CHAPTER 8

IS MENTAL ILLNESS JUST A BRAIN DISEASE?

The first time I got into an MRI scanner, I had a severe anxiety attack. The scanner had a panic button that I could press to alert the operator that I needed help, but this was such a major-league freak-out that I ended up crawling out of the scanner before they could get into the room and wheel me out gracefully. I've now been in MRI scanners more than 100 times (as you learned in chapter 5), and I've gotten pretty comfortable with it, but I sometimes still have flashbacks to that first scan whenever the bed starts sliding into the scanner. That panic attack in the scanner was not my first encounter with anxiety—in fact, at that point I had been dealing with it for a number of years. The first anxiety attack that I can remember happened just after I had started as a graduate student. I raised my hand to ask a question in a seminar, and suddenly was overcome with all of the telltale signs of panic: my heart was racing, I wasn't sure if I could breathe, and my face suddenly felt very hot. For an aspiring academic, this is not a good start to one's career. And throughout the next decade, every encounter with public speaking became an occasion for fear and loathing. It was only through many sessions of cognitive behavioral therapy that I was able to finally kick the fear of speaking in public, or at least tamp it down to a level that doesn't make me miserable.

Anxiety is just one of a set of mental health problems that takes an enormous toll on modern society. It is estimated that roughly 1 in 5 people in the United States experiences some

kind of mental illness every year, and 1 in 25 suffers from a severe mental illness that affects his or her ability to function in society. The costs to society are enormous, in dollars and lives; major mental illness costs the United States almost $200 million in lost productivity every year, and suicide is the second most common cause of death for adolescents and young adults. And while death and disability from many other diseases are on the decline, disability from mental disorders is actually rising, despite the massive investment of research dollars by countries around the world.

Until relatively recently, mental health problems were not viewed as diseases of the same sort as cancer or diabetes. Instead, they were seen as manifestations of personal weakness or of spiritual problems such as demonic possession, witchcraft, or undue influence of the moon (which is the source of the term "lunatic," after Luna, the Roman goddess of the moon). Sigmund Freud tried to explain severe mental disorders in terms of sexual urges and our need to repress them; for example, in describing the case of a German judge who became schizophrenic, he said that "we may regard the phase of violent hallucinations as a struggle between repression and an attempt at recovery by bringing the libido back again on to its objects."[1] It wasn't until the twentieth century that physicians and scientists began to view mental illnesses as brain diseases. A major factor in this change was the introduction of drug treatments for major mental illnesses in the 1950s, which convinced many physicians and scientists that these diseases must reflect a "chemical imbalance" that is corrected by the drug. Another important contributor was increasing knowledge about the genetics of mental illness.

What Genetics Has Taught Us about Mental Illness

Genetics plays an important role in all of the major mental disorders, which shows that they must have a biological underpinning. One way to see the role of genetics is to compare identical twins (who share almost exactly the same genome) with fraternal twins (who on average share half of their genome with one

another). If one identical twin is diagnosed with schizophrenia, then the other twin has a 30%–50% chance of being diagnosed; for comparison, if they have a fraternal twin with schizophrenia then the rate is 5%–10%, whereas the rate for the entire population is about 1%. Another way to describe the influence of genetics is *heritability*, which is a notoriously difficult concept that describes the degree to which differences across people in some characteristic (such as a diagnosis of schizophrenia) are due to genetic differences versus other differences (such as experience or environment).[2] If a disease has a heritability of 100%, that means that any differences between people in the presence of the disease are due entirely to differences in their genetics; but, importantly, this doesn't mean that the effects of the gene are necessarily inevitable. The best example of this is a rare disease called *phenylketonuria* (PKU), in which a person is born without the ability to process a specific amino acid called phenylalanine. If untreated, the disease results in brain damage and intellectual disability. PKU is 100% heritable, meaning that if both parents carry the gene then the child is certain to have the disease. However, despite the certain inheritance of the disorder, the consequences of the disease can be reduced or eliminated simply by minimizing the amount of phenylalanine in the diet; if you have ever noticed the warning "Phenylketonurics: Contains phenylalanine" on a can of diet soda, this is why.

PKU is due to mutation in a single gene; for this reason it's called a "simple" genetic disorder. Another tragic example of a simple genetic disorder of the brain is Huntington's disease, which causes uncontrollable movements of the body as well as psychiatric symptoms such as mood problems and psychosis. Huntington's disease is caused by a mutation in a single gene, and its inheritance is described according to the rules that Gregor Mendel first discovered in his studies of plants; if a parent has the Huntington's disease gene, then the children have a 50/50 chance of inheriting the disorder, in which case they are guaranteed to develop the disease later in life (usually by about 50 years of age). Unlike Huntington's disease, most major mental disorders are called "complex" genetic disorders because, while they all have a substantial degree of heritability, they are not

inherited in a way that would suggest that they are caused by a single gene.

The powerful genetic technologies that were the fruits of the Human Genome Project have enabled researchers to begin to clarify the genetic underpinnings of complex disorders such as schizophrenia, depression, and autism, providing a more direct biological explanation for the heritability of these disorders. An important tool that has enabled the search for genes involved in complex brain disorders is the *genome-wide association study*, or GWAS. GWAS relies on the fact that there are a relatively small number of places among the roughly three billion locations in the human genome where people differ from one another very often—where "relatively small" means something like a few million places, and "very often" means that at least about one percent of people have a different letter in their genome (or *variant*) at that location. The rest of the genome is identical across nearly all humans. To perform a GWAS, researchers collect genetic material from a large number of individuals (from either blood or saliva), and then identify which version of each of those million or so "common variants" is carried by each individual. They then compare all of these variants between a set of people who have the disorder of interest (who are known as "cases") and a similar set of people who don't have the disorder (known as "controls"), to see whether there are any variants that are more or less common in cases versus controls.

As researchers began to use GWAS to investigate diseases such as schizophrenia, it became clear that there were many different genes that appeared to play a role in these diseases, but each individual gene appeared to play a very small role; none of them accounts for more than about one percent of the differences in the presence or absence of the disease. That is, there is no "schizophrenia gene." However, these studies have provided important new insights into the biology of schizophrenia. Surprisingly, the strongest differences in the genomes of schizophrenic individuals are not found in genes with any obvious relation to brain function; instead, they are found in genes related to the function of the immune system, specifically the part that helps the body decide which cells are foreign and which are

not (known as the *major histocompatibility complex*). Detailed studies of the genomes of schizophrenic individuals allowed Steven McCarroll and his colleagues at Harvard Medical School to identify one specific gene known as *C4* that differed on average between healthy and schizophrenic people, with the schizophrenics being more likely to have a version of the gene that is more active, meaning that it generates more of its particular protein.[3] They then used studies of mice to understand the role of C4 protein in the brain, and found that it plays a role in the elimination of synapses between neurons, which happens during early brain development; greater C4 activity during early brain development could in theory lead to later brain dysfunction by causing too much elimination of synapses. This work is a shining example of how genetics can lead to a deeper understanding of the biology of mental illnesses, though it's worth remembering that it's still only a small part of the explanation for the disease, because most people with schizophrenia do not have a disordered version of the *C4* gene, so other genes must also be playing a role, given the high heritability of schizophrenia.

What can we conclude from genetic differences in case-control studies? Think back to our discussion of reverse inference. There we saw that the presence of activation in the context of some particular psychological function (such as activation of the amygdala when a person experiences fear) does not tell us that the region is a "fear" region; we have to know what other psychological functions also activate the region. Similarly, finding an association between a genetic variant and a disease doesn't tell us that the gene is specific for that disease; just because a gene is more common in people diagnosed with depression doesn't make it a "depression gene." To ask that question, we need to ask whether the gene is specifically related to the disease, or whether the same genetic variant is also related to other brain disorders. As genetics researchers have begun to ask those questions, the answer has become clear: there is very strong overlap in the genetics of seemingly distinct mental health disorders. In particular, there is a large amount of overlap in the genetics of severe mental illnesses such as schizophrenia, bipolar disorder, and major depression, with

weaker overlaps between these and disorders such as ADHD, obsessive-compulsive disorder, and autism. There are many ways to interpret this, but one of the simplest is that a diagnosis of a particular mental disorder, while it might be useful for the practicing psychiatrist, may not be a very useful description at the biological level. As neuroimaging researchers have examined psychiatric disorders, a very similar story has emerged.

Imaging Mental Illness

If mental illnesses are truly brain diseases then we should see evidence of them using brain imaging, and it should come as no surprise that a large number of studies have examined this question. The majority of these studies have examined the structure of the brain, focusing on measurements such as the thickness or density of the gray matter. This is a relatively easy measure to obtain, requiring only a few MRI scans taking 20–30 minutes.

Many of the individual studies published on this topic have demonstrated differences between patients and control subjects, but interpreting these differences is much more challenging because many of the studies have been relatively small, owing in part to the fact that collection of MRI data is much more difficult than taking a cheek swab for a genetics study. However, it is possible to combine the data across many studies, using a technique called a "meta-analysis," which gives us more confidence in the results. The largest meta-analysis of structural MRI in mental illness to date was led by Amit Etkin, a psychiatrist at Stanford. Etkin and his group combined data from almost 200 published case-control studies examining a wide range of mental disorders: schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety.[4] Their analysis focused on studies that measured differences in the amount of gray matter across the entire brain.

The findings of the meta-analysis were impressive. Across all of the different disorders, there was evidence for less gray matter in people with mental disorders in three regions of the brain: the anterior cingulate cortex, and the left and right

anterior insulae (see color plate 10). These are regions that are strongly connected to one another, and a large body of research has suggested that this network is particularly important for *executive function*—the ability to control one's behavior and act in a goal-directed manner. Indeed, when Etkin's group looked at another data set of healthy people they found that gray matter density in this network was correlated with a measure of executive function derived from several different psychological tests. There were some differences between different patient groups; for example, people with "internalizing disorders" (including depression, anxiety disorder, and obsessive-compulsive disorder) showed reduced gray matter in the hippocampus and amygdala, and people with psychotic disorders showed greater overall gray matter loss than nonpsychotic individuals. However, the relative overlap between these seemingly different disorders suggested that their biology may be much more similar than their different symptoms would suggest—a message strikingly similar to the genetics findings that we discussed above, where it was seen that different psychiatric diagnoses can have overlapping genetic causes.

One difficulty with interpreting studies of gray matter density or thickness is that there is not a direct relationship between the amount of gray matter and its function. It might seem that a thicker cortex would be better, but this is not always the case—in fact, the thickness of the cortex decreases from the day we are born through old age, such that a babbling 18-month-old child has thicker gray matter than a 30-year-old math genius. Sometimes thinner cortex is bad, as in Alzheimer's disease, where the cortex becomes overly thin. However, sometimes thicker cortex is bad; for example, many studies have reported that autistic individuals have thicker cortex in some parts of the brain compared to healthy controls. Structural MRI studies can thus tell us whether the brain differs in these disorders, but can't really tell us what it means.

Psychiatric researchers have also used fMRI to look for differences in brain function between healthy people and people with different mental health disorders. Here too there are many individual studies that report differences in brain function

between cases and controls, but the studies are often very small, so once again meta-analysis can provide us a consensus view. Emma Sprooten and her colleagues at the Mount Sinai School of Medicine performed such a meta-analysis using data from 537 published fMRI studies of schizophrenia, bipolar disorder, major depression, anxiety disorders, and obsessive-compulsive disorder.[5] The results of this analysis were consistent with those from the structural MRI meta-analysis by Etkin and his colleagues: when Sprooten looked at analyses that examined the whole brain (which are less biased than analyses focused on specific regions), she found that there were consistent differences in functional activity in a number of brain regions between healthy people and people with mental illness, but these brain differences were largely the same across all of the disorders. That is, people with depression, bipolar disorder, and schizophrenia show differences in brain function compared to healthy people, but the differences are largely similar across all of those disorders. As I will discuss later, results like these have led some to question whether our approach to studying mental disorders needs to be completely rethought.

Challenges of Imaging Mental Illness

One problem with interpretation of many neuroimaging studies of mental illness is that it's difficult to disentangle the disease process itself from the effects of the disease, including the drugs used to treat the disease. The best example of this effect is seen in schizophrenic individuals who have been treated with so-called "typical" antipsychotic drugs (such as haloperidol), which block a particular kind of dopamine receptor (known as D2 receptors). Studies that have followed individuals over time after they started taking these drugs have found that in most parts of the brain there is a decrease in gray matter, but in the basal ganglia (which have a large number of dopamine D2 receptors) there is actually an increase in volume. In addition, the lifestyles of mentally ill people are often not conducive to healthy eating, exercise, or social engagement, all of which can have an impact

on the brain. Any study that compares healthy individuals with people with a long history of mental illness will be confounded by the effects of medication and other consequences of the disease rather than the disease process itself. One way to address this is to study people when they first become ill, which lets us see the effect of the disease without the confounding effects of years of drug exposure and (in some cases) social isolation. Getting an unmedicated actively psychotic person into an MRI scanner is very difficult, but some studies have succeeded in doing this, and they have shown us that there are indeed differences in brain function between healthy people and people diagnosed with major mental disorders. For example, research by Jong Yoon at Stanford and Cameron Carter at the University of California at Davis has shown that even in schizophrenic individuals having their first psychotic episode and who have never been exposed to antipsychotic drugs, the brain response in regions related to the dopamine system is abnormal.[6]

Another approach that can sidestep the effects of drugs is to study unaffected first-degree relatives (siblings, parents, and children) of mentally ill people. First-degree relatives should, on average, share about half of their genome, and the heritability of mental illness tells us that these individuals should thus share at least some of the genetic vulnerability that contributes to the disease in their affected relatives. Thus, by studying unaffected relatives we can better understand the brain differences that are associated with risk for the disease. Studies of first-degree relatives have indeed shown that they exhibit some of the same brain abnormalities as mentally ill people. For example, research by the late Larry Seidman and his colleagues from Harvard Medical School examined the size of the hippocampus, a brain area involved in forming new memories, in people with schizophrenia and their unaffected relatives. They found that both the schizophrenics and their relatives (especially those from families with multiple people with the disease) had smaller hippocampi, as well as having worse memory compared to healthy controls from families without any schizophrenic relatives. This provides perhaps even stronger evidence that mental illness

really is a brain disease, because we can see the lingering traces of genetic risk for the illness even in people who have not actually developed the disease. Neuroimaging has been uniquely important to obtain these insights; while in theory it would be possible to examine the brains of people after their death and compare the size of brain areas across people, in practice such studies are almost impossible to perform, whereas neuroimaging data can be collected fairly easily.

Rethinking Mental Disorders

Results like those outlined above have left researchers who study the biology of psychiatric disorders increasingly frustrated, and much of the blame for this frustration has been laid on a single book: the *Diagnostic and Statistical Manual of Mental Disorders*, better known as the *DSM*. This is the book that defines how psychiatrists diagnose particular disorders. For example, in order to diagnose someone with panic disorder, they must have recurrent panic attacks that include at least four of the following symptoms:

- palpitations, pounding heart, or accelerated heart rate
- sweating
- trembling or shaking
- sensations of shortness of breath or smothering
- feelings of choking
- chest pain or discomfort
- nausea or abdominal distress
- feeling dizzy, unsteady, light-headed, or faint
- chills or heat sensations
- paresthesias (numbness or tingling sensations)
- derealization (feelings of unreality) or depersonalization (being detached from oneself)
- fear of losing control or "going crazy"
- fear of dying[7]

Other disorders are similarly defined in terms of checklists, requiring that the individual experiences a minimum number

of the symptoms in order to receive the diagnosis. This smorgasbord approach means that two people can have completely different sets of symptoms—for example, one with palpitations, sweating, shaking, and choking sensations, and another with nausea, dizziness, chills, and tingling—but both would be diagnosed with the same disorder.

There is something clearly very different about this approach compared with how most other nonpsychiatric diseases are diagnosed. For example, the symptoms of diabetes can include extreme thirst or hunger, frequent urination, and fatigue. However, physicians would never diagnose a person with diabetes simply because he or she reports some number of these symptoms. Instead, they draw blood and measure the level of specific chemicals in the blood, which we refer to as "biomarkers," such as glucose or hemoglobin A1C. Similarly, an emergency room physician would never diagnose someone as having a heart attack simply based on a symptom of chest pain. The genomics revolution has taken this even further for cancer diagnosis. Previously, cancer would have been characterized in terms of where it occurred ("brain cancer") or the kind of cells that are involved ("glioblastoma"), but research has shown that this is not very useful in determining how to treat the cancer effectively. With the development of the ability to determine the exact genetic mutations within a tumor, physicians can now use this knowledge to determine the appropriate care; for example, there are four different types of glioblastoma (an aggressive form of brain cancer) that are characterized by different patterns of genetic abnormalities, and which differ in their response to treatment. It is this kind of "precision medicine"—using the knowledge of biology to drive personalized treatments—that inspired one psychiatrist to try to change the way that psychiatric disorders are defined and studied.

Tom Insel was not the person who many would have expected to lead a revolution in psychiatry. He was trained as a psychiatrist, but then spent many years as a basic neuroscience researcher. He was best known for his pioneering research into the sex lives of prairie voles (a small rodent known for being especially social), which showed that specific neurochemical systems were

responsible for making these animals monogamous. However, in 2002 Insel was appointed as the director of the National Institute for Mental Health (NIMH), which provides funding for the majority of research into mental health disorders in the United States. This put him into a position to set the research agenda for mental health, and he took full advantage of his bully pulpit. He was particularly struck by the fact that while death and disability from most diseases such as cancer and heart disease have decreased over recent decades, the toll of psychiatric disorders has increased over the same time. He realized that the field of psychiatry had failed to deliver on the promise of making people healthier, and as he said in a 2013 blog post: "Patients with mental disorders deserve better."[8]

The solution that Insel conceived along with psychologist Bruce Cuthbert is known as Research Domain Criteria, or RDoC. The basic idea is that if mental health disorders are brain disorders, then we need to understand the brain systems that go awry in mental illness before we can understand how to diagnose and treat them properly. However, Insel felt that the traditional diagnostic labels of psychiatry (like depression and schizophrenia) were more of an impediment than a help in understanding how the brain leads to mental illness. We already saw that research from both genetics and neuroscience has shown that those different diagnoses don't map well onto biology—just as one would not expect a symptom like chest pain to have a simple biological basis. Instead, he proposed that we study the different systems in the brain that might give rise to these symptoms, just as we study biological systems in order to understand other diseases. During his tenure as director (which ended when he moved to Google in 2015), Insel pushed the entire NIMH research program away from studying people based on their DSM diagnoses and more toward studying the basic brain systems that underlie those diagnoses. Groups of neuroscientists were convened to discuss each of a number of different domains that are thought to play a role in mental illness, with each group developing a "matrix" describing how that specific process is related to different genes, molecules, brain systems, and behaviors.

Fear in the Brain

One of the RDoC domains is "negative valence systems," which encompasses a set of negative emotional experiences including fear, anxiety, loss, and "frustrative nonreward." Of these, fear is probably the best understood in terms of the underlying brain systems. Fear is a natural emotion, acquired through evolution in order to help protect us from predators and prevent us from standing too close to the edge of a cliff. Most people experience fear from time to time, and some sensation-seeking people even relish it, but for other people fear can become debilitating. For a person suffering from post-traumatic stress disorder (PTSD), the most subtle reminder of a traumatic experience can trigger intense fear, and for someone with panic disorder the fear can often seem to come from nowhere. In some cases the concern about these attacks can lead a person to become *agoraphobic*, a term that translates from Latin as "fear of the marketplace" but for us refers to a fear of crowds or public places, that leads the person to avoid interactions with the world. Fortunately, my fear of public speaking never led me to avoid it, but for many people social anxiety severely limits their ability to achieve their professional or personal goals.

Neuroscience research has provided a detailed picture of how fear works in the brain. Say that you are walking down the street and someone approaches you with a gun and asks for your wallet and phone. Humans are not born with a fear of guns; we learn this from experience, and this learning occurs through changes in the connections between neurons in a brain circuit that includes the amygdala as well as a number of other areas connected to it. This circuit sends messages to the rest of our body that ultimately cause the unpleasant physical sensations that we experience, but they also can allow us to regulate the anxiety response, such as when we realize that the gun is actually a toy and the perpetrator is a friend playing a Halloween prank. Much of our knowledge of the detailed circuitry of the fear response has come from studies of nonhuman animals like rats and mice, but neuroimaging has also shown us what fear looks like in the human brain. One way that this has been studied

is through what is called "fear conditioning." In this kind of experiment, the volunteers are presented with cues (such as pictures or sounds); some of these are presented alone, while others are followed by a mild electric shock. Over time, the individuals start to fear being shocked whenever they see the cues that were paired with shock, and it's possible to examine brain activity when the subjects are experiencing that fear. What this research has found is that when a person experiences fear of an impending shock, there is activity throughout the brain's fear circuit, which shows that the brain function of humans and rats is not so different when it comes to basic emotional experiences like fear. It is worth pointing out that there are still many questions about how fear works in the brain, and it is increasingly thought that there are different brain circuits involved in the conscious experience of fear and the physiological responses and behavioral responses (such as freezing or avoiding) that are associated with fear.

Fearing a shock in the fear conditioning experiment is normal, but what about when fear goes awry? Researchers think that what happens in PTSD is that the brain's fear system generalizes the fear response to otherwise nonthreatening cues in the world, and is unable to extinguish this response even in the face of experience showing that no harm will come from those cues. Several meta-analyses have shown that people with PTSD and anxiety disorders exhibit an exaggerated response in the amygdala and insula to negative emotional stimuli. It also appears that the strength of the response in the brain's fear circuit is related both to the likelihood of developing PTSD following a traumatic event and to the likelihood of successful treatment. One particularly interesting study recruited individuals from an emergency room following a traumatic event, and then used fMRI within about two months after the event to assess their brains' response to viewing fearful faces.[9] When they followed up with these individuals a year after the traumatic event, they found that people with higher activity in the amygdala within two months of the traumatic event were more likely to show symptoms of PTSD a year later. It is this kind of approach, focusing on the prediction of specific psychological symptoms

using neuroscience, that RDoC has championed and that many hope will move psychiatry beyond its current messy state. At the same time, the past decade of research using the RDoC approach has not provided the level of breakthroughs that was initially hoped for, highlighting just how far we are from a deep understanding of these disorders.

Computational Psychiatry

The RDoC approach focuses on understanding which brain systems go awry in mental illness, but doesn't really tell us what specifically those brain systems are doing wrong in these disorders. To solve this problem, an emerging approach known as "computational psychiatry" is trying to link the brain dysfunction in mental illness back to the basic computations being performed by the brain, using sophisticated mathematical models.

Michael J. Frank is a neuroscientist at Brown University who has used computational models to study a number of different neurological and psychiatric disorders, and his work has been at the vanguard of the computational psychiatry movement. His research has focused on how people learn from either good or bad experiences, using reinforcement learning models like those that I described briefly in chapter 7. You may remember from the earlier discussion that dopamine plays a critical role in reinforcement learning. The role of dopamine in reinforcement learning comes at least in part from the effects that it has in the basal ganglia, which receive a major input from dopamine neurons. Specifically, the effects of dopamine on learning appear to come from its effects on changes in the connection strength of neurons in the basal ganglia. However, as you might have expected, it turns out that the dopamine story is much more complicated.

One complication is that there are different sets of neurons in the basal ganglia that respond differently to dopamine. One set of neurons, which Frank calls the "go pathway," causes us to engage in action when it is activated, while another set of neurons, called the "no-go pathway," drives us to avoid action when it is activated. Both of these sets of neurons are

affected by dopamine, but in different and largely opposite ways, owing to the fact that they have different kinds of dopamine receptors. If neurons in the go pathway fire in the presence of dopamine, then the synaptic connections between the neurons and their inputs will be strengthened; conversely, if they fire in the absence of dopamine, those connections will be weakened. Exactly the opposite thing happens in the no-go pathway: firing in the presence of dopamine causes their connections to become weaker, and in the absence of dopamine to become stronger. Based on this, Frank had the idea that dopamine should have different effects on learning from positive outcomes (which should cause dopamine increases) and negative outcomes (which should cause dopamine decreases). His early work tested this idea in people with Parkinson's disease, who have dysfunctional dopamine systems. He found that unmedicated patients (who have low dopamine levels) had problems learning from positive outcomes, but not from negative outcomes; on the other hand, when they were medicated (which causes high dopamine levels), they showed the opposite pattern, having trouble learning from negative outcomes but not from positive outcomes.[10]

The ideas developed in Frank's early studies of Parkinson's disease have since been used to begin understanding how brain computations malfunction in people with schizophrenia.[11] Dopamine clearly plays an important role in schizophrenia—most of the drugs used to treat psychosis have their effects by blocking dopamine receptors—but an understanding of exactly what role it plays has eluded researchers. Frank and his colleagues have shown that individuals with schizophrenia behave similarly to unmedicated people with Parkinson's disease on their test: they are impaired at learning from positive feedback but normal at learning from negative feedback. Further, this impairment is related to the strength of so-called "negative symptoms" of schizophrenia, such as flattened affect (reduced expression of emotions), apathy, and a general lack of engagement with the world. The models that Frank and his colleagues have developed also suggest that part of the problem in schizophrenia might be related to *when* the dopamine neurons fire, proposing that dopamine neurons may fire more often

at inappropriate times. This kind of computational analysis of behavior using brain-inspired mathematical models is likely to become a central feature of psychiatric research in the coming years, as the computational psychiatry movement gains steam. It remains to be seen whether it will help us understand psychiatric disorders better than our previous approaches have, but it's hard to imagine that it could do much worse.

Is Addiction a Brain Disease?

Addiction is a problem that touches almost everyone's life today in some way. Since my childhood, I have heard stories of one of my great-grandfathers whose alcoholism shattered the family. As an adult, I have had friends whose lives have been turned upside-down by their addiction to drugs, and have also watched as some of my favorite musicians and artists succumbed to their addictions. I'm not unique in this respect: across the world drug addiction takes a substantial toll. The most prevalent addiction is tobacco; it is estimated that more than 10% of deaths in men and 5% of deaths in women across the world are directly related to smoking. Addiction seems on its face to be different from other mental disorders because it is ultimately a disorder of choice: the addict could in principle simply choose to stop taking the drug, whereas it's much harder to imagine that psychotic people could choose not to listen to the voices in their head or depressed people could just will themselves into a good mood. But it's clear that stopping once one is addicted is very difficult; for example, studies of people trying to quit smoking or drinking have found that only about one-third of those who try to quit will still be successful a year later, and the outcomes for people addicted to opiates like heroin are usually much worse.

Addiction has been defined by the US National Institute on Drug Abuse (NIDA) as "a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences."[12] What does it mean for addiction to be a "brain disease"? There is a trivial sense in which addiction is a brain disease, since addicts' health is clearly impaired owing to their behavior, and all behavior arises from our brains, but the

real story is much more complex. Rather than thinking of it as a disease of the same kind as schizophrenia, I tend to think of addiction as the result of a mismatch between our evolved brain and our modern environment.

In chapter 7 we discussed the brain's system for making choices, and the central role of dopamine in creating habits. All forms of addiction seem to involve dopamine; in fact, many of the most powerful drugs of addiction are those that directly affect the dopamine system in the brain. Cocaine causes a flood of dopamine in the synapses between neurons by turning off a chemical pump that usually sucks extra dopamine from the synapse back into the cell so that it can be recycled and used again. Amphetamines can actually cause these pumps to go in reverse, spewing out even more dopamine into the synapse. Other drugs of abuse (including alcohol and nicotine) have more indirect effects on dopamine, but ultimately it seems that dopamine is the key to all forms of addictive behavior. The fact that dopamine agonist medication for Parkinson's disease can cause strange addictions (as I mentioned in chapter 7) provides even stronger evidence for this idea. All of this is due to two of dopamine's main effects: it causes us to be motivated to obtain rewards ("wanting") and it increases the likelihood that any action that results in dopamine release will be repeated in the future, turning behaviors into habits.

Our brains evolved in a world where the strongest stimulation that our dopamine system ever received was probably from sexual intercourse. The foods that our hunter/gatherer ancestors ate were almost certainly healthier than those that most humans eat today, but it's doubtful that they were particularly tasty given that there was little access to salt, sugar, or spices, and whatever fruits they scavenged had not been bred for flavor like the supersweet strawberries and apples that we eat today. Fast-forward to modern society, and we now have access to an enormous number of ways to stimulate our dopamine system that go far beyond what evolution had prepared us for, from highly palatable junk foods to both legal and illegal drugs that stimulate dopamine release in ways that were unprecedented in our evolutionary history.

Neuroimaging research has shown that the brains of addicts exhibit specific changes in the dopamine system. Dopamine levels can't be measured using MRI, but they can be measured indirectly with PET imaging using radioactive tracers that are attached to a molecule that binds to dopamine receptors, such as raclopride. Several studies have found that there is decreased binding of these molecules in the brains of people addicted to stimulants such as cocaine. Because these molecules bind less strongly than real dopamine, they will only attach to receptors if there are no extra dopamine molecules available to take those spots. A lower level of binding thus could mean two things: more dopamine is present (taking up all the open spots), or there are fewer available receptors to latch on to. However, it's also possible to test how much dopamine is released in the brain by using the same PET imaging method while administering a drug that causes dopamine release; because of the difficulty of doing research with an illegal drug like cocaine, this has generally been done using other drugs with similar effects on dopamine, such as the prescription drug Ritalin (methylphenidate). Studies using this approach have found that drug abusers appear to show decreased release of dopamine when given these drugs, which suggests that their lower levels of binding probably indicate lower numbers of receptors present. This probably reflects the fact that, just like our bodies, our brains adapt to our circumstances, always trying to keep us within a range of healthy function. When the brain experiences abnormally high levels of dopamine, it adapts by both decreasing its response to dopamine (turning down the number of dopamine receptors) and reducing the amount of dopamine that it releases. This adaptation is probably part of why over time the abuser goes from feeling high from the drug to needing the drug just to feel normal.

The fact that drug use causes changes in the brain fits with the idea that addiction is a "disease," but it's worth noting that changes in the body due to experience happen for many reasons, not all of which we would think of as diseases. If I lift heavy weights regularly my muscles will grow, and if I eat too much junk food I will gain body fat, both of which are caused by the body's natural mechanisms for adapting to its environment. We

certainly wouldn't refer to large biceps as a disease, and we only treat that extra fat as a disease if it gets too far out of hand.

Many drug treatment programs claim that drug addiction is a chronic disease that can be managed (usually through complete abstinence) but never cured, but there is some reason to question this idea. The most compelling evidence comes from a landmark study of heroin addicts returning from military service in Vietnam.[13] Narcotics were remarkably easy to obtain in Vietnam; almost half of the army's enlisted men in Vietnam in 1970–71 had tried narcotics, and 20% claimed to be addicted. If addiction is a chronic disease, then we would expect their addiction to continue when they returned to the United States after their service, but the data showed otherwise. A study by Lee Robins and her colleagues found that only about 5% of those soldiers who had been addicted in Vietnam had become readdicted a year after being back home. This was in stark contrast to the findings on drug addicts in the United States who had been sent to a "narcotics hospital," two-thirds of whom relapsed within six months. This tells us that context is very important, which is not surprising at all to anyone who has ever smoked; even if one can resist the impulse to smoke during the day, being in a smoky bar at night makes it much harder to say no. On the other hand, many of these individuals went on to develop other addictions (particularly alcohol), which suggests that they may have traded one addiction for another.

In fact, context is central not just to the desire to consume drugs but also to our brain's reaction to those drugs. When a person consumes a drug over time, the drug has increasingly weaker effects, which scientists call *tolerance* (and Australians call "piss fit"). The work of Shepard Siegel and his colleagues has shown that this tolerance occurs through learning and is specific to the context in which the drug is taken.[14] This fact explains an interesting aspect of heroin "overdoses"—in many cases, the amount of drug that results in death is no larger than the amount that the user has consumed in the past, but the drug is consumed in a different context than the user had previously consumed in. Siegel reported one particularly striking case of a cancer patient who received morphine at home for his pain. For about a month

he had received his treatments in the bedroom, but one day decided to take the treatment in his living room instead. The dose was no different from what he had received previously, but in this new context he developed the signs of an overdose and died shortly thereafter. The context sensitivity of addiction helps to explain the low rate of readdiction in the returning Vietnam veterans, but also leads us to question the description of addiction as a "chronic disease."

The Stigma of Mental Illness

One motivation for treating addiction and other psychiatric illnesses as "brain diseases" is that it is thought that this might help alleviate the stigma associated with these disorders. Research into stigma has found that it can take three forms: fear that the mentally ill person will become violent and dangerous, concern that the individual is not responsible enough to make their own life choices, and feelings that the individual needs to be taken care of.[15] These societal stigmas can boomerang, leading mentally ill individuals to engage in "self-stigma" that can cause them to feel even worse about their disease. They can also lead to structural discrimination against mentally ill people; for example, in about one-third of states in the United States, people with mental illnesses may be denied the right to vote.

It's less common for people with physical diseases to be stigmatized (though it does sometimes happen, as in the case of HIV/AIDS), and one might hope that treating mental illness as a biological illness would decrease stigma. Studies of public perception of mental illness have confirmed that people across the world have become increasingly likely to consider major mental illnesses such as schizophrenia and depression as "brain diseases."[16] However, these changes in attitudes about the causes of mental illness have not necessarily translated into greater acceptance of mentally ill individuals; the same study that found increasing belief in biological causes for these illnesses also found that the willingness to accept a mentally ill person as a neighbor or coworker actually went *down* over the same period. According to the researchers Nick Haslam and Erlend Kvaale, the belief in

what they call "biogenetic" explanations for mental illness has been a "mixed blessing": while it leads people to be less likely to blame the mentally ill for their problems, it actually makes them *more* likely to think that the mentally ill are dangerous, and also makes them more pessimistic about the ability of mentally ill people to improve through treatment.[17]

It's also interesting to look at how people with mental illnesses think about this question. Carla Meurk and her colleagues have done extensive interviews with people suffering from alcohol and drug addiction, delving specifically into the question of how they think of the idea of addiction as a brain disease. Their views are remarkably diverse. Some are clear in their rejection of the label:

> "I just don't think it could be a brain disease because it's something that it's by choice." [ID04, female]

Others embraced the label:

> "Well I'm happy if it is a disease because it helps me. Takes that pressure off—I'm a fuck up. [. . .] Ah I can say it's not just me and it's a disease. It's not just me being a screw up that is by drinking all the time, so yeah that made me feel better. [. . .] [If it's a disease] then at least I know all right there's a problem there and it can be fixed hopefully." [ID06, male]

Interestingly, some also raised concerns consistent with the mixed-blessings model that the disease label might lead them to be viewed as inferior:

> "Brain disease might sort of infer that—like brain injury. If you hear that somebody's got a brain injury or an acquired brain injury, you sort of get that image in your head of slow, low intelligence, as a result." [ID07, male][18]

Together, these studies show that the impacts of biogenetic explanations for mental illness and addiction are complex, and almost certainly there will be both positive and negative impacts on people suffering from those illnesses. Hopefully, with improved treatment for these disorders, the stigma will be reduced as they come to be viewed like other curable diseases.