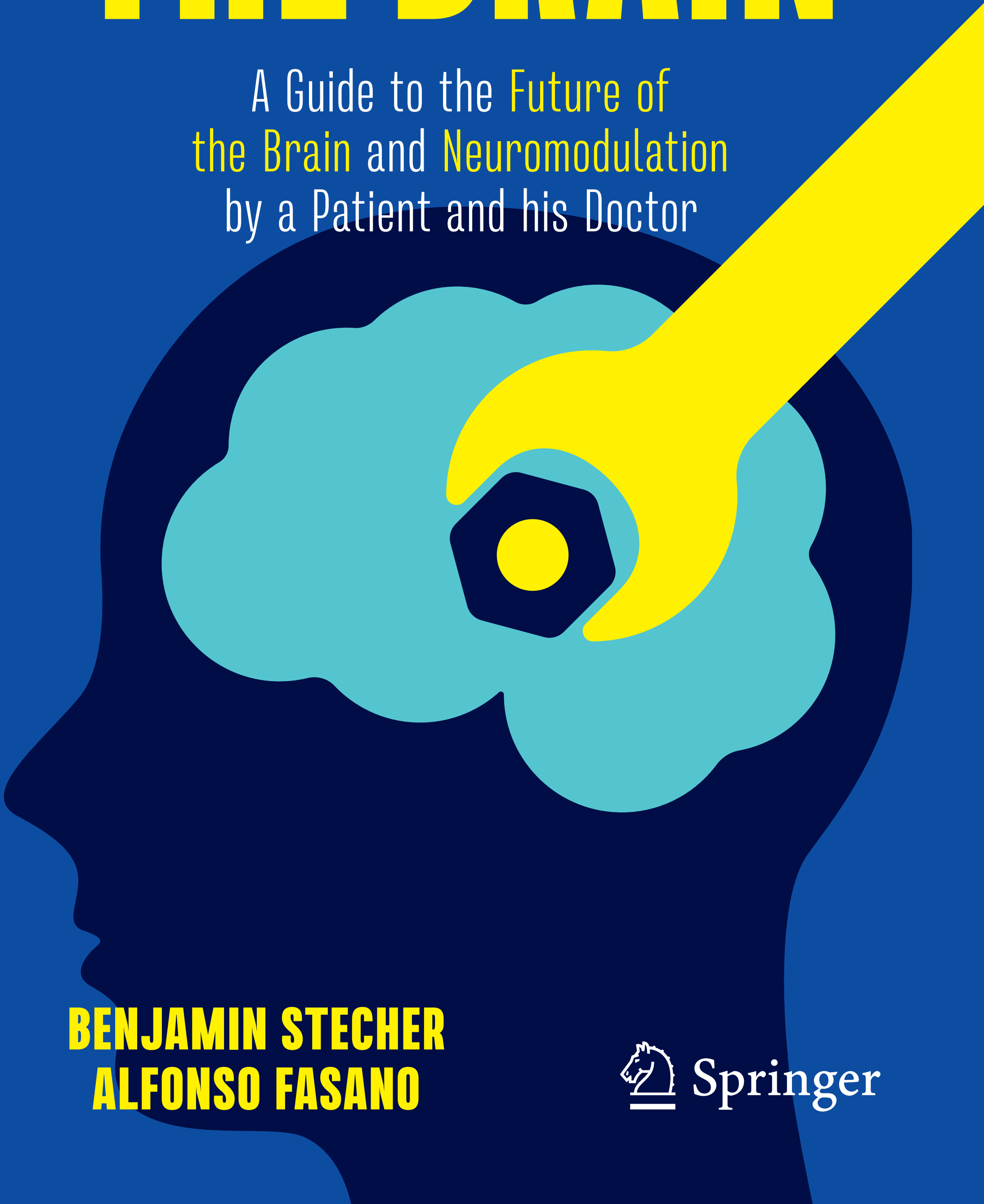
REPROGRAMMING THE BRAIN

A Guide to the Future of the Brain and Neuromodulation by a Patient and his Doctor



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Springer

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Introduction

In June 2021, we decided that time had come to surgically implant two six-inch-long metal alloy electrode-tipped spikes all the way through Ben's brain. We did so because we felt the medications Ben was taking to control his Parkinson's disease had become unmanageable.

Back then Ben was taking about 20 different pills a day. Each pill, if it absorbed properly, would activate the dopamine pathways in his brain and induce uncontrollable writhing movements that would last for about an hour. He would then get about 20 min where he'd feel ok before the slowness and tremor kicked in again. So, he'd take another pill and the cycle would repeat.

After months of titrating and finding just the right settings on his deep brain stimulator, we decided, for the first time ever in a clinical trial in Canada, to flip on the adaptive settings.

This is the story of how we made that decision and what happened next.

Mama Fasano, Papa Fasano, Benjamin Stecher, and Dr. Alfonso Fasano taken on November 23, 2022 (Mama Fasano's b-day) in Nusco, Italy, Fasano's home

Patient Prelude

On June 1, 2021, I took part in an experimental procedure to have an adaptive deep brain stimulator (aDBS) surgically implanted to treat my Parkinson's disease (PD).

The day began by getting that lovely looking frame shown below bolted on to my skull (Fig. 1). It didn't feel quite as bad as it looks. They froze the areas where the bolts go so other than the weight and some added pressure around my skull, I didn't really feel it. But, after they turned me into a cartoon supervillain, I was told an emergency case had come in that would delay my surgery by an hour or two. So, I sat there in the cramped pre-op room staring at the other patients who were doing their best not to look horrified when we made eye contact.

Fig. 1 A selfie taken by Ben on the morning of his surgery

Eventually I got wheeled into the OR. Like a guest of honor there were many onlookers waiting for me when I arrived. In addition to the surgical team itself of at least 7 or 8 people, there were a couple rows of students who had come to watch and learn.

First, I was laid out on the table and had that frame locked into a much larger contraption that would keep my head securely in place no matter how much I wriggled and writhed about. Then there was about half an hour of prep the team did in a flurry of activity happening all around me. During which time my hair was cut, but only the parts that might get in the way of the procedure, giving me that classically handsome Friar Tuck look. Then all sorts of sterilizing ointments were applied. Between that, the oxygen, and the mild sedatives I was given, it was almost starting to feel like a trip to a spa (Fig. 2).

Almost…

Throughout the morning I had felt very ready for what I was about to experience. I'm not sure exactly what to attribute that to, but in the days preceding it my mind was completely at ease with what I was about to experience. One fear I thought I might have was that I would start to doubt the decision I had made. DBS was not the only option available to me. What if I got into the OR and started to second guess myself?

Well, thankfully I was as well prepared as any patient could possibly be. You see, I had spent much of the 8 years prior preparing myself for that day. I had traveled to the far corners of the world and back again to better understand what was happening in me and what the best options were to treat it.

Despite my preparations, I still was not as prepared as I should have been. I hope that in writing this book I can help those who may be thinking of going through something similar prepare themselves for the arduous weeks and months ahead while giving some insight into all that this ordeal has to teach us about what we are.

But, before I go into all of that I do have to note that I've lived a blessed life. I may have been unfortunate enough to develop a degenerative neurological disorder

Fig. 2 Photo taken by Dr. Suneil Kalia during Ben's surgery

Fig. 3 The third day after being released from the hospital and just after Ben had been instructed to remove the bandages on his head

at 29 (PD), but despite the inconveniences it has brought, I find myself feeling incredibly lucky to be alive in the time and place that I am (Fig. 3).

You see, of all the planes of existence that I could have been on, I somehow found myself living in the one that not only had developed just the procedure (DBS) that I needed to live as comfortably as possible, but I also happened to grow up within 50 km of a hospital at the forefront of its development and have access to one of the few teams in the world spearheading its growth. Not sure what I did to deserve all of that, but I find myself very grateful to be when and where I am and to have what I have.

Anybody who has followed my journey will know that I owe a lot to two doctors that have helped shape my thinking and my recovery around this disease. One is Prof. Alberto Espay who had these now prescient words to say to me just before my surgery…

"You are living proof that there is no 'Parkinson's' but people living with some form of what we call PD for lack of a better name—and everyone is different. I fully agree with Alfonso. Yours is a pure nigrostriatal form, unlikely to spread to non-motor regions and, as such, not that critical if we never learn of its biology (which, in turn, is critical to many others with far less benign variants, and the reason we created CCBP).[1] A confirmation will be that post-DBS life barely reminds you of any symptoms of PD […] Much, much love from Cincinnati!"

I guess it shouldn't really have come as much of a surprise to hear, after all, we did write the book 'Brain Fables' together that basically said the same thing.[2] Still, when he did clue me in to just what it might mean for me, I shed a tear. With it I also committed to shedding the label of PD for myself and for others.

However, most are not so lucky. The majority diagnosed with a neurodegenerative disease will never know which form they have or how best to treat it. And even if they did, they likely will never have access to the team and support system needed. It's a sad state of affairs we find ourselves in if for no other reason than one day that person in the neurologists or psychologists office will be you. What kind of care would you like to receive on that day is a question that should haunt us all.

The second doctor to whom I owe the world to is the coauthor of this book Dr. Alfonso Fasano. When I was first diagnosed, I was a 29-year-old kid doing pretty well for myself living and working as an education consultant in China. It was on a trip back home to Toronto one fall when my aunt, Dr. Rochelle Schwartz, noticed my hand was shaking and immediately made me an appointment with a movement disorder specialist, a profession I did not even know existed at the time. I went through a standard battery of tests and was told the news right then and there. That specialist was nice enough, but he did tell me not to go back to China. I, being the kid I was, was defiant and ended up spending the next three years ignoring his advice and trying to go about my life as if nothing were wrong.

When I did eventually return, I did so on a mission to seek out the best minds the world had to offer me. It began in Toronto where I went about emailing every specialist in town. I got only one reply, from Dr. Alfonso Fasano. Below is the first of many email exchanges I would have with him which would eventually culminate in this book you are now reading:

(July 20, 2016)

"Dear Dr. Alfonso Fasano,

My name is Benjamin, I am a 31-year-old Canadian who was diagnosed with Parkinson's Disease 3 years ago. I am currently looking for ways I can participate and contribute to PD research and take part in clinical trials. Please let me know if you are aware of any such opportunities.

Thank you, BS"

"Dear Mr. Stecher

Your thought is very nice as patients like you can certainly contribute to our understanding of this disease. However, to better help you, it would be better to

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[1] Cincinnati Cohort Biomarker Program, whose aim is to "separate neurodegenerative diseases into their proper biological subtypes and then match each one to therapies that will be able to alter disease progression" (https://ccbpstudy.com).

[2] Espay A, Stecher B. Brain fables: the hidden history of neurodegenerative diseases and a blueprint to conquer them. Cambridge: Cambridge University Press; 2022.

know more about you. Have you spoken to your neurologist about it? You're quite young, did you undergo any genetic test?

AF"

I was struck by the sentiment. Can patients really make a difference to our understanding of this disease? Or was he just being considerate? So, I asked if I could come to his office for a "quick" visit. He spent hours with me that first meeting, patiently answering my many naïve questions. I recall drawing with him a very crude looking neuron and he taking the time to label with me all the most relevant parts and describing the function of each. It felt like my first big break and I have been riding the high of that first encounter since.

Physician Prelude

Walks and Talks

I grew up rootless. Thanks to my dad, who was an official in the Italian army, we had moved 5 times when the choice of where and what to study at university came up. My high school days were spent reading philosophy, mostly existentialist texts with a blend of religious and psychoanalytic undertones. I particularly loved Jacques Maritain's humanism and Victor Frankl's existential analysis. Yet, when the time came, I chose medicine. I used to tell myself that it was part of a natural process; human beings had always been at the center of my interests. Used to. Truth be told, I do not really know why I ended up studying Ohm's law, the Krebs cycle, or any of the other mysteries of biology that describe how and why humans are what we are.

Why I chose Neurology is a much simpler story. It was 1999 when I had my epiphany. I was in the midst of my painful journey through the pages of a cytology book, preparing for my exam on the inner workings of cells… when boom! I realized that a neuron is just matter that becomes aware of its own existence (Fig. 4).

Fig. 4 Alfonso in October 2022 at the Real Academia Nacional de Medicina de España—Madrid, Spain, on the occasion of Semana Cajal, a week in honor of Santiago Ramón y Cajal, the Spanish neuroscientist who discovered the major structures of neurons by applying the staining method of Camillo Golgi, an Italian pathologist. Next to him Prof José A. Obeso.

Later that year I saw my first DBS patient. I was 20. A woman with PD was wheeled into our anatomy class to show the effects of functionally inhibiting the subthalamus (STN). She was one of the first Italian patients treated with DBS at the Gemelli Hospital in Rome, one of the first cases treated outside of Grenoble—France, where STN DBS was first done. Nowadays we neurologists take for granted what we saw in that classroom: a tremor-dominant PD patient suddenly "cured" by this revolutionary technique. Back then it was a revelation and a resolution: I wanted to become a neurologist.

I soon learned how to manage the frustration of dealing with thousands of rare diseases, very rarely being able to accurately diagnose—let alone cure—any of them. Movement disorders seemed different, quite far from the "diagnose and adios" mantra of Alzheimer's or ALS. We had levodopa, botulinum toxin, DBS, and a general idea that something was always possible. However, from those years what stuck with me were the words of my mentor Dr. Anna Rita Bentivoglio: "we rarely help our patients, being nice to them is the very least we can do".

I believe that *voluptas sciendi* (Latin for intensely craving knowledge) was and is my strongest motivator. It was for that reason I went to Kiel—Germany to complete my PhD in neuroscience. At this point I only wanted to answer one question: why are some of my DBS patients having so many troubles with gait and balance?

During the years of my training, medicine was still a paternalistic business based on sterile scales and objectives set by physicians.[1] We thought that PD was all about motor fluctuations and tremor. However, my patients have always had a knack for showing me just how flawed my textbooks were. Most couldn't care less about their tremor, what they really wanted was to be pain-free, to talk, to walk… and to go to the bathroom. I have come to believe that Patients' needs must be where research begins and ends.

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Kiel is a cold and dark city in Northern Germany with not much to do, outside of work. Yet it has a beautiful fjord that I used to walk by every morning on my way to the gait lab, where walking itself is meticulously analyzed. Humans are bipedal hominids; we are defined by our seemingly unique ability to walk around on two feet. So I went full circle back to my high school interests: humans.[2] Those walks, and the inspiring talks with my mentor Prof. Günther Deuschl, were the fuel of my thesis on walking problems after DBS.[3] Prof. Deuschl is one of the minds behind the EarlyStim trial, which you'll hear more about later on.

I had just come back to Rome when Prof. Anthony E. Lang (Tony to most of us) phoned me on a Saturday afternoon wondering if I was interested in leading the

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[1] The TEDx talk "From God to Guide" by Bastian Bloem is an extraordinary manifesto of how medicine was about to change (www.youtube.com/watch?v=LnDWt10Maf8).

[2] The Roman playwright Publius Terentius Afer, a.k.a. Terence nicely summarized it with the sentence: *Homo sum; humani nil a me alienum puto* (Latin for "I am a human being; I consider nothing human alien to me").

[3] Fasano A, Herzog J, Seifert E, Stolze H, Falk D, Reese R, Volkmann J, Deuschl G. Modulation of gait coordination by subthalamic stimulation improves freezing of gait. Mov Disord. 2011;26:844–51.

Fig. 5 Alfonso flanked by Drs. Alberto Espay and Francesca Morgante in February 2010 during the 1st Knowledge Gap in Movement Disorders International Conference held in Taormina, Sicily

DBS program at Toronto Western Hospital. We had previously met at the first "Knowledge Gap" meeting in Sicily, during which I presented the findings of my German studies. It was morning in Toronto and Tony was about to go play tennis while I was about to make the most important decision of my life: should I leave my home and move to Canada? (Fig. 5)

In the end I chose Canada. Did I really have a choice? Toronto Western Hospital is one of the most important centers in the world for movement disorders, I couldn't have dreamed of a better place for me to harness my craft, and under the brilliant tutelage of Tony Lang, it felt like paradise. Back then we all used the Toronto Western Spasmodic Torticollis Rating Scale, TWSTRS a.k.a. "twisters", still nowadays the most common scale for the assessment of cervical dystonia, a painful condition in which muscles in the neck contract involuntarily causing the individuals neck to twist or bend.

So, it was not a coincidence that I ended up visiting the main hall of the hospital on my first trip to Toronto in 2011, during the Movement Disorders Congress which the city was hosting. Who knew that few years later I'd be walking those halls every morning.

It was a morning like any other when I opened Ben's email from July 20, 2016. I probably regretted agreeing to talk with Ben for "a few minutes". My clinic was probably running late, as usual, and I probably had a stack of unread papers I had been meaning to get to strewn about my desk. This kid couldn't stop asking questions. At times he sounded cocky and pretentious. He came in with no prior knowledge of biology, but thought he could not only learn about all of PD, but also neurobiology and the entirety of clinical neurology. However, I remembered that patients don't go to doctors for fun. Having traveled the world, having spoken with thousands of patients, Ben was there in front of me asking for the one thing I could provide—hope, hope through knowledge. Who was I to preclude him of it?

That is how this story begins. Now I can proudly say: I am Ben's neurologist! When researchers worldwide started to invite him for lectures, I realized why he embodied the Latin sentence I had taught him: *nemo propheta in patria* (no man is a prophet in his own land). We share that fate.

Contents

List of Abbreviations

aDBS	Adaptive deep brain stimulator
cDBS	Continuous deep brain stimulator
DBS	Deep brain stimulation
EEG	Electroencephalogram
EKG	Electrocardiogram
EMG	Electromyography
GPi	Globus pallidus pars interna
LFP	Local field potential
ICD	Impulse control disorder
iPS cells	Induced pluripotent stem cells
MDS	Movement disorder specialist
MRI	Magnetic resonance imaging
PD	Parkinson’s disease
PPN	Pedunculopontine nucleus
PSD	Power spectral density
PwP	People with Parkinson’s
STN	Subthalamic nucleus or subthalamus
VTA	Volume of tissue activated