CHAPTER 5

HOW DO BRAINS CHANGE OVER TIME?

On September 24, 2012, I got into an MRI scanner at the University of Texas at Austin, where I was the director of the Imaging Research Center. It's not uncommon for MRI researchers like myself to get scanned; often when we are testing out a new technique we just need a warm body in the scanner to see if it works. But this was different, as it was the first of a large number of scans taking place over the course of more than a year. Over the next 18 months I would get into the MRI scanner 104 times at the University of Texas, as well as being scanned at Washington University in St. Louis and at Stanford. Why would anyone do this? For me it was a means to start answering a fundamental scientific mystery about how the brain changes over time.

When we think about how the brain changes, we first need to distinguish the time scale: Are we talking about changes over the course of years, weeks, or seconds? Second, we need to ask what is causing the change. Early brain development relies largely on our genome's plan for how to build a brain, but most changes in the brain rely upon an intimate interaction between our genes and our environment. In fact, every experience you have leaves an imprint (however tiny) on the structure and function of your brain, through a set of brain mechanisms known as "neural plasticity." The brain's mechanisms for plasticity are complex and still being heavily studied, but several facts are well established. When two neurons fire at the same time, the connections between them (that is, the synapses) get stronger,

such that the same amout of input from one neuron will cause a stronger response in the other. This idea was first proposed by the neuroscientist Donald Hebb in 1949, and for that reason it is usually referred to as "Hebbian plasticity"—but a common parapharasing is "neurons that fire together, wire together." Neuroscientists now understand a great deal about the biology of this kind of plasticity, including the molecules and genes that are necessary for it to occur. We also know that this kind of plasticity is necessary for learning; if we administer a drug to an animal that blocks it, the animal's ability to learn will be diminished. It is these plastic changes in neurons that underlie nearly all of the ways in which we learn and remember, but *where* in the brain the plasticity happens matters for what is being learned. For example, our ability to remember events and replay them in our mind (which psychologists call "episodic memory") requires plasticity in a part of the brain called the *hippocampus*, while learning a new motor skill involves plasticity in a different part of the brain, called the *basal ganglia*.

Brain Development Across the Life Span

Our brains change continuously throughout our lives, from their emergence during fetal development through old age when their function often starts to decline. Interestingly, we are born with nearly all of the neurons that we will have in our lifetime. It's true that some parts of the brain can make new neurons throughout our life and that this is very important for learning, but the human newborn has nearly all of the 100 billion neurons that it will have for the rest of its life. The connections between those neurons, which are the key to learning, develop rapidly up until about the end of the first year of life, when the brain then starts to pick them off, through a process called *pruning* that continues throughout one's life. However, neuroimaging has shown us that this development doesn't happen equally across the brain. Research by Jay Giedd, Elizabeth Sowell, and many others has shown that the prefrontal cortex is the last part of the brain to develop in terms of its structure, not reaching its mature state until early adulthood, well after other parts of the brain.

Another aspect of brain development has to do with its wiring. I previously mentioned myelin in the context of imaging the white matter of the brain using diffusion weighted imaging. This fatty substance surrounds the neurons and helps them transmit information faster and more accurately. Research using diffusion weighted imaging has shown that the white matter develops very slowly, not fully maturing until well into the third decade of life. And just like the cortex, the white matter also doesn't develop evenly across the brain. The long tracts that connect the frontal lobe to the rest of the brain are some of the slowest to develop, while others reach their mature state by about 10 years of age. As I will discuss in chapter 6, the underdeveloped state of the prefrontal cortex and its wiring to the rest of the brain during adolescence provides part of the explanation for why teenagers can sometimes seem so out of control.

At the other end of the life span, a depressing reality of aging is that brain function starts to decline once we round our 30s. While some neurons die as we age, the bigger change comes in the connections between neurons that store our memories and knowledge, which start to deteriorate over time.[1] In addition, the myelin that insulates the brain's wiring also starts to degrade. These changes occur even in healthy aging, while another set of more insidious changes occurs in people suffering from age-related dementias such as Alzheimer's disease. In these diseases, the accumulation of damaging proteins in the brain's neurons causes them to start to malfunction and ultimately die. Some of the earliest changes happen in a part of the temporal lobe called the *entorhinal cortex*, which sends input to the hippocampus; this explains why memory problems are often the first sign of dementia, though it's important to note that a decline in memory function is a normal part of aging even for people without dementia. However, changes also occur throughout a network of regions in the cerebral cortex that are connected to the hippocampus. Research by Randy Buckner of Harvard and others combined structural MRI, fMRI, and PET imaging to show that there is a specific set of brain regions that is important for memory that starts to malfunction early in the development of Alzheimer's disease.[2] In particular, they used

a newly developed type of PET imaging that allowed them to quantify the amount of the damaging protein known as amyloid throughout the brain. Using this technique, they were able to demonstrate that the network of regions involved in memory also had the highest levels of amyloid, as well as showing the greatest amount of atrophy. Buckner's work provides an outstanding example of how neuroimaging can provide new insights into brain diseases.

How Experience Changes the Brain

The brain can often repair itself in response to insults such as stroke or brain injury. It was once thought that the brain lost most of its plasticity after puberty, but we now know that the ability of the brain to change in response to damage extends well into adulthood. Remember the case of Lisa, who I introduced in chapter 1, who had undergone a radical surgery to remove her left hemisphere at age 16 in order to treat her severe epilepsy. She was a right-handed child, which means that her left hemisphere was almost certainly the dominant side for processing language; this is also consistent with the fact that she did not speak for about a year after her left hemisphere was removed. However, her brain retained a remarkable amount of plasticity, which was evident when we studied her several years later. While her language function was far from normal, she was able to read simple sentences aloud and have a basic conversation. To find the areas in her brain that were supporting this newfound language function, we scanned her with fMRI while she listened to words or made judgments about the meaning of printed words. In each case, what we saw was that there was activity in the areas of her right hemisphere that matched where we would have expected it in the left hemisphere of a healthy person. Somehow, over the course of those several years, her brain rewired itself so that her intact right hemisphere could take over the functions that had relied upon her left hemisphere before it was removed.

There is also evidence that experience across the lifetime can change the brain, even in the absence of brain damage or illness. One of the best test-beds for the study of these kinds of changes

is in musicians, who usually spend many years learning and perfecting their complex combination of knowledge, auditory perception, and motor skills. Gottfried Schlaug from Harvard Medical School has spent more than two decades studying how musical experience changes the brain, and the results from his work as well as from others are very clear: musical experience changes both the structure and function of the brain, in direct relation to the amount of experience. One of the best-established findings is that the corpus callosum (the bundle of fibers connecting the brain's two hemispheres) is thicker in musicians compared with nonmusicians, and these changes are particularly evident in musicians who started learning music at an early age. This probably reflects the need for greater communication between the two hemispheres during musical performance, especially for players of keyboard instruments who have to coordinate their two hands. Other studies have looked at the size of the motor cortex, which in nonmusicians is usually larger on the dominant side (for right-handers that would be the left hemisphere, since everything is crossed over between the brain and the body). However, in pianists the motor cortex is much more equal in size across the two sides, primarily because it is larger on the nondominant side. It seems that the need to use both hands equally when playing the piano causes growth in the cortex that controls the nondominant hand, compared with nonmusicians who don't use the nondominant hand for fine motor skills as often.

The changes I have discussed so far happen over years or decades, but the brain's activity can also change much more quickly with experience. One of the most reliable findings in neuroimaging is that when a person does the same thing repeatedly, the amount of activity in the brain goes down.[3] A common example of this is a phenomenon known as "repetition suppression," in which repeatedly presenting a specific stimulus (such as a particular word or picture) leads to a decrease in the amount of activity in the areas of the brain that process the stimulus. For example, let's say that I present you with a noun (such as "hammer") and ask you to generate a verb that goes with the noun (you might say "hit"). The first time you do this,

there will be activation in a set of networks in your brain that are involved in reading and language processing as well as executive control networks that are engaged more generally whenever you do a novel cognitive task. If I were to show you the same word again and ask you to do the same task, there would be much less activation across all of these networks (see color plate 7). This probably reflects a couple of different things. First, when you do the same task a second time, you will almost always do it more quickly, which means that these brain systems are turned on for a shorter period, leading to less overall activity when we average it over time. Research by Tal Yarkoni has shown that there is a large set of brain networks whose level of activity is correlated with reaction time regardless of the specific task that the person is doing, meaning that their activity probably indexes something very general about how difficult a task is.[4] Second, when we do something for a second time, we will often do it differently. The first time you generate a verb related to the word "hammer," you have to search your word knowledge to find the right word. However, if I ask you to do the same thing again a short time later, now you could either once again search your word knowledge, or you could simply remember that you said "hit" the last time you did the task. Because remembering the answer is often going to be faster and easier than searching through your knowledge base for an answer, it's generally going to evoke less activity in the brain.

Brain Fluctuations

The research that I just described has told us a lot about changes that happen very slowly (over years or decades) or very quickly (over minutes). My lab had worked on both of these topics for years, but at some point it started to occur to me that there was a serious missing link in our understanding of how the brain changes over time—namely, how does it change over the course of days, weeks, and months? This is important because it's exactly this time frame over which people with mental illness can exhibit huge fluctuations in their psychological function, which must reflect changes in their brain over that time scale. Detailed

studies of individuals with schizophrenia and bipolar disorder have shown that their symptoms as well as their overall level of daily life functioning can fluctuate drastically from week to week: one week a person can be fully functional, and a couple of weeks later that person can be completely disabled.[5] Because we can't understand these kinds of changes in illness without first understanding how the healthy brain fluctuates over time, this seemed like a major void in our scientific knowledge—at that point there were no studies that had examined these kinds of fluctuations.

The reasons for such a scientific blind spot are not hard to see. First, cognitive neuroscientists have largely viewed the brain as a relatively static entity. We realize that the brain changes with experience, but nonetheless we generally assume that when we scan a person we are taking a representative snapshot of their brain function, and researchers have generally not thought that fluctuations over weeks or months are very interesting. Second, doing this kind of longitudinal research is really hard. Getting a person to come in for a single MRI scan is usually easy, but getting them to return for multiple scans over many months would be very difficult—just imagine that I asked you to come and get in an MRI scanner once a week every week for a year. In theory we could pay people enough to make sure that they come back for every visit, but in general the ethics boards that approve our research will not let us pay people an amount that they feel would be coercive; our subjects are supposed to be able to freely walk away from the research if they want to, but if they depend on the money to pay their rent or buy food then they don't really have that option.

Even if I could find willing volunteers, there is also the challenge of how to obtain research funding for such a study. In a perfect world, I would be able to apply for grant funding to study brain function in a group of volunteers over time, and given my track record I should have a good shot at receiving funding for such a study. However, most grant programs (such as those from the National Institutes of Health [NIH] and National Science Foundation, which fund most neuroscience research in the United States) will not support exploratory research where

the answer is not obvious. Instead, this kind of research is often labeled pejoratively as a "fishing expedition"; in fact, even when I later applied for a grant to do this kind of work from one of the NIH programs designed to support exploratory new research, it was rejected because the reviewers thought that it was too exploratory. Thus I was stuck on the horns of a dilemma: I could not hope to obtain research funding to answer the question without having some preliminary results to provide hypotheses to test, but at the same time I could not secure the funding necessary to obtain those pilot data.

"My Crazy Study"

Just as I was starting to think deeply about the variability of human brain function over time, an unlikely source of inspiration drove me to begin thinking about using myself as the first test subject. Laurie Frick is a former high-tech executive turned artist, whom I met in 2011. After her interest in our research became clear, we appointed her as our imaging center's "artist in residence." This meant two things for us: First, she joined us for scientific discussions, often bringing an interesting outside perspective on the questions that we were asking. Second, she allowed us to borrow some of her art pieces, which helped make our austere scientific laboratory a lot more beautiful. Laurie was deeply entrenched in the Quantified Self movement, which is a group of people who record as much data as possible about themselves, and her art is based on data that reflect the patterns in her life or others' lives. As Laurie began to push me to take advantage of my unique position as an fMRI researcher to collect brain imaging data on myself, a paper appeared that would prove to be the added inspiration that I needed to begin seriously studying myself.

Michael Snyder, a molecular biologist from Stanford, published a groundbreaking paper in 2012, in which he described what has come to be called the "Snyderome" (or as the journal *Nature* jokingly referred to it, the "narcissome").[6] Snyder's lab at Stanford studies many of the different "-omes" that are central to modern biology: the genome that describes our genetic code,

the transcriptome that describes how those genes are expressed, the proteome that describes the proteins generated from that expression, the metabolome that describes many of the small molecules involved in bodily metabolism, and more. His team developed an approach that they called "integrated personal-omics profiling," which involves quantifying almost everything that can be quantified about a human's biological function, and they used this to follow Snyder's personal biology over the course of more than a year. Analyses of Snyder's genome showed that he had genes that put him at risk for type 2 diabetes, and during the course of the study this genetic risk became destiny; after a respiratory infection, his blood glucose levels spiked and he developed full-blown diabetes. Now, no one wishes to develop a major disease such as type 2 diabetes, but Snyder's illness became a medical gold mine, because the blood collected over the course of his illness allowed his lab to generate the most detailed biological picture ever of how the disease develops. In particular, his results provided a set of new hypotheses about the relationship between inflammation and diabetes, which are now being tested in larger groups of prediabetic individuals.

Snyder is one of the world's leading molecular biologists, and his study showed me that serious researchers can make major discoveries by studying themselves. The idea of self-experimentation is of course not new; many researchers throughout history have experimented on themselves before studying others. In his memoir, Marcus Raichle recounts his experience as a young researcher when he spent several hours hyperventilating with catheters stuck in his jugular vein and femoral artery, in order to test how carbon dioxide affected brain metabolism. Self-experimentation has not always ended well (eight deaths of self-experimenters were recorded in the first half of the twentieth century),[7] but in some cases self-experimentation has led to discoveries that have changed the course of science and medicine. Take the case of stomach ulcers. It was long thought that these ulcers occurred as a result of stress or diet, but Dr. Barry Marshall had a theory that they could instead be caused by a bacterium called *Helicobacter pylori* (*H. pylori* for short). In order to establish that an organism

causes a disease, researchers must show that introducing the organism into a healthy individual results in the disease, and that eliminating the organism cures the disease. Dr. Marshall established this by drinking a liquid containing *H. pylori*; soon thereafter he developed an ulcer, which was cured by a course of antibiotics that killed the bacteria in his stomach. This self-experiment has revolutionized the treatment of stomach ulcers, and gained Marshall a Nobel Prize in Medicine.

In early 2012 I began discussing my planned study with many of my colleagues, usually describing it as the "crazy study I'm thinking about," and in September 2012 I began the study. I started out with the plan of scanning myself three times a week. It was important that these scans be performed under the most controlled conditions possible, so we performed them at very specific times of day and days of the week—every Monday at 5.00 p.m., and every Tuesday and Thursday at 7.30 a.m. We also planned the collection of blood every Tuesday, so that we could perform some of the same kinds of -omics analyses that Snyder performed in his study. Because food can drastically affect these results, this meant that I needed to fast and avoid caffeine every Tuesday morning until after my blood draw.

One of the not-so-important questions we had to answer early on was what to call my study. Some of my collaborators on the project had taken to calling it either the "Russome" or the "Poldrome" but I didn't like either of those, partly because they seemed too self-aggrandizing but also because they didn't really highlight what was most important about the study. I settled on calling it the "MyConnectome study," riffing on Sebastian Seung's well-known TED talk titled "I Am My Connectome," which I mentioned in chapter 3. This name highlighted the fact that we were particularly interested in understanding how brain connectivity, by which we mean the relationships in activity levels across different brain regions measured using fMRI, changes over time within one person.

Soon after we began the study, a potential snag appeared. While planning the study, we had considered the potential side effects of repeated MRI scanning. Fortunately MRI does not involve ionizing radiation (like an X-ray or a CT [computed

tomography] scan), and a large body of research suggested that the effects of repeated scanning should be minimal. The worst that I had expected was possibly some dizziness due to the crystals in my inner ear being pulled around by the magnetic field. However, in the first few weeks something worrisome happened. I suffer from tinnitus, or ringing in my ears, probably because of shooting guns without ear protection as a child (a hazard of growing up in small-town Texas) and too many loud rock concerts in my teens and twenties. It's like a little friend who is always there in the background, waiting to blow its whistle whenever I get bored or anxious. Soon after the study began, I noticed that my tinnitus became more intrusive. Anyone who has had an MRI scan will understand why—the scanner makes very loud noises, and the research scans used for my tests are even louder and more annoying. As much as I like scientific discovery, I like my hearing a lot more, so I quickly arranged to get tested at the campus hearing center, so that we could follow my hearing to make sure that I wasn't damaging it. The results of the first tests were not surprising—I had fairly significant hearing loss in the high frequencies, consistent with noise-related hearing damage, which predated my scanning endeavor. I continued to get tested monthly, and for many months the results were very consistent, but in April 2013 we noticed a worrisome reduction in my hearing. In retrospect this was probably a fluke (I had a bit of a cold on the morning of the test), but it concerned me enough that I decided to take a break from the study for a couple of months. Fortunately, follow-up tests later that summer showed that my hearing was unchanged from the beginning of the study, and we started back up with the study in June 2013.

I began the study with a plan of collecting one year's worth of data, but real life intervened in a number of ways, including work-related travel, holidays, MRI scanner problems, and a number of campus closures due to icy weather in the spring of 2014. I also had to stop doing the Monday afternoon scans, as they just took too much time out of my day. In the end, it took about 18 months to collect 48 samples of blood data (that's about a quart of blood in total) and 104 MRI scanning

sessions. I moved to Stanford soon after the study ended, and I spent the summer of 2014 digging deeply into the data from a temporary apartment in Palo Alto, using the supercomputers at the University of Texas to process the massive data sets.

How One Brain Changes over Time

We performed many different types of MRI scans in the course of the project, but the one type of scan we focused on in particular was resting fMRI, which you have already encountered in chapter 3. The goal of resting fMRI is generally to understand the relationships between the activity of different regions across the brain over time. We record data from about 100,000 small cubes ("voxels") within the brain, but then we collapse the data from nearby voxels into regions (which we generally call "parcels"), through an operation that we call "parcellation." The idea behind parcellation is that there are regions of the brain whose connectivity with the rest of the brain is highly similar, so we can treat them as a single unit for the purposes of our data analysis. We worked with a group led by Steve Petersen at Washington University in St. Louis, which has developed some of the most state-of-the-art methods for parcellation of the brain. In fact, Petersen's group first contacted me because they had heard about the study and wanted to use my data set to test the reliabilty of their parcellation methods—they had never had enough data from one person to do so. This turned into a remarkably effective and enjoyable collaboration between our groups, spearheaded by a brilliant graduate student in Petersen's lab named Tim Laumann. Tim applied their methods to my data and found that they were indeed quite reliable; when he applied the same method to two different sets of scans collected on different days, the results came out very similar, giving us added confidence in the method. The parcellation results told us that my cerebral cortex was composed of 620 different regions. This was many more regions than previous research had suggested, but that work had been based on much less data for each individual. Subsequent research by David Van Essen and his colleagues in the Human Connectome Project has identified a similar but

somewhat smaller number of regions (360) across many more people, using a different set of methods.

Once we had identified the 620 regions in my brain, we took the average activity from each region and performed all of our analyses on those data, which greatly reduced the computational burden of the analyses; instead of needing a supercomputer, I could now do most of the analyses on my laptop. We calculated the correlations between each pair of the 620 regions within each 10-minute-long resting fMRI scan, which gave us almost 200,000 correlations, which we then used to sort the 620 regions into a smaller number of "resting state networks"—-basically, sets of regions whose activity is more highly correlated with one another than with the rest of the brain. This showed that there were 13 networks, which corresponded quite well to the networks that the Petersen group had previously identified in larger groups of people. However, there were also some idiosyncratic features of my brain. For example, there is a network that is always found in the middle of the brain called the "default mode" network (shown in red in color plate 8), which was first identified by Marcus Raichle and his colleagues and which seems to be most active when a person is thinking introspectively, as we do when we are resting in an MRI scanner. My default mode area sits in the same place where we would have expected it to sit based on the previous studies. There is another network, called the "salience" network, that usually spans different parts of the frontal lobe and is involved in orienting to surprising things in the environment. I also have one of these (shown in light blue in color plate 8), and again it's mostly in the right place. However, if you look in the middle of the default mode area in my prefrontal cortex, you will see several blue areas surrounded by the red default mode areas—these regions are basically in the wrong place, at least according to what we expected based on studies of groups of people (with much less data for each person).

One of the other important questions that we wanted to answer with the study was this: How do the differences in resting state connectivity between days for a single person compare to the differences across people? If the differences in my brain from one day to the next were similar to the differences among people,

then this would mean that we might not actually need to study individuals longitudinally over time—we could just compare different people. It turned out that the fluctuations in my brain from day to day were very different from the way that people's brains vary from one to another: in fact, when we looked at the regions that varied the most in their connectivity from day to day within my scans, those turned out to be some of the *least* variable among people. This is important because it tells us that if we want to understand the fluctuations in brain function over time within a single person, then we need to do the kind of intensive studies over time that I did in my study; we can't simply look across different people and ask how they differ from one another.

Because I needed to be fasted and caffeine-free on Tuesday mornings in order to get valid results from the blood analyses, we had a built-in experimental comparison of the effect of caffeine and food between Tuesdays and Thursdays. We have long known that caffeine affects blood flow to the brain, and some labs keep a coffee machine near the MRI scanner because of the lore that it produces better data when subjects are caffeinated during a scan, so I expected brain connectivity to be generally lower and more variable on days when I was uncaffeinated. When we analyzed the data we were surprised by the results. First, we found that overall connectivity was actually *greater* on days when I was caffeine-free. Second, when we looked at where this happened in the brain, we found that it was specific to a small subset of areas, which were some of the most primitive parts of the cerebral cortex: the visual areas that process basic visual input, and the sensory/motor cortex that is responsible for touch and movement. These areas were relatively unconnected when I was caffeinated, but became highly interconnected when I was fasted and uncaffeinated. It was almost as if, in its tired and uncaffeinated state, my brain moved into a more basic mode that focused on sensory input rather than higher-order cognitive functions. We assume that this is due to caffeine, but we can't rule out that it might also reflect the effects of food, since the two were always changed together.

Tim Laumann drafted the first paper describing our findings and we submitted it for publication in early 2015. The reviewers of the paper were quite enthusiastic, but also raised some

questions about the analyses that we had presented. In the paper we had compared my brain with the data from a large group of individuals who had been scanned in less detail at Washington University. There were two major differences between how we had collected the data in Austin and how the data had been collected from the subjects at Washington University. First, they were scanned on a different model of MRI scanner than I had been. We don't generally expect different scanners to give us radically different results, but a large study called the Biomedical Informatics Research Network has shown that results can differ from scanner to scanner, so this was a legitimate concern. Another difference between the studies was subtle put potentially very important: in my scans I had kept my eyes closed, while the subjects in the Washington University studies had their eyes open, staring at a point on a gray screen. In order to address these questions, I flew to St. Louis on April 3, 2015, and spent about six hours lying in the MRI scanner at Washington University, doing resting fMRI scans with my eyes either open or closed, in order to address the questions raised by the reviewer (see figure 5.1). It turned out that having my eyes open did indeed result in a substantial difference in the connectivity of my brain, not just in the parts of my brain that process visual information, but also in the sensory/motor areas that showed such big effects of caffeine and food. This meant that any comparisons between the data sets had to be interpreted with that factor in mind. With this question answered, the paper was accepted and published later that year.[8]

What did we learn from all of this work? First, we now have an initial glimpse into how the function of a single human brain changes over time; it is not at all surprising that the brain changes over the course of weeks and months, but until our study it had not ever been measured. In addition, we have discovered some of the factors that cause brain function to fluctuate, including caffeine and food as well as my mood. We have also discovered that these differences in brain function within a person over time are not the same as the differences across people. This is essential, because it says that we need to study individuals over time more intensively if we want to

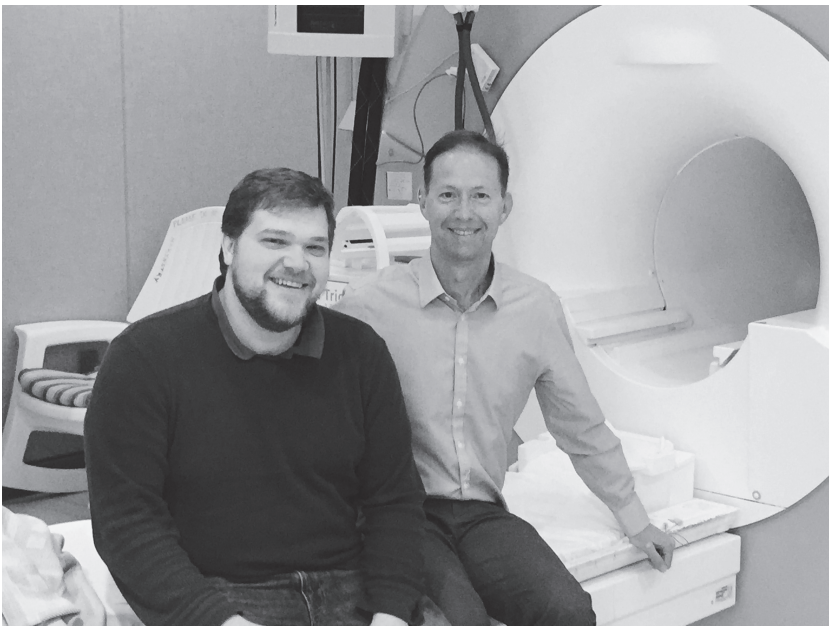

Figure 5.1. A photo of Tim Laumann (*left*) and me (*right*), just after I emerged from about six hours of MRI scanning at Washington University. Photo courtesy of Tim Laumann.

understand these fluctuations, which we think are crucial if we want to understand how the brain changes in mental illnesses such as depression or bipolar disorder. The results also showed us that if we want to obtain highly reliable measurements of an individual brain, we need to collect much more data about each person than most studies have done: behind the gross concepts of brain organization that had come from earlier studies (in which a small amount of data was collected from a large set of people) was hiding a level of fine-grained differences between people that have started to emerge from more detailed studies of individuals.

These findings have also inspired a number of other researchers to start looking at individuals in much more detail, and the findings have already started to change how we think about the functional organization of the brain. In one example of such a study, Rodrigo Braga and Randy Buckner from Harvard University scanned four individuals extensively and

then examined how the default mode network in their brains was organized.[9] What they found was that within the areas where the default mode network should be found, based on the group studies, there were actually two separate networks next to each other, which differed in how they were connected to the rest of the brain. Because this organization differs from person to person, it had been lost in previous research that had combined data across individuals. The power of this "dense-scanning" approach is so strong that Buckner, one of the pioneers of fMRI research, has switched his entire research program to focus on the intensive scanning of individuals.

Toward a Personalized Neuroscience?

I am often asked what I learned about myself from all of the data that we collected as part of the MyConnectome study, and my answer is usually: "depressingly little." The data led us to some very important *scientific* findings, and those have been deeply edifying for me. It has also changed how I think about doing neuroimaging research, leading me to an interest in collecting more data on each individual in order to be able to better characterize individual brains. However, in terms of insights into how to live my life, there really have not been any. In part this is because while the project involved collection of an astounding amount of data, there is still too little data for me to confidently make decisions about how to change my life.

The most promising analysis for telling me something useful was what we called a "phenome-wide" analysis. The *phenome* refers to all of the different ways in which humans can vary, which come about through the interaction of our genomes and our environments. A phenome-wide analysis is one that examines the relationships between many different types of variables—in my case this included brain imaging, gene expression and metabolite levels in my blood, the foods that I had eaten each day, and all of the various psychological measurements that we made during the study. We examined the correlations between all of these different variables, which involved more than 38,000 statistical tests. After performing statistical corrections for

this large number of tests, there were still a large number of statistically significant relations between variables. Some of these made very good sense; for example, the severity of my psoriasis (which I rated every evening) was related to the expression of genes related to T cells, which are known to play a central role in the disease. Others were potentially useful, such as a relationship between eating beef and the level of expression of genes related to inflammation. However, even though that relationship was statistically significant after correcting for the large number of analyses, it still only accounted for a few percent of the expression in those genes, and it's hard to know whether it's a false positive or a real result.

One central problem is that because this is correlational research, we don't know what causes what. Anyone who has ever taken a statistics class is familiar with the dictum that correlation does not imply causation. In reality, the presence of a correlation tells you that something is causing something else, but doesn't tell you which way the causal arrows point; in the case of the beef result, there are three possibilities. First, it could be that eating beef causes those inflammatory genes to be expressed more. Second, it could be that high levels of expression in those genes caused me to be more likely to eat beef (for example, as "comfort food" when I wasn't feeling as good). Third, something else could be causing both of these things to change. For example, perhaps I eat more beef when I am exercising more, and the latter also causes changes in gene expression. Because our data are purely observational, we can't tell these apart. For this reason, I didn't feel confident enough in any of the results to make big changes in my life (especially something as drastic as cutting beef from my diet).

In recent years there has been great excitement about the idea of "precision medicine," or "personalized medicine," with the NIH in the United States putting more than $50 million into a project called "All of Us," which is meant to gather data from more than one million people in order to more precisely treat their diseases. There are already some success stories for personalized medicine, such as the ability to effectively cure some cancers with treatments that are based on the specific

genetic mutations in the cancer or the ability to tailor drug dosages based on a person's genetics. Much of the current excitement around precision medicine comes from the hope that data collected from mobile devices will provide physicians with new ways to understand disease and possibly intervene earlier in the course of a disease. For example, what if your smartphone could monitor your movements and use them to predict that you are about to become depressed? I also hold out hope that this kind of measurement will lead to more effective prevention and treatment of diseases. But my experience with the MyConnectome project suggests that it will be challenging to scale this up to studies that require more intrusive measurements, such as MRI scans. Even simple things like writing down all of the foods that I had eaten in a day became very tiresome after a few months, so anything that requires effort from the individual will likely be difficult to sustain unless it can be automated. I certainly hope that the All of Us project succeeds in showing new ways to prevent or treat diseases, but I think it's always important to disentangle hype from realistic expectations.