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INTRODUCTION

A Memory of a Memory

MAY 26, 2011 might have been a sunny day in Boston, perfect for a brisk jog along the Charles River. Or it might have been a gloomy day, just right for a pint and a movie in Harvard Square. It could have been the ideal day for baseball if the Red Sox were back in town. But I can't tell you for sure. I can't tell you what I had for breakfast, lunch, or dinner that day. I can't tell you who I called, what news I read, what music I listened to. There are bits of experience I don't remember because, well, I'm relying on my memory.

And yet, somehow, I do remember that I was in a windowless dark room at the Brain and Cognitive Sciences building at MIT that afternoon, transferring a small, black mouse from the palm of my hand into an almond-scented box about the size of a milk crate, with white floors, transparent walls, and a camera mounted overhead.

The mouse began sniffing its surroundings. It was no stranger to the box, having investigated the same corners just yesterday. The fact that nothing monumental had occurred during its initial journey in the box was important: it meant that the mouse had no reason to be afraid this time around. It could go about its business without fear as I recorded its behavior with my lab partner, Xu Liu.

Ten days earlier, I watched as Xu anesthetized this very same mouse. We both felt similarly regarding the lab mice we worked with: we approached them with veneration for their biological revelations and with tremendous care for the life that they experience. Xu in particular took this relationship seriously, and that day I could tell how much this

dynamic meant to him as he carefully lowered two glass barrels into two small holes through the top of the skull of the mouse. Like miniature flashlights, about the width of cocktail straws and shorter than the nail on your pinky finger, these glass barrels are capable of funneling and focusing light onto the part of the mouse's brain in which they are nestled—in this case, in the mouse hippocampus. Why did we want to shine light onto the mouse's hippocampus though? As part of our experiment, we'd made this particular mouse special using some genetic trickery called optogenetics. Put succinctly, optogenetics entails hand-crafting special bits of DNA that make a cell light-sensitive, and delivering those bits into very specific cells into the brain. Once these brain cells are made light sensitive, researchers can turn them on or off with light, much like a switch. Xu and I planned to focus beams of light directly onto our light-sensitive cells in the hippocampus, and voilà, those cells would turn on. It's these particular hippocampus cells, we hypothesized, that contained a memory.

Based on what we knew about the inner workings of the brain, Xu and I had every reason to believe that the hippocampus is like a mental time machine: an area that is active when a mouse is trying to remember the shortest path to return to the tasty crumbs in the kitchen pantry, or in one of us humans, when you recall the memory of your first kiss, or hearing your baby coo for the first time, or last Friday's delicious steak frites dinner. The hippocampus contains millions of brain cells, which chunk space and time into our personally experienced events. The hippocampus, in short, is crucial to the process of memory, in both our mouse and in humans. It teleports us to relive the past.



Xu and I were playing with an idea that day in the lab, as our mouse scurried about its box: Could we “turn on” a memory if we triggered the parts of the brain where it lived?

We were in essence testing a hypothesis first put forth over one hundred years ago by the German zoologist Richard Semon. Semon proposed that memories are a kind of lasting physical imprint, or “trace” in

the brain—somehow, the marvelous waters of memory carve measurable grooves in the neural riverbeds of the brain. For the savvy enthusiast, there's an official term for this so-called memory trace, and it was first proposed by Semon himself: *engram*.

The holy grail of memory neuroscience, the engram is thought to be the key to unlocking the power of our brain's mental time machine. Once we find the engram, Semon's prescient idea goes, we could probably find a way to reverse engineer memory and, ultimately, control it.

Xu and I used to refer to memory researchers as the auto-mechanics of the brain, taking apart the fleshy machine between our ears one piece at a time in an attempt to understand what each piece does and how it enables our smooth mental time-travel. "If you can break it and make it, then you can understand it," he'd say.

By 2011, memory researchers had already done just that. They had discovered that it was possible to "erase" memories—to "break" them. If scientists could do *that*, well, why couldn't we find memories and reactivate them instead? Breaking something lets us know how it works by preventing some output from happening, Xu and I reasoned, but if we could manually recall a memory—if we could stimulate this same output—then we could get the mental time machine to run again . . . and again and again at will.

Our goal was initially nonscientific in its basis: we'd break into and jump-start the brain's time machine. The project had a name in the lab, one that we felt had a mysterious grandeur to it: Project X. It all sounded pretty sci-fi to us, and that was exactly what hooked us in. The idea of *activating* a memory? Very *Total Recall* with a bit of *Inception* thrown in. We felt like kids again, and our playground was the science lab. Sometimes an idea for an experiment just feels "too important and too damn cool not to do," we'd say.

We thought activating cells that held onto a memory would cause a domino effect in the brain that ultimately led to recollection of that memory. After all, external stimuli in the world do this to us all the time: walking past a bakery and smelling the maple bacon doughnuts might remind you of the last time you cheated on your diet; the sight of a particularly unfashionable shirt at the mall might remind you of an ugly

Christmas sweater party with the family; the smell of tequila might remind you of that time you dulled your grief with alcohol and woke up in even more pain the next morning. These sights and sounds and smells force us to relive the worlds of the past. They bring engrams back to life.

We just wanted to bypass the external stimuli.

Say that Xu and I were able to reactivate a memory. What next? One of the central goals of doing this kind of science is to discover fundamental truths about how the brain works and to use these truths to help people. Our biggest ambitions for our work included applying a new understanding of the mechanics of memory to treat disorders of the brain. We wondered if we could one day suppress a negative memory to prevent the debilitating effects of PTSD, or toggle down a bout of overwhelming anxiety to prevent a panic attack. If we could activate a memory, then we could think of memory as something our brain naturally produces *as well as* a potential antidote that the brain contains to rid itself of suffering. The possibilities would be endless: What if we activated positive memories to curb symptoms of depression, or what if we brought a memory back that was thought to be lost to Alzheimer's, or what if we could etch in entirely new memories to produce a cognitively enhanced brain? All of these possibilities relied on one thing—the ability to control memory, which was what Xu and I had within reach.

Given how far the field had already come, we thought a repair shop for the brain wasn't all that far-fetched.

A perceptive, soft-spoken, Shanghai-born scientist, Xu Liu came off as proper, formal—fully buttoning up his lab coat was a rather ritualistic act—and the level of intention and respect he brought to the study of science was like nothing I had ever witnessed. When he was locked into his science, everything else became background noise, as if the only two things in the world that mattered in those moments were him and the experiment at hand. Watching Xu do science felt like watching pure discipline in motion.

But Xu was also a kindhearted mentor, a big brother in the lab. His discipline in the experimental testing rooms transformed into thoughtfulness in his daily mentorship—and it was in this mentorship role that he was *really* in his element. I often felt like Xu had a career-length road map for how he would train me in neuroscience. He told me he decided to take me under his wing and become my day-to-day mentor because our friendship was “organic” from day one in the lab. As he put it: “I knew we’d have chemistry doing science together. Get it?” It was a terrible joke, and yet I couldn’t help but laugh.

Xu joined MIT as a postdoc fellow a few years before I arrived there for grad school. He spent years mastering the surgeries and techniques needed to test Semon’s engram hypothesis. It was his passion. Late one night, after yet another nail-biting round of Jenga with me, he told me that memory was the most mysterious thing he knew of, but it was a mystery he was confident he could solve with science. In graduate school, he studied how memories are formed and retrieved—and he did this using the tools of molecular biology to study how individual neurons represent memories in the fly brain. Like the human brain, the fly brain also consists of neurons, and it is much easier to play around with fly neurons than human neurons. He moved on to study mouse brains because they’re “big fly brains solving mouse problems,” as he put it.

But Xu didn’t just have the fly, mouse, or even the human brain in mind—no, he was thinking on a much grander scale: Xu wanted to understand the phenomenon of *memory* itself. He believed that memory isn’t just recalling what you ate yesterday or your high school graduation; memory is nothing less than the perpetual beating heart of life. It appears everywhere, from single cell organisms to jellyfish, fungi to flies, mice to humans, and from life that started billions of years ago to life that exists today. We are all endowed with this biological machinery capable of preserving what once was. Memory takes many forms, but it is a biological constant.

It follows, then, that knowledge of memory in any organism will inform our grander understanding of how memory works in general and, in some capacity, will be applicable to humans. For Xu and me, rodents

were the perfect model organism in which to use our neuroscience tool kit to study how to activate a memory.

We began our experiments by trying to manipulate fear memories. Our reasoning: we know a great deal about the neural circuitry underlying fear in both rodents and humans (it's similar enough), and we know that this circuitry also intersects with a variety of psychiatric disorders, including PTSD and anxiety. So we had a leg up in knowing how fear memories are created and where in the brain to look for them, and we knew that manipulating fear memories could have beneficial effects for patients suffering from fear-based disorders. Fear memories are also incredibly potent; so we figured that when we activated one, we'd know because the mouse's behavior would change immediately, making it a scientifically measurable output. For example, if you think about the impossibly high-pitched noise of a dentist's drill, a hair-raising, "why-god-why" cringe immediately ensues. Your brain made a powerful association—it was *conditioned*—because at some point in the past that noise was followed by pain and pressure while you were told to sit still.

Our first step was to create a fear memory that we could then try to manipulate. One of the most common ways that we can create fear memories in rodents is to place the animals in a new environment—in the lab, this means a small box with a metal grid for a floor, dim lighting, and a black triangular roof scented in this case with a particularly zesty orange aroma—and then send a very mild shock to their feet so they associate this area with an important event. They're thus conditioned: they're trained to associate the environment with a negative stimulus. After they acquired this fear memory, whenever the rodents were placed in the box, they would *freeze* in place to protect themselves from the looming threat of a negative stimulus. Xu and I kept track of how often the mice were freezing as our measurable readout of recalling a fear memory.

Xu and I figured we could activate the brain cells in the hippocampus that produced a fear memory—and that we could do this with light. We used the optogenetic tools Xu had spent so long creating in the lab to finally test Semon's hypothesis. The mouse's brain was primed: its hippocampus cells had been manipulated so that they could be controlled with light, and the tiny glass barrels that would funnel that light had been implanted.

On May 26, 2011, the day after we first created the fear memory, we placed our mice in a “safe” box—a box where nothing had happened, where no shock had been delivered. We began by connecting the glass barrels implanted in the mouse’s brain to a laser that emitted a brilliant Avatar-blue light. To turn on the laser, we simply had to click a switch. One *click*—that was all that separated us from a scientific triumph, from a completely puzzling result, or from the tediousness of . . . nothing. But that’s science in nutshell: maybe you’ll get lucky and see something that has never been seen before; maybe you’ll finish the day scratching your head wondering what in the world just happened. Or both.

On the day of our big experiment, we funneled pulses of light through the surgically implanted optic fibers, bombarding the mouse’s neural tissue with photons, attempting to awaken the dormant memory. Xu and I sat and watched, eager, nervous, the lab like a command center during the first few seconds of a rocket’s lift-off.

We turned on the laser, the mouse’s ears perked up—and it immediately stopped moving. It tensed up, vigilant and frozen in place, perhaps experiencing the echoes and murmurs of a fearful engram flicker in and out of its mind.

I finally broke the silence: “So . . . did that . . . just freaking work?”

“We have to run controls,” Xu responded briskly. “We have to do the experiment large-scale and double blind. We have to replicate it. But, let’s just call it a day and go have a drink across the street because, yes, I think it actually freaking worked.”

“I knew it!” I yelled, splashing Xu with the water I was using to clean the floors in the mouse cage. That day, at the end of my first year working with Xu at MIT, I realized that we had made the discovery of a lifetime.

I gave Xu a hug, the first of only two we would share.

That Xu and I thought the mouse was recalling a bona fide memory was, of course, anthropomorphic conjecture. No one knows exactly what a memory looks like in the brain, and we certainly don’t know what it’s like to be a mouse. We do, however, have a rough idea of how cells and

mice often behave when they're recalling an experience that was negative. A mouse reliving a negative memory will freeze in place. The objective description of our scientific findings is this: Xu and I turned on the mouse's brain cells that were previously active during the formation of a fear memory, and we caused the mouse to freeze in place. A mouse may never be able to tell us otherwise, but we have very good reason to believe that our objective description can be translated as: we shot pinpoint lasers into the mouse's brain that made the mouse relive the fear-provoking memory.

The objective description would also tell you that memory is multifaceted. It is how the brain processes every experience you've ever had and turns each one into cellular signals that contain information about the past. And what are these "cellular signals" exactly? Well, a wealth of research lets us know that there are processes, stages of memory that transform over time, and we can label them this way: Encoding, Storing, Retrieving, and Updating. All of these processes simply describe the larger phenomenon of memory itself: it is a dynamic integration of the past with the present to permit future livelihood. In other words, memory recalls the past in the present to help us better navigate the future. It is a history with the breadth of all that we've felt and the depth of all that we've experienced. Just as we learn history to learn *from* history, our brain keeps a record of our past so that we can learn from it.

Let's dwell on this definition of memory for a second. For starters, memory isn't *only* about preserving the past. Recalling a memory in the present helps us understand the environment that we find ourselves in, and it helps us decide what to do next. This means that memory has a purpose that is much grander than being a neural photo album of your life. In fact if you gave me five seconds on a talk show to give the world the answer to "What is memory?"—since *everyone* is tuning in to find out—I'd say the following: "Memory is what the brain does. It is a fundamental property of any biological living organism. Memories are at the core of being human because they thread and unify our overall sense of being."

This is indeed a much grander description and may feel a little nebulous. So let's break memory down into its four processes. Encoding, the

first step of memory formation, is all about your senses—the sights, sounds, tastes, smells, and touches that bring together the richness of an ongoing experience into the cohesive whole that becomes a memory. These general sensory categories might feel arbitrary—Can you really separate the *smell* of an onion from its *taste*?—but there is good reason for this “batching” of the Encoding process. It helps scientists find patterns in how the brain *takes in information over time*. The first time I visited my family in El Salvador, when I was about six years old, every moment was entirely new to me, something I had never experienced before. It was like having my senses dialed up to high definition: the warm pebbles tickled my feet when I stepped into the lake near my grandparents’ house; the carne asada that my grandma cooked would waft through the rooms of the house, and soon the entire block would smell like a steakhouse; I could see the country’s volcanoes from miles away and wonder if they might erupt again, all while hearing roosters crowing and horses galloping by me. My brain was taking in and encoding every bit of sensory detail, putting together my wonderful experience of being in the place where my parents grew up.

The next stage of memory is Storing, a process that begins the moment after an experience is over. In this phase, the brain creates a record of the past by storing information in its own cellular terms. In contrast to Encoding, Storing is the basic way that an experience creates a mappable, observable change in the brain at the cellular level. These changes are stored copies of experiences that allow us to mentally time-travel back to the past.

Let’s deconstruct that early memory of El Salvador as an example. The night of my first visit, I went to sleep on my grandma’s hammock and was thinking about everything that happened that day. My mind was effortlessly replaying the parts that stood out to me the most—the lake, the pupusas, the mountainous landscape fading into the horizon. Storing a memory doesn’t have to be a conscious effort—our brain will do it whether we’re aware of the process or not—but it was as if my brain was rehearsing the day’s events to help solidify all the details, big and small, into a memory. From the brain’s perspective, conscious and subconscious rehearsal makes a memory, and so the brain rehearses its own

experience day and night to effectively store it away for later use. And best of all, there's no test at the end of this kind of practice rehearsal—just my brain's ability to store what I considered to be a memorable day.

Once a memory is stored, it is ready to be retrieved when called upon, and the things that memories then do are marvelous. When I retrieve my memory of my first visit to El Salvador, I mentally time-travel back to specific moments and swell with the admiration and curiosity that comes with thinking about my family's deep history. Retrieving a memory means I can “rewind” to a snippet of my past and then zoom in and out to replay the granular details of pebbles or to gaze at a spectacularly star-speckled sky or to relive scenes of breakfast with my family, again and again. Retrieving these kinds of memories is when we begin to find that thing called “fulfillment” and all the moments in which it has been sprinkled throughout our past.

These phases of encoding, storing, and retrieving a memory, however, don't happen in some vacuum. From the brain's perspective, experience never stops, and this means that we're always encoding bits and pieces of this, while storing bits and pieces of that, while retrieving some aspect of our past. If I were to give memory a movie title, it would be *Everything Everywhere All at Once-ish*. And it doesn't end here: the act of recalling a memory leads us to one more magnificent property of memory, and that is its malleability. Memories become updated with new information each time we recall them. This Updating process taps into our “library” of memories and scribbles new information into one of our books. I *know* that there were pupusas on my first trip to El Salvador, but no matter how hard I try to recall what else was on my plate or what clothes I was even wearing at the time, the surrounding details of the meal simply shape-shift with every attempt. Sometimes there's a bit of yellow rice at the edge of the blue ceramic plate, and other times there's a slightly burnt tortilla; sometimes there's a coconut cut open to my right ready for drinking, and other times it's a Cola Champagne. Sometimes I'm wearing a gray Nike T-shirt and other times I'm wearing a purple soccer jersey. All of these details infiltrate my memory and warp it into something new each time—into some version of *my truth* that, like memory, is defined and redefined every time I remember.

Okay. But what does a memory *mean* to you? What does it mean to remember, to forget, to choose what to try to remember with greater clarity, and what to let go of? Do we even have a choice? For example, I'm attempting to remember past events for this book. What challenges does that pose?

No one can claim that they've solved the mysteries of the brain, let alone of memory, but Xu and I saw this as a challenge (even if it took dedicating our lives to getting an answer). We could start with the four main components—Encoding, Storing, Retrieving, Updating—which at least allow us to break this complicated part of cognition down to some of its constituent parts and to tackle each with neuroscience.

Six months after Xu and I successfully shot lasers into the mouse's brain and reactivated a fear memory, we submitted our work to the journal *Nature*, and in 2012 our paper was published. We had localized a memory in the brain and had artificially triggered that memory. Our paper used words like *hippocampal dentate gyrus* and *engram* and *Channelrhodopsin-2 (ChR2)*, but the international news coverage referenced movies like *Memento* and *Eternal Sunshine of the Spotless Mind*. Media calls and interviews followed, as people pushed us to contextualize our findings and speculate on the future of memory research.

For once, the international news coverage was apt. Within just three years of our discovery, between 2012 and 2015, the scientific advances in memory control and manipulation in our memory research community were mind-bending: creating false memories, erasing memories, manipulating positive memories in the context of depression, bringing back memories that were once thought to be lost in Alzheimer's, tinkering with memories of social experiences, turning good memories bad and bad memories good.

If all of this sounds too good to be true, that's because it is still wildly incomplete; it is all part of a larger revolution brewing in science to make memory manipulation a commonplace practice in the lab. Even before our paper was published, several labs around the world were

working on the same project, in a race to publish first. Egos, funding, awards, and recognition meant navigating a—scientifically speaking—suboptimal future. In other words: it was stressful as shit. A race over bragging rights, and not necessarily the significance of the discoveries or how scientists might combine efforts and work toward a common cause, took over.

You might say that Xu and I were naive. I prefer to say that we were young scientists with far fewer encoded and stored memories of professional slights and nursed reputational injuries to retrieve, and we tried to operate outside of the rat race. For us, turning the process of discovery into a career-long race would kill the part of science that felt most essential and human to us. What we were in practice, however, was frustrated by this competitive aspect of experimental science, especially since we were still learning how to navigate the politics within academia.

Xu gave me some advice, which he would often repeat: When faced with the nastier side of science, don't just put your head down and ignore it. These feelings aren't just something to be brushed off; they're exactly the things we can learn from. They're our mind's way of putting what we value into focus. "Fight fire with water," Xu would say. Fighting fire with fire burns the edifice of academia down; fighting fire with water wins by solving the problem.

Xu's guidance always came in a measured voice, a calm cadence that showed me a diplomatic approach to problem solving, even if the environment bothered him too. He was like that, a scientist firmly grounded by the gravitational pull of the meticulous practice of his craft. I admired his composure. Neither competition nor ego would sway Xu.

Xu and I found ways to manage the competition, but the *ad hominem* criticisms of our "place" within academia were, for me, difficult to endure—infuriating in fact. Here's a common criticism we heard: "Xu Liu and Steve Ramirez only got the paper accepted in *Nature* because the journal has a minority quota." This kind of statement was nothing new. People spewed similar judgments in my direction all the time: "MIT had a minority quota," "*Forbes* must have needed to include a minority," "TED had a quota," "Harvard *clearly* had to increase the number of Latinos," "NPR had a DEI mandate." I started to wonder if people

thought I'd somehow managed to *turn* Latino just to get an edge in academia. And Xu started to wonder if he'd ever be able to talk about his science without someone criticizing *him* as opposed to critiquing his work. He once said to me, "If you think being a minority in science makes it *easier* to get an award or a job, then you don't understand why minorities are, well, not a majority."

In my first few years of graduate school, these kinds of comments made me livid. As did admonishments like, "Don't let them get to you," and "You've got to ignore the haters," and "Just stick to the science." I didn't want to feel like I had to be thick-skinned and bulletproof to survive. Why did I need to dismiss my humanity to do good science? These things *should* hurt, I thought. Desensitizing myself to them made it all too easy to become complacent about the toxicity present in some academic circles. But the relentless nature of the "minority quota" comments had a cumulative effect. Each one did its part in deflating my sense of accomplishment that came with a scientific discovery. My response wasn't to become desensitized but to double down. "I have to discover more" was my ever-present thought, my solution, my mind's way of coping. It's the one thing I felt I could do really well: I knew how to work my ass off.

One evening in the not-too-distant past, I was at the top of the Prudential building in Boston listening to a jazz band that played on Wednesdays in an open lounge area surrounded by a floor-to-ceiling panoramic view of the city. It was one of the highest places I could possibly be in Boston, away from the ground-level of reality, and I'd come to this nook of the city alone when I needed time to just *be*. Halfway through the evening, a bouncy bass line emerged from the stage with the kind of weight and rhythm that begins in your belly and radiates outward to tip-tapping feet and tempo-following head nods. The jazz lick was the backbone of Glenn Miller's "In the Mood," a song that gave me so much trouble when trying to learn it on the piano as a kid that I still sometimes hear it in my dreams. I closed my eyes and, after one big sigh, let

myself *be*. My left hand began playing the arpeggio on my thigh as each note rose up from my childhood and . . . suddenly . . .

Xu and I were at the top of the Prudential and smiling back at Boston's bright lights as they shimmered over the Charles River. We were having a fancy dinner together (all expenses paid for by our boss) to celebrate the publication of our discovery on memory manipulation. I could see my childhood hometown; my alma mater, Boston University; my current apartment by MIT; and Xu's reflection on the window, fifty-two stories in the sky, all in a single field of view. The music filled the lounge with the kind of kinetic cadence that synchronizes everyone in the room.

I've never been so happy and so fully alive.

I knew I'd repeatedly come back to this moment in my mind. The music and Xu's voice were becoming part of my life's soundtrack.

"Are you in the mood for dessert?" I asked, while the jazz band played on.

"I'm a little drunk," he responded, grinning at me. "So . . . yes."

His peppy, vulnerable, and playful confession caught me off guard, but I accepted the moment as one we had earned: a bit of debauchery amid the stress of science.

"Xu, you're not going to believe me, but just ignore the entire menu and trust me here. I bet you my left hippocampus that if we ask the waiter what to order, they'll one thousand percent say the cookies and milk."

"Deal."

When the waiter came over, I asked what their best dessert was, and he simply took our menus, folded them up, and said, "I got you. It'll be about fifteen minutes."

While we were waiting for our dessert, Xu asked, "Does it ever scare you that you can hold your thumb out, close one eye, and see where ninety-nine percent of your life has played out?" He was motioning toward the window.

"I find it weirdly calming," I said.

"It's crazy to think where we'll be in a few years, given how much has happened since we published our paper," Xu said. "It's kind of scary, but I think we'll be okay."

“I think we’ll be more than okay. Above average. Let’s shoot for above average,” I said.

“I like that. Do you want the rest of my above-average drink?” Xu slid his golden ale toward me.

“I got you,” I said instinctively, as I traded my empty glass for his full one.

The waiter came over and ceremoniously placed a glossy porcelain dish in the center of our table. A dozen freshly baked cookies were stacked on top of each other—some oozing chocolate chips, others smelling of nothing but pure butter and sugar, some with crumbly oatmeal and raisins, and others infused with a velvety peanut butter. Berries lined the dish, powdered sugar dusted the top of the stack, and a side of French vanilla Chantilly cream tied it all together. This was served with a cup of cold milk because what else does one wash down the Platonic ideal of cookies with anyway?

“Enjoy,” the waiter said, while a handful of people in the lounge looked over to see what on earth smelled like heaven.

“I didn’t want your left hippocampus anyway,” Xu remarked.

“After you!” I declared, anticipating Xu’s reaction to his first bite. He picked up a chocolate chip cookie that began folding in on itself, dipped it quickly into the cream, and crunched off half of it in one go. He nodded approvingly . . . and fixed his glasses.

It was a childlike moment, paired with our adult scientific achievements, one that I could store in my memory bank in the “Feel Good” folder.

Xu started to laugh, perhaps realizing that the cookies and milk were as damn good as I’d claimed they would be. The music came into the foreground with a lone bass line . . . which brought the room back to baseline.

“Last call!”

My left hand finished playing the arpeggio on my thigh, as each note brought me back to where and when I was. I was alone. Boston glimmered in the background.

I realized in that moment, wishing Xu were sitting across from me again, that the power of encoding, storing, retrieving, and even updating an ordinary memory was changing me as a person. I was at once becoming more aware, frightened, and reverent of what memory was doing *to me* because the force of memory lasts well beyond its wake. Sometimes I'd recall this memory with Xu and feel empowered to continue doing science. I'd emerge from the memory having grown a bit in my confidence to navigate science and the world without my friend. There are always more cookies and milk to be shared in life.

Other times, this same memory led me to imagine all that could never be with Xu. I'd feel overwhelming sadness because it was a moment I could never recreate with him. Instead of trading my empty glass with Xu's full one, I'd trade my empty glass with the bartender.

And sometimes I'd remember for the sake of learning something new. I'd go to the top of the Prudential to get lost in the music and memories until they all brought Xu back. And when they did, I would say the things I wish I'd said to him years earlier. I would hug him for longer than I ever had before. And I would order dessert again to see him laugh out of pure joy. Retrieving this memory was a miniature miracle in its ability to bring the past back to life, so I'd go to the lounge to relive this moment with my memory of him again and again. Each time felt full of purpose—I was learning to rewrite what my past meant to me.

Just what *exactly* that purpose is continues to change and will evolve throughout the narrative in this book. All I know is that learning about memory brought me to Xu, one of the closest friends I'd make in my life. Memories now bring me back to him. In a way that I find biologically meaningful, Xu and I are still connected. I sometimes even dream about our time at the Prudential together and relive it with fantastical details. The music plays the same, but the skyscape behind the lounge shape-shifts into the buildings on MIT's campus or some of the playgrounds from my childhood. Retrieving a memory offers a chance to change what it means to us, to update it, regardless of whether we're even awake. The meaning of our memory together at the Prudential is mercurial, but it's where the *should haves* of my life with Xu find resolution. This is comforting because a memory may transform me entirely,

but I have the power to transform it as well—both with my mind and with my science.

At its heart, *How to Change a Memory* is about these transformations: your brain transforms moments into engrams, the theorized physical units of memory imprinted in your brain, and these engrams are controllable—they can be transformed and in turn can transform us as human beings. That memory has so much transformational power is the most astonishing thing that I know, and I have dedicated my career to understanding just how far we can push this power in the lab. In this book, I will take you on the journey that I myself traveled, both professionally and personally, to understand the new science of memory manipulation. I've started the story of that journey in this chapter, with my and Xu's breakthrough in artificially activating a memory in a rodent brain. In many ways this experiment—and our friendship—was indeed the breakthrough that jump-started my career and propelled me forward into a new chapter in my life. But like all stories, this story has deep roots, a backstory that did not start with me, or with Xu; our research in memory manipulation rests on a foundation of contemporary triumphs in neuroscience, which we explore in part I.

Twenty-first-century neuroscience has successfully tracked where memories reside (chapter 1), and it has measured how they change over time (chapter 2). This work has permitted neuroscientists to erase and activate memories of all kinds (chapter 3), as well as to create and implant false memories (chapter 4), all with extraordinary clinical applications (chapter 5). We'll follow the path of some incredible scientists whose work has brought us to the very cutting edge of memory research. We'll unpack their breakthroughs and build a new understanding of how memory works, as well as how we can begin to artificially change memories to enable biological well-being. The goal of part I, therefore, is to provide a framework for the neuroscientific basis of memory and its manipulation.

In part II, we look at how artificially controlling memory changes our very understanding of the nature of what memory is for and how it intersects with our lives. Memories build our futures through dreams and imagination (chapter 6), and they sculpt our overall sense of being to endow us with an identity (chapter 7). Manipulating memory has the

power to change life as we know it: our quest concludes in chapter 8 with a forward-thinking account of the promises and perils of memory manipulation. The goal of part II, therefore, is to illuminate just how intertwined the human condition is with memory so that we emerge with a profound appreciation for the very thing that enables our livelihood and sense of self.

My quest to manipulate a memory is as scientific as it is personal. In each chapter I fold in some of the most valuable memories I've made in my life, both in and out of the lab. These personal stories are meant to showcase how the scientific process works from the perspective of the people who did the discovering. There's a very human element at play in every discovery, which is sometimes overlooked or not told at all. Just as the work that Xu and I have done to manipulate memory builds on the foundational neuroscience that came before us, my own personal journey as a scientist is the product of my past, of my own memories, and of memories that predate me. My parents and siblings came to the United States from El Salvador, fleeing civil war, many years before I was born; their memories and their love for me form the foundation of who I am as a scientist.

I've struggled along the way, as we all do, but I've also experienced the joy of true friendship and the fulfillment that comes from making my parents proud, both of which have imbued my work with meaning. I've learned so much about how memories can outlive us and the heartbreak that occurs when the things we love become memories themselves. There is a pulse to memory that beats on, far beyond the biological lifespan of the brain which housed it first.

My quest to manipulate a memory began with a friendship. Xu and I belonged to each other.¹ The truth is that we all contain engrams of each other—engrams of those who are living and engrams that outlive those who are gone. This book is my attempt to make sense of the enigma of memory—the snippets of remembrances, the brief moments in time, the decisions we make, the blackouts, the imagined, and the dreamt of—all the things the brain does to breathe life into the past so that we can heal and become whole again. This book is my engram of Xu, and how my engram managed to outlive him, too.

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