This and the following chapters are from *Brain on Fire: My Month of Madness*, by Susannah Cahalan, Published in 2012 by Simon & Schuster

CHAPTER 24

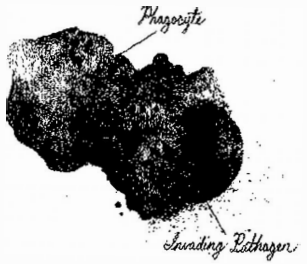
IVIG

On April 2, the nurses started my first round of five intravenous immunoglobulin (IVIG) infusions. The clear IV bags hung on a metal pole above my head, their liquid trickling down into my vein. Each of those ordinary-looking bags contained the healthy antibodies of over a thousand blood donors and cost upwards of $20,000 per infusion. One thousand tourniquets, one thousand nurses, one thousand veins, one thousand blood-sugar regulating cookies, all just to help one patient.

IVIG is made up of serum antibodies called immunoglobulin G, or IgG, which are the most common type of antibody found in the human body. IVIG is approved by the U.S. Food and Drug Administration to treat problems relating to transplants, leukemia, and pediatric HIV, among other conditions; its off-label uses have often been considered "experimental" and denied by insurance companies.

Antibodies are created by the body's immune system to counteract an unwanted, external element, such as when a pathogen of some sort—a virus, bacterium, fungus, or other foreign substance—enters the body. This sets off a series of reactions beginning with the body's basic alarm system, the innate response, which is a one-size-fits-all process designed to get rid of unwanted visitors quickly. If the innate system can't eradicate the pathogen, the next defense stage is the "adaptive response," which tailors itself to the specific intruder, using an arsenal of white blood cells and antibodies. This takes much longer to mobilize than the innate response, ten days versus the innate system's minutes or hours. Usually the collateral damage of these internal battles

results in familiar flulike symptoms such as headache, fever, muscle ache, nausea, and enlarged lymph nodes.



An immune cell, called a phagocyte, "eating" a pathogen.

One type of white blood cell, the B-cell, also can morph into plasma cells that create antibodies. Under normal conditions, each antibody fits exactly to only one pathogen, like Cinderella's glass slipper, with the purpose of blocking the spread of infection by either disabling that specific kind of pathogen or flagging it for destruction. But autoantibodies, which everyone has in healthy doses, can sometimes transform into the most malicious type of biological shadowboxer, if they begin to attach to and destroy the healthy host tissue, like the brain. An IVIG infusion introduces fresh, healthy antibodies to fuse with those "bad" rogue autoantibodies created by a sick person's immune system, helping to neutralize them and rendering the autoantibodies harmless.

Beep, beep, beep. It's dark. There's the beeping of a massive machine to my right. There's a wire hooking me up to heaving bags of white liquid. I put Stephen's headphones on and close my eyes. I am far, far away from here. I am myself again.

"This next song is to my friend Leah who couldn't be here tonight . . ."

The hum of the guitar. The soft tap on the drums. The swell of the music. It's Halloween night at Harlem's Apollo Theater. I'm at a Ryan Adams concert. I can see him onstage, strumming on his guitar, but I can't keep my eyes open to watch the scene. I feel a touch on my skin. It makes me shudder. I hear a voice.

"SuSHana, time to take vitals."

The concert disappears, dissolving into the dark hospital room, the nurse next to me. I'm back, back in the place where there is no night and there is no day. It's this woman's fault I'm back here. I'm suddenly filled with blinding, focused rage. I wind my right arm back and punch her in the chest. She gasps.

The next morning, my mother took her usual place beside me in a chair by the window when her phone rang. It was James. My parents had been keeping him uninformed about the severity of my illness, not wanting to worry him and disrupt his studies. He and I had always been close, despite the five-year age difference, and our parents knew he would drop everything and come home if he discovered how bad off I was. But today, for the first time, she decided to hand off the phone to me.

"James . . . James . . . James," I said, hearing my brother's voice on the other line. "James . . . James . . . James."

In his dorm room in Pittsburgh, James choked back tears. I sounded so different, so unlike his big sister. He insisted, "I'm going to come home soon. And you're going to get better."

The following day, while I was on my second course of IVIG treatment, Dr. Arslan, the psychopharmacologist, came by on rounds and noticed that my speech problems had worsened. He wrote the following in his progress note:

Some sleep problems overnight and increased speech latency, the latter a concern because it may be an initial catatonic sign. Seroquel less effective for sleep last night than previously.

It was the first time that anyone had mentioned the term *catatonia,* a stage defined by absence, by inability, by nonbehaviors. The mnemonic that doctors use to diagnose catatonia is WIRED 'N MIRED:

- Waxy flexibility/catalepsy (muscular rigidity and fixedness of posture)
- Immobility/stupor
- Refusal to eat or drink
- Excitement
- Deadpan staring
- Negativism/negative symptoms
- Mutism
- Impulsivity
- Rigidity
- Echolalia (automatic repetition of words or statements said by another person)
- Direct observation

Catatonia comes from the misfiring of neurons. That "muscular rigidity," also called posturing, occurs when the chemical link is severed between the patient's awareness of her body and the feeling of comfort and appropriateness of movement. In other words, a catatonic patient cannot sense his or her body in space, and therefore cannot appropriately adjust. The result is that a person sits very still in awkward, atypical, unnatural poses. Cata-

tonia is more akin to the results of a botched lobotomy than a persistent vegetative state because the person is technically still active. There are behaviors of a sort, as bizarre, nonresponsive, and inappropriate as they may be.

Meanwhile, a comment that the nurse had made the night before was haunting Stephen. She was a young Asian immigrant who had just begun working at New York University. While examining me, she said offhandedly, "Has she always been so slow?"

Stephen shook his head violently, struggling to control his temper. *How dare she say something like that. Susannah is not, and never was, slow.*

The next morning, Stephen ran into my father in the hallway. At first, they spoke about superficial things—the cold weather, how Stephen's work was, and so forth. But the conversation quickly turned to me.

"She's still in there," Stephen said. "I can see her. She's still there. I know it."

"I agree. And that's who we're fighting for. None of the doctors and nurses see it, but we do," my dad said. "And we have to remain strong for her."

"Agreed." The two men shook hands. My dad wrote about his new impression of Stephen in his journal: "The one friend who did come everyday was Stephen. He was terrific. I wasn't that sold on him when I first met him, but he grew in my respect and regard with every day that passed."

Go to the next page.

Compare the explanations and language on pages 149 - 151 to the language used in research articles.

CHAPTER 29

DALMAU'S DISEASE

Dr. Russo arrived later that day to explain which diseases they could now tick off the list of possibilities, including hyperthyroidism, lymphoma, and Devic's disease, a rare disease similar symptomatically to multiple sclerosis. They still suspected that I had been exposed to hepatitis, which can cause encephalitis, but they didn't have proof.

After the conversation, my mother followed Dr. Russo into the hallway. "So what do *you* think it is?" my mom prodded.

"Actually, Dr. Najjar and I have a bet going."

"What kind of a bet?"

"Well, Dr. Najjar thinks the inflammation is caused by autoimmune encephalitis; I think it's paraneoplastic syndrome." When my mother pressed for more details, Dr. Russo explained that paraneoplastic syndrome is a consequence of an underlying cancer, most often associated with lung, breast, or ovarian cancer. The symptoms—psychosis, catatonia, and so forth—are not associated with the cancer but with the immune system's response to it. As the body gears up to attack the tumor, it sometimes begins to target healthy parts of the body, such as the spine or the brain. "I think because of her history of melanoma, it makes sense," Dr. Russo concluded.

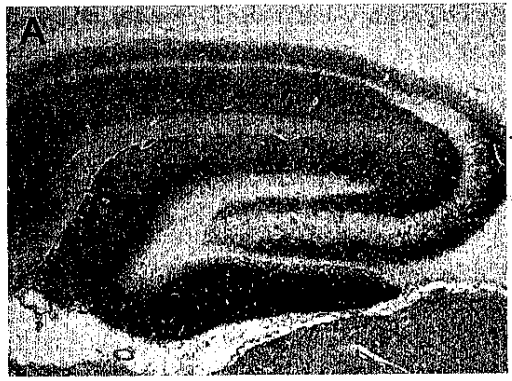
This was not what my mother wanted to hear. Cancer had always been the greatest fear, the word she dared not utter. Now this doctor was tossing it off casually as part of a bet.

Meanwhile, two plastic tubes, placed securely in Styrofoam boxes, had arrived at the University of Pennsylvania, transported in a refrigerator in the back of a FedEx truck; one contained transparent cerebrospinal fluid, as clear as unfiltered water, and another held blood, which started to look like dehydrated urine as, over time, the red blood cells dropped to the bottom. The test tubes were coded 0933, labeled with my initials, SC, and placed in a negative-80 degree freezer waiting for the lab to conduct its tests. They were addressed to the lab run by neuro-oncologist Dr. Josep Dalmau, whom Dr. Najjar had mentioned during his first visit and whom Dr. Russo had since e-mailed to ask if he would take a look at my case.

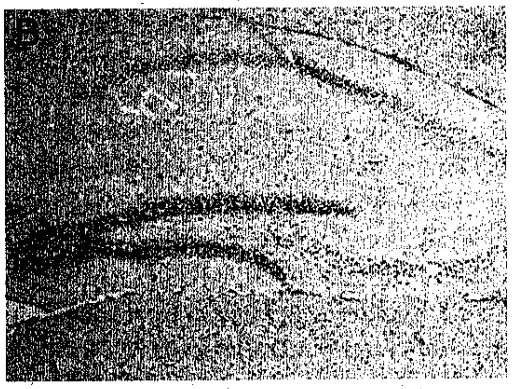
Four years earlier, in 2005, Dr. Dalmau had been the senior author on a paper in the neuroscience journal *Annals of Neurology* that focused on four young women who had developed prominent psychiatric symptoms and encephalitis. All had white blood cells in their cerebrospinal fluid, confusion, memory problems, hallucinations, delusions, and difficulty breathing, and they all had tumors called teratomas in their ovaries. But the most remarkable finding was that all four patients had similar antibodies that appeared to be reacting against specific areas of the brain, mainly the hippocampus. Something about the combination of the tumor and the antibodies was making these women very sick.

Dr. Dalmau had noticed a pattern in these four women; now he had to learn more about the antibody itself. He and his research team began to work night and day on an elaborate immunohistochemistry experiment involving frozen sections of rat brains, which had been sliced into paper-thin pieces and then exposed to the cerebrospinal fluid of those four sick women. The hope was that the antibodies from the cerebrospinal fluid would bind directly to some receptors in the rat brain and reveal a characteristic design. It took eight months of tinkering before a pattern finally emerged.

Dr. Dalmau had prepared the rat brain slides all the same, placing a small amount of cerebrospinal fluid from each of the four patients on each. Twenty-four hours later:



A: Section of rat brain in the hippocampus that shows the reactivity of the cerebrospinal fluid of a patient with anti-NMDAR encephalitis. The brown staining corresponds to the patient's antibodies that have bound to the NMDA receptors.



B: A similar section of hippocampus of an individual without NMDA receptor antibodies.

Four beautiful images, like cave drawings or abstract seashell patterns, revealed the antibodies' binding to the naked eye. "It was a moment of great excitement," Dr. Dalmau later recalled. "Everything had been negative. Now we became totally positive that all four not only had the same illness, but the same antibody."

He had clarified that the pattern of reactivity was more intense in the hippocampus of the rat brain, but this was only the beginning. A far more difficult question now arose: Which receptors were these antibodies targeting? Through a combination of trial and error, plus a few educated guesses about which receptors are most common in the hippocampus, Dr. Dalmau and his colleagues eventually identified the target. Using a kidney cell line bought from a commercial lab that came with no receptors on their surfaces at all, a kind of "blank slate," his lab introduced DNA sequences that direct the cells to make certain types of receptors, allowing the lab to control which receptors were available for binding. Dalmau chose to have them express only NMDA receptors, after figuring out that those were the most likely to have been present in high volume in the hippocampus. Sure enough, the antibodies in the cerebrospinal fluid of the four patients bound to the cells. There was his answer: the culprits were NMDA-receptor-seeking antibodies.

NMDA (N-methyl-D-aspartate acid) receptors are vital to learning, memory, and behavior, and they are a main staple of our brain chemistry. If these are incapacitated, mind and body fail. NMDA receptors are located all over the brain, but the majority are concentrated on neurons in the hippocampus, the brain's primary learning and memory center, and in the frontal lobes, the seat of higher functions and personality. These receptors receive instructions from chemicals called neurotransmitters. All neurotransmitters carry only one of two messages: they can either "excite" a cell, encouraging it to fire an electrical impulse, or "inhibit" a cell, which hinders it from firing. These simple conversations between neurons are at the root of everything we do, from sipping a glass of wine to writing a newspaper lead.

In those unfortunate patients with Dr. Dalmau's anti-NMDA-receptor encephalitis, the antibodies, normally a force for good in the body, had become treasonous persona non grata in the brain. These receptor-seeking antibodies planted their death kiss on the surface of a neuron, handicapping the neuron's receptors,

making them unable to send and receive those important chemical signals. Though researchers are far from fully understanding how NMDA receptors (and their corresponding neurons) affect and alter behavior, it's clear that when they are compromised the outcome can be disastrous, even deadly.

Still, a few experiments have offered up some clues as to their importance. Decrease NMDA receptors by, say, 40 percent, and you might get psychosis; decrease them by 70 percent, and you have catatonia. In "knockout mice" without NMDA receptors at all, even the most basic life functions are impossible: most die within ten hours of birth due to respiratory failure. Mice with a very small number of NMDA receptors don't learn to suckle, and they simply starve to death within a day or so. Those mice with at least 5 percent of their NMDA receptors intact survive, but exhibit abnormal behavior and strange social and sexual interactions. Mice with half their receptors in working order also live, but they show memory deficits and abnormal social relationships.

As a result of this additional research, in 2007, Dr. Dalmau and his colleagues presented another paper, now introducing his new class of NMDA-receptor-seeking diseases to the world. This second article identified twelve women with the same profile of neurological symptoms, which could now be called a syndrome. They all had teratomas, and almost all of them were young women. Within a year after publication, one hundred more patients had been diagnosed; not all of them had ovarian teratomas and not all of them were young women (some were men and many were children), enabling Dr. Dalmau to do an even more thorough study on the newly discovered, but nameless, disease.

"Why not name it the Dalmau disease?" people often asked him. But he didn't think "Dalmau disease" sounded right, and it was no longer customary to name a disease after its discoverer. "I didn't think that would be wise. It's not very humble." He shrugged.

By the time I was a patient at NYU, Dr. Dalmau had fine-tuned his approach, designing two tests that could swiftly and accurately diagnose the disease. As soon as he received my samples, he could

test the spinal fluid. If he found that I had anti-NMDA-receptor autoimmune encephalitis, it would make me the 217th person worldwide to be diagnosed since 2007. It just begged the question: If it took so long for one of the best hospitals in the world to get to this step, how many other people were going untreated, diagnosed with a mental illness or condemned to a life in a nursing home or a psychiatric ward?

CHAPTER 31

THE BIG REVEAL

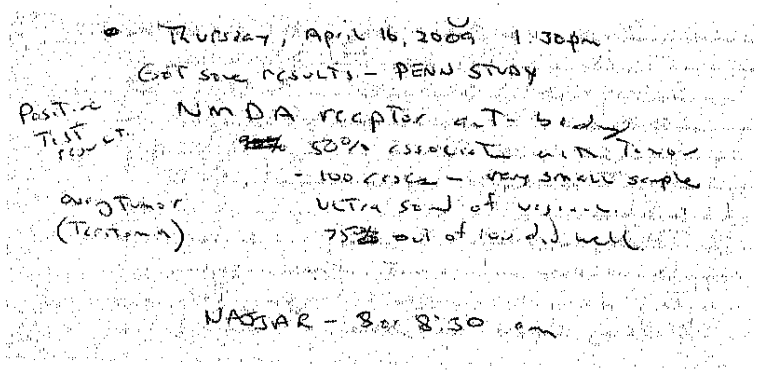
Later that afternoon, my dad had been trying to interest me in a game of gin rummy when Dr. Russo and the team arrived.

"Mr. Cahalan," she said. "We have some positive test results."

He dropped the playing cards on the floor and grabbed his notebook. Dr. Russo explained that they'd heard back from Dr. Dalmau with a confirmation of the diagnosis. Her words flew at him like shrapnel—bang, bang, bang: *NMDA, antibody, tumor, chemotherapy.* He fought to pay close attention, but there was one key part of the explanation that he could hold on to: my immune system had gone haywire and had begun attacking my brain.

"I'm sorry," he interrupted the barrage. "What is the name again?"

He wrote the letters "NMDA" in his block lettering:



Anti-NMDA-receptor encephalitis, Dr. Russo explained, is a multistage disease that varies wildly in its presentation as it progresses. For 70 percent of patients, the disorder begins innocuously, with normal flulike symptoms: headaches, fever, nausea, and vomiting, though it's unclear if patients initially contract a virus related to the disease or if these symptoms are a result of the disease itself. Typically, about two weeks after the initial flulike symptoms, psychiatric issues, which include anxiety, insomnia, fear, grandiose delusions, hyperreligiosity, mania, and paranoia, take hold. Because the symptoms are psychiatric, most patients seek out mental health professionals first. Seizures crop up in 75 percent of patients, which is fortunate if only because they get the patient out of the psychologist's chair and into a neurologist's office. From there, language and memory deficits arise, but they are often overshadowed by the more dramatic psychiatric symptoms.

My father sighed with relief. He felt comforted by a name, any name, to explain what had happened to me, even if he didn't quite understand what it all meant. Everything she said was matching up perfectly to my case, including abnormal facial tics, lip smacking, and tongue jabbing, along with synchronized and rigid body movements. Patients also often develop autonomic symptoms, she continued: blood pressure and heart rate that vacillate between too high and too low—again, just like my case. She hardly needed to point out that I had now entered the catatonic stage, which marks the height of the disease but also precedes breathing failure, coma, and sometimes death. The doctors seemed to have caught it just in time.

When Dr. Russo began to explain that there are treatments that have been proven to reverse the course of the disease, my father nearly sank to his knees and thanked God right there in the hospital room. Still, Dr. Russo cautioned, even once you have a diagnosis, there are still substantial question marks. Though 75 percent of patients recover fully or maintain only mild side effects, over 20 percent remain permanently disabled and 4 percent die anyway, even despite a swift diagnosis. And those aforementioned

"mild" side effects might mean the difference between the old me and a new Susannah, one who might not have the humor, vitality, or drive that I did before. *Mild* is a vague and undefined term.

"About 50 percent of the time, the disease is instigated by an ovarian tumor, called a teratoma, but in the other 50 percent of cases, the cause is never discovered," Dr. Russo continued.

My dad looked at her quizzically. *What the hell is a teratoma?*

It was probably best that he didn't know. When this type of tumor was identified in the late 1800s, a German doctor christened it "teratoma" from the Greek *teraton,* which means monster. These twisted cysts were a source of fascination even when there was no name for them: the first description dates back to a Babylonian text from 600 B.C. These masses of tissue range in size from microscopic to fist sized (or even bigger) and contain hair, teeth, bone, and sometimes even eyes, limbs, and brain tissue. They are often located in the reproductive organs, brain, skull, tongue, and neck and resemble pus-soaked hairballs. They are like those hairy, toothy creatures in the 1980s horror film franchise *Critters*. The only good news is that they are usually—but not always—benign.

"We will need to do a transvaginal exam to see if there are any signs of tumors," said Dr. Russo. "We'll also check her over to see if there's any link with her history of melanoma. If so, we'll have to move on with chemotherapy."

"Chemotherapy." My father repeated the word in the hope that she had gotten it wrong. But she hadn't.

My dad looked over at me. I had been staring off to the side, disassociated from the exchange, not seeming to gauge the magnitude of the moment. Suddenly, though, at the word *chemotherapy,* my chest began heaving, and I let out a deep sigh. Tears streamed down my face. My dad ran from his chair and threw his arms around me. I continued to sob without saying a word, as Dr. Russo waited quietly while he rocked me. He couldn't tell if I understood what was going on or if I was just attuned to the amplified electricity in the room.

"This is killing me," I said, my voice high yet unemotional, despite the sobs. "I'm dying in here."

"I know, I know," he said. With my head in his arms, he could smell the glue on my hair. "We're going to get you out of here."

After a few moments, my sobs stopped, and I lay back on the bed, my head against the pillow, staring straight ahead. Quietly, Dr. Russo continued. "Overall, this is good news, Mr. Cahalan. Dr. Najjar believes that there is a possibility that Susannah could get back as much as 90 percent of her former self."

"We could get her back?"

"There seems to be a strong possibility."

"I want to go home," I said.

"We're working on doing just that," Dr. Russo replied with a smile.

Over the weeks, I had gone from being a notoriously difficult patient to a favorite, the ward's "interesting consult" for a host of attending doctors, interns, and residents hoping to catch a glimpse of the girl with the unknown disease. Now that we had a diagnosis that had never before been seen at NYU, young MDs, hardly a day older than me, stared at me as if I were a caged animal in a zoo and made muffled assessments, pointing at me and craning their heads as more experienced doctors gave a rundown of the syndrome. The next morning, as my father fed me oatmeal and chopped-up bananas, a group of residents and medical students arrived. The young man leading the group of nascent MDs introduced my case as if I weren't in the room.

"This is a very interesting one," he said, leading a gang of about six others into the room. "She has what is called anti-NMDA-receptor autoimmune encephalitis."

The group ogled me and a few even let out a few quiet "ooohs" and "ahhhs." My father gritted his teeth and tried to ignore them.

"In about 50 percent of the cases, there is a teratoma in the ovaries. If this is the case, this patient may have her ovaries removed as a precaution."

As the spectators nodded their heads, I caught this somehow, and began to cry.

My father bolted from his seat. This was the first time he had heard anything about my ovaries being removed, and he certainly didn't want either of us hearing it from this kid. A born fighter and a strong man for his age (or for any other age), my dad bum-rushed the scrawny young physician and pointed a finger in his face.

"You get the fuck out of here right now!" His voice bounced around the hospital room. "Never come back. Get the fuck out of the room."

The young doctor's confidence deflated. Instead of apologizing, he waved his hand, urging the other interns to follow him toward the door, and made his escape.

"Forget you heard that, Susannah," my dad said. "They have no idea what the hell they're talking about."

Required reading is done.

CHAPTER 32

90 PERCENT

That same day, a dermatologist arrived and conducted a full-body skin exam to check for melanoma, which took about thirty minutes because my body is covered in moles. But after a thorough search, the dermatologist concluded that, happily, there was no sign of melanoma. That evening, they wheeled me down, yet again, to the second-floor radiology department, where they would conduct an ultrasound of my pelvis in search of a teratoma.

I am awakened, even though I hadn't been asleep. I had imagined this moment: the time when I would find out the gender of my child. Momentarily, I think, "I hope it's a boy." But the feeling passes. I would be happy with either a girl or a boy. I can feel the cool metal of the transducer against my belly. My chest wall leaps up into my throat in reaction to the cold. It was almost exactly how I imagined it to be. But then again not at all.

Distraught by the first ultrasound, I refused a transvaginal one, the more invasive pelvic examination. Still, even from the imperfect first test, there was good news: no sign of a teratoma. The bad news was that, ironically, teratomas were *good* news, because those with them tend to improve faster than people without them, for reasons researchers still don't understand.