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CHAPTER 1

The Grand Plan

No one had ever suggested it could be hereditary, it was just seen as a terrible coincidence. But on my little A5-size Basildon Bond paper, I drew the family tree. There were my grandma and grandad, both of whom I suspected had Alzheimer's, and in the next line I put their 10 children and marked the three who had been diagnosed. In the letter I said we'd love to take part in any research. I wasn't necessarily thinking they would find a missing link, but that if they could give us any information, any idea about how to treat it, it would be worth it.

CAROL JENNINGS, 1999

The first signs of Alzheimer's include forgetting little things here and there—symptoms that are difficult to distinguish from the consequences of fatigue, the hormonal changes that accompany menopause, and normal age-related cognitive decline. As the disease progresses, it causes more severe memory problems, and individuals increasingly become unable to do everyday tasks. Alzheimer's is a heartbreaking, slowly progressing neurodegenerative disease that typically escalates over ~4–8 years (but sometimes as many as 20) until complications from it (like choking or pneumonia) lead to death. It is responsible for approximately 70% of all cases of dementia and afflicts 10% of individuals 65 and older. Worldwide, more than 35 million individuals are currently suffering from it. The disease inevitably brings tragedy to those who suffer and to

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their families. But the biggest tragedy of all is that we do not have *any* highly effective cures or treatments.

Alzheimer's is not a new disorder—we've known about it for more than a century. Dr. Alois Alzheimer was the first to report clumps in the brain of one of his dementia patients in 1906, following her death. He described the clumps as a "deposition of a peculiar substance in the cortex." We now know these clumps as the plaques typically associated with Alzheimer's.

In the 1970s and 1980s, the causes of Alzheimer's were not thought to be genetic. Viruses, aluminum exposure, and other environmental toxins were all suspected. However, when Carol Jennings's father and two of his siblings were all diagnosed with the disease at the atypically young ages of 54–59, Carol suspected her family carried a genetic form of the disorder. She began writing letters to Alzheimer's researchers asking whether her family could contribute to some type of study. She wrote one of those letters to Dr. John Hardy at St. Mary's Hospital in London in response to an ad he had placed in the *Alzheimer's Society Newsletter*. In Carol's letter, she described her family tree, highlighting the individuals with Alzheimer's and the inheritance pattern. That letter triggered a cascade of events that changed the course of Alzheimer's research for over 30 years.

The genetics of Alzheimer's are complex, involving many genes. Most of these genes, if inherited, increase the risk that an individual will acquire the disease but do not ensure it. But if an individual inherits one of a few rare genes (accounting for <1% of all cases of the disease), there is an exceedingly high probability that they will develop Alzheimer's. Likewise, if an individual's parent is afflicted but does not pass on the gene to them, their own offspring are not at increased risk. Carol's family carries that type of autosomal dominant Alzheimer's gene. Because her father was afflicted, Carol herself had a 50% chance of developing the disease, and if she was a carrier, so did her two children.

Upon receiving Carol's letter, Hardy's team responded, eager to learn more about her family. Based on previous work, they suspected that the family's mutation would be somewhere on the long arm of chromosome 21, but it was unclear which gene would be involved. Carol rallied her family to contribute blood samples and participate in clinical tests.

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With the genetic material from Carol's family, Hardy's team proceeded to do the laborious work of finding the mutation. It took 4 years. The culprit turned out to be a mutation in a single DNA base pair in a gene called APP—a "C" changed into a "T." That mutation led to a swap of a single amino acid (an isoleucine instead of a valine) in the protein amyloid-beta. The researchers confirmed the same mutation in a second afflicted family.

Many lauded the discovery as a "breakthrough." The *New York Times* reported, "Gene mutation that causes Alzheimer's is found." The junior researcher who made the discovery, Alison Goate, remembers thinking, "Sometimes in science, you generate the data gradually. This was like, boom, a eureka moment." Hardy recalls the discovery similarly, "I felt we'd cracked Alzheimer's. I felt we'd done something that had made a real difference." One researcher speculated, "I would bet you a great deal of money that if you could prevent the accumulation of amyloid, you could stop dementia."

With this knowledge in hand, Hardy and other researchers went on to develop the "amyloid hypothesis." They already knew that the plaques Alois Alzheimer first identified were composed of amyloid-beta. The fact that a mutation in the gene for this protein caused Alzheimer's in Carol's family and others suggested that the plaques might be a cause (not a consequence) of the disorder. The gist of the amyloid hypothesis is that mutations in APP (and other factors) lead to the accumulation of amyloid into plaques, and because these are toxic, they trigger a cascade of events that leads to neurodegeneration; in turn, this leads to cognitive decline. This hypothesis quickly became the dominant focus of Alzheimer's research.

Launching from it, researchers set out to discover how to clear amyloid plaques from the brain. After a number of false starts, brain researchers successfully produced a drug to do just that, and the FDA approved the first amyloid-clearing drug, aducanumab, in 2021 and then a second, similar drug, lecanemab, in 2023. These drugs are both antibodies that bind to amyloid-beta, triggering the body to clear plaques from the brain. They both do that job quite well, and that in and of itself is remarkable.

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Up to this point, everything about the story of Alzheimer's is so incredible that it breaks my heart to tell you the twist. There was so much hope that these amyloid-clearing drugs would stop Alzheimer's, but clinical trials have demonstrated only modest effects in slowing cognitive decline. Of the two drugs, the lecanemab clinical trials were the most promising, showing a modest slowing projected to extend the course of the disease by ~9 months. Unfortunately, the drug also has side effects, like an increased risk of brain swelling. It helps; it's a crucial step, but sadly, it's not the final solution.

Why hasn't the amyloid-clearing approach worked better? That's unclear. There's still hope that these drugs do work well, but they weren't given early enough in the course of the disease to prevent neurodegeneration. Evidence from families with autosomal dominant genetic mutations (like Carol's family) suggests that the biomarkers for Alzheimer's probably begin to appear more than 15 years before the onset of cognitive symptoms; in the clinical trials, however, the drugs were administered much later in the course of the disease. Clinical trials are underway to determine whether earlier administration of the drugs will yield better results, and everyone has their fingers crossed. In parallel, some suspect that the amyloid hypothesis, as stated, may not be quite right or may be incomplete. Hardy has taken this position: "Although [the amyloid hypothesis] almost certainly has some elements of truth to it . . . it clearly does not capture the complexity of the disease process in several ways." Still others speculate about alternative triggering causes, such as the accumulation of another protein inside neurons, tau, as well as viruses and environmental toxins. At this point, no one knows for sure.

The unfinished story of Alzheimer's is a remarkable account of scientific achievement but one that does not have a happy ending, at least not yet. Carol spent the 30 years following the discovery of the APP mutation as a patient advocate for the disorder, sharing the story of her family and inspiring connections between individuals afflicted with Alzheimer's and researchers searching for a cure. Absent that cure, she refused to get a genetic test to determine if she was a carrier herself. Sadly, she was diagnosed with the disease in 2012 and we had no way to help her. After experiencing all stages of Alzheimer's, she died from it in March

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2024. Let's pause to reflect on this timeline: more than 30 years have passed since Carol wrote her letter and Hardy's group identified APP, and we *still* do not have a highly effective treatment or cure for Alzheimer's, even for families like Carol's where we can trace it to a genetic mutation. As Carol's devoted husband, Stuart, says, "It's the kids we're fighting for now."

So, what's holding back a cure for Alzheimer's? Tragically, we can ask the same question for so many other brain disorders, including Huntington's, Parkinson's, multiple sclerosis, epilepsy, depression, schizophrenia, and so many more. Though we have ways of mitigating some of the effects of these disorders, we cannot cure any of them. Worldwide, the numbers are staggering. For the 8.5 million individuals afflicted with Parkinson's, we have treatments to help mitigate the symptoms but no way to slow down the neurodegeneration associated with it. A striking 970 million people around the world are living with a mental disorder such as depression, anxiety, or psychosis, and for approximately one-third of those (323 million), their symptoms are resistant to existing treatments. A remarkable 1.2 billion individuals suffer from chronic pain, and while the most extreme cases can be treated with opioids, those drugs can lead to both cognitive impairment and addiction. These are just a few examples. In 2010 brain disorders cost the European Union (EU) €800 billion per year—an amount larger than the entire gross domestic product of the Netherlands and more than cancer, cardiovascular disease, and diabetes together. Similar estimates for the United States in 2016 suggest a cost of $1.5 trillion, or 9% of its gross domestic product.

Humanity can do so many amazing things. We can fly to the moon; we can battle many types of cancers into remission. So, what's holding us back from curing brain dysfunction? Or, in the absence of cures, what's holding back more effective treatments?

I am a neuroscientist, and I have been engaged in brain research for over two decades. For a long time, I've been convinced that I have the best

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of all possible jobs: I get paid to think up new questions about how the brain works and answer them. A large part of what inspires my research is my intense curiosity about how the brain gives rise to the mind, and to ourselves. To answer these questions, I focus on memory. I investigate questions like: When we have the experience of remembering that we've seen something before, what is happening in our brains? How do our brains manage to remember so much? And how do our brains curate what we remember and forget?

My work is not driven just by curiosity; I believe that a foundational understanding of how memory works will contribute to future treatments and cures for memory dysfunction, including age-related dementias such as Alzheimer's. In fact, part of my research program focuses on transforming what we've learned about memory into the earliest stages of developing a new treatment for memory impairment. Ours is but one example of what is known as the *bench to bedside* approach, where fundamental research discoveries are the first step toward developing new clinical treatments.

The bench to bedside narrative is so deeply ingrained in brain research that it's not typically questioned or even discussed. Brain researchers all have their own analogs of the things that I state in all my research grants: "The goal of this proposal is to understand how the brain stores memories. These results could inform new treatments for deficits in memory such as age-related dementia." After all, to fix something it's helpful to understand it, right? Obviously.

But are we learning the right types of things? In the past few years, I have started to question the broader bench to bedside narrative when it comes to brain research. Simply put, when it comes to brain disorders, the orderly progression of discovery in brain research has not led to an orderly progression of new treatments and cures for brain dysfunction. In other words, there has been a lot of perceived success on the *bench* and very little on the *bedside*, at least so far. There are exceptions—very important ones. But the bedside has been dominated by frustrations, variations of the frustrations encountered with Alzheimer's.

Around 2011 something alarming happened: six of the world's largest pharmaceutical companies decided to pull back their brain drug

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development efforts following years of failed and expensive attempts to bring drugs through clinical trials. Together, they had invested several billion dollars in developing new drugs, including $18 billion in Alzheimer's alone, and they had very little progress to show for the venture. What was going wrong? Reports suggest that, en masse, these companies concluded that we do not yet know enough about the brain to create new drug therapies for its dysfunction; it simply is not a good investment. In other words, progress at the bedside would be limited unless and until we make more progress at the bench.

In the grand scheme, not much has changed since 2011. We still do not understand the causes of most brain disorders. For Alzheimer's and Huntington's disease, we still lack *any* highly effective treatments. For disorders like depression and schizophrenia, existing treatments work for some individuals but not for many others. That isn't to say nothing has been happening—it has! Progress in the nuts-and-bolts arm of brain research is exploding in any way you measure it: papers published (fig. 1a; a proxy for facts collected), or even the number of pages in neuroscience textbooks. And it has been for several decades. However, progress in developing new treatments has not followed as expected: the number of new brain drugs introduced annually has been steady for the past 30 years (fig. 1b). So work at the bench has been progressing, but for some reason it has not translated efficiently to the bedside. The big question we need to answer is: What's been missing?

Unless you are really (really!) in the know, the arc from discovery to treatments in brain research—the bench to the bedside—probably is not happening as you suspect. At least that was true in my case. Even after working for decades in the field, I misunderstood how new treatments for brain dysfunction are developed. To drive this home, consider that in 2019 Joshua Gordon, director of the National Institute of Mental Health (NIMH) from 2016 to 2024, lauded the approval of a new drug to treat postpartum depression (brexanolone) as "a cause for celebration for psychiatric neuroscience, as it represents a true bench to bedside success for our field. The promise of basic neuroscience to provide truly novel and effective treatments for psychiatric disorders has for a long time been only that, a promise. But not anymore." Note

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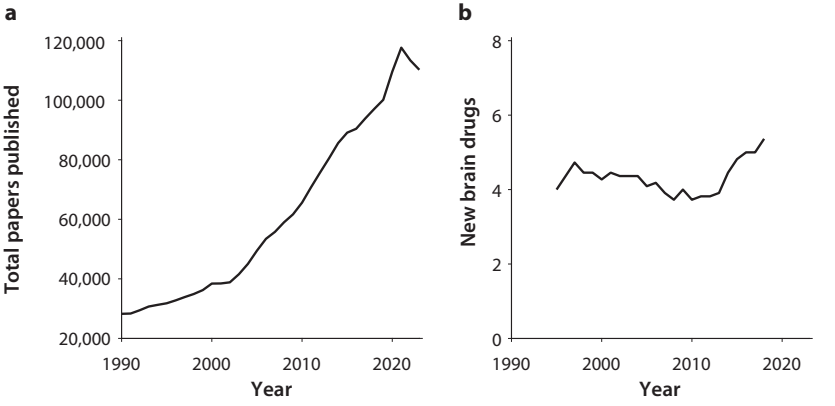


FIGURE 1. *The disconnect between papers published about the brain and the introduction of new brain drugs.* a) Total number of papers published per year 1990–2023, indexed on the search engine PubMed.gov with "brain" in the title, keywords, or abstract. b) Total number of new brain drugs introduced per year across the same 33-year period, computed via a 10-year running average.

that brexanolone was one of the first realizations of the bench to bedside narrative leading to a genuinely novel treatment for a psychiatric disorder. It didn't come until 2019, and it was one success in a rich and varied history in which successes were few and far between.

You might wonder: How can this possibly be true? After all, we have plenty of drugs to treat depression, anxiety, psychosis, and many other psychiatric disorders. Well, while these existing drugs work for some individuals, they fail to work for many others. And further, we don't have a complete understanding of *how* these drugs work. It turns out that many of these drugs were not developed based on understanding how the brain operates, but rather during a time when we did not understand much about the brain at all. In fact, when these drugs were developed, the field hadn't even reached a consensus that neurons in the brain use neurotransmitters to communicate. Instead, many of these brain drugs were discovered either serendipitously or by a process I'll call "try it and see what happens." The first antidepressant (iproniazid) was created in 1952 while researchers were looking for a treatment for tuberculosis. The first drug

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to treat anxiety (meprobamate) was created in 1945 while they were looking for a treatment for penicillin-resistant bacteria. Ritalin, one of the first drugs for attention deficit hyperactivity disorder (ADHD), was created in 1944 via "try it and see." A nontrivial fraction of the drugs that we have today are actually not new drugs, but rather refinements of old drugs created before 1960. And, while we now better understand how the old (and new) drugs work, many of the newer drugs operate in the same ways as the original ones.

One of the most powerful statements of frustration comes from Thomas Insel, the director of NIMH who preceded Gordon and served from 2002 to 2015:

> I spent 13 years at NIMH really pushing on the neuroscience and genetics of mental disorders, and when I look back on that, I realize that while I think I succeeded at getting lots of really cool papers published by cool scientists at fairly large costs—I think $20 billion—I don't think we moved the needle in reducing suicide, reducing hospitalizations, improving recovery for the tens of millions of people who have mental illness. I hold myself accountable for that.

Twenty billion dollars spent across 13 years did not move the needle. What will it take?

During his tenure at NIMH, Insel was a tremendous and effective force in directing mental health research toward investigations of brain dysfunction. One of the explicit goals during that era was to redefine "mental disorders" as "brain circuit disorders" to focus the search for new therapeutics on the brain. Since leaving his position a decade ago, Insel has redirected his efforts toward facilitating access to treatments that already exist. As he explains, "I still believe we need better science and a deeper understanding of the biology, the psychology, and the environmental factors underlying mental illness. . . . But there are pioneers who have taken a broader view of the problem . . . they are finding faster ways to put out the fire." While I admire this move tremendously, the fact that one of the once biggest and most influential proponents of brain research is now questioning the efficacy of the enterprise should prompt us all to pause and reflect, to say the least.

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When thinking about these issues, it's natural to ask: Won't new treatments naturally emerge once we fully understand the brain? Perhaps, but there are two complications to this question. The first is that what's happening in the brain is not the only thing we need to consider when trying to understand brain dysfunction and develop treatments. Social, economic, and environmental factors and trauma can cause brain disorders; behavioral interventions, as well as social support, are important routes to treatment. In other words, it's not *just* the brain that we need to understand—we also need to understand how brains are influenced by (and interact with) the world. The second is that we are far from understanding everything about the brain. In the case of drugs and other brain-based therapies (like brain stimulation), interventions typically lag scientific discoveries by decades. To ensure that the intervention is effective and safe, an intervention must first be created and then tested in multiple stages of clinical trials. For instance, a new generation of game-changing drugs designed to treat and prevent migraine that were first approved in 2018 evolved from discoveries about a specific neurotransmitter pathway (CGRP) that happened more than 30 years prior, in the early 1980s. Patients with neurological and psychiatric disorders need solutions now. So the question we need to answer is: How do we expedite learning the things about the brain that we need to know to treat brain dysfunction?

I've looked, and the information needed to answer this question is hard to find and synthesize, even if you are an expert. So I decided to write a book to try to answer it. I wanted to understand the challenges blocking progress to new treatments for all types of brain dysfunction, including mental illness. Neuroscience has seen so much progress in the past 30 years—we've seen multiple forms of technology revolutionize the field, including CRISPR, genome-wide association studies (GWAS), connectomics, optogenetics, large-scale neural recording, machine learning, and artificial intelligence. We've invested tremendous resources to pursue brain research globally, including the US BRAIN Initiative and similar efforts in Australia, Canada, China, the EU, Japan, and South Korea. And we've learned a lot about the brain through these efforts. So why have we struggled so much to translate the exploding

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number of discoveries that are happening at the bench to the bedside? How can we get better at understanding and treating neurological and mental health? What does the path from where we are now to successful treatments look like?

This book began as my own personal journey, as a brain researcher, trying to answer these questions for myself. In all honesty, I began the journey quite pessimistically, as I realized that I could not describe the current "grand plan" for the field—a description, in broad strokes, of how neuroscience plans to discover the things it needs to know about the brain to develop new treatments and cures for brain disorders. I suspected the same was true for most of my colleagues. If we cannot even articulate the field's current plan, how can we identify why or how it is going wrong?

I thus became compelled to spell out a Grand Plan for brain research that I could believe in. And so I spent the better part of a few years sifting through neuroscience and medicine well outside my typical wheelhouse, as well as history and philosophy. By the end, I realized that a new path forward is emerging in brain research just where we need it, one that I am optimistic will lead to more and better treatments. Some researchers are already on this path, and it is exciting to think about where it will bring us. It's a significant shift, however, relative to how we've been thinking about the brain up to this point, and it requires us to rethink how we approach treatments entirely. Before we can think about this new path, we need to understand the Grand Plan as it has existed in neuroscience to date. In a nutshell, we've been oversimplifying our ideas about what type of thing the brain is and how it breaks. It's not that simplification in and of itself is bad; in fact, simplification is inevitable. As the saying goes, "All models are wrong, but some are useful." In that famous phrase, "wrong" refers to the fact that any model, by design, is a simplification that captures some aspects of reality while disregarding others. The problem in brain research is that we've *over*-simplified how we think about the brain in ways that aren't just wrong but also *aren't useful* for treating brain dysfunction because they fall short of what we need to know. The Grand Plan up to this point has rested on these oversimplifications.

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What's the current Grand Plan?

One of the biggest slices of the Grand Plan is so central to the modern research agenda that it appears in the popular undergraduate introductory textbook *Neuroscience: Exploring the Brain*. It's called *molecular medicine*. The first step involves identifying a gene whose mutation is responsible for the disorder of interest. Next, researchers create an animal model of the disease by mutating that gene in a mouse, and they use it to determine what is going wrong in the brain. The mutation might lead to the absence of something the brain needs to function. Or it might lead the brain to produce something toxic. Whatever is happening, once it's understood, researchers create a drug to fix it.

The rationale here is that the mouse brain serves as a proxy for the human brain. While we cannot perform invasive experiments in humans, we can (with much thought, care, and compliance with ethical and regulatory guidelines) purposefully recapitulate a mutation in a mouse. If that gene has a similar function in mice and humans, learning what happens when it is mutated in a mouse can help us develop a potential treatment. And once we have a treatment that works in mice, we can then test it in humans. Finally, if the drug makes its way through clinical trials, voilà, we have a new treatment! Molecular medicine had tremendous optimism behind it as recently as a few decades ago. Today, the plan—at least stated in this simple way—is regarded as naive. Among the many reasons is that we've learned most brain disorders cannot be linked to individual genes or even a handful of them. So why did we initially think that they could be?

Molecular medicine followed tremendous discoveries in genetics and molecular biology in the 1950s–1990s, including the discovery of the genetic code (loosely: DNA base pair triplets code for amino acids and amino acid sequences are configured into proteins, the building blocks of the body and brain). The excitement surrounding these discoveries spilled over into brain research and was described by the psychiatrist and Nobel laureate Eric Kandel in a brilliant paper in 1998 titled "A new intellectual framework for psychiatry." In this paper, Kandel described the new, emerging way to think about psychiatric disorders

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as tied to physical changes in the brain. He was tapping into the same ethos that Insel was channeling during his tenure at NIMH when he sought to redefine "mental disorders" as "brain circuit disorders"; it was the same ethos that led to the description of molecular medicine that is reflected in today's textbooks. Because it reflects the ideas of not just one individual but an entire era, I'll refer to it throughout the book as the *molecular neuroscience framework*.

This way of thinking was a notable shift away from how mental disorders were regarded in the 1960s, where only a few such disorders were regarded as "organic" (brain) disorders. The majority were regarded as "functional" (mental) disorders with unspecified causes that need not be tied to the brain in any way and were most often treated through psychodynamic therapy. If, as Kandel proposed, all psychiatric disorders arose from the brain, then perhaps we could understand them by understanding the brain.

The first two principles, the core of the framework as Kandel described it, conceptualize psychiatric illness as the end of a domino chain: genes code for mRNA, which codes for proteins; proteins create neurons; neurons combine into neural circuits; and activation of the brain's neural circuits leads to all mental and behavioral function and dysfunction (fig. 2). Consequently, all psychiatric illness is a disturbance of brain function. Even in cases where the causes of disease are environmental, brain function is still implicated because the environment is causing changes in the brain that lead to the illness.

Kandel's third and fourth principles acknowledged that genes alone do not determine mental illness. Rather, social and developmental factors also play a crucial role. Together, these two principles specified a mechanism by which this happens: behavior and social factors feed back to modify genetic expression, leading to changes in how neurons function and how neural circuits are wired (in other words, "learning"). As a consequence of this feedback loop, Kandel proposed that "all of 'nurture' is ultimately expressed as 'nature.'" Conceptually, this was a big step forward for the field.

Finally, the fifth principle captured the idea that the long-term effects of psychotherapy and counseling operate via this same mechanism: by

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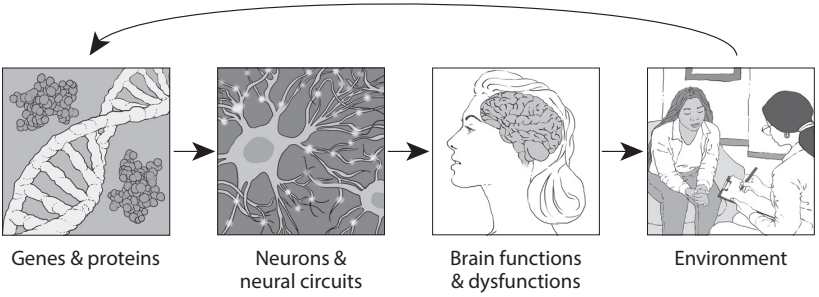


FIGURE 2. *The molecular neuroscience framework*. Genes code for mRNA, which codes for proteins; proteins create neurons; neurons combine into neural circuits; and activation of the brain's neural circuits leads to all mental and behavioral function and dysfunction. Influences from the environment happen via a feedback loop to the brain to influence gene expression. In this framework, dysfunction is presumed to happen following deficits at one (or more) of these four stages.

learning. Therapy changes gene expression and, in turn, reshapes neural circuits. In this framework, both psychotherapy and brain drugs operate via a common pathway.

In sum, the molecular neuroscience framework is largely set up as a domino chain where changes in genetic expression ultimately change brain activity and brain function. It allows for a singular feedback loop whereby information from the environment can be fed back to the brain (to influence gene expression; fig. 2). Crucially, this framework is not limited to descriptions at the molecular level, but it does emphasize gene expression as a crucial node through which everything must pass. In the case of neurological disorders, the presumption is that changes in something about the brain lead to neurological dysfunction. Take Alzheimer's, for instance. The amyloid hypothesis fits within this framework, with its emphasis on a domino-chain cascade of events that begins with a mutated gene that produces a protein and ends in cognitive impairment; in the case of Carol's family, that gene is APP, and the protein is amyloid-beta.

I am not arguing that the molecular neuroscience framework, with its emphasis on domino-chain causality, is exclusively how researchers

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have been thinking about the brain—there are plenty of examples of brain researchers thinking in other ways. Instead, my argument is that it has implicitly been the predominant way of thinking about the brain in the past few decades of brain research and has, therefore, guided how we have thought about treatments for brain disorders. The framework has led us to several important discoveries, including some that are recognized by Nobel prizes, and it has also led to transformative new therapies to treat brain disorders. At the same time, we can now see how it's problematic, and why it's time to evolve beyond it.

Three problems with the molecular neuroscience framework

Now that more than 25 years have passed, the problems with the molecular neuroscience framework are apparent. The biggest problem is that the framework sets brain researchers off along the wrong path regarding how the causes of brain dysfunction will manifest. Domino chains are devilishly tempting because they are among the simplest and most satisfying accounts of how a system works: you set up the dominos in a row, you knock the first one down, and they all fall in turn. But thinking about the brain this way presumes that brain dysfunction follows from an aberrant domino; it leads researchers to focus on pinpointing *that one* domino (such as a genetic mutation or the reduced vigor of activity in a brain area). Once a cause for a disorder is pinpointed, the thinking goes, researchers can develop treatments for it either by targeting that domino directly or by compensating for the broken domino somewhere downstream. In other words, the framework can be summarized by the phrase, "find the broken domino and fix it."

Why is this a problem? Because the brain is not a domino-like system. It is instead a system that is designed to adapt to changing conditions. A changing brain means that many dominos and their interactions might change over time, and we may not be able to reliably point to a single domino as a culprit. One well-understood example is blood pressure. Our blood pressure is regulated by our brain: brain mechanisms compare what our blood pressure is with what it should be, and when it's off target, our

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brain sends signals to our body to adjust it. When our blood pressure chronically deviates from what is healthy for us, the specific cause is most often unknown. Instead of thinking about blood pressure as a chain with a broken domino, we think about it as a system that is constantly incorporating feedback but is set to the wrong point. To fix unhealthy blood pressure, we focus on recalibrating the system (for instance, with drugs that change the dilation of blood vessels) as opposed to finding and fixing one broken piece of it. This is an entirely different way to conceptualize how dysfunction manifests. We'll elaborate on what kind of system the brain is later on, but for now, the upshot is that we need to seriously consider whether the reason we still do not understand the causes of many brain disorders is that we've been primarily focused on pinpointing broken dominos, and this is just not how the brain works.

The second problem with the molecular neuroscience framework is closely aligned with the first. Our focus on broken dominos not only has led researchers to search for the causes of dysfunction in individual dominos, it has also led to a laser focus on creating treatments that target those individual dominos with exquisite selectivity. When those treatments are drugs, the approach is called rational drug design, and it's captured with the phrase "one gene, one drug, one disease." In 2011, when pharmaceutical companies abandoned brain drug development efforts en masse, some researchers pointed to this type of oversimplification as the problem—a drug targeting a single domino can fail when that domino interacts with other dominos.

One example of this from cancer research is drug resistance. It happens when a drug that is initially effective at treating an individual's cancer stops working, leading to cancer relapse. Cancer drugs are often designed to target specific elements of a genetic network (dominos), and the reason drug resistance happens is that the genetic networks that lead to cancer are set up not as domino chains, but instead as complex networks in which there are multiple pathways that lead to a cancerous state—when one route is blocked, the cancer cells adapt and find another path. Consequently, when developing effective treatments for cancer, researchers consider full genetic networks, not just individual genes, and oncologists will often administer combination therapies designed

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to block multiple paths to cancer, not just one. Given that the brain's components (like genes) are more often than not components of complex networks, we need to seriously consider whether the reason that attempts to treat brain dysfunction have not worked is that, as with cancer, targeting singular dominos is often the wrong approach.

The third problem with the molecular neuroscience framework is that it is incomplete. When Kandel first described it, he intentionally left details about how the brain gives rise to the mind and behavior unspecified, explaining that "the great challenge for biology and psychiatry at this point is to delineate that relationship in terms that are satisfying to both the biologist of the brain and the psychiatrist of the mind." Thus, this framework not only leaves out missing facts (like details about specific genes and genetic expression) but is *missing concepts* about how we should think about the link between the brain and the mind. How can we possibly understand how changes in the brain lead to mental dysfunction in the absence of solid ideas about how they connect together?

I don't expect that my call to rethink how brain researchers have been approaching things will be controversial. It captures the pulse of what's happening in the field right now. Brain researchers in all divisions of the field are sounding the alarms, and funding agencies are listening. There's a growing sense that we've been oversimplifying the brain, and it's time to evolve the current Grand Plan as it's described in textbooks. What's much less clear is what comes next. What should we replace the existing Grand Plan with?

How do we move forward?

A fable written in 1963 titled "Chaos in the Brickyard" likens the scientific enterprise to building large, imposing edifices, and the facts that scientists acquire via their experiments to bricks. The tale begins by describing science as a type of thoughtful construction that relies on producing bespoke bricks, as needed, to build solid and sound structures while also avoiding waste. It then transitions into the misguided notion that "bricks are the goal," with bricks collected into large piles

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with great pride—ultimately at the cost of actually building anything, because the builders can't find the right bricks in the big mess. The fable ends with the warning, "Saddest of all, sometimes no effort was made to maintain the distinction between a pile of bricks and a true edifice."

It's time for us all to consider whether we have arrived at our own form of chaos in the brickyard of brain research. Have we transitioned into piling up bricks (data)? To be clear, I am not questioning the value of nuts-and-bolts, curiosity-driven research. The history of biomedical research offers up many examples of why this type of research is so essential: investigations of retroviruses before the discovery of HIV; investigations of the light-sensitive proteins in algae before they became the foundation of optogenetic biotechnology; investigations of the chemicals released by parasitic snails before anyone suspected that they might be useful to treat pain. Curiosity-driven or "basic" research is crucial for laying the foundation for treating brain dysfunction. Moreover, understanding the brain because we are curious about it—to gain insights into ourselves and how we work—is a worthy and impactful goal in and of itself.

It's time, however, to reconsider the edifices we've presumably been building as we mass-produce bricks. In other words, it's time to evolve curiosity-driven research beyond the molecular neuroscience framework and its domino-chain ethos because it's both wrong and too simple. As I've mentioned, different and more complex ways of thinking about the brain have already been suggested. All reflect a shift away from simple domino-chain descriptions that emphasize things like candidate genes and proteins or which brain areas are activated in human fMRI studies, and a shift toward examining brain systems more holistically. In place of domino chains, these approaches appreciate that the whole may not easily be predicted by understanding how the brain's parts operate when studied in isolation. None of these new ways of thinking have reached a broad consensus, however, and more consensus is what we need if we are going to move the needle on more successfully treating the brain and its dysfunction.

Let's take another look at Alzheimer's disease, this time to understand what kinds of new ways of thinking about the brain have been proposed. The amyloid hypothesis that John Hardy championed in

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1991 and its focus on the accumulation of the protein amyloid-beta as the triggering cause for Alzheimer's fit squarely into the molecular neuroscience ethos. In 2023 Hardy and his colleagues began advocating for a different approach to Alzheimer's in which we stop assuming that the events causing Alzheimer's are reflected as domino chains, and we begin to embrace more of the system's complexity. Hardy now advocates for modeling the brain systems associated with Alzheimer's as a *nonlinear dynamical system*; in these systems, typically the whole (like cognitive function and dysfunction) is not easily predicted from the operation of its parts (like proteins). Calling this a shift in perspective doesn't begin to describe it: "For non-linear systems, correlation does not imply causation, causation does not imply a correlation, and even the concept of cause-effect can be difficult to define when multiple interactions, feedbacks, and time delays are involved." Indeed, these types of systems are far from intuitive. They can be understood; they just require different approaches, including mathematical models. Suppose the parts of the brain that go awry in Alzheimer's operate as a nonlinear dynamical system (which, as we will discuss, is likely). In that case, Hardy is right—tackling the problem through the lens of such systems may be the only path to a cure for Alzheimer's.

This is just one example of what's happening at the cutting edge of brain research today, and we will discuss many more examples throughout this book. As we will see, researchers are beginning to shift their perspectives of the brain away from the domino-chain ethos of the molecular neuroscience framework to ways that better capture its complexity. But navigating the path forward is exceedingly tricky. To embrace more complexity, we can shift our perspectives about the brain in a multitude of ways. What ideas about the brain will be vital to making impactful progress toward treating—or even curing—brain dysfunction?

In this book, I will take you along a streamlined version of the same path I traversed to ask and answer the hard questions I've posed in this introduction. We'll begin in part 1 by exploring how we arrived where we are

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today, launching with the history (which even many brain researchers don't know) of how we've developed the treatments that we have thus far. To explore the relationship between understanding the brain and fixing it, we'll trace the discovery stories behind the treatments for disorders such as psychosis, depression, and extreme paralysis, pinpointing the scientific breakthroughs that led to them. As a spoiler, unless you are really in the know, it probably hasn't worked quite like you think (and the phrase *bench to bedside* certainly is not a good account of it).

In part 2 we'll explore how brain researchers are elaborating the molecular neuroscience framework to address its three big problems. The first elaboration seeks to fill in the gap between the brain and the mind by treating the brain as a type of "computer": an information-processing machine that receives sensory input and performs computations to determine how it should behave. While this approach holds much promise for designing new drugs (and has facilitated impactful developments in artificial intelligence, or AI), it gets us only partway to where we need to go because it continues to oversimplify the brain, treating it as a domino chain. The second elaboration proposes that we think about the brain not as a domino chain, but as something that regulates its stability and flexibility in ways that require feedback. It regards the brain as a complex adaptive system that processes information while regulating itself, thereby maximizing its fitness. We'll see how this approach is much more promising.

In part 3 we will explore how this newfound appreciation of the brain's complexity changes how brain researchers go about finding the causes of brain dysfunction and how to treat it. I'll lay out in broad strokes the next steps for brain research that will be required to unlock the brain's biggest mysteries and lead to new treatments to help the billions of individuals who are suffering. In the final chapter I'll describe the reasons that I'm so optimistic that the next few decades in brain research will be more impactful than the last.

This book was inspired by my growing pessimism about the path forward for brain research. On the other side of writing it, I'm unequivocally optimistic. This new ethos will have a profound impact on how I approach research at the "bench," but I'm ready to embrace these

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changes wholeheartedly. Brain research is on the cusp of a new era. Now that I can see how things are transforming, I'm excited to share that vision with you.

Before we dive in, a quick note on the level at which this book is written. I firmly believe that brain research will benefit from a combination of clear-headed thinking and straightforward explanations accessible to nearly anyone. While the brain is complicated and brain research is technical, it is our good fortune that these issues are conceptual, and the concepts themselves are pretty straightforward. Ideas about the path forward for brain research are important for experts engaged in brain research, but not just for researchers; they are also important for anyone who is affected by some type of brain dysfunction or has a loved one who is, as well as for policymakers, journalists, and anyone who wants to better understand the brain. Understanding the brain concerns all of us. It makes sense that we should all be privy to the solutions.

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