Chapter 1

The Shaky Six and the "Second Reality"

The crucial importance of cognitive dissonance. Humans have an amazing capacity to believe in contradictory things. For example, to believe in an omnipotent and benevolent God, but somehow excuse Him from all the suffering in the world. Or our ability to believe from the standpoint of law that humans are equal and have free will and from biology that humans are just organic machines. Our medical system and our legal system are built on contradictory assumptions. Yet we somehow live with this contradiction.

Yuval Noah Harari, in answer to "What's the most misunderstood fact about the history of our species?", posed by Arik Gabbai, Smithsonian, February 2015

In *Sapiens,* Yuval Noah Harari argues that humankind's greatest invention is our ability to create and believe fictions. While all other animals communicate realities with which they interact, humans create a separate layer of subjective, interpretative realities. The fiction most universally embraced today is money. "Dollar bills have absolutely no value except in our collective imagination, but everybody believes in the dollar bill," says Harari.

Harari goes on to state that humans have been living in a dual reality. "On the one hand, the *objective reality* of rivers, trees, and lions; and on the other hand, the *imagined reality* of gods, nations, and corporations."

In medicine, humans have also created two realities.

Clinicians describe what they see, an *objective* reality, but the medical community then tries to explain and give meaning to what they see, creating a second, *imagined* reality. When a sufficient collection of objective realities are viewed, patterns emerge and an idea of a disease starts to form. The validity of the second, imagined reality gets verified by the accumulation and replication of the emergent patterns. When this second reality spreads far enough, it becomes the accepted reality. In so doing, it also becomes resistant to any evidence to the contrary.

In 1817 Dr. James Parkinson published his interpretations of physical features shared by three patients he examined in his office and three other individuals he observed on the streets of London: tremor in one hand, slowness of movement, stiffness, stooped posture, and difficulties with walking and balance. He proposed the term *paralysis agitans* to describe those who were affected. Parkinson was the epitome of the astute clinician living in an era in which observation was the greatest instrument of medicine. His detailed notes meticulously described the collection of abnormalities he observed. When read today, his monograph, *An Essay on the Shaking Palsy,* remains a remarkably elegant and vivid piece of neurology.

So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow its progress, that it rarely happens, that the patient can form any recollection of the precise period of its commencement. The first symptoms perceived are a slight sense of weakness, with a proneness to trembling in some particular part; sometimes in the head, but most commonly in one of the hands and arms. These symptoms gradually increase in the part first affected; and at an uncertain period, but seldom in less than twelve months or more, the morbid influence is felt in some other part. Thus assuming one of the hands and arms to be first attacked, the other, at this period becomes similarly affected. After a few more months the patient is found to be less strict than usual in preserving an upright posture: this being most observable whilst walking, but sometimes whilst sitting or standing.

[. . .]

But as the malady proceeds, even this temporary mitigation of suffering from the agitation of the limbs is denied. The propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and fore part of the feet, whilst the upper part of the body is thrown so far forward as to render it difficult to avoid falling on the face. In some cases, when this state of the malady is attained, the patient can no longer exercise himself by walking in his usual manner, but is thrown on the toes and forepart of the feet; being, at the same time, irresistibly impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace. In some cases it is found necessary entirely to substitute running for walking; since otherwise the patient, on proceeding only a very few paces, would inevitably fall.

An Essay on the Shaking Palsy, by James Parkinson, monograph published by Sherwood, Neely, and Jones (London, 1817)

In 1861 the famous French neurologist Dr. Jean-Martin Charcot recognized and extended Parkinson's observations on the *paralysis agitans*, but emphasized that patients were neither markedly weakened nor necessarily plagued with tremor.[5] Nevertheless, Charcot suggested applying to this cluster of neurological difficulties the name "Parkinson's disease" in honor of Parkinson's seminal description.

The most important elements of the "second, imagined reality" was completed nearly a century after the Shaky Six from London came to the attention of the medical field. In 1912 a German neurologist, Dr. Friedrich Heinrich Lewy, working on the brains of individuals who had died with the symptoms Parkinson identified, found unusual clumps of proteins inside neurons in certain parts of the brain.[6]

The *corps de Lewy* – or Lewy bodies, as coined by Dr. Konstantin Trétiakoff, a Russian neuropathologist – provided the first evidence of clinical observations converging with brain tissue observations, validating the label Parkinson's *disease* (Figure 1). This was to become the "clinico-pathologic" model enshrined by nineteenth-century physicians. The recognition of specific brain proteins at autopsy became the gold standard for definitive diagnoses of all diseases of brain aging. With the proliferation of new staining methods and advances in microscopy, the type of proteins to be identified during postmortem studies was to grow in diversity in the twentieth century.

As the same type of protein was observed in brains from people who died with or without dementia, with or without tremor, with rapid or slow progression, Parkinson's and other age-related diseases cemented themselves as heterogeneous, but ultimately single diseases.

An easily overlooked implication is that neuropathologists became the arbiters of diseases and disease classifications. Clinicians could achieve "possible" or, at best, "probable" categories of diagnostic certainty when examining a patient, but they couldn't be "definitive." The elevation of the diagnostic certainty to "definitive" was reserved for the outcome of microscopic examination of brain tissue after death.

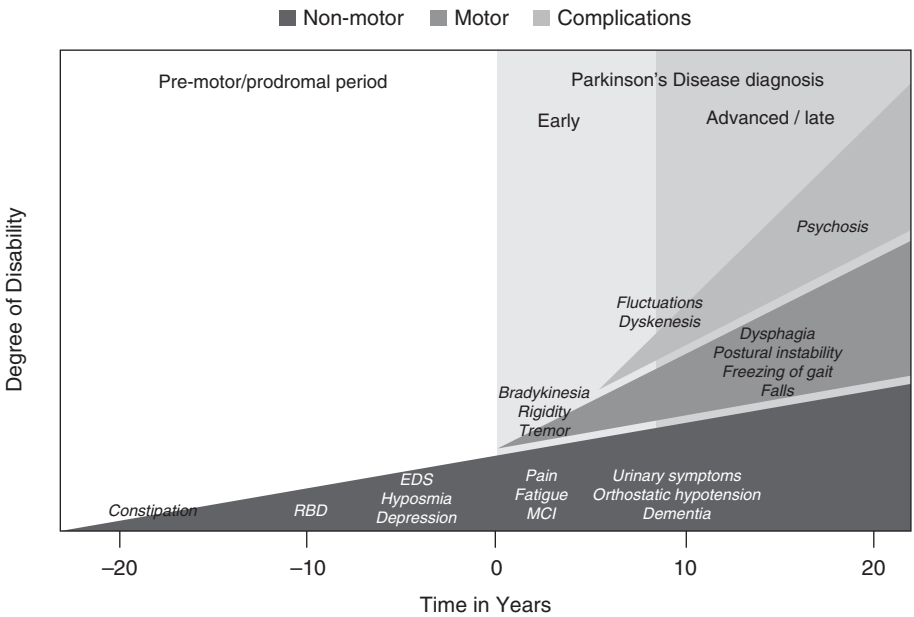

Figure 1 A heterogeneous disease. The "confirmation" of Parkinson's disease by Lewy bodies identified at autopsy increased the spectrum of manifestations thought to represent the same disease. This diagram depicts the range of motor and non-motor features believed to arise from Lewy bodies at "Time 0," defined arbitrarily as the time when the first motor symptom appears, which is when the disease becomes recognizable to physicians and can be diagnosed at the bedside (adapted by Marcia Hartsock, from Lang and Kalia, *Lancet* 2015;386 (9996): 896–912). RBD: REM sleep behavior disorder; EDS: excessive daytime sleepiness; MCI: mild cognitive impairment.

The importance of the study of brain tissue in the classifications of diseases (*nosology*, in the jargon of medicine) was eventually going to give birth to the concept that neurodegenerative diseases, or diseases of abnormal brain aging, were "proteinopathies." According to this model, I can tell you what disease you have if you tell me what proteins your brain accumulates. (More on these proteins and what they mean in Chapter 5.)

One final wrinkle worth considering. When James Parkinson was hard at work describing the Shaky Six, he probably thought he was describing a set of features that were common to selected individuals and distinguishable from other diseases. If we could ask him today, he might say that he was describing a syndrome, a collection of discrete symptoms and signs that formed a clinical pattern. It is unlikely he was proposing a distinct molecular entity.[1]

Yet 200 years later we celebrate James Parkinson because the field still sees in his work something beyond what he intended. In this narrative we have embraced, he was describing

[1] If biological or molecular abnormalities affect function, they produce symptoms. Conversely, symptoms cannot be expected to reflect a specific biological or molecular abnormality. Most symptoms are non-specific manifestations of many abnormalities. A *disease* is considered a reflection of specific biological/molecular abnormalities, often yielding a set of heterogeneous symptoms. A syndrome is defined as a collection of diseases and, as such, cannot be specific to any biological/molecular abnormalities.

not just a syndrome but a biological and molecular construct – which, we anticipate we are on the brink of finally demonstrating. In the chapters to come, we shall uncover the pitfalls of this deeply ingrained "second reality."

Commentary – What Is and What Isn't

The universe seeks equilibriums; it prefers to disperse energy, disrupt organization, and maximize chaos. Life is designed to combat these forces. We slow down reactions, concentrate matter, and organize chemicals into compartments; we sort laundry on Wednesdays. "It sometimes seems as if curbing entropy is our quixotic purpose in the universe," James Gleick wrote. We live in the loopholes of natural laws, seeking extensions, exceptions and excuses. The laws of nature still mark the outer boundaries of permissibility – but life, in all its idiosyncratic, mad weirdness, flourishes by reading between the lines.

Siddhartha Mukherjee, The Gene: An Intimate History

The most challenging part of my diagnosis has been trying to figure out what and who to believe in. Not a week goes by that a family member or friend doesn't send me news of some therapy or supplement that supposedly does wonders for Parkinson's. Early on I followed up on every one. Some took me down some very bizarre rabbit holes. Almost all ended in disappointment.

Over time I became better at sniffing out which were worth exploring and which I could ignore. One of the few good things about Parkinson's is that it tends to progress slowly, giving most who get it enough time to come to a pretty good understanding of it. But it is a long slow road to comprehension, one born out of fear, frustration, and endless trial-and-error.

Here is one such rabbit hole I fell into: On a trip back to China in December of 2016, a friend brought me to a lecture hall in Shanghai to meet a renowned practitioner of traditional Chinese medicine (TCM). Going in I was more than a little skeptical, but I promised to be open minded enough to see what, if any, insight this doctor might have for me. What I didn't know when I walked in was that I would be interrupting her class so that she could use me as a live guinea pig for her techniques, and as a foreign prop to impress her audience.

She started by having me sit in a chair while she passed her hand over me to examine my qi (a force that can be harnessed and used as a measure of one's vitality). Afterwards she took out a small container of seeds and started taping them to my ear while the class gathered around. According to some branches of TCM, the entire body can be mapped to pressure points on the ears, hands or feet, and certain seeds can trigger neurological connections between the various parts of the body that stimulate healing. So, for about 20 minutes I sat there as dozens of tiny seeds were pressed into both ears.

Figure 2 "The Experiment." Class gathers for a live demonstra-tion of the therapeutic benefits of a bold new technique for people with Parkinson's.

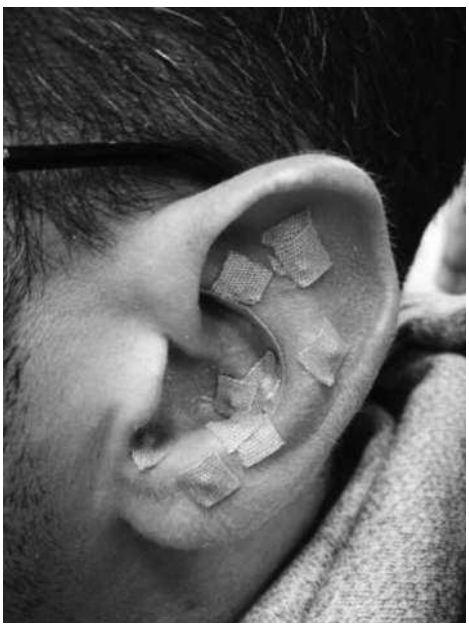

Figure 3 "The Aftermath." A dozen or so tiny seeds, renowned for their healing powers, were pressed onto my ear. . .still awaiting supposed benefit.

She then took out a hand-carved wooden comb and started delivering vibrating pulses against my scalp. She did this for about 10 minutes while she explained the mystical powers of the wood it was carved from. I could hear the hushed words from those in attendance: "Look, he's getting better" and "wow, it's working." I only felt the tremor-like scrapes of the comb against my head.

Afterwards she gave me the comb and a beaded wooden bracelet to wear and told me to walk West for one hour a day until I was cured.

Yuval Noah Harari has been one of the most helpful guides I have had in helping me separate fact from fiction. He has a knack for cutting through the noise and getting right to the most important details. From him I learned that when trying to understand a truth of our world, you must remove any form of narrative. All stories are the creation of our subjective experiences, and often they blur the line between what is and what isn't. He seems to apply this to everything he studies, from our mythologies and religions, to money and nations. I wonder if he would say the same thing about biomedical science?

At a fundamental level there are enormous gaps between what we know about our biology and what there is to know. We know there are 20 organic compounds called amino acids that make up everything we think of as life. But how they assemble into all the pieces that make us who we are, and how those pieces interact with one another, is, for the most part, a black box. This makes it very difficult for us to properly intervene when things go wrong.

This was explained to me in an interview I did with Dario Alessi, professor at the University of Dundee in Scotland and one of the most revered biochemists in the field:

> *Generally, I think we understand less than 1/10,000 of all that there is to understand in biology. We know virtually nothing about how biology is controlled and how it works.*
>
> *We have 20,000+ genes, each with many different variants, which are all expressed at different levels, in different ways, in different cells. They probably make hundreds of thousands of RNA molecules and millions of forms of proteins that get modified in a number of ways. All of these things interact and form the various parts of the cell. Also, as you interact with your environment and consume energy, DNA accumulates damage that also affects how cells function. All of this is like a big boiling pot with millions of things thrown in; you can't really understand it.*
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> Posted September 18, 2018, *tmrwedition.com*

So, what do humans do when they try to make sense of something that they don't really understand? They make it up, filling in the gaps with stories about what we think is happening. Our most probable stories now get called hypotheses, which we then test to see if we can accept as truth. In medicine those "truths" lead to potential treatments which we push through the clinical trial process hoping some make it out the other side.

As Dario went on to say in that interview: "There isn't a lot of funding to do the fundamental research on one gene or one protein that would be needed to really understand these things. You could spend your whole life studying one protein, but getting the funding to do that is hard. Funding bodies want us to solve diseases and work with companies to figure out shortcuts that can be made into a drug. But we don't have the fundamental basis needed to really solve these problems."

And therein lies the crux of this problem. How can we intervene in something we don't understand? How many of the pieces of this puzzle have we uncovered? How many more do we need to be able to purposefully intervene?

Here some would say: "But medical science is filled with stories of accidental breakthroughs; maybe if we continue doing as we have done up till now we will stumble across a solution." As George Church, world-renowned geneticist and professor at Harvard University, put it in an interview with me, "We developed effective smallpox prevention back when we had close to zero understanding of virology and immunology." Sure, it is possible, but is that the strategy you would bet your life on?

Our Best Bets

So what is the field placing its bets on? What do the experts think we should be devoting our limited resources to? I wanted to find out, so I took a poll, asking many of the experts I know to list their top five disease-modifying targets for Parkinson's; 43 of them responded (Figure 4).

Of the 43 experts polled, 35 said that alpha-synuclein (*SNCA* is the name of the corresponding gene) represents our best target to modify the course of this disease. This wasn't really a surprise, one of my first interviews was with Jeffrey H. Kordower, an international authority on movement disorders and professor at Rush University, who

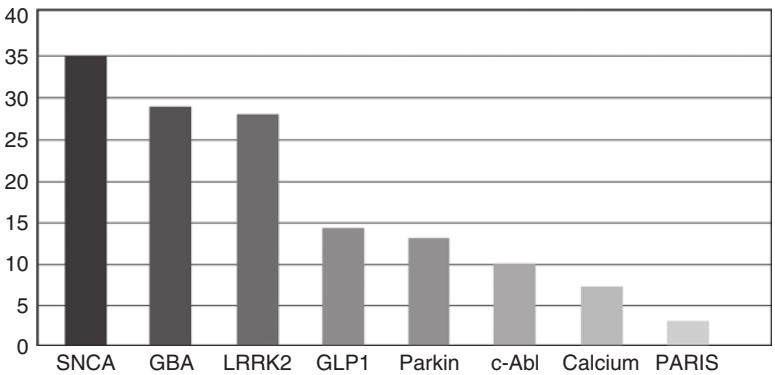

Figure 4 Unscientific survey of scientists. Experts were given a list of presumed genetic and molecular targets for therapeutic development and asked which ones they thought were most likely to succeed.

told me, "In terms of cures, I am for testing everything that modifies synuclein. I often say, synuclein now, synuclein forever."

At first this was comforting, a single misfolding protein seemed like a nice tidy explanation and a clear target to go after. Stop these clumps from forming, and we'll stop the disease. I dug a little deeper and saw that the evidence was pretty compelling. For one, families with a rare duplication or triplication of the *SNCA* gene have drastically higher rates of the disease. Additionally, autopsies revealed that the vast majority of people who have died with Parkinson's had these proteins aggregating in their brains. These pieces of evidence were enough to get alpha-synuclein labelled *pathogenic*, meaning the *cause* of disease.

But dig a little deeper and you start to see that there are a few holes in this theory. For one, despite a couple of decades of research into this misfolding protein, we still know very little about what the healthy version of it is supposed to do.

Kelvin Luk, a protein-folding expert at the University of Pennsylvania, which may be the world's leading center in the study of synuclein, explained to me, "We know that once this protein starts to misfold (that is, adopt an abnormal shape), it triggers a cascade of more misfolding. The cause for the initial misfolding is still a black box because we still know very little about the correct shape that alpha-synuclein should be in for it to function properly."

To me this seems like trying to fix a broken car radiator without even knowing what a radiator does or why it was there in the first place. At some point I started to question, if we know so little about this protein, why are we so sure that it is the cause of this disease?

I went back and reread an interview with Simon Stott, then a research associate at Cambridge University and now deputy director of research at the Cure Parkinson's Trust. "While I hope that it is a cause because we have all these clinical trials going on targeting it, I think the community needs to prepare itself that it isn't that simple. The brain is so complicated, I seriously doubt that it comes down to one protein. If it really was that simple, then we would probably be too simple to understand it."

The more I came to know about this disease, and the more I examined our failures of the past, the more I started to realize that time and time again we had fallen short because we

believed that the problem was simpler than it really was. Yet almost every book ever written about the brain starts by marveling at its complexity, astounding readers with its hundred billion cells and the hundred trillion connections between them that together form the most sophisticated clump of matter in the known universe. How do we even begin to look for all the pieces needed to make sense of such a complicated puzzle, let alone decide that any one puzzle piece is responsible for things that go wrong?

What if, as Alberto will elaborate in the next chapter, we have been looking for pieces to a puzzle that doesn't even exist?