of any manner cause neurogenesis levels to drop as well, regardless of the amount of exercise that comes before or after it. Surprisingly, this is contrasted with the discovery that eating hard foods (anything that requires a substantial amount of chewing) can greatly increase neurogenesis due to the amount of mastication and movement of the jaw involved.

Things are also much easier to understand in regards to exercise -- to nobody's surprise, any form of exercise is in any respect beneficial, regardless of if it is aerobic or not. Weight-lifting, yoga, and even speed walking all give their own benefits to neurogenesis as they contribute to spatial memory improvement in the brain. If anything, it is consistent, moderate exercise that seems to be the most effective when improving adult neurogenesis, as single-instance exercise continues to have proportionally lower levels of neurogenesis when compared to more consistent plans. On the other hand, extreme exercise, at its worst, can be physically and mentally detrimental as it has the possibility to disrupt normal metabolic processes in the body,

accelerating cell death in the body instead of doing the exact opposite.

These three factors are all common recommendations that are given in order to encourage others to lead healthier, and happier lives. But what are some more rare -- and arguably, fun -- lifestyle choices that can improve adult neurogenesis in the brain?

“The Good Stuff”

Drugs, sex, and alcohol may not be the first thing to pop into your head when you consider “brain cell development”, and for good reason. These three vices can do more harm than good if taken in excess, but without a doubt, still retain some positive side effects -- including but not limited to, adult neurogenesis.

To start off, only one drug of abuse (drugs of abuse being: opiates, nicotine, cocaine) has proven to have a substantially positive effect on neuron development in an adult mouse brain. While cocaine and nicotine can considerably suppress the amount of new neuron growth, both plant-derived and synthetic cannabinoids can improve levels of neurogenesis in the hippocampus.² And to make things more interesting, these increased levels of neuron development only occur given chronic administration of marijuana, rather than one-time occurrences.

The next factor on the list is one more closely connected to its effect on human stress levels, as well as daily activity. While detrimental levels of stress may also suppress neurogenesis in the adult brain, sexual experience instead amounts as a more rewarding stressor that can not only greatly reduce anxiety, but increase levels of neuron development in the adult brain as well. And when comparing the amount of sexual experience between an acute and more chronic schedule, both parties were found to have a promoted growth in adult neurogenesis, despite proportionality.

Alcohol, being the last of the three, has had a long-standing history with its detrimental effects on the brain's hippocampus. Alcohol consumption, whether it be merely intake, addiction, or both, consistently has a negative relationship on brain structure as well as hippocampus function. Yet, one alcoholic compound proves to have the opposite effect on adult neurogenesis, particularly on those over the age of 35. Resveratrol, an anti-

oxidant found on the skin of red grapes and subsequently in red wine, can help contribute to memory improvement as well as neuron growth in the adult brain. Despite other forms of alcohol interrupting neurogenesis and having an adverse effect at all stages (whether it be growth, maturity, or migration), the resveratrol flavonoid seems to have the exact opposite effect.

All of these existing factors, useful or not, prove to have a substantial role in improving the rate at which new neurons are developed within the adult brain -- particularly that of the hippocampus. And though it may be an oversimplification to assume that “more brain cells = good”, there are many more positive results that come out of increased levels of neurogenesis. Researching adult neurogenesis is not just a way to improve our brain function and keep ourselves healthy as we age, but an innovative form of treatment that can be utilized to treat pre-existing diseases as time goes on.

Mental Health and Diseases -- Battling Against Time

There are a wide array of neurodegenerative diseases that could be battled by researching adult neurogenesis, and Parkinson's Disease is only one of them. This disorder is a progressive disease that gradually worsens movement and can cause nerve cell damage overtime, and is clinically considered to be a multi-system disorder as it affects the Central Nervous System, rather than one portion of the brain.

While there is not one specific part of the brain that can be focused on when considering Parkinson's, it is important to consider the ability of adult neurogenesis to build new neurons not limited to one region. While hippocampal adult neurogenesis is the most known and most widespread form of neuron growth at the moment, the possibility of using NSPCs to migrate to different regions of the brain and mature into specialized neurons is enough reason for interest in the topic. As Parkinson's Disease is known to begin ~5-10 years before the onset of motor symptoms, and symptoms of depression and anxiety pre-dating ~20 years, adult neurogenesis offers a possible treatment for the widespread disease by looking into the migration and integration potential of NSPCs in the brain other than the hippocampus. This is especially vital when regarding the benefit of adult neurogenesis on symptoms of depression and anxiety alone.

² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1253627/>

The reason that adult neurogenesis is vital to the treatment of depression is due to its use in conjunction with antidepressants. Because patients who have experienced major depressive episodes begin to have significantly reduced hippocampal volume, it is vital that new neurons are developed in order to bring the hippocampus back to its normal size. This neurogenesis, when used in conjunction with antidepressants, is meant to balance the detrimental effect of chronic stress and reduced volume on the brain and ultimately help the patient to better regulate possible depressive behaviors.

Like all issues with mental health and illnesses, it is important to consider that the effectiveness of neurogenesis can vary widely from person to person. However, this variation does not deny the fact that increased levels of adult neurogenesis can significantly help those who may have trouble with depression due to major episodes and chronic stress. Just like any other form of treatment, there are multitudes of factors to consider and various ways to implement them.

If current research has proved anything, it's shown that there is still so much more that can be done with adult neurogenesis. While there still remains some doubt over its efficiency in the adult human brain compared to that of other nonhuman primates or rodents, its existence in the hippocampus alone proves that there is much more that can be done in order to master the migration and maturation components of neurogenesis. And if the multitude of factors that contribute to adult neuron growth say anything, it shows that we have plenty of neurons to spare.

So, what will you do with your newfound brain cells? —○

Picture This

A Discussion About Human Memory

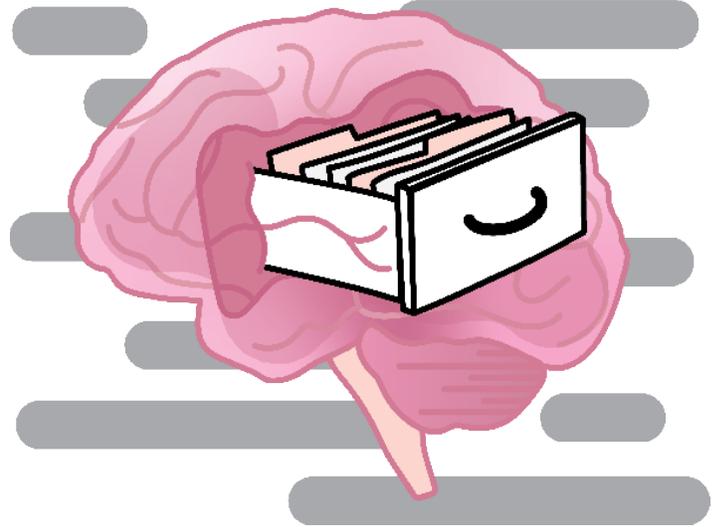
By Jandy Le

Our brains are plastic. The human brain has the capacity to continually change throughout our lifetime, creating new neurons and new neural connections, simply through experience. How is it that such random *external* factors such as our relationships, jobs, and education change the *internal* biological structure of one of the human body's most important anatomical features? You can't change the structure of your kidneys, or your lungs, or your stomach through such activities; yet, somehow the brain can accommodate all of our embarrassing memories, momentous achievements, and academic endeavours.

The brain also works in the opposite way- neurons that aren't regularly used eventually deteriorate; thus, it is important to keep mentally "sharp," as this can be referred to as the "use it or lose it" phenomenon. With the average adult brain containing about one hundred trillion synaptic connections, it is no lie that we are constantly impacted by our external surroundings; however, the consistency of each neural connection being used is important in their preservation.

Unlike other body cells, often which can continually divide to replace old cells, most neurons in the human brain are only able to divide to make new cells during fetal development and until a few months after birth, through a process called neurogenesis. With this knowledge, healthcare providers encourage many different measures to be taken to ensure the brain is forming properly during fetal development. Additionally, major conditions such as fetal alcohol syndrome evidently reflect permanent consequences in brain structure and function due to the absence of proper neurogenesis. Effects include immature neuronal cell death, inaccurate synaptic connections, memory deficits, and learning disabilities -- all of which are irreversible.

Reported to occur in animals such as rats, birds, and other primates, there is continuing research for evidence that adult humans can undergo neurogenesis-- specifically in the hippo-



Graphic by Amy Wang

campus, a brain structure well known for its major roles in the formation and storage of new memories. However, it is already known for a fact that the aging process has a direct effect on cognitive decline, especially in the function of the hippocampus, leading to just ordinary memory loss, or even dementia and neurodegenerative diseases. Starting from as early as age 45, decline in cognitive function can be first-handedly observed through daily tasks; one can notice that they are quickly forgetting names and faces, or have difficulty recalling what events happened from just the previous week.

Without a purpose, neurons die. If a connection is not used frequently, it fades away. Brain circuits constantly change, and as people grow older, they are simply going through day-to-day routines, and may not be learning as frequently as a school-child.

Research about adult neurogenesis is still in progress, but despite whether this evidence is true or not, everyone's brain still exhibits neuroplasticity: the brains' amazing ability to form and remodel synaptic connections between neurons (not making new neurons). Neuroplasticity explains the concept of memory. For new knowledge to be retained, and for such information to be recalled, neural connections must be strong and accessible. During learning, neurons can either internal-

<https://human-memory.net/brain-neurons-synapses/>

<https://faculty.washington.edu/chudler/plast.html>

<https://www.scientificamerican.com/article/why-is-synaptic-pruning-important-for-the-developing-brain/>

ly change their structure, namely in the area of the synapse, or there can be an increase in the number of synapses-- thus forming more connections. To slow down the consequences of aging on the brain, health experts encourage people to engage in mentally stimulating activities that strengthen and improve memory naturally. Besides the obvious healthy lifestyle choices such as physical exercise, getting enough sleep, and drinking less alcohol, many believe in “brain exercises” that stimulate intense concentration, thus activating areas of the brain that may not be used frequently from day-to-day. Trivia games, card games, and infamous puzzles such as Sudoku have been proven to increase retention of information and enhance recall, as well as increase mental alertness and creativity.

However, age-related cognitive decline inevitably continues to persist, despite any preventative measures one takes. This could be due to genetic or environmental conditions; however, modern technology allows scientists to harness this neuroplasticity and develop devices that promise to improve memory drastically. For those who have envied photographic memory, it may soon be possible. Picture this: imagine being able to recall an entire music festival and replay your favorite sets, or being able to remember exactly what your house robber’s face looked like and what he wore. But most importantly, this would also mean that neurodegenerative disorders such as Alzheimer’s could be prevented.

Currently, researchers have a few methods to attain memory improvements. For instance, noninvasive transcranial magnetic stimulation (TMS) sends electromagnetic pulses to specific areas of the brain, especially targeting the hippocampus. It has been proven to boost memory, but TMS is also used for conditions such as depression, epilepsy, and obsessive-compulsive disorder. In this method, patients are typically confined to a chair, lying under a helmet attached to a bulky machine.

There is also transcranial direct current stimulation (tDCS), in which the machine used is a simple headband, with a smaller dose of electricity. This method manipulates the neuroplasticity of our brains, and builds new neural pathways, which can then improve memory.

Other prototypes are more invasive, including Dr. Robert Hampson’s “hippocampal neural prosthetic” that focused more on the process of memory encoding, rather than just retrieval.

It uses the subject’s own memory patterns; simply, a person’s neural patterns could be recorded, reinforced, and fed back into the brain by the prosthetic in what is called a closed loop. When an error pattern is detected, electrical stimulations interfere to correct it. From this, effects showed evidently prolonged working memory and long-term memory retention. With success in both animals and humans, Dr. Hampson hopes that this machine could soon be tweaked to become an implant.

Devices like this neural prosthetic will prosper when targeted to patients suffering from neurodegenerative disorders, or those of old age experiencing significant cognitive decline. Patients with Alzheimer’s will be able to remember family members, age-related memory issues will be delayed to even later life stages. There could also be possible applications toward people with other cognitive disorders.

Much of this future form of technology would involve invasive procedures, in order to place some sort of device or microchip in the brain, thus hindering the accessibility and financial ability for many people. Now let’s imagine if future versions are reliable, supposedly risk-free, and available to the general public regardless of whether people exhibit symptoms of dementia... how far would people be willing to insert this foreign device into their bodies? Would it increasingly become the norm?

For example, take cochlear implants, now a very widely used biomedical device amongst patients that experience loss of hearing. In the past, it used to be seen as a risky method of “hacking into the auditory nerve,” leading to an unnecessary fear that we see as absurd today. Would it also eventually become socially accepted if a large number of people start adopting memory-enhancing devices?

The brain is completely different from organs such as the ear, and mental privacy issues arise as people’s brain information could very realistically be hacked (I’ve written about this in a previous Mind issue!). At this point, we are still unsure as to how someone’s thoughts or memories could be retrieved into an external device available for viewing or usage-- for instance, recalling a memory is not as simple as replaying a video; memory is not vividly cinematic like that. But if we are able to get to the point of enhancing memory recall, isn’t it just as possible to be able to translate people’s private mental information in the same way as one would hack a computer?

In addition, it is still unclear as to how much memory we would be able to encode and retrieve. And to what detail? Could there be an extent where our brains feel overloaded? Currently, estimates of our current brain usage vary from 1 to 1000 terabytes-- a very broad range, evident of the fact that we know very little about brain storage so far. However, even with this trivial fact, we are viewing our brain as data storage instead of a problem-solver; the brain replaces the role of memory cards, SD cards, computers.

As a consequence, people could “store” as many facts as they want. This could greatly affect students and workers who rely on memory to execute daily responsibilities. This actually opens up opportunities for higher levels of learning: to reduce the educational advantage that people with the implants would have, schools would adapt to test students not based on rote memorization, but rather problem-solving skills, which beneficially, in turn, would strengthen brain synapses. Jobs would execute more critical thinking questions during interviews, and graduate school tests such as the MCAT no longer tests merely factual recall, but applicable skills for the workforce.

How important would this specialized photographic memory be to our daily lives? How much of our current lifestyle would be different if we were able to just recall more things? Being able to just remember a few more digits to successfully recite a new phone number, maybe even remember a shopping list of twenty items, would make our routines slightly more convenient, but we already use our smartphones to write down lists like that.

A photographic memory is especially more important in dangerous situations, such as when an intruder enters, or when someone kidnaps a child on the street. For humans, vision is one of the less reliable senses, as visual memory and history could easily be distorted during recall. Typically, people are not good eyewitnesses, especially in emergency circumstances, which is why it is difficult to report what color shirt a suspect is wearing, or if they had facial hair, and especially important details such as the license plate of the kidnapper.

A powerful superhuman gadget like this could be very costly, and most people would not be able to afford it-- leading to yet another material advantage that upper class people could acquire, giving them a headstart in educational and work roles

that have not yet adapted to this quick-evolving technology. The development of the Apple Watch led to the possibility of students cheating on exams, and schools implemented guidelines to promote fairness... how would it work in this scenario?

Lastly, the most important question: is this ethical? Would we be treating our brains as a self-aware machine, or is this simply just a bodily modification like a prosthetic leg, or a commercial technological device, like a typical smartphone? Could the government be involved with these neurotechnological companies, or regulate such an intrusive and personal machine? Surely there would be some set of health and safety regulations put in place before everyone is able to have access to such an impressive machine.

While a photographic memory sounds appealing, there are still societal and ethical concerns to deal with before such a device is introduced to the general public. Maybe for now, it's a good thing that we have not adopted such a drastic form of technology. Maybe it's relieving to not have perfect recollection of your day. Imagine being able to remember every line from the allergy medicine TV commercial; instead of having a catchy song stuck in your head, you would be reciting the side effects of the pill all day. You remember the sequence of red and green lights on your commute to work? There's not really a point to that-- waste of brain capacity. You wanted to use your favorite knock-knock joke as an ice-breaker... well, too bad, because everyone else heard that one in third-grade.

This hypothetical exploration of such devices and superpower abilities seem too good to be true, and too far to be true, but with the pace of the neurotech advancements today, it wouldn't be surprising to soon see ads of products claiming to enhance your memory. So picture how your life could be like if everything you said or everything you did was memorized-- permanently recorded-- by the people around you. Would you change your behavior? 

Music and the Mind

A Novel Remedy

By Abraham Niu, Nehchal Kaur

When Darwin popularized the idea of ‘survival of the fittest’, he changed the way humanity viewed the circle of life: the very act of existence became a competition. Even so, humans are social animals, and if there’s anything that history has taught us, it’s that survival depends more on cooperation than it does on competition.

Enter Music.

From the primal, ritualistic drums banged by the first humans to walk the earth, to the lyrically advanced wordplay of Kendrick Lamar, music has been an integral aspect of the human experience affecting every known culture, past and present. There is something omnipresent in the various manifestations of music that has allowed it to stand the test of time. It doesn’t matter if it’s rock ‘n roll, jazz, classical, or hip-hop, from Bach to the Beatles, music has been there to accompany human activity and emotion in every step of life. But beyond the usual head-bobbing or foot-tapping we typically find satisfying, music possesses the properties to serve as a medium for deeper human connection, and in doing so, can effectively be used for curative purposes.

But what is it about music that makes us tick?

Sound is a vibration and music is the act of coupling the affective, lyrical, temporal and rhythmic characteristics of those vibrations. We are all simply an amalgamation of the tunes our atoms weave and the harmonies that result. But beyond the poetic cooperation that music embodies, it also represents the unity of something more concrete: us. The validity of this perspective is being specifically explored through the neural sciences. At microscopic levels, neuroscience has begun to discover that for the neural oscillatory activity in our brains, music may be the unifying force that helps cells and brain regions harmonize their activity with each other. In fact this applicability goes beyond a single person as research has elucidated,

that being engaged with the same piece of music synchronizes the brainwaves of the audience despite each individual being a unique blend of thoughts and experiences (Madsen et al., 2019).

The centrality of music to human cognition has found an application through something called music therapy. A kind of expressive arts therapy, music therapy is a form of evidence-based clinical intervention for improving and maintaining psychological, behavioral, sociological and neurological symptoms of various diseases and disorders. This method, which involves listening to music, playing instruments, or even composing, has already been proven as a natural and potent tool in therapy, often leading to stress relief, a better sense of motivation, along with aiding in physical and mental rehabilitation. Perhaps of even greater fascination is how music helps in alleviating some of the damage present in diseases of neurodegeneration. In patients with dementia, studies have shown that music-based rehabilitation interventions lead to improvements in attention, orientation, verbal skills, episodic, short-term, and working memory, as well as broader executive function. At the same time, patients with Parkinson’s Disease exhibited drastic improvements in mobility, along with reductions in disease-specific motor symptoms. But beyond those areas, music therapy has been shown to enhance personal and social experiences



Graphic by Chris Seo

by lessening neuropsychiatric symptoms including reduced depression, agitation, and anxiety, along with mood improvements and overall increase quality of life reports (Sihvonen et al., 2017). The capacity for these effects has been under debate for its acute or chronic reach but a recent study by Chen et al. provided interesting results: they exposed juvenile rats to regular music and found that it facilitated fear extinction and reduced anxiety in adulthood.

In his book *Musicophilia*, Oliver Sacks writes about a music therapist who worked at Beth Abraham in the 1960's. At the time when he joined the hospital, he encountered many patients who seemed to be in a 'trancelike' state of motionlessness. Some of them had been 'frozen' for over 40 years. This was a characteristic symptom of encephalitis lethargica, the sleeping sickness epidemic that swept the world around the time. With very little prior success in treatment, it was only Kitty Stiles, a therapist who played music for the patients, that would succeed in inducing some balanced movement despite their catatonic state.

Another well known example is that of Samuel S. After having suffered a stroke, Samuel developed severe expressive aphasia, rendering his ability to produce language so ineffective that even intensive speech therapy had little to no effect. A music therapist noticed him humming "Ol' Man River" with complete tonal and affective expressiveness, lacking only in the lyrics. She began to work with him for half an hour, thrice a week and soon from being able to sing Ol' Man River completely and many other songs he had learnt growing up to responding with appropriate phrases to questions, he completed the journey in two months.

Similarly, after a tragic snowboarding accident, Forrest Stone Allen suffered catastrophic brain trauma and found himself unable to control his breath, let alone communicate. Blowing a feather off a hand, humming - these were all outside of his ability at the time. Standard therapy efforts were to no avail, but in the end, it was music therapy that opened the doors for his recovery. His music therapist employed beginning tactics of playing a piano note and having Allen try to the best of his ability to give him sound back. Month after month of humming and breathing, Forrest was able to rewire his brain and attach pitch to verbal sound. Eventually, he was able to sing songs and communicate normally, reactivating his vocal cords

which had been almost completely dormant for over a year and a half. In both the case of Samuel S and Forrest Stone Allen, music was able to do what other modes of therapy couldn't - help patients rediscover the voice they had lost.

Although pinning down the exact mechanisms behind these miracles is a complex task that is still out of the reach of modern science, researchers have some idea of what may be going on in our brains.

Music, as a hierarchical, compound language built out of counts is physically complex as it recruits multiple neural networks. Along with rule-based analysis and combination of sound patterns, such stimuli require attention, memory, semantic and syntactic processing as well as imagery to work together to understand and enjoy the song. This widespread engagement helps facilitate an equally widespread network in the brain which sustains its functioning even after some local neural damage due to the described interwoven working mechanism. It possesses the unique ability to access affective and motivational systems in the brain, providing time structures that enhance perception processes, mainly in the range of cognition, language and motor learning.

Further, music serves to modulate the emotional as well as cardiovascular systems of the body. Depending on the state induced by the kind of tempo, rhythmic meter and timbre, these effects are brought about by feedback loops between psychological and physiological responses.

Prior conditionings and personal memories associated with the music can stimulate defined emotional states that in turn regulate our heart rate, blood pressure level and breathing. The neurochemistry also points to increased levels of dopamine and serotonin when we are listening to pleasant music. Similar effects are produced by the momentary experience that music brings. Specifically, the pleasure brought about by music is described in a recent study (Koelsch et al., 2019) as a function of our predictions about the next tone in a melody. Music, due to its rhythmic flowing nature constantly provides the opportunity to prove or disprove hypotheses our brains have made about various stimuli. When your brain predicts correctly, it triggers the associated neural circuits bringing about pleasure.

Thus, cognitively, music serves to use the past, present, and

future evaluations of the environment together to induce biological changes. The discussed biological changes in turn regulate hormone levels that have an impact on the anxiety and stress of an individual. Excess of corticosteroid is detrimental to health and surprisingly, the levels of these steroids are balanced out by music, increasing it in subjects with lower hormone levels and decreasing it in subjects with high hormone levels.

Specifically, music is specially known to affect steroid and corticosteroid hormones along with the BDNF (Brain Derived Neurotrophic Factor) which in turn not only attenuate stress but also directly affect cerebral plasticity. They are known to contribute to expression, regeneration and repair of nerve cells (Fukui & Toyoshima, 2008;Marzban et al., 2011).

Following a study for stroke recovery with 60 patients where three sections were assigned to control, language and music groups, Särkämö et al., found that there were significant improvements seen in the music group over the control as well as the language group. After 6 months of rehabilitation, verbal memory and focussed attention improved along with depressive and confused symptoms (2008).

Besides cell protection and reparation, oscillatory activities like the ones stimulated by music play an important role in recovery. Neurologic Music Therapy (NMT) has recently been developed substantially as a concrete, widespread implementation of music therapy. This evidence-based treatment model focuses specifically on music and rhythm's physical effect on the brain and neural pathways. Neurologists involved with NMT describe everyday human movement as kinetic melody and biological processes as circular rhythmic patterns. Perhaps it is then poetic justice that the deep fundamental relationships between neural workings and music are successful in re-tuning this melody when conscious instruction fails.

Listening to music is as much an active process as creating it is. This dedicated involvement with the process perhaps is what leads to revolutionary ideas for utilizing this tool; socially, psychologically, as well as academically. If music therapy can help us blur the lines between abled and disabled, everyone - trained and amateur members of the music community alike, as well as those receiving health benefits from it - can share a little bit of what makes us all human. Music Mends Minds, a non-profit organization based in Los Angeles, is one such community

that seeks to vitalize patients suffering from neurodegenerative diseases through music. By creating musical support groups amongst diagnosed patients, they foster a sense of community between musicians and singers, as well as their friends, families, and caregivers, all of whom thrive on socialization and music-making. This empowerment and engagement of patients suffering from neurodegenerative diseases through unique and novel services like Music Mends Minds helps in providing them with some semblance of shared beauty still left to experience. In 2018, a documentary aired on Youtube that highlighted the experiences of these band members, many of whom spoke highly about their overall sense of well-being after joining. In her early diagnosis, band member Carol Hicks felt that Parkinson's Disease had defined her life. But the weekly band sessions in her words elevated her moods and became reminders and reaffirmations of her true identity — a friend and a musician. Dorothy, a member of the Santa Barbara chapter band, had also begun feeling really frustrated when she first started out because she felt she wasn't playing her mbira very well. The inclusive and uplifting nature of the community, however, catalyzed not only her motor skill development and ability to play well, but also her overall self-esteem and confidence. While pharmaceuticals are great when addressing brain chemistry, stories like these — though they may not see the light of day in the statistics or in scientific articles — successfully grapple with the daily issues of being a human being and having one's own identity, heart, and claim to be who they are.

In a world of chaos and conflict, music is able to spark a flame in each and every one of us that transcends any socially constructed barrier that has ever divided us. Culturally, music has served as both a practice and a tool in forming strong bonds amongst people by expressing common interests, shared histories, and collective hopes for their lives. It is only now that we are discovering a similar expression by the human body and its constituent systems. Neurodegeneration has been on many occasions defined as irreversible. Whether it is our misclassification of symptoms as irreversible (as described by a study by Hinz et al., 2016) or a lack of deeper understanding about the degeneration itself of neural cells, music has forced us to change our dooming ideas about related diseases. The empirical evidence of regulatory consequences brought about by a music-induced balance of internal systems gives hope for the management and perhaps someday, cure for neurological diseases.



OLD AGE

“How body from spirit slowly does unwind, until we are pure spirit at the end”

Theodore Roethke

BCI's and Neurorehabilitation

By Shanaya Sidhu

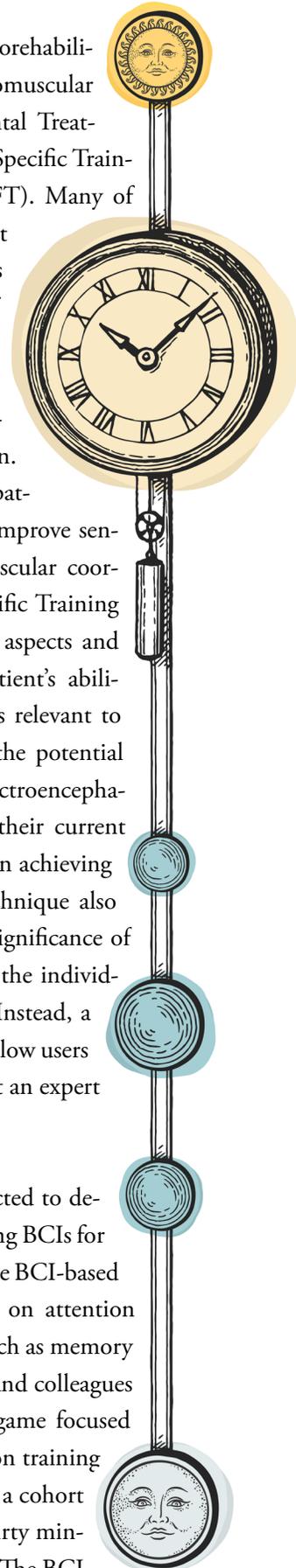
Aging is a natural process that is inevitable for all people. As society makes advancements in technology and healthcare, life expectancy and the proportion of elderly that make up our population have increased: 22% of the world's population will be 60 years old or older by 2050.

When we think of aging the more obvious physical changes often come to mind: grey hair, wrinkles, and poor posture. But there is something much more profound going on inside of us. As we age, our brains undergo many changes not only in size and vasculature, but also in cognitive ability. We experience a natural decline in memory and attention, which are further exacerbated in the most common neurodegenerative disorders impacting older adults, such as dementia, Parkinson's disease, and Alzheimer's disease. This natural decline in functioning of older adults' nervous systems affect various aspects of their lives beyond just memory and attention, such as movement, thinking, learning, sensory perception, sleep, behavior, judgement, speech and language, mood, and problem solving.

Despite these neurological changes, there is one important capability of the brain that is maintained over time. Neuroplasticity, the ability to reform and develop new connections between neural synapses in response to learning. While the rate and extent of learning declines as we age, neuroplasticity still remains intact, contrary to the prevailing notion that "you can't teach an old dog new tricks". So how can we use neuroplasticity to combat the natural effects of aging? The main method is neurorehabilitation, which is the medical process of recovering from an injury to the nervous system. Although neurorehabilitation is normally administered in a medical setting, the recent and rapid development of brain-computer interfaces (BCIs) has allowed for technological, user-friendly means of administering neurorehabilitation. BCIs are computer-based systems that record, analyze, and transform brain signals to use them as commands for technology, allowing for example, a person to type out words or control a wheelchair using purely their brain signals. With the development of BCIs targeted towards our ageing populations, it is important to reflect on current models of neurorehabilitation for geriatric populations.

Some of the current models of neurorehabilitation include Proprioceptive Neuromuscular Facilitation (PNF), Neurodevelopmental Treatment (NDT), Task-Analysis and Task-Specific Training, and Neurofeedback Training (NFT). Many of these techniques focus on movement and neuromuscular aspects and thus require a medical setting and team of professionals. PNF, for example, uses muscle strengthening and stretching to improve joint stability, neuromuscular coordination, and range of motion. NDT similarly focuses on movement patterns and motor learning in order to improve sensory-motor functioning and neuromuscular coordination. Task-Analysis and Task-Specific Training moves away from the focus of motor aspects and instead focuses on improving the patient's ability to complete certain functional tasks relevant to them. NFT is where we start to see the potential applications of BCIs; NFT uses electroencephalography (EEG) to show individuals their current brain waves and trains them to focus on achieving an optimal pattern. However, this technique also requires a professional to explain the significance of brainwave patterns and identify when the individual has achieved the optimal pattern. Instead, a BCI can interpret the brainwaves and allow users to undergo neurorehabilitation without an expert present.

Current clinical trials are being conducted to develop a cognitive training system utilizing BCIs for healthy elderly individuals. Most of these BCI-based cognitive training interventions focus on attention since it is critical for other processes, such as memory and problem solving. A study by Lee and colleagues in 2013 tested the effectiveness of a game focused on individualized memory and attention training using a BCI. The training was done on a cohort of healthy elderly individuals for 24 thirty minute sessions over the course of 8 weeks. The BCI



analyzed EEG waves to quantify attention level, therefore allowing individuals to use their attention to control a computer game. The system calibrated one's baseline attentive state and EEG profile before playing the actual game, creating an experience tailored to each subject. The actual memory game consists of computerized card-pairing, during which individuals can open and close cards on the screen by using their attention and focus. Before and after the use of BCI over the course of 8 weeks, there were significant improvements in immediate and delayed memory, visuospatial skills, and attention.

In another study conducted by Laiz and colleagues evaluated similar cognitive domains, including memory, attention, intellectual, spoken language, and visuospatial domains, via BCI-based cognitive training programs designed for elderly individuals to avoid cognitive impairment. Elderly participants were asked to participate in 10 training sessions spanning over 5 weeks, including one 60 minute neurofeedback training using BCI and one 20 minute working memory training session per week, for a total of 10 training sessions throughout the course of the trial. The training sessions included activities focused on pictorial recognition, visual perception, expressive and receptive speech, spatial orientation, and immediate and logical memory. For example, the test of immediate memory involved memorizing and retaining 10 words whereas the logical memory test focused on relationships participants made to memorize items. All activities aimed to resemble common daily activities in order to make the training more functionally useful and improve quality of life. Before and after the 5 weeks of training, results showed that the experimental group had significant improvements in all cognitive domains mentioned earlier in comparison to the control group.

Another successful study by Jiang and colleagues used scalp EEG and neurofeedback training to create an BCI-based cognitive training intervention focusing on attention levels. The test presents a series of superimposed transparent images of a scene and a face. The participant, who wears an EEG headset that can record brain signals related to attention, is asked to then focus on one of the images, either the scene or the face, and ignore the other. Based on known EEG markers, which are brain signals known to be associated with certain brain processes, the experimenter could measure the level of attention and focus the subject was applying to the target image. A high level of attention would cause the target image to become clearer,

thus rewarding the participant for their focus.

All of these successful clinical trials point to the promising efficacy of a BCI-based cognitive training system for older adults, and BCI-based interventions are beginning to be seen as more preferable over traditional neurorehabilitation and cognitive interventions. They do not require trained professionals and can be completed from the comforts of one's own home, which is particularly useful for older adults with financial or mobility issues. These interventions are also user-friendly, interactive, and usually non-invasive. As the elderly population continues to increase, using such accessible interventions can help easily improve the quality of life of older individuals and potentially reduce national healthcare costs tied to age-associated cognitive declines. Additionally, since BCI uses neurotechnology to record and analyze brain signals, these systems can also be used to identify early EEG markers of cognitive disorders and issues with brain connectivity, allowing older individuals to be diagnosed and seek medical care earlier.

Despite the benefits of BCI-based cognitive training systems, there are some issues with their large-scale implementation. The success of the system truly depends on the individual, first and foremost. For example, older individuals must have a high level of motivation to stick to a training routine, since such biofeedback interventions are only useful if they are practiced over regular repetitions over the course of a certain time period, often lasting several weeks. The distribution and regulation of these devices also leave us with more questions than answers. How many older individuals will have access to such BCI-based cognitive training systems, both on a national and global level? How much will these systems cost? How can these systems be utilized in developing countries and in underserved communities? Other issues with implementation of these systems concern regulation. What medical regulations and policies will be put in place to ensure successful implementation of these devices?

These are questions we must answer if we want to reap the cognitive rewards of a BCI-based cognitive training system. BCIs can be extremely helpful for improving the cognitive functioning and quality of life of our growing elderly population, but it is important to consider their limitations in order to assess the impact and feasibility of such incredible technological interventions.

Molecular Symphonies and Neurodegeneration

By Sameer Rajesh

The Tiniest Philharmonic Orchestra

Anyone who has watched a symphony can see the beauty of moving parts working in unison. Philharmonic orchestras composed of nearly a hundred musicians playing instruments from the octobass to the piccolo produce amazingly harmonious, euphonic sounds despite having so many individual components.

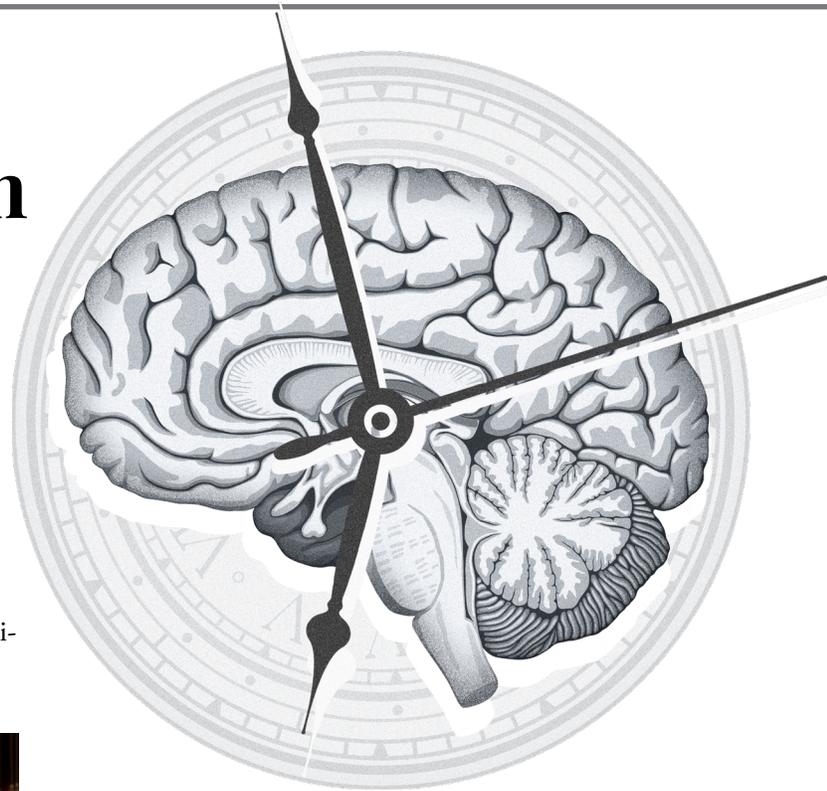


The Berlin Philharmonic

The same thing happens on a larger (and smaller) scale inside a cell. The basic units of life, cells contain an immense number of individual molecules dynamically interacting with each other to perform specific functions. There are many different classes of such molecules, from the energy-producing carbohydrates to the information storing nucleic acids DNA and RNA. But on a much deeper level, the real molecular machines are proteins. The set of different proteins that exist within a cell is called the proteome—and just like a real symphony, all the different proteins in the proteome must work together to create the harmony we call life.

Little Musicians

Proteins are polymers. This means that they are composed of

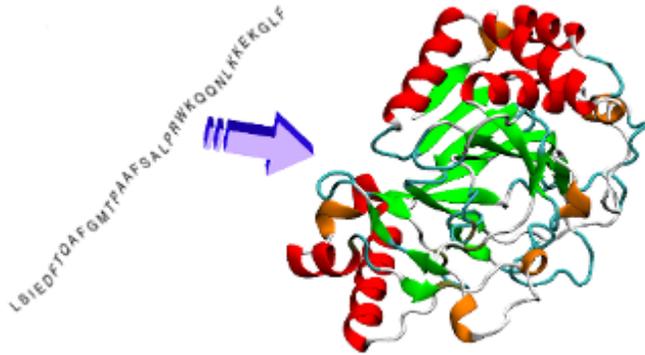


Graphic by Chris Seo

many individual building blocks, referred to as monomers. In the context of proteins, the monomers in question are amino acids, and there are a set of 20 amino acids that are used to build nearly every protein that has ever been identified in any organism on Earth. Proteins are essential to a cell's ability to survive and reproduce. Some proteins provide structural support, such as collagen or keratin while others facilitate movement, such as dynein, actin, and kinesin. A class of proteins called enzymes function as catalysts and help make biological reactions more favorable. Just as the number of instruments in an orchestra is vast, so too is the number of different proteins in the proteome—in fact, the latter is far more diverse in both structure and function.

In addition to being a linear chain of many individual amino acid units, a protein can also be folded into a three-dimensional structure. This protein folding process is facilitated by the formation of interactions between different parts of the protein with each other, as well as interactions with the environment. Much in the same way that each instrument in our symphony should be tuned appropriately, so too should a protein's structure be tuned to the correct conformation, called the native state. The most fascinating thing about this process is its repeatability. For example, when taught how to fold an origami

swan, most children will not be able to reproduce exactly what they were shown, and several different swans made by the same child may not all look the same. The natural process of protein folding, however, is much more accurate. In a healthy cell, two chains composed of the same sequence of amino acids will almost infallibly form the same 3-dimensional structure—much in the same way that two violins would be tuned to the same frequencies in an orchestra.



Basic schematic of a protein chain folding. Each amino acid is represented as a single letter in a chain.

A protein's structure is intimately connected to its function. For example, a channel protein that allows small molecules and ions to pass through the cell membranes of cells must adopt a tube-like shape. Other proteins that catalyze specific reactions must have a section of their structure that selectively binds to the reactants of that reaction; this is known as the active site of an enzyme. Just as an instrument should be tuned properly in order to produce the proper notes, so too should a protein's be folded nearly perfectly for it to be able to perform its function well.

A Delicate Balance between Harmony and Chaos

It's easy to tell when someone hasn't tuned their instrument; it just sounds wrong. Protein folding is susceptible to the same sort of error, imaginatively referred to as protein misfolding. The process of a linear protein chain folding up into its stable 3D native conformation primarily takes place in the endoplasmic reticulum (ER) of a cell. The ER is a subcellular component known as an organelle and shares the same relation to a cell as does an organ to a human, for example. The ER is a rather intelligent organ, in that it is able to detect proteins that are folding incorrectly and degrade them to recycle their component amino acids. This allows the ER to maintain "proteostasis", an equilibrium state of fully functional proteins within the cell. But sometimes proteins misfold too quickly for

the ER to cope on its own. This activates a large-scale cellular response known as the unfolded protein response (UPR). The UPR takes more drastic action towards restoring a cell's proteome to the equilibrium. To maintain proteostasis throughout the cell, the UPR causes misfolded proteins to be degraded, inhibits the production of new proteins, and often even leads the cell towards programmed cell death, called apoptosis. In short, the UPR would prefer to kill a cell rather than allow misfolded proteins to accumulate. Hopefully, the violists reading this will now think twice before coming to practice untuned.

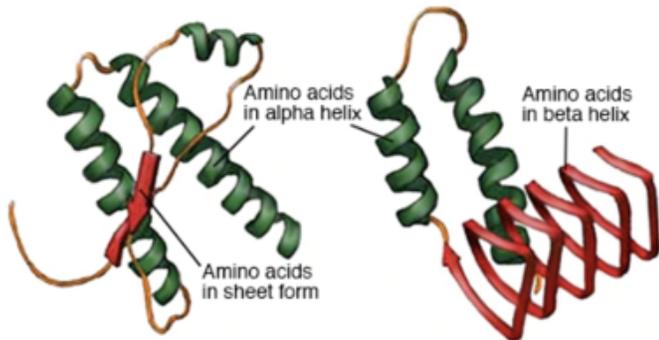
Maintaining proteostasis is an essential aspect of all living organisms, and the UPR is an effective, but oftentimes overactive means to regulate it. Though healthy human cells can regulate the UPR well, diseased cells containing large amounts of unfolded proteins can trigger overactivity of the UPR. Once the UPR begins to act hyperactively, it can result in widespread cell death and lead to many disorders. Notably, hyperactivity of the UPR has been implicated in the pathology of many neurodegenerative disorders including Alzheimer's and Parkinson's diseases.

Seeds of Doom

There are several different neurodegenerative disorders which are deeply rooted in the misfolding of proteins and the hyperactivity of the UPR. These disorders are referred to as proteopathic disorders, due to their pathologies being fundamentally based in the disruption of proteostasis. Among these disorders is Creutzfeldt-Jakob disease (CJD). CJD and the closely related "variant CJD" (vCJD) are classified as Transmissible Spongiform Encephalopathies (TSEs). To break down this mouthful of words, a spongiform encephalopathy is a disease that infects and degrades the tissues of the brain, leaving behind a network of spongy brain tissue riddled with holes, which can be seen under a microscope. These diseases are fatal within weeks. In addition, CJD is transmissible. You cannot, of course, contract CJD when someone sneezes near you—but vCJD, in particular, was observed in many individuals who ate beef coming from a certain subpopulation of cows affected by the well-known "Mad Cow Disease". Scientists posited that there was a transmissible agent that caused both Mad Cow Disease (or bovine spongiform encephalopathy, BSE) and vCJD. It was hypothesized very early on that it was a protein particle that was responsible for this transmission, but it was only in the late 80s'

that the protein infectious particle—called a prion—was discovered and isolated by Stanley Prusiner of UCSF. Prusiner would go on to win the Nobel Prize in Physiology and Medicine in 1997 for his discovery of the human prion protein PrP.

Prions are not bacteria. They're not viruses either, although just like viruses, they are nonliving and require another organism's molecular machinery in order to replicate. A prion is a misfolded protein that is stable enough to not be degraded quickly by cellular responses to unfolded proteins.



The structure on the above left represents a properly folded segment of a protein. The structure on the right is a misfolded, stable version of the same chain, indicating it may have pathogenic properties.

These prions are especially resistant to degradation after they clump together and aggregate. Prusiner had discovered only one such example of a stable, misfolded protein. Since then, several other prions have been discovered. In addition, it was found that most of these prions were misfolded versions of proteins that had relevant roles to play in the normal cellular context when folded correctly, leading scientists to study how misfolded prion forms of protein should interact with the stable, normally folded versions. The dominant theory now is that misfolded prion forms can induce the same misfolds in other proteins of the same type. Prions are able to “communicate” with functional proteins and refold it into a prion form, much like a cellular version of Agent Smith. This process is known as prion seeding and is the basis of transmission for transmissible spongiform encephalopathies. Beef from infected cows likely contained a variant of the prion protein which was able to enter nervous tissue and cause widespread misfolding of more prion proteins, which eventually led to the aggregation of plaques of misfolded proteins, inhibited neural signaling, and caused neuronal death. The protein plaques (referred to as amyloids or aggregates) composed of abnormally folded proteins were actually responsible for causing the sponge-like appearance of brain tissue by initiating the widespread and rapid neuron death. Protein plaques and aggregates become increas-

ingly relevant in the context of many other neurodegenerative diseases, especially Alzheimer's disease.

The prion basis of CJD transmission and pathology sparked a new era in the study of molecular bases for diseases. The playing field had changed, and a new type of foreign invader, completely different in function from both bacteria and viruses, had come into play. Many labs are working on studying the prion basis of neurodegeneration in other contexts, most notably in Alzheimer's and Parkinson's diseases.

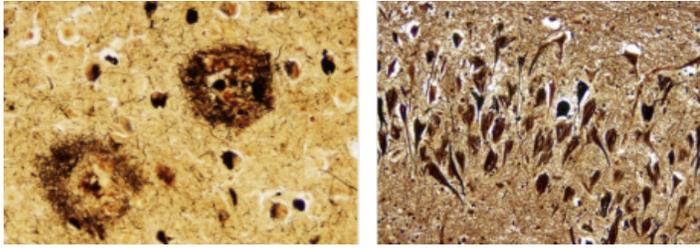
The Infamous Amyloid Beta

The Alzheimer's Association indicates over 5 million Americans are affected by the disease today. In 30 years, that number is projected to rise to nearly 14 million. The statistics are grim, but they have also fueled research into the mechanisms of Alzheimer's, and have led to the development of treatments that attack the disorder from many different directions.

Alzheimer's disease is most famous for causing rapid dementia, among other neurological problems. Sufferers quickly lose the ability to function independently, and life expectancy falls to between 3 and 9 years after diagnosis. Alzheimer's disease is difficult to detect until symptoms develop, which is after the quality of life has already decreased for the patient. Several hypotheses exist regarding the molecular mechanisms by which Alzheimer's is caused. Two of the most popular hypotheses are that Alzheimer's is caused by the aggregation of prion forms of the Amyloid Beta peptide $A\beta$ and related peptides (a peptide is a small protein or a section of a protein), or the aggregation of the tau protein prions.

Both $A\beta$ and tau are known to exist in the normal cellular context, and it is thought that they do serve important functions. Some studies have pointed towards their involvement in the structural stability of neurons and intracellular neuron signaling, both of which are essential for a healthy nervous system. $A\beta$, the less understood of the two, is especially (in) famous because plaques composed of misfolded $A\beta$ prions are found in the brains of nearly all individuals who suffer from Alzheimer's disease. The aggregation of tau proteins results in tau amyloid fibers, which along with $A\beta$ plaques interfere with normal cell signaling. These disruptions cause neural circuits degradation and eventually neuronal death, similar to CJD and

other spongiform encephalopathies. Another scary similarity between CJD and Alzheimers is transmissibility.



Above left: Large amyloid plaques.
Above right: Fibrous tangles composed of tau prions.

Studies have shown that there is significant evidence that the tau and A β aggregates are formed similarly to the prion protein aggregates in CJD, and seeding has been demonstrated for tau and A β as well. There is evidence that introduction of prion forms of tau and A β to healthy mouse brains (which are good models for human brains) can cause protein aggregation and amyloid formation, leading some to wonder if contaminated surgical tools used on patients with Alzheimer's disease can transmit prions to the brains of healthy individuals. Though no definite cases of human-to-human transmission Alzheimers, a 2015 study done on individuals who had passed away due to CJD found that they had contracted the disease as a result of contaminant prions being present in growth hormone supplements they had been receiving for hormone therapy. Upon autopsy, their brains were unexpectedly found to contain advanced aggregates of A β peptides, suggesting that perhaps a misfolded A β variant was also present as a contaminant in the supplements (or that the CJD prion protein was able to induce misfolds in A β), and that had the CJD not killed them first, they may have developed Alzheimer's. Researchers recently confirmed that Alzheimer's could be transmitted to mice by injection of the A β prion. This suggests that neurosurgical tools that are contaminated with A β prions can transmit Alzheimer's to uninfected humans, indicating that this is a public health concern that should not be neglected whatsoever.

Although there is a good molecular framework for understanding some of the causes and pathologies of Alzheimer's disease, we are still unable to use that information well in a diagnostic capacity. The most common way to diagnose Alzheimer's is through many brain images to first rule out other diseases, and subsequent analysis of the medical history and mental capacity of the patient. To get a definitive diagnosis of Alzheimer's, a biopsy of brain tissue must be analyzed under a microscope through imaging techniques to find A β plaques—this technique

is invasive and generally used only postmortem. Still, the ubiquity of A β and tau amyloid plaques in the brains of Alzheimer's patients suggests that perhaps diagnostic techniques focused around these aggregates could provide methods for earlier detection and risk screening.

The information we have about A β plaques and tau aggregates has provided promising information and has led to new directions in the pharmaceutical industry as well. Researchers have investigated Alzheimer's disease in a mouse model and found that medications that decrease or degrade A β have been able to combat symptoms of Alzheimer's, but far more work has to be done in this field. Other scientists, such as Dr. Marc Diamond, are also working on studying Alzheimer's from the standpoint that it is a prion based disease, similar to CJD. Diamond's lab works to analyze tau protein amyloids from a prion standpoint so that one day therapeutics can be developed that target the prion seeding mechanism and the aggregation process. Discovering new ways to target the protein aggregates implicated in Alzheimer's disease may eventually lead to medications and treatments that can greatly restore quality of life for patients. One day, we may even have a cure.

Tremors

The second most common age-related disease globally, Parkinson's disease is a degenerative motor neuron disease. Parkinson's is marked by rapid neuronal death in the basal ganglia, specifically the substantia nigra, a portion of the brainstem involved in regulating movement. Studies have shown that animals with dysfunctional substantia nigras, particularly in the pars compacta region (Substantia Nigra pars compacta), are unable to coordinate fine motor movements. Neurons in the SNpc are called dopaminergic because they are involved in secreting the neurotransmitter dopamine. Because of the rapid death of dopaminergic neurons in the SNpc, Parkinson's patients gradually lose control over fine motor movements. This has led to scientists developing dopamine based treatments for Parkinson's. Indeed, the most common medication for Parkinson's is Levodopa, a specific form of the dopamine molecule which is taken to supplement the lack of dopamine caused by the death of dopaminergic neurons.

After performing a biopsy or autopsy of the substantia nigra of a patient who has Parkinson's, one observes large protein

aggregates. These aggregates are named Lewy bodies, after their discoverer Fritz Lewy. Upon analysis, it was discovered that these aggregates are composed of α -Synuclein proteins. α -Synuclein is a structural protein thought to be involved in several neural signaling pathways and primarily regulates the release of different neurotransmitters, dopamine in particular. It is no surprise then, that aggregates of misfolded forms of α -Synuclein disrupt and kill neurons involved in dopamine release.

Our understanding of α -Synuclein aggregation is not at the same level as our understanding of A β and tau amyloids. It is likely that α -Synuclein aggregation is caused by misfolds seeding other misfolds, as is the case in other proteopathic disorders. Evidence has shown that α -Synuclein is capable of this. But due to the large focus of therapeutics involving dopamine for Parkinson's disease, there has only recently been a surge of interest in understanding the prion biology of α -Synuclein. Perhaps as we continue to study the prion biology of Parkinson's disease we can learn more about its molecular pathology and develop new treatments.

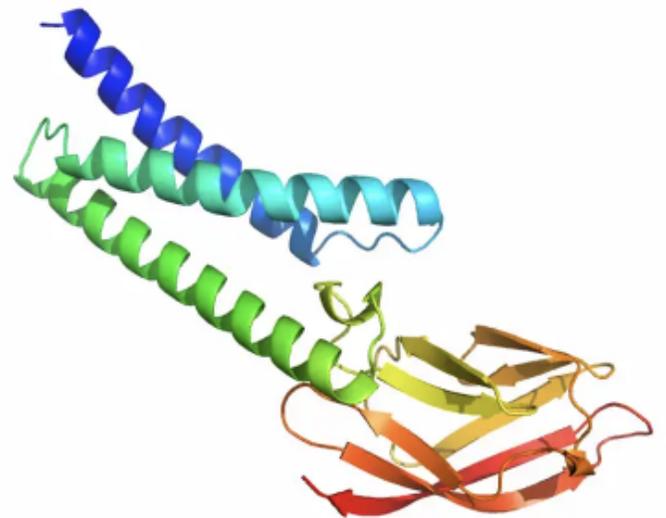
It is interesting to note that many other neurodegenerative diseases, such as Huntington's or ALS, are also related to protein plaque aggregations—it is hypothesized by some that the prion basis for disease is common to many neurodegenerative disorders. If this is true, our understanding of prion biology could be crucial to improving treatments for many different disorders which were previously not considered very similar. The true ubiquity of prions as causative agents of these disorders remains to be seen, but current insights seem extremely promising.

Google It!

Living in an era dominated by data and computing, it should come as no surprise that scientists have been working on developing algorithms that can predict a protein's folded, stable, native conformation from just its primary sequence of amino acids. The problem of predicting structure from sequence is creatively referred to as the protein folding problem, and is incredibly complex from a computational standpoint, despite sounding quite simple. The problem is referred to as an NP-hard problem. This means that given a primary sequence of amino acids, it is very difficult to come up with a solution for a 3-dimensional folded structure—however, given an arbitrary folded structure for a particular sequence, a program can verify

how stable the fold is. In recent years, the task has gotten easier as computational biologists can use the tools from the world of data science, such as machine learning, to come up with predictive structures much faster than was previously possible. The field continues to grow explosively

But why bother solving the problem at all? As was mentioned earlier, a protein's function is intimately linked to its structure. By predicting structures of proteins, we can determine the effect different mutations have on a protein's function. We can artificially engineer small proteins to carry out specific functions as well. Relevant to our discussions, we may even be able to study how prions can induce misfolds in normal proteins if we are able to learn more about prion structures. In the advent of new predictive structure determination algorithms, molecular biology has been revolutionized globally and new discoveries are being made that might not have been thought of a decade or two ago.



AlphaFold generated structure prediction of a protein involved in COVID-19

The push to develop newer and better algorithms is so great that there is even a competition between computational biologists to see whose algorithm is the best. This year's winner of the Critical Assessment of Structure Prediction (CASP) competition was Google's AI-based algorithm called AlphaFold from DeepMind Technologies. AlphaFold works by using several different neural networks, machine learning models that are based on how neurons function, to construct structures for small segments of a protein. The algorithm then anneals these substructures together and optimizes certain parameters repeatedly until it finally settles on a steady-state "best" solution. Scientists at Harvard have since claimed to have developed

even faster (though less accurate) algorithms, and while the details of the algorithms are rather complex, the success they have achieved is extremely promising. Google's AlphaFold has already been put to work in analyzing and predicting protein structures for proteins involved in COVID-19. In short, studying the protein folding problem from a computational standpoint can pave the way towards understanding how prions are generated and how they seed misfolds. Studying entire aggregates and plaques from a computational standpoint, though extremely challenging, could provide new insights towards the development of novel therapeutics that target these aggregates.

The Last Movement

I hope that by now, you've managed to gain a little more appreciation for the tiny orchestras of molecules that keep us alive and well. These ensembles and systems in equilibrium help us construct models for disease, and provide insights towards solving some of the biggest problems that affect the medical field today. There is much more information to be gleaned from studying these little musicians that play in the majestic symphony of life. 

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3514124/>

<https://www.nature.com/articles/s41586-018-0790-y>

<https://www.utsouthwestern.edu/labs/diamond/research/>

<https://www.nature.com/articles/nature15369>

<https://blogs.scientificamerican.com/artful-amoeba/the-case-for-transmissible-alzheimers-grows/>
www.nature.com/news/autopsies-reveal-signs-of-alzheimer-s-in-growth-hormone-patients-1.18331

How to Treat a Graying America

By Jessica Singh

In 10 years, 1 in 5 individuals will be of retirement age within the United States.¹ With baby boomers continuing to age and fertility rates decreasing, the 2030's will represent a radical shift for population demographics globally and bring a new set of challenges. Namely, an older population will mean an increase in patients due to a wide variety of medical concerns. "Incidence of stroke, white matter lesions, and dementia rise with age, as [do] level[s] of memory impairment"². We like to believe that the pills and treatments doctors prescribe are well thought out and equipped to handle this influx of aged patients, but is that really true?

Every medication that the FDA approves is subjected to foundational investigation, pre-clinical research, and multiple phases of clinical trials. The system is extensive and laborious, but it is still failing our growing elderly population. The very clinical trials that are designed to decide the treatments for the elderly, often fail to include them. Fifty percent of all clinical trials have upper age limits. If there isn't an age limit, exclusion criteria such as "comorbid conditions, cognitive impairment, and polypharmacy" eliminate older patients.³ Unfortunately, upper age limits are rarely justified, but ethical review boards often disregard that. Pharmaceutical companies will even eliminate older patients to boost their internal validity and increase the marketability of their product.

Simultaneously, there are very real challenges when trying to include the elderly in clinical trials. Cognitive impairment can make obtaining informed consent extremely difficult, and comorbidities and external factors such as limited transportation can cause increased attrition.³ However, there are ways around these limitations. "The Interventions on Frailty Working Group has developed recommendations to screen, recruit, evaluate, and retain frail older persons in clinical trials". Initial screenings should be used to eliminate "too well" and "too ill" patients. In supplementary stages, the researchers should work



Graphic by Jessica Singh

to find patients that would both benefit from the trial and are valuable for the researchers. Finally, strategies to limit attrition should constitute an integral part of the study design and disability outcome measures should have both self reported and objective measures to gather accurate information.⁴ These parameters to circumvent eliminating geriatric patients may seem tedious, but they are worth it.

The current lack of representation among the elderly compromises the external validity of medications. Even though neurological disorders disproportionately affect geriatric patients there is an astonishing age gap between the individuals studied and those afflicted with the disorders. A review looking at 165 Alzheimer's trials found that 72% of patients with Alzheimers are 80 years of age or older, but 78% of subjects in trials are younger than 80. In fact, only 5% of the studied subjects were 85 or older.⁵ When medications are not studied on populations representative of the one they seek to treat, their efficacy is questionable at best. Geriatricians are left to extrapolate with insufficient data as they clumsily decide treatments for their patients.

Senescence, the gradual deterioration of our cells with age, can drastically alter our bodies and consequently how our bodies react to medications. There are changes in metabolism, absorption, blood flow, renal function, liver mass, and various other pharmacokinetic parameters. Decreased liver mass results in a decreased capacity for phase 1 metabolic oxidation reactions-- a chemical reaction which breaks down the drugs we

1 <https://www.census.gov/newsroom/press-releases/2018/cb18-41-population-projections.html>

2 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2596698/>

3 <https://www.todaygeriatricmedicine.com/archive/MA19p30.shtml>

4 <https://pubmed.ncbi.nlm.nih.gov/15066083/>

5 <https://alzres.biomedcentral.com/articles/10.1186/s13195-016-0201-2>

consume into pharmacologically inactive or less active metabolites. Therefore, elderly patients are more likely to have higher concentrations of the unmetabolized, active version of the drug in their bloodstream and are consequently more susceptible to drug toxicity. Lowered renal function can relate to diminished filtration causing older patients to retain medications for longer. Finally, decreased hepatic blood flow correlates with a diminished first pass effect (a phenomenon of drug metabolism, where drug concentrations plummet before reaching the systemic circuit). Once again since less of the drug is metabolized, there are higher serum concentrations of the drug leading to a greater potential for toxicity. There is no definite way to decide based on information collected from younger patients on how to dose an older individual. Dependent on the type of drug, how that specific drug is generally broken down, the patient's age, and their individual characteristics, doctors have to determine a specialized dose that can mean either higher or lower concentrations of the medication. What is definite is that all of these changes and their effects on how we process drugs tell us one thing: one size does not fit all. It is simply impossible to test a medication on a 20 year old and expect similar results on a 70 year old patient.

As of January 2019, the NIH has enacted the Inclusion Across the Lifespan Policy requiring grant applicants to justify any age-related restrictions, and provide deidentified age data in progress reports. While this is a step in the right direction, it is insufficient on its own. For starters, the majority of clinical trials are conducted by private pharmaceutical companies and the FDA does not have a similar inclusion policy. Though the FDA has repeatedly advocated for geriatric trials, there needs to be policy changes to fully combat these issues. Additionally, to address attrition and limited volunteers there needs to be active recruitment and education of elderly patients. Unless patients understand why it is important they join such trials and how it will benefit them, the elderly are unlikely to take the initiative to participate.³ By creating policies that require involvement, companies and researchers alike will be forced to take extra steps to accommodate elderly patients and increase their participation in trials.

The Bove lab at UCSF, which studies multiple sclerosis (MS) over the female lifespan, is already addressing this concern and including older women in their work. Differing levels of estrogen can affect the disease course in many neurodegenera-

tive disorders, and MS has clear trends correlating decreasing estrogen levels with increased neurodegeneration and demyelination.⁶ Intriguingly, humans are one of only a few species where people have 30-40 years of somatic longevity even after the ovaries stop functioning. To study this unique phenomenon and address the concerns of post-menopausal women—who are particularly vulnerable to plummeting estrogen levels, the lab is currently conducting a clinical trial to test out a new hormonal therapy. Gender-based and age-conscious care is not the norm because it is difficult to pursue and brings a whole host of challenges. Dr. Riley Bove, the principal investigator at the Bove lab, added that prior to disease modifying therapies, MS patients above 50 were often not physically fit enough so such therapies were not considered valuable. However, as MS therapies have improved, the patient demographics have shifted. While MS affects individuals starting at the age of 25-35, the median age of people living with MS are 50+. Furthermore, the lab has found that patients above 50 are extremely enthusiastic and have joined many of their digital health studies and clinical trials. Thus, Dr. Bove has used her lab and research to try and set up her patients for healthy aging.⁷ Similarly, Dr. Katherine Possin at the UCSF Memory and Aging Center is developing the Care Ecosystem, a phone based intervention program for patients with dementia. Older patients and those with debilitating neurological conditions have trouble coming in to medical providers, so the Care Ecosystem trial is aimed at creating an innovative approach to medical care. A community of caregivers, nurses, dementia care providers, and patients are able to communicate via phone to provide preventative care and allow older patients to actively monitor their health from the comfort of their homes.⁸ This allows for specialized care for older patients who may otherwise be overlooked. Challenging the norms in medicine, the Bove lab and Dr. Katherine Possin represent the future of medicine and an ideal all of medicine should work towards.⁶

A graying America needs representation. Geriatricians have been voicing their concerns for more than a decade, and an aging population will only compound these worries and exacerbate the current crisis. Changes in how we recruit patients, implement clinical trials, and approve medications can drastically increase elderly participation and create the change we need. We need to address these concerns today, so that we are prepared to treat the changed population that awaits us tomorrow.

6 <https://www.ncbi.nlm.nih.gov/pubmed/30696729>

7 Interview with Dr. Riley Bove

8 <https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002260>

Meditation with My Dad

By Saarang Panchavati

As a child, I'd often find myself sitting in my dad's lap while he meditated. I'd watch his slow, steady breaths till they turned to soft snores — becoming more and more convinced that he was napping instead. I'd shake him awake and laugh as he groggily came to life, always with a smile. For almost 30 years now, my dad, like many, has turned to meditation as a means to re-center, improve mental state, and gain clarity. Growing up, I was always skeptical — how could closing your eyes for 30 minutes make you feel better? And even if it did, what made it so?

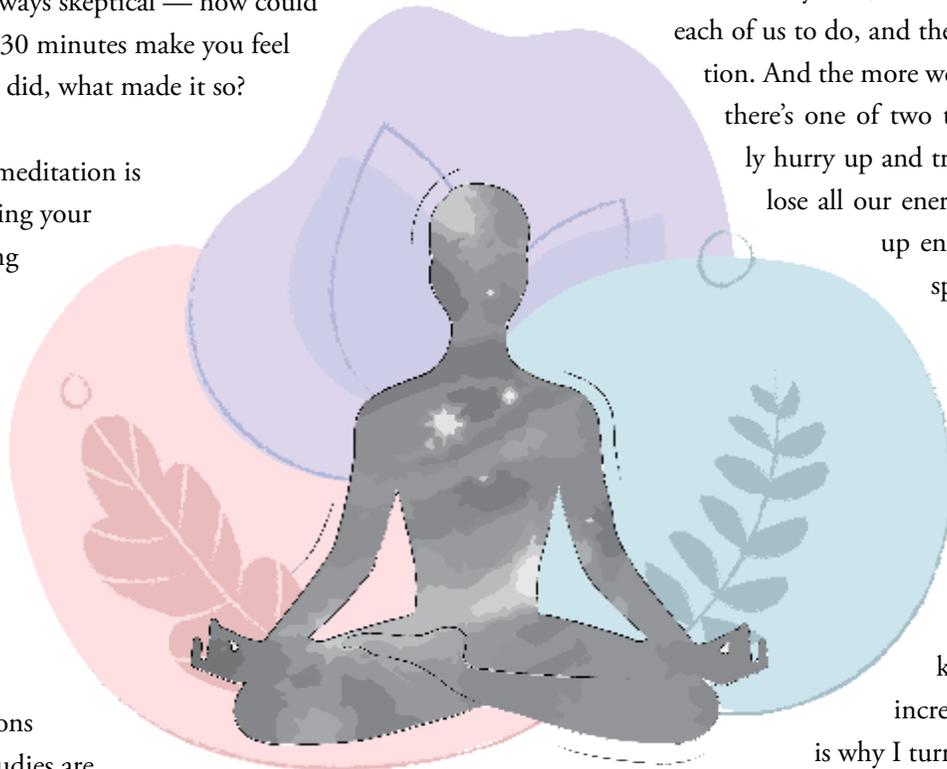
At the highest level, meditation is the process of observing your thoughts, and learning to regulate attention and awareness to promote mental clarity, emotional understanding and mental “peace.” Research into the effects of meditation is still in the early stages, leaving many of these questions unanswered. Most studies are smaller studies with few participants, and even larger studies often to capture the variety of meditation techniques practiced around the world. However, certain highly specific, well constructed studies offer us a glimpse into the biological phenomena behind the clear beneficial effects of meditation.

A lack of hard evidence has not put a damper on meditation practices, as millions of people around the world practice mindfulness every day. For most, the question of how meditation works is not as important to ask because it does work. For this article, I wanted to synthesize some of the stories of how meditation has helped the people around me as they get

older, and identify (and perhaps provide some biological basis for) some of the common mental and physiological effects of a daily practice, starting with the person who inspired me to write this article: my dad. Below is an abridged transcript of a conversation with him regarding the effects and benefits of his daily meditation, and what he's learned through the years.¹

Me: What did you hope to gain when you started a daily practice?

Dad: So in our daily lives, there are so many things for each of us to do, and there is so much distraction. And the more we have to do, the more there's one of two things: either we really hurry up and try to squeeze time and lose all our energy, or we try to build up energy and keep up our spirits but still have to run around in a hurry. Either way we end up kind of getting burned out, which is what was happening to me. I realized that the other alternative is to keep up my spirit and increase my energy, which is why I turned to meditation.



Graphic by Amy Wang

In a meta-analysis,² Young found that “studies suggest that [meditation] decreases depression, anxiety and psychological distress in people with chronic somatic diseases and that it reduces stress, ruminative thinking and trait anxiety in healthy people.” Aging and meditation go hand in hand, as we progress through life, our stresses (both mental and physiological) seem to compound. Meditation appears to have significant physiological and mental impacts on older adults, perhaps because they stand the most to gain. For instance, 50% of adults 55 years and older experience some problems with sleep. Black et al. demonstrated³ that meditation practice could significantly improve side effects of sleep impairment as opposed to other methods.

¹ For context, my dad has been practicing the meditation practice taught by the Art of Living Foundation, a breathing practice focused method that has been taught to millions of people worldwide.
² Young SN. Biologic effects of mindfulness meditation: growing insights into neurobiologic aspects of the prevention of depression. *J Psychiatry Neurosci.* 2011;36(2):75-77. doi:10.1503/jpn.110010
³ Black DS, O'Reilly GA, Olmstead R, Breen EC, Irwin MR. Mindfulness Meditation and Improvement in Sleep Quality and Daytime Impairment Among Older Adults With Sleep Disturbances: A Randomized Clinical Trial. *JAMA Intern Med.* 2015;175(4):494-501. doi:10.1001/jamainternmed.2014.8081

Me: What makes you continue to keep up a daily practice?

Dad: There is a lot of uncertainty across the board, and for me as well, there is a lot of uncertainty in terms of jobs, supporting a family, and providing for others, and it saps people's energy. Every day brings a new challenge. I found that doing a daily practice ends up releasing all the stresses that accumulate throughout the day and also prepare oneself on how to deal with tomorrow. We are creatures of habit, and you have to build up those habits that push you forward and not those that drain you. Meditation is one that pushes me forward.

Me: What style of practice do you follow?

Dad: I got introduced to the Art of Living Foundation in '95, and since then I've been able to utilize the techniques that are taught. I found this very powerful simply because I don't have to invest in anything other than in spending time with myself, my breath, and in learning techniques that more effectively optimize the value of the very thing because of which we live.

Me: Why is the breath so important in the practice that you do?

Dad: There are four ways to increase energy, one is we can eat food. Of course, it provides energy, but we know what happens when we are stressed. We end up overeating or binge eating, making the problem worse. The other one is sleep, but when we are stressed we undersleep and when we are too stressed and don't want to deal with stuff we oversleep. Both the third and the fourth are kind of related. The third source of energy to keep up his breathing techniques, which I do very regularly. And coupled with breathing techniques, when we learn to breathe properly, it takes you into the fourth — a meditative state giving you deep rest that you need and you come out more energized.

Me: Why did you choose this style of meditation as opposed to other ones?

Dad: What we end up doing is typically exploring multiple things. Some people call it spiritual shopping looking for a quick fix. We are always looking for a quick fix these days. You want to have an answer Now, now, now. So if something doesn't provide results in one day or two days or a week, we have a tendency to drop it and move on. My take is that it does not matter what practice you do as long as you're committed and do it for a period of time before exploring others.

At the end of the article I've provided resources and links to explore other types of meditation.

Me: What is it like to meditate?

Dad: One of the most misconstrued notions of meditation that I've found is that meditation is concentration. Meditation is de-concentration or letting go. You let the mind go wherever it wants to go with awareness. Like I already told you, one of the most powerful techniques that I found was what my physics professor told me to do: sit on the bus, observe. Just see where your mind is. It's fascinating. The idea is to keep the mind as crystal clear as possible. How can you keep a mind clear? It is only when we let go.

Mindfulness practices and meditation go hand in hand. Mindfulness can be practiced anywhere at any time, and is most often related to "being in the moment", and being aware about one's mental state. Mindfulness, like meditation, is a skill, and can be developed through meditation practice. What my dad describes here is applying mindfulness in the context of meditation.

Me: What do you feel immediately after you meditate, what's different?

Dad: Soon after meditation as you're letting go, the relief that you feel is very, very palpable. You can do this simple exercise. Just hold your fist, very very tight fist, and then let go. That feeling of relief is a sense of calm, a sense of relief when you are consciously letting go. We let go in the night. If you don't let go in a night, you cannot sleep. But that is nature pushing us to do that. Imagine doing it at will consciously. That is what meditation does.

Elder⁴ et al. demonstrated a significant improvement in perceived mental health for teachers in a high-stress school after repeated daily meditation practice. They showed that in all metrics measured (perceived stress, depression, burnout) and a meta-analysis by Bamber et. al showed promising results across meditation studies in stress reduction among college students.⁵ Meditation's physiological effects on cortisol (the stress hormone) levels and oxidative stress can explain why many daily meditators report reduced stress levels and anxiety.

Me: What are some of the permanent changes you've noticed after practicing for so long?

Dad: Emotions are also related to the breath. If you become

⁴ Elder C, Nidich S, Moriarty F, Nidich R. Effect of transcendental meditation on employee stress, depression, and burnout: a randomized controlled study. *Perm J*. 2014;18(1):19–23. doi:10.7812/39

⁵ <https://www.sciencedirect.com/science/article/pii/S1747938X15000676>

aware of these emotions, you're going to step back and look at your breath pattern. You're able to moderate your emotions through the breath as well. So I have noticed this in myself that I'm able to manage my emotions very well. I'm not saying I don't get angry. I'm not saying I don't get anxious. All I'm saying is to be more aware when I'm getting angry. And in that, I pulled back and then my self-centered and moved on with life. So this awareness has helped me be able to shift the perspective in and around me as well.

A 2005 study⁶ demonstrated permanent changes to brain structure and cortical thickness in long term meditators. These are changes in areas involved with somatosensory, auditory, visual and interoceptive processing. Meditation has also been shown to increase gray matter concentration in regions involved with learning and memory processes, emotion regulation, and perspective taking.⁷ The increased cortical thickness and grey matter concentration may affect brain plasticity in areas involved with cognitive and emotional processing — perhaps explaining the increased awareness and clarity that many meditators commonly cite.

Me: You're getting old, have you noticed any ways that meditation has helped you compared to your friends who might not meditate?

Dad: A side benefit is definitely on how meditation has given me extra energy to focus on other things to take better care of myself. I can't really highlight any big differences because I didn't measure anything before and after. I'm positive that there have been control studies that you could get data from — but I don't have any quantitative data other than my experience. I have noticed that after meditation some of the ailments like back pain and other things have gone away. As I am getting older, physically I have to do more exercise than what I'm doing. But from a mind, intellect, and ego perspective I can definitely say that it has improved in leaps and bounds.

Meditation seems to have a neuroprotective effect — rebuilding gray matter,⁸ myelination or restructuralization of white-matter tracts.⁹ These neuroprotective effects are indicators of a reduced risk of neurodegenerative disease. A reduction in grey matter loss can help maintain neuroplasticity, helping with memory loss, attention decline and a reduced risk for neurodegenerative

diseases. Many older adults present subjective cognitive decline, a condition characterized by decline in mood, health concerns and biomarkers for diseases like Alzheimer's. In adults with SCD, a pilot study showed significant improvements in memory and cognitive function after 6 months of daily meditation practice. A 2015 paper titled "Greater widespread functional connectivity of the caudate in older adults who practice kripalu yoga and vipasana meditation than in controls"¹⁰ showed that this increase in functional connectivity in older adults led to increased behavioral flexibility and well being.

Me: A lot of people think that you should only meditate in times of anxiety and stress. What do you say to that?

Dad: One line answer: Prevention is better than cure.

Me: What advice do you have for people that want to start meditating or mindfulness?

Dad: Please don't wait any longer. You're not doing it for everyone, you're doing it for yourself. If you're not living what you're telling your kids and others to do, then it doesn't matter. Jump on it and get going. We are in an interdependent world, meditation gives you the self-realization to realize how much you're getting caught up in this rat race and help you to include everyone around you in this.

Fueled by growing awareness for mental health, mindfulness activities are taking the world, and the App Store, by storm. Simple practices are becoming increasingly accessible, and people are taking it in stride. Here I am, writing this after a 30-minute meditation, inspired to let everyone in on this well-known secret. As we grow older, we must learn to face the existential dread of our own mortality, and the degradation of our body and minds. Meditation seems to offer a way for us to deal with this, and perhaps slow the erosion of time. [Here](#) are some resources I've compiled for you to try meditating yourself. And most importantly, don't forget to breathe.

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I Have Something to Say, But I Can't Tell You...

By Cris Micheli, Utkarsh Sarawgi, Lucas Steuber, Andreas Forsland

The majority of nations have successfully extended the average lifespan of their citizens. However, the quality of life in the extra years gained from this extension is often overlooked. While it's difficult to approach this from a medical perspective, the widespread adoption of current technologies of human-computer interaction such as portable devices, wearables, mixed reality products, and brain-computer interfaces (BCIs) have made it possible to complement the healthcare infrastructure and augment the quality of life of geriatric populations.

Primarily, these devices can improve their lived experience by facilitating person-to-person communication. This article presents some of those cutting-edge technologies available to support the elderly and those with limited communication abilities, followed by a few prominent use-cases for the aging population.

Technology for Augmentative Alternative Communication (AAC)

Technology can assist the elderly in a variety of ways by leveraging a diversified selection of access interfaces and assistive technologies that augment or compensate for deficits in their physical and cognitive abilities. These portable human-technology interfaces aid humans, without substituting or invading their bodies. This non-invasive approach is called 'assistive technology' as it gently assists human function similar to a walking stick providing stability to an elderly person.

As people age, communication becomes more and more challenging, eventually leading to social isolation. As such, all available instruments able to support or 'augment' communication will assume a very important role in the years to come for aging populations. These technologies are referred to as Augmentative Alternative Communication, or AAC. Specifically, AAC is described as "encompass[ing] the communication methods used to supplement or replace speech or writing for those with impairments in the production or comprehension of spoken or written language."¹

The most ubiquitous modern form of AAC is accessed via a touch screen – often on a commercially available device. Such devices allow for solutions that assist or augment the interaction of users with their surroundings, thereby solving communication roadblocks with their peers. In fact, a substantial percentage of the population (7.6% of adults in the US ²) has some form of speech impediment. As a consequence, the market has shown lately a high adoption rate of portable devices with AAC technologies across all ages, including the geriatric segment.

In particular, there are an increasing number of apps on the market that use the built-in accessibility functions of mobile devices to produce synthesized or recorded language. These apps also employ specialized interfaces designed for specific target populations to provide access to communication (Figure 1). In addition to speaking aids, most portable devices can

Graphic by Amy Wang

¹ https://en.wikipedia.org/wiki/Augmentative_and_alternative_communication

² <https://www.nidcd.nih.gov/health/statistics/quick-statistics-voice-speech-language>



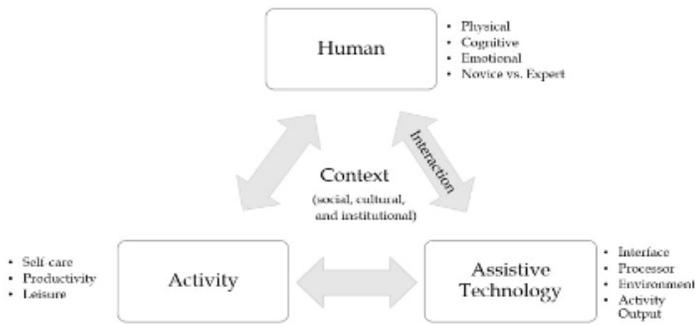


Figure 1: A useful depiction of Augmentative Alternative technologies or AAC (from Elshahar et al 2019). [Licensed under creative commons by 4.0](#)

help communication by easing cognitive functioning. For example, by engaging the user’s attention and memory systems through gaming or providing dashboards that produce simple sentences, the cognitive workload of communication can be distributed and made easier.

Due to recent innovations - like the consumer-grade touch-screen devices mentioned above - we can now design and create affordable high-tech solutions with the potential to exponentially improve the abilities of aging individuals affected by speech or general communication impediments. A handful of companies with clearly defined missions have taken upon this task of delivering consumer-level products that will help solve these challenges, forming a niche technological ecosystem described below.

A Brief and Incomplete Overview of the Tech Ecosystem

CTRL-Labs, originally based in New York, developed an armband to decode arm gestures. This assistive device could be used to convey intended movement or to decode a simple hand or arm gesture with a stipulated meaning. Facebook recently acquired CTRL-Labs for over 500 million dollars, making it part of the Facebook Reality Labs. The financial scale of this acquisition, among many others, demonstrates the consumer electronics industry’s commitment to transform what we currently call “accessibility” into simply another component of user “personalization”, where the product adapts to the consumer rather than the other way around.

Another company, Neuralink, adopts an invasive approach that substitutes the loss of function with technology. Their interface rests on top of the user’s head and transmits information wirelessly from tiny flexible electrode threads embedded

in the brain. It is supposed to provide a near-to-the source interface to assist decoding movement or language intentions where the biological systems are no longer able to do so. As opposed to the earlier mentioned approaches, Neuralink advances an invasive framework by reaching into the human body, rather than having an external product that can be used as a ‘plug-and-play’ device.

Cognixion, a company based in Santa Barbara and Toronto, provides a speech-generating device as an assistive communication solution that interacts with users via multiple non-invasive access points. The app efficiently serves as a prosthetic to provide speech to non-verbal individuals through a user-friendly tablet or phone interface which generates grammatically accurate sentences from a fast access interface with the goal to increase their speed of communication. In technical terms, it seeks to enhance ‘word rate’, a measurement of the amount of words effectively communicated in one minute. The interface is completely customizable and supports eye-tracking, multiple keyboard layouts, and a range of gesture swipes corresponding to the desired messages. For example, a swipe or tap on the iPad screen could select the ‘I love you dad’ tile; alternatively, a blink during directed eye gaze could generate a spoken request for water. The company is also developing a cutting-edge brain-computer interface to augment daily-life conversational skills for people in need (Figure 2).



Figure 2: Three of the many interfaces available in Speakprose® (Cognixion’s AAC app): swipe or tap on an iPad and eye-tracking (above) and Augmented Reality (below). Among other features (not pictured): brain-machine interface. The app vocalizes the desired statement on behalf of the user from a customizable vocabulary

Another striking example of AAC technology is project AlterEgo from MIT Media Lab. It is a non-invasive and wearable real-time silent speech interface that helps people communicate in natural language without using their voice or externally observable movements. All the user has to do is articulate their words internally, and the peripheral neural

interface records electrical activity using multiple surface electrodes around the speech articulators (mouth and throat areas), which are then decoded into speech. The feedback to the user is given through audio, via bone conduction, without disrupting the user's usual auditory perception, and making the interface closed-loop. This feature is commonly adopted in rehabilitation protocols, and in this specific case it leverages neuroplasticity by providing feedback via the bone conduction device about the correctness of a silent speech word.

As opposed to brain-computer interfaces which record electrical activity from the brain, this wearable merely acquires intended speech signals, i.e. internal articulations which are inherently silent and unobtrusive. While a primary focus of this project is to help support communication for people with speech disorders in conditions like Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) among others, the system has the potential to seamlessly integrate humans and computers such that computing, The Internet, and AI would weave into our daily life as a "second self" and augment our cognition and abilities. This can thereby help facilitate unobtrusive and real-time access to personalized content and publicly available information for the elderly people and any other target population with similar needs, while also providing an AI assistant to help form intelligible speech for the affected. (Figure 3).



Figure 3: An elderly Multiple Sclerosis patient using an early prototype of AlterEgo

Many other companies have joined the effort to restore, augment, or supplement the ability to communicate for affected individuals. The use cases detail how technology can aid

communication among the elderly.

Aging and Stroke

The use of portable devices is important among the aging population. Their general availability and accessible interface make them useful for a population with senses that often are naturally in decline. In some cases, this decline is abrupt, such as after a cerebrovascular insult (CVI), more commonly known as a stroke. One frequent consequence of stroke is aphasia, a structural disruption in the brain conducive to impaired language comprehension and/or production. Aphasia is a complex syndrome that presents itself with different symptoms and, while individuals with aphasia can benefit from AAC, their needs are often unique. Thus, a customizable interface with images describing the items to be selected would support such recovering patients. For them, a picture is really worth a 1000 words. The ideal app would support recovering patients affected by stroke and aphasia by providing an effective neurofeedback tool; by viewing the image and accompanying verbal or textual stimulus, they quite literally are able to "recall" a forgotten word or phrase.

Aging and Mild Cognitive Impairment

AAC technology can also support individuals affected by age-related mild cognitive impairment. The symptoms of such conditions are memory loss as well as working memory impairment, which is the inability to retain a thought for a medium to long span of time.

Working memory impairment has a clear impact on communicative efficacy because it makes communication much more cognitively difficult. Assistive technologies can provide resources to help this by reducing the cognitive workload of communication and helping the elderly remember the sentences they want to communicate. For example, having graphic elements that reinforce the context of the discourse within a speech generating app facilitates the retainment of words in working memory and therefore promotes fluid communication.

In general, AAC interfaces can assist communication by lowering the cognitive workload related to word selection by visualizing, or otherwise facilitating the understanding of, both concepts and context relevant to conversation. Such

solutions, paired with personalized vocabulary that learns from patients' routines and the myriad factors that constitute their immediate context, can boost communication and give useful neurofeedback to the user, over time improving their cognitive and communicative abilities. The promise of such AAC technologies is to promote cognitive plasticity and reinstate weakened verbal abilities.

Aging and Hospitalization

Every so often, in a clinical environment, patients wake up in the Intensive Care Unit and find out that their ability to speak is temporarily impaired. Some individuals must receive invasive surgeries such as tracheostomy to restore respiration, and the lack of verbal communication affects the patients as well as their families.

Critical care is a dramatic example of AAC as a communication aid. Most often, aging individuals in assistive nursing conditions or under caretaking regimens experience a gradual decline in their ability to speak. In such cases, speech-generating devices can make a difference in communicating intentions and needs. Portable lightweight solutions with a set of contextual sentences can also make a difference in constrained clinical settings where visiting times are often limited (Figure 4).



Figure 4: Portable solutions as communication aids in critical care can make the difference for non-speaking patients (Speakprose ©, from Cognixion)

The previous examples cover use cases within wearable or lightweight portable assistive technologies. Speech assistive technologies can also compose emergency numbers on behalf of the customer. Another example of such technologies is the fall-detection device, an automatic dialing switch hanging

from the neck of elderly people. The device contacts family members with an emergency preprogrammed call in instances of sudden falls. All these discussions lead towards a question that still remains unanswered— with such apparent diversity of options, how does this all come together for the user – and why would an industry develop dedicated solutions to generating such tools?

Why This Is Important

Let's briefly review how assistive technologies affect the quality of life of elderly people. Due to recent technological innovations such as portable and wearable devices to aid communication by supporting different levels of functionality and human interaction, especially for non-speaking individuals: - they provide neural feedback mechanisms. By providing visual or audio feedback to the elderly, they stimulate more communication and improve quality of life and interaction with other individuals:

- They are lightweight, easily concealed, and cost-effective therapeutic solutions;
- Some solutions allow the caretaker or the individual to personalize the vocabulary;
- Multimodal access for items selection such as eye tracking, gestures, touchscreen displays, brain-computer interfaces, further improve customizability as the elderly can choose their preferred communication modality.

Where once a nonverbal or a minimally verbal individual was limited by the options presented to them, they now have personalized access to the ability to communicate, control their environment, and contribute in ways that were until recently very difficult, causing profound implications at the individual, familial and societal levels.

For the individual, it is not a significant recovery of cognitive function due to effective communication support and neurofeedback of such tech solutions is not unlikely. We, as tech contributors and developers, are motivated to imagine the improved relationship with family and friends, the feelings of integration or diminished isolation, and a better sense of agency and control over their own life. Importantly, such interfaces enable the elderly to communicate their life experiences as part of the human need to pass on their culture and

experience to the next generations.

The impact of AAC on society is already – and will continue to be - profound. Among other benefits, assistive technologies help reduce the burden on staff and caretakers, thus reducing costs for palliative care and psychological therapies and reducing the possibility of misunderstandings and errors.

Every human being deserves to be given the opportunity to share their thoughts and experiences. Communication is not just a functional or transactional act; it is the means by which they expand the span of their well-being; it is a form of self-actualization. For many of us, this key facet of our identity will slowly slip away as we continue to age. Fortunately, we can prevent this with the right technology, allowing the oldest members of society to participate in it once again. —○

Using The Dead to Reinvent The Future

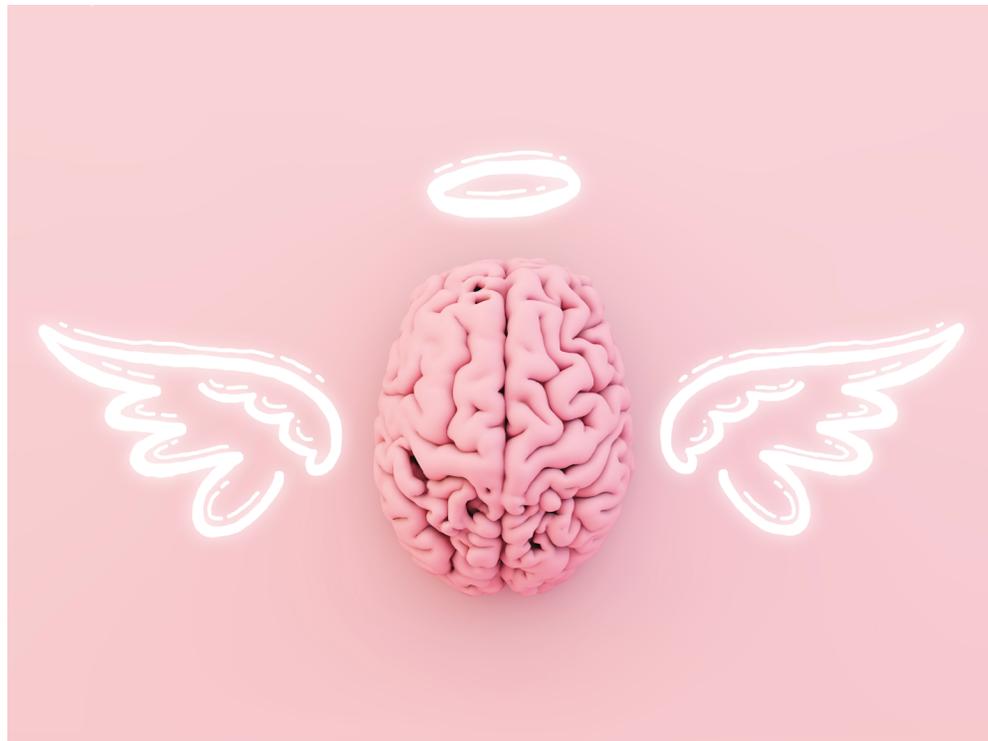
By Hunter Alves

As we journey through life, we create memories of our favourite experiences. Our first love, going to college, becoming a parent, getting married. These memories make us who we are. But, for millions of people, there will come a day when these memories that they have cherished will slowly be forgotten because of a biological inevitability -- the degradation of the mind.

The current treatments for neurodegenerative diseases like Alzheimer's and Parkinson's disease only mitigate the symptoms. The lack of a viable cure is a source of fear and desperation for patients and their family members, and whilst those suffering from these conditions experience the effects first-hand, the healthcare workers and researchers that devote their lives to these diseases face their own set of demoralising challenges; it is these experts who grapple daily with the burden of communicating how the onset of disease will dramatically change their patients' quality of life.

The key to developing the cures to these disorders is rooted in detecting the early symptoms and first signs of progression. From that crucial first level of understanding, researchers can then attempt to reverse or halt degradation and ideally, significantly improve the quality of life for billions of potential patients.

Leading scientists and experts in medical fields have gradually been picking apart and unveiling the underlying causes to these seemingly incurable disorders. Of these, neurotechnology has proven to be an attractive option - showing great promise in its ability to provide answers and clarity concerning why our brains function the way they do. Over the past few decades, with the relatively recent creation of tools/equipment for visu-



Graphic by Chris Seo

alizing the brain, people have assessed the efficacy of neuroimaging to be a stepping stone for understanding the relationship between the activity of specific brain regions and their correlation to certain neurological functions. Specific areas of brain activation have been measured with a few popular devices such as fMRIs, PET, and EEGs - all connected under the umbrella term of functional neuroimaging. Unfortunately, common drawbacks and criticisms to these devices stem from their inability to generate well-trusted statistical analyses. Although it is a major benefit that these technologies can isolate regions of the brain, their inability to provide information on a neuronal level raise lingering questions for researchers as to what interactions could be happening in those localized regions. Although functional neuroimaging has yielded insight for neuroscience researchers, it is important to recognize that due to their more shallow imaging capabilities these technologies do not give many clues about what neurodegenerative disease looks like, nor do they help clinicians and diagnosticians understand a likely prognosis.

However, in 2019 there was a glimmer of hope. The first instance of quantifiable visual data for what an Alzheimer's patient's brain looks like was finally developed.

The efforts of a research team from the Icahn School of Medicine at Mount Sinai yielded a new solution for detecting symptoms associated with Alzheimer's. Coined as the Precise Informatics Platform, it is a novel dynamic between machine learning and microscope technology. In order to visualize and observe anything that we are incapable of seeing with the naked eye (neurons in this case) researchers use microscopes to take images of these objects and particles. Using computer science concepts from artificial intelligence with existing microscope technology to study intracellular interactions, the team analyzed postmortem brains to distinguish between a variety of these disorders. This provided a great amount of information in aid of forming future diagnoses.

To achieve this specialized visualization, the team integrates machine learning capabilities with digitized microscope slides of brain tissue. The images of the samples get transmitted to an associated monitor, where the research team can then visually analyze the biochemical components of the brain samples. The neuroscience behind the creation of this technology is derived from tauopathies – a classification of neurodegenerative disorders that affect primary motor and cognitive functions. The name stems from the intracellular deposition of hyperphosphorylated tau proteins that have been hypothesized to underlie the process.

Unpacking this further, tau proteins are present in different forms - and within the brain as a type of soluble protein, meaning that they can be dissolved in water, and exist freely in intracellular components of cells such as the cytoplasm and nucleus. Tau proteins exist abundantly in our central nervous system and have been discovered to be essential for microtubule stability. Microtubules are proteins that also exist in the cytoplasm of our cells which serve to support and help their shape and structure ensuring that the transport of neurotransmitters across the long distances of our axons can occur seamlessly.

When tau proteins get phosphorylated, the phosphate groups that bind to the protein cause destabilization and the release of the protein's latch onto the microtubules. This is an extremely common biological mechanism occurring on a daily basis. The protein kinase enzyme responsible for this process chemically modifies the binding capabilities of the cells they target through the addition of these phosphate groups.

Without tau, this leads to an immediate impairment of microtubule activity, causing their subsequent instability and disintegration. The combination of these two events elicit neuronal cell death and deactivation of connections within the brain. When tau proteins across neurons detach from their associated microtubules, the phosphorylated tau molecules stick to one another, forming clumps and tangling together. They have the tendency to form neurofibrillary tangles (NFTs), becoming a primary biomarker of how researchers have identified Alzheimer's disease.

Pre-existing studies with microscope technology and stained post-mortem brain samples currently act as the only method of tauopathy diagnosis. In order to provide definitive diagnoses for specific diseases, accuracy and precision are key. Unfortunately, the current microscope technology techniques contribute a substantial degree of inter-and intra-observer variability and are also highly time and cost consuming. Recent interest in analyzing pathological changes of the brain with artificial intelligence has helped improve two aspects of pre-existing research: decreasing the human error rate and bringing uniformity and accuracy in patient diagnoses. This approach hopes to remedy the aforementioned issues that come along with using microscope technology alone.

An advanced form of AI technology being used for analyzing whole slide images (WSI) of post-mortem brain tissue is deep learning (DL). Deep learning is a unique type of machine learning that is based on artificial neural networks, which are algorithms inspired by biological networks such as how neurons communicate. This form of AI is distinct from others because it has the ability to draw conclusions in its own way, generating self-organized outputs from unlabeled data. Deep learning has shown benefits in medical image analysis, sorting through individual patient data and drawing conclusions. Furthermore, and of particular interest to this study, DL has demonstrated the ability to organize WSI based on pathology. With the lack of existence of datasets to apply in machine-based learning for neurodegenerative disease research, the team from Mount Sinai decided to create and test a novel deep learning algorithm to bring us one step closer to understanding the patterns of these disorders.

Directly from their study published in Nature, the team introduces their goals to “recognize, classify, and quantify diag-

nostic elements of tauopathies on WSI of postmortem human brain tissue specimens from patients with tau-associated neurodegenerative conditions in order to better stratify patients for clinical and other correlative studies". Their methodology in the study includes taking de-identified autopsy brain tissues from 22 individuals with Alzheimer's, progressive supranuclear palsy, and/or chronic traumatic encephalopathy. While the latter two diseases have different aetiologies: gradual death of specific brain regions and repeated head injuries respectively, all three share the clinically relevant symptom of dementia. They ensured that within their patient selection criteria, the individuals had a variety of histo-morphological features, possessed minimal or no neuropathological comorbidities, and that the samples were effectively stained.

The tissue samples isolated for testing represented the hippocampal formation and dorsolateral prefrontal cortex. The hippocampus is responsible for consolidating our memories from short term memory to long term memory, while the prefrontal cortex is responsible for activating our working memories. All of the samples were digitized to generate digital whole slide images using various image scanners, and then were uploaded to the Precise Informatics Platform (PIP) for the team to begin their analysis. Throughout the study, PIP takes advantage of the incredible precision of deep learning technology to rapidly classify and visualize different features of the sample. Along with the functionality of PIP, they engineered a fully convolutional network (FCN) for their testing. In order for deep neural networks such as FCN to classify images, the data inputs (i.e. the samples) get processed through convolutional layers and filters. Within each layer, a single convolution represents the application of a filter to an image, and produces an output by the technology - but when done once, only detects vague features of the sample being processed. With repeated applications of these layers and filters on the same image, the final output is a map of all the activations. This map organizes the complex features of specific regions of interest (ROI) from the slide images, and sorts the unlabelled data into categories set by the researchers.

By implementing deep learning algorithms as a computational tool, this novel solution demonstrates the unique ability to provide a more easily reproducible approach in speeding up the otherwise labor-intensive process of collecting data from tissue samples. DL has its own challenges as it requires more

advanced computational infrastructure and datasets to be able to visualize and annotate whole slide images quickly and efficiently. However, when provided the necessary data, it far surpasses the regular imaging techniques. With regular imaging, researchers are unable to provide trustworthy and reliable diagnoses. But the specificity of the neural networks when integrated with microscope technology make diagnoses possible through the detection of NFTs.

Although there are clear benefits of deep learning at giving a clue to the features of these diseases, the Mount Sinai team is making plans for furthering the capabilities of the technology. The pathological annotations utilized for image analysis were able to recognize distinguishable features between the tauopathies studied specifically in this study. With the accomplishments thus far, they aim to increase the capabilities of the DL algorithm and add more annotations for the system to recognize. The team wants to further the level of performance of what they have created and provide accurate diagnoses for other types of neurodegeneration as well - looking beyond the three diseases they analyzed.

In a field where there is still so much that is unknown and yet to be understood, deep learning has undoubtedly created a fresh perspective for tackling the prevalent issue of neurodegeneration. It seems as though this team has only grazed the surface of the true capabilities of these algorithms, as the possibilities of what researchers will be able to program in the future are continuously being explored. Through established visual imaging analysis methods, incredible feats such as reconstructing memories with these networks or creating definitive diagnoses are no longer far-fetched ideas, but actually attainable in this generation and preserve hope for a world free of these diseases in the near future.

Contributors



writer
Abraham Niu

Abraham Niu is a second-year undergraduate student at UC Berkeley studying Cognitive Science and Data Science. In his spare time, he enjoys snowboarding, meddling with music, and watching basketball highlights.



design lead
Amy Wang

Amy is a sophomore at Berkeley studying Neurobiology and Data Science. She is also co-lead of NT@B's Education Division and is on the Cal Figure Skating Team. She enjoys baking, listening to podcasts, and exploring coffee shops!



design
Chris Seo

Chris Seo is a first-year at Berkeley pursuing Computer Science and maybe Cognitive Science. In quarantine, he's been taking photos and learning Beatles songs on the guitar.



guest writer
Andreas Forsland

Andreas Forsland is an entrepreneur with a background in human factors, human-computer interaction design and innovation strategy. He is the Founder and CEO of Cognixion, a company currently focused on unlocking communication as well as environmental controls for individuals with cognitive, speech, and motor disabilities that help them interact with the world at their full speed using their eyes, facial gestures, and a direct brain-computer interface.



guest writer
Cris Micheli

Cris Micheli is a PhD is a senior software engineer, BCI / biosignals researcher and project manager with Cognixion. He currently serves also as co-organizer of NeuroTechX Toronto chapter. He holds a PhD in Cognitive Neuroscience from the University of Tuebingen, Germany and a master's and bachelor's degree in biomedical engineering from Politecnico di Milano, Italy.



writer
Hunter Alves

Hunter Alves is a junior at UC Berkeley studying Molecular and Cell Biology on the Immunology track.



writer
Iris Lu

Iris Lu is a first-year student at Berkeley intending to major in Cognitive Science or Molecular and Cell Biology.



writer
Jandy Le

Jandy Le is a sophomore at UC Berkeley studying Integrative Biology and Public Health.



guest writer
Jessica Singh

Jessica Singh is a third-year at UC Berkeley double majoring in Molecular and Cell Biology and Data Science. She currently serves as the President of NT@B.



writer
Josephine Tai

Josephine is a freshman studying Molecular and Cell Biology and Business Administration.



editor
Jwalin Joshi

Jwalin Joshi is a second year Applied Math and Computer Science major at UC Berkeley. He currently serves as the co-lead of NT@B's publications division, and is passionate about increasing accessibility and ensuring equity in the neurotech space. He enjoys practicing yoga, playing the guitar and going on hikes. He has often been described as NT@B's "token vegan".



writer
Kyle Giffin

Kyle Giffin is a junior at UC Berkeley studying Cognitive Science and Data Science, and he is fascinated by the future of neuro-technological influence. In his free time, you can find him climbing, hiking, or running the hills of Berkeley. Kyle won a pi competition in 3rd grade and has since been on a slow downward trend. He is known for his controversial take on Tik-Tok and poor sense of humor.



guest writer
Lucas Steuber

Lucas Steuber, MA Applied Linguistics, MS CCC/SLP, is Linguist and Speech-Language Pathologist (SLP). He served as clinical SLP in schools and home health, with a speciality in rare and complex communication needs, before joining Cognixion as Director of Clinical Product and Marketing. He is a two-time recipient of CES' "Technology for a Better World" award. He holds positions in the core working groups of the Autism Society of America and Adler's Voice, and serves in a variety of advisory roles for both United States and international Speech-Language Pathology and rehabilitation engineering licensing Bodies.



writer
Michael Xiong

Michael Xiong is a first-year at UC Berkeley majoring in Chemical Biology.



writer
Sameer Rajesh

Sameer Rajesh is a rising sophomore at UC Berkeley intending to major in Molecular and Cell Biology. When he's not waiting for someone to drop the latest protein structure determination algorithm, he can be found watching Netflix, reading popular science, or playing ultimate frisbee with his friends. Sameer hopes to become a medical doctor and work in either neurology or neurosurgery.



editor
Lillian Shallow

Lillian is a second year Berkeley undergrad, studying Microbial Biology, Spanish, and Public Health. She is co-editor and co-lead of the publications division for Spring 2020. In her free time she likes to read brain books, collect fun earrings, and spend time with her rescue pups.



writer
Malachi Tran

Malachi is a sophomore studying Molecular and Cell Biology and Psychology at UC Berkeley.



guest writer
Nehchal Kaur

Nehchal Kaur studies Msc. Cognitive Systems at Ulm University, Germany and is pursuing a thesis on neurological understanding of music therapy. She believes that through music we can hope to bring about social, psychological as well as neurological healing that can be applied on both micro and macro levels of society.



guest writer
Shanaya Sidhu

Shanaya Sidhu is a second-year Neuroscience student at UCLA.



guest writer
Saarang Panchavati

Saarang Panchavati is a third-year Bioengineering and EECS student at Berkeley. He has served as NT@B's Software Division lead and will be VP of Projects next semester.



guest writer
Utkarsh Sarawgi

Utkarsh Sarawgi is currently a graduate student at MIT and a researcher with the Fluid Interfaces group in the MIT Media Lab. His recent works include creating human-centric AI systems for healthcare, intelligence augmentation, and social good, among others. His interests include machine learning and perception, cognitive neuroscience,⁵⁰ and rapid prototyping.