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Phantoms in the Brain. Human Nature and the Architecture of the Mind.

HARPER PERENNIAL London, New York, Toronto and Sydney

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Foreword

The great neurologists and psychiatrists of the nineteenth and early twentieth centuries were masters of description, and some of their case histories provided an almost novelistic richness of detail. Silas Weir Mitchell—who was a novelist as well as a neurologist—provided unforgettable descriptions of the phantom limbs (or "sensory ghosts," as he first called them) in soldiers who had been injured on the battlefields of the Civil War. Joseph Babinski, the great French neurologist, described an even more extraordinary syndrome—anosognosia, the inability to perceive that one side of one's own body is paralyzed and the often-bizarre attribution of the paralyzed side to another person. (Such a patient might say of his or her own left side, "It's my brother's" or "It's yours.")

Dr. V.S. Ramachandran, one of the most interesting neuroscientists of our time, has done seminal work on the nature and treatment of phantom limbs—those obdurate and sometimes tormenting ghosts of arms and legs lost years or decades before but not forgotten by the brain. A phantom may at first feel like a normal limb, a part of the normal body image; but, cut off from normal sensation or action, it may assume a pathological character, becoming intrusive, "paralyzed," deformed, or excruciatingly painful—phantom fingers may dig into a phantom palm with an unspeakable, unstoppable intensity. The fact that the pain and the phantom are "unreal" is of no help, and may indeed make them more difficult to treat, for one may be unable to unclench the seemingly paralyzed phantom. In an attempt to alleviate such phantoms, physicians and their patients have been driven to extreme and desperate measures: making the amputation stump shorter and shorter, cutting pain or sensory tracts in the spinal cord, destroying pain centers in the brain itself. But all too frequently, none of these work; the phantom, and the phantom pain, almost invariably return.

To these seemingly intractable problems, Ramachandran brings a fresh and different approach, which stems from his inquiries as to what phantoms are, and how and where they are generated in the nervous system. It has been classically considered that representations in the brain, including those of body image and phantoms, are fixed. But Ramachandran (and now others) has shown that striking reorganizations in body image occur very rapidly—within forty-eight hours, and possibly much less—following the amputation of a limb. Phantoms, in his view, are generated by such reorganizations of body image in thc sensory cortex and may then be maintained by what he terms a "learned" paralysis. But if there are such rapid changes underlying the genesis of a phantom, if there is such plasticity in the cortex, can the process be reversed? Can the brain be tricked into unlearning a phantom?

By using an ingenious "virtual reality" device, a simple box with a transposing mirror, Ramachandran has found that a patient may be helped by merely being given thc sight of a normal limb—the patient's own normal right arm, for example, now seen on the left side of the body, in place of the phantom. The result of this may be instantaneous and magical: The normal look of the arm competes with the feel of the phantom. The first effect of this is that a deformed phantom may straighten out, a paralyzed phantom may move; eventually, there may be no more phantom at all. Ramachandran speaks here, with characteristic humor, of "the first successful amputation of a phantom limb," and of how, if the phantom is extinguished, its pain must also go—for if there is nothing to embody it, then it can no longer survive. (Mrs. Gradgrind, in Hard Times, asked if she had a pain, replied, "There is a pain somewhere in the room, but I cannot be sure that I have got it." But this was her confusion, or Dickens's joke, for one cannot have a pain except in oneself.)

Can equally simple "tricks" assist patients with anosognosia, patients who cannot recognize one of their sides as their own? Here too, Ramachandran finds, mirrors may be of great use in enabling such patients to reclaim the previously denied side as their own; though in other patients, the loss of "leftness," the bisection of one's body and world, is so profound that mirrors may induce an even deeper, through-the-looking-glass confusion, a groping to see if there is not someone lurking "behind" or "in" the mirror. (Ramachandran is the first to describe this "mirror agnosia.") It is a measure not only of Ramachandran's tenacity of mind but of his delicate and supportive relationship with patients that he has been able to pursue these syndromes to their depths.

The deeply strange business of mirror agnosia, and that of misattributing one's own limbs to others, are often dismissed by physicians as irrational. But these problems are also considered carefully by Ramachandran, who sees them not as groundless or crazy, but as emergency defense measures constructed by the unconscious to deal with sudden overwhelming bewilderments about one's body and the space around it. They are, he feels, quite normal defense mechanisms (denial, repression, projection, confabulation, and so on) such as Freud delineated as universal strategies of the unconscious when forced to accommodate the intolerable or unintelligible. Such an understanding removes such patients from the realm of the mad or freakish and restores them to the realm of discourse and reason—albeit the discourse and reason of the unconscious.

Another syndrome of misidentification that Ramachandran considers is Capgras' syndrome, where the patient sees familiar and loved figures as impostors. Here too, he is able to delineate a clear neurological basis for the syndrome—the removal of the usual and crucial affective cues to recognition, coupled with a not unnatural interpretation of the now affectless perceptions ("He can't be my father, because I feel nothing—he must be a sort of simulacrum").

Dr. Ramachandran has countless other interests too: in the nature of religious experience and the remarkable "mystical" syndromes associated with dysfunction in the temporal lobes, in the neurology of laughter and tickling, and—a vast realm—in the neurology of suggestion and placebos. Like the perceptual psychologist Richard Gregory (with whom he has published fascinating work on a range of subjects, from the filling-in of the blind spot to visual illusions and protective colorations), Ramachandran has a flair for seeing what is fundamentally important and is prepared to turn his hand, his freshness, his inventiveness, to almost anything. All of these subjects, in his hands, become windows into the way our nervous systems, our worlds, and our very selves are constituted, so that his work becomes, as he likes to say, a form of "experimental epistemology." He is, in this way, a natural philosopher in the eighteenth-century sense, though with all the knowledge and know-how of the late twentieth century behind him.

In his Preface, Ramachandran tells us of the nineteenth-century science books he especially enjoyed as a boy: Michael Faraday's Chemical History of a Candle, works by Charles Darwin, Humphry Davy and Thomas Huxley. There was no distinction at this time between academic and popular writing, but rather the notion that one could be deep and serious but completely accessible, all at once. Later, Ramachandran tells us, he enjoyed the books of George Gamow, Lewis Thomas, Peter Medawar, and then Carl Sagan and Stephen Jay Gould. Ramachandran has now joined these grand science writers with his closely observed and deeply serious but beautifully readable book Phantoms in the Brain. It is one of the most original and accessible neurology books of our generation.

Oliver Sacks, M.D.

Preface

In any field, find the strangest thing and then explore it. JOHN ARCHIBALD WHEELER

This book has been incubating in my head for many years, but I never quite got around to writing it. Then, about three years ago, I gave the Decade of the Brain Lecture at the annual meeting of the Society for Neuroscience to an audience of over four thousand scientists, discussing many of my findings, including my studies on phantom limbs, body image and the illusory nature of the self. Soon after the lecture, I was barraged with questions from the audience: How does the mind influence the body in health and sickness, How can I stimulate my right brain to be more creative? Can your mental attitude really help cure asthma and cancer? Is hypnosis a real phenomenon? Does your work suggest new ways to treat paralysis after strokes? I also got a number of requests from students, colleagaes and even a few publishers to undertake writing a textbook. Textbook writing is not my cup of tea, but I thought a popular book on the brain dealing mainly with my own experiences working with neurological patients might be fun to write. During the last decade or so, I have gleaned many new insights into the workings of the human brain by studying such cases, and the urge to communicate these ideas is strong. When you are involved in an enterprise as exciting as this, it's a natural human tendency to want to share your ideas with others. Moreover, I feel that I owe it to taxpayers, who ultimately support my work through grants from the National Institutes of Health.

Popular science books have a rich, venerable tradition going as far back as Galileo in the seventeenth century. Indeed, this was Galileo's main method of disseminating his ideas, and in his books he often aimed barbs at an imaginary protagonist, Simplicio—an amalgam of his professors. Almost all of Charles Darwin's famous books, including The Origin of Species, The Descent of Man, The Expression of Emotions in Animals and Men, The Habits of Insectivorous Plants—but not his two-volume monograph on barnacles!—were written for the lay reader at the request of his publisher, John Murray. The same can be said of the many works of Thomas Huxley, Michael Faraday, Humphry Davy and many other Victorian scientists. Faraday's Chemical History of a Candle, based on Christmas lectures that he gave to children, remains a classic to this day.

I must confess that I haven't read all these books, but I do owe a heavy intellectual debt to popular science books, a sentiment that is echoed by many of my colleagues. Dr. Francis Crick of the Salk Institute tells me that Erwin Schrödinger's popular book What Is Life? contained a few speculative remarks on how heredity might be based on a chemical and that this had a profound impact on his intellectual development, culminating in his unraveling the genetic code together with James Watson. Many a Nobel Prize-winning physician embarked on a research career after reading Paul de Kruif's The Microbe Hunters, which was published in 1926. My own interest in scientific research dates back to my early teens, when I read books by George Gamow, Lewis Thomas, and Peter Medawar, and the flame is being kept alive by a new generation of writers—Oliver Sacks, Stephen Jay Gould, Carl Sagan, Dan Dennett, Richard Gregory, Richard Dawkins, Paul Davies, Colin Blakemore and Steven Pinker.

About six years ago I received a phone call from Francis Crick, the codiscoverer of the structure of deoxyribonucleic acid (DNA), in which he said that he was writing a popular book on the brain called

The Astonishing Hypothesis. In his crisp British accent, Crick said that he had completed a first draft and had sent it to his editor, who felt that it was extremely well written but that the manuscript still contained jargon that would be intelligible only to a specialist. She suggested that he pass it around to some lay people. "I say, Rama," Crick said with exasperation, "the trouble is, I don't know any lay people. Do you know any lay people I could show the book to?" At first I thought he was joking, but then realized he was perfectly serious. I can't personally claim not to know any lay people, but I could nevertheless sympathize with Crick's plight. When writing a popular book, professional scientists always have to walk a tightrope between making the book intelligible to the general reader, on the one hand, and avoiding oversimplification, on the other, so that experts are not annoyed. My solution has been to make elaborate use of end notes, which serve three distinct functions: First, whenever it was necessary to simplify an idea, my cowriter, Sandra Blakeslee, and I resorted to notes to qualify these remarks, to point out exceptions and to make it clear that in some cases the results are preliminary or controversial. Second, we have used notes to amplify a point that is made only briefly in the main text—so that the reader can explore a topic in greater depth. The notes also point the reader to original references and credit those who have worked on similar topics. I apologize to those whose works are not cited; my only excuse is that such omission is inevitable in a book such as this (for a while the notes threatened to exceed the main text in length). But I've tried to include as many pertinent references as possible in the bibliography at the end, even though not all of them are specifically mentioned in the text.

This book is based on the true-life stories of many neurological patients. To protect their identity, I have followed the usual tradition of changing names, circumstances and defining characteristics throughout each chapter. Some of the "cases" I describe are really composites of several patients, including classics in the medical literature, as my purpose has been to illustrate salient aspects of the disorder, such as the neglect syndrome or temporal lobe epilepsy. When I describe classic cases (like the man with amnesia known as H.M.), I refer the reader to original sources for details. Other stories are based on what are called single-case studies, which involve individuals who manifest a rare or unusual syndrome.

A tension exists in neurology between those who believe that the most valuable lessons about the brain can be learned from statistical analyses involving large numbers of patients and those who believe that doing the right kind of experiments on the right patients—even a single patient—can yield much more useful information. This is really a silly debate since its resolution is obvious: It's a good idea to begin with experiments on single cases and then to confirm the findings through studies of additional patients. By way of analogy, imagine that I cart a pig into your living room and tell you that it can talk. You might say, "Oh, really? Show me." I then wave my wand and the pig starts talking. You might respond, "My God! That's amazing!" You are not likely to say, "Ah, but that's just one pig. Show me a few more and then I might believe you." Yet this is precisely the attitude of many people in my field.

I think it's fair to say that, in neurology, most of the major discoveries that have withstood the test of time were, in fact, based initially on single-case studies and demonstrations. More was learned about memory from a few days of studying a patient called H.M. than was gleaned from previous decades of research averaging data on many subjects. The same can be said about hemispheric specialization (the organization of the brain into a left brain and a right brain, which are specialized for different functions) and the experiments carried out on two patients with so-called split brains (in whom the left and right hemispheres were disconnected by cutting the fibers between them). More was learned from these two individuals than from the previous fifty years of studies on normal people.

In a science still in its infancy (like neuroscience and psychology) demonstration-style experiments play an especially important role. A classic example is Galileo's use of early telescopes. People often assume that Galileo invented the telescope, but he did not. Around 1607, a Dutch spectacle maker, Hans Lipperhey, placed two lenses in a cardboard tube and found that this arrangement made distant objects appear closer. The device was widely used as a child's toy and soon found its way into country fairs throughout Europe, including France. In 1609, when Galileo heard about this gadget, he immediately recognized its potential. Instead of spying on people and other terrestrial objects, he simply raised the tube to the sky—something that nobody else had done. First he aimed it at the moon and found that it was covered with craters, gullies and mountains—which told him that the so-called heavenly bodies are, contrary to conventional wisdom, not so perfect after all: They are full of flaws and imperfections, open to scrutiny by mortal eyes just like objects on earth. Next he directed the telescope at the Milky Way and noticed instantly that far from being a homogeneous cloud (as people believed), it was composed of millions of stars. But his most startling discovery occurred when he peered at Jupiter, which was known to be a planet or wandering star. Imagine his astonishment when he saw three tiny dots near Jupiter (which he initially assumed were new stars) and witnessed that after a few days one disappeared. He then waited for a few more days and gazed once again at Jupiter, only to find that not only had the missing dot reappeared, but there was now an extra dot—a total of four dots instead of three. He understood in a flash that the four dots were Jovian satellites—moons just like ours—that orbited the planet. The implications were immense. In one stroke, Galileo had proved that not all celestial bodies orbit the earth, for here were four that orbited another planet, Jupiter. He thereby dethroned the geocentric theory of the universe, replacing it with the Copernican view that the sun, not the earth, was at the center of the known universe. The clinching evidence came when he directed his telescope at Venus and found that it looked like a crescent moon going though all the phases, just like our moon, except that it took a year rather than a month to do so. Again, Galileo deduced from this that all the planets were orbiting the sun and that Venus was interposed between the earth and the sun. All this from a simple cardboard tube with two lenses. No equations, no graphs, no quantitative measurements: "just" a demonstration.

When I relate this example to medical students, the usual reaction is, Well, that was easy during Galileo's time, but surely now in the twentieth century all the major discoveries have already been made and we can't do any new research without expensive equipment and detailed quantitative methods. Rubbish! Even now amazing discoveries are staring at you all the time, right under your nose. The difficulty lies in realizing this. For example, in recent decades all medical students were taught that ulcers are caused by stress, which leads to excessive acid production that erodes the mucosal lining of the stomach and duodenum, producing the characteristic craters or wounds that we call ulcers. And for decades the treatment was either antacids, histamine receptor blockers, vagotomy (cutting the acid-secreting nerve that innervates the stomach) or even gastrectomy (removal of part of the stomach.) But then a young resident physician in Australia, Dr. Bill Marshall, looked at a stained section of a human ulcer under a microscope and noticed that it was teeming with Helicobacter pylori - a common bacterium that is found in a certain proportion of healthy individuals. Since he regularly saw these bacteria in ulcers, he started wondering whether perhaps they actually caused ulcers. When he mentioned this idea to his professors, he was told, "No way. That can't be true. We all know ulcers are caused by stress. What you are seeing is just a secondary infection of an ulcer that was already in place."

But Dr. Marshall was not dissuaded and proceeded to challenge the conventional wisdom. First he carried out an epidemiological study, which showed a strong correlation between the distribution of Helicobacter species in patients and the incidence of duodenal ulcers. But this finding did not convince his colleagues, so out of sheer desperation Marshall swallowed a culture of the bacteria, did an endoscopy on himself a few weeks later and demonstrated that his gastrointestinal tract was studded with ulcers! He then conducted a formal clinical trial and showed that ulcer patients who were treated with a combination of antibiotics, bismuth and metronidazole (Flagyl, a bactericide) recovered at a much higher rate—and had fewer relapses—than did a control group given acid-blocking agents alone.

I mention this episode to emphasize that a single medical student or resident whose mind is open to new ideas and who works without sophisticated equipment can revolutionize the practice of medicine. It is in this spirit that we should all undertake our work, because one never knows what nature is hiding.

I'd also like to say a word about speculation, a term that has acquired a pejorativc connotation among some scientists. Describing someone's idea as "mere speculation" is often considered insulting. This is unfortunate. As the English biologist Peter Medawar has noted, "An imaginative conception of what might be true is the starting point of all great discoveries in science." Ironically, this is sometimes true even when the speculation turns out to be wrong. Listen to Charles Darwin: "False facts are highly injurious to the progress of science for they often endure long; but false hypotheses do little harm, as everyone takes a salutary pleasure in proving their falseness; and when this is done, one path toward error is closed and the road to truth is often at the same time opened."

Every scientist knows that the best research emerges from a dialectic between speculation and healthy skepticism. Ideally the two should coexist in the same brain, but they don't have to. Since there are people who represent both extremes, all ideas eventually get tested ruthlessly. Many are rejected (like cold fusion) and others promise to turn our views topsy turvy (like the view that ulcers are caused by bacteria).

Several of the findings you are going to read about began as hunches and were later confirmed by other groups (the chapters on phantom limbs, neglect syndrome, blind-sight and Capgras' syndrome). Other chapters describe work at an earlier stage, much of which is frankly speculative (the chapter on denial and temporal lobe epilepsy). Indeed, I will take you at times to the very limits of scientific inquiry.

I strongly believe, however, that it is always the writer's responsibility to spell out clearly when he is speculating and when his conclusions are clearly warranted by his observations. I've made every effort to preserve this distinction throughout the book, often adding qualifications, disclaimers and caveats in the text and especially in the notes. In striking this balance between fact and fancy, I hope to stimulate your intellectual curiosity and to widen your horizons, rather than to provide you with hard and fast answers to the questions raised.

The famous saying "May you live in interesting times" has a special meaning now for those of us who study the brain and human behavior. On the one hand, despite two hundred years of research, the most basic questions about the human mind—How do we recognize faces? Why do we cry? Why do we laugh? Why do we dream? and Why do we enjoy music and art?—remain unanswered, as does the really big question: What is consciousness? On the other hand, the advent of novel experimental approaches and imaging techniques is sure to transform our understanding of the human brain. What a unique privilege it will be for our generation—and our children's—to witness what I believe will be the greatest revolution in the history of the human race: understanding ourselves. The prospect of doing so is at once both exhilarating and disquieting.

There is something distinctly odd about a hairless neotenous primate that has evolved into a species that can look back over its own shoulder and ask questions about its origins. And odder still, the brain can not only discover how other brains work but also ask questions about its own existence: Who am I? What happens after death? Does my mind arise exclusively from neurons in my brain? And if so, what scope is there for free will? It is the peculiar recursive quality of these questions—as the brain struggles to understand itself—that makes neurology fascinating.

Phantoms in the Brain.

Contents

> By the deficits, we may know the talents, by the exceptions, we may discern the rules, by studying pathology we may construct a model of health. And — most importrant — from this model may evolve the insights and tools we need to affect our own lives, mould our own destinies, change ourselves and our society in ways that, as yet, we can only imagine. LAURENCE MILLER
>
> The world shall perish not for lack of wonders, but for lack of wonder. J.B.S. HALDANE

CHAPTER 1: The Phantom Within

> For in and out, above, about, below,
> 'Tis nothing but a Magic Shadow-show
> Play'd in a Box whose Candle is the Sun,
> Round which we Phantom Figures come and go.
> The Rubáiyát of Omar Khayyám
>
> I know, my dear Watson, that you share my love of all that is bizarre and outside the conventions and humdrum routines of everyday life. SHERLOCK HOLMES

A man wearing an enormous bejewelled cross dangling on a gold chain sits in my office, telling me about his conversations with God, the "real meaning" of the cosmos and the deeper truth behind all surface appearances. The universe is suffused with spiritual messages, he says, if you just allow yourself to tune in. I glance at his medical chart, noting that he has suffered from temporal lobe epilepsy since early adolescence, and that is when "God began talking" to him. Do his religious experiences have anything to do with his temporal lobe seizures?

An amateur athlete lost his arm in a motorcycle accident but continues to feel a "phantom arm" with vivid sensations of movement. He can wave the missing arm in midair, "touch" things and even reach out and "grab" a coffee cup. If I pull the cup away from him suddenly, he yelps in pain. "Ouch! I can feel it being wrenched from my fingers," he says, wincing.

A nurse developed a large blind spot in her field of vision, which is troubling enough. But to her dismay, she often sees cartoon characters cavorting within the blind spot itself. When she looks at me seated across from her, she sees Bugs Bunny in my lap, or Elmer Fudd, or the Road Runner. Or sometimes she sees cartoon versions of real people she's always known.

A schoolteacher suffered a stroke that paralyzed the left side of her body, but she insists that her left arm is not paralyzed. Once, when I asked her whose arm was lying in the bed next to her, she explained that the limb belonged to her brother.

A librarian from Philadelphia who had a different kind of stroke began to laugh uncontrollably. This went on for a full day, until she literally died laughing.

And then there is Arthur, a young man who sustained a terrible head injury in an automobile crash and soon afterward claimed that his father and mother had been replaced by duplicates who looked exactly like his real parents. He recognized their faces but they seemed odd, unfamiliar. The only way Arthur could make any sense out of the situation was to assume that his parents were impostors.

None of these people is "crazy"; sending them to psychiatrists would be a waste of time. Rather, each of them suffers from damage to a specific part of the brain that leads to bizarre but highly characteristic changes in behavior. They hear voices, feel missing limbs, see things that no one else does, deny the obvious and make wild, extraordinary claims about other people and the world we all live in. Yet for the most part they are lucid, rational and no more insane than you or I.

Although enigmatic disorders like these have intrigued and perplexed physicians throughout history, they are usually chalked up as curiosities— case studies stuffed into a drawer labeled "file and forget." Most neurologists who treat such patients are not particularly interested in explaining these odd behaviors. Their goal is to alleviate symptoms and to make people well again, not necessarily to dig deeper or to learn how the brain works. Psychiatrists often invent ad hoc theories for curious syndromes, as if a bizarre condition requires an equally bizarre explanation. Odd symptoms are blamed on the patient's upbringing (bad thoughts from childhood) or even on the patient's mother (a bad nurturer). *Phantoms in the Brain* takes the opposite viewpoint. These patients, whose stories you will hear in detail, are our guides into the inner workings of the human brain—yours and mine. Far from being curiosities, these syndromes illustrate fundamental principles of how the normal human mind and brain work, shedding light on the nature of body image, language, laughter, dreams, depression and other hallmarks of human nature. Have you ever wondered why some jokes are funny and others are not, why you make an explosive sound when you laugh, why you are inclined to believe or disbelieve in God, and why you feel erotic sensations when someone sucks your toes? Surprisingly, we can now begin to provide scientific answers to at least some of these questions. Indeed, by studying these patients, we can even address lofty "philosophical" questions about the nature of the self: Why do you endure as one person through space and time, and what brings about the seamless unity of subjective experience? What does it mean to make a choice or to will an action, And more generally, how does the activity of tiny wisps of protoplasm in the brain lead to conscious experience?

Philosophers love to debate questions like these, but it's only now becomrng clear that such issues can be tackled experimentally. By moving these patients out of the clinic and into the laboratory, we can conduct experiments that help reveal the deep architecture of our brains. Indeed we can pick up where Freud left off, ushering in what might be called an era of experimental epistemology (the study of how the brain represents knowledge and belief) and cognitive neuropsychiatry (the interface between mental and physical disorders of the brain), and start experimenting on belief systems, consciousness, mind-body interactions and other hallmarks of human behavior.

I believe that being a medical scientist is not all that different from being a sleuth. In this book, I've attempted to share the sense of mystery that lies at the heart of all scientific pursuits and is especially characteristic of the forays we make in trying to understand our own minds. Each story begins with either an account of a patient displaying seemingly inexplicable symptoms or a broad question about human nature, such as why we laugh or why we are so prone to self-deception. We then go step by step through the same sequence of ideas that I followed in my own mind as I tried to tackle these cases. In some instances, as with phantom limbs, I can claim to have genuinely solved the mystery. In others—as in the chapter on God—the final answer remains elusive, even though we come tantalizingly close. But whether the case is solved or not, I hope to convey the spirit of intellectual adventure that accompanies this pursuit and makes neurology the most fascinating of all disciplines. As Sherlock Holmes told Watson, "The game is afoot!"

Consider the case of Arthur, who thought his parents were impostors. Most physicians would be tempted to conclude that he was just crazy, and, indeed, that is the most common explanation for this type of disorder, found in many textbooks. But, by simply showing him photographs of different people and measuring the extent to which he starts sweating (using a device similar to the lie detector test), I was able to figure out exactly what had gone wrong in his brain (see chapter 9). This is a recurring theme in this book: We begin with a set of symptoms that seem bizarre and incomprehensible and then end up—at least in some cases—with an intellectually satisfying account in terms of the neural circuitry in the patient's brain. And in doing so, we have often not only discovered something new about how the brain works but simultaneously opened the doors to a whole new direction of research.

But before we begin, I think it's important for you to understand my personal approach to science and why I am drawn to curious cases. When I give talks to lay audiences around the country, one question comes up again and again: "When are you brain scientists ever going to come up with a unified theory for how the mind works? There's Einstein's general theory of relativity and Newton's universal law of gravitation in physics. Why not one for the brain?"

My answer is that we are not yet at the stage where we can formulate grand unified theories of mind and brain. Every science has to go through an initial "experiment" or phenomena - driven stage - in which its practitioners are still discovering the basic laws—before it reaches a more sophisticated theory-driven stage. Consider the evolution of ideas about electricity and magnetism. Although people had vague notions about lodestones and magnets for centuries and used them both for making compasses, the Victorian physicist Michael Faraday was the first to study magnets systematically. He did two very simple experiments with astonishing results. In one experiment—which any schoolchild can repeat—he simply placed a bar magnet behind a sheet of paper, sprinkled powdered iron filings on the surface of the paper and found that they spontaneously aligned themselves along the magnetic lines of force (this was the very first time anyone had demonstrated the existence of fields in physics). In the second experiment, Faraday moved a bar magnet to and fro in the centre of a coil of wire, and, lo and behold, this action produced an electrical current in the wire. These informal demonstrations—and this book is full of examples of this sort—had deep implications:[1] They linked magnetism and electricity for the first time. Faraday's own interpretation of these effects remained qualitative, but his experiments set the stage for James Clerk Maxwell's famous electromagnetic wave equations several decades later—the mathematical formalisms that form the basis of all modern physics.

My point is simply that neuroscience today is in the Faraday stage, not in the Maxwell stage, and there is no point in trying to jump ahead. I would love to be proved wrong, of course, and there is certainly no harm in trying to construct formal theories about the brain, even if one fails (and there is no shortage of people who are trying). But for me, the best research strategy might be characterized as "tinkering." Whenever I use this word, many people look rather shocked, as if one couldn't possibly do sophisticated science by just playing around with ideas and without an overarching theory to guide one's hunches. But that's exactly what I mean (although these hunches are far from random; they are always guided by intuition).

I've been interested in science as long as I can remember. When I was eight or nine years old, I started collecting fossils and seashells, becoming obsessed with taxonomy and evolution. A little later I set up a small chemistry lab under the stairway in our house and enjoyed watching iron filings "fizz" in hydrochloric acid and listening to the hydrogen "pop" when I set fire to it. (The iron displaced the hydrogen from the hydrochloric acid to form iron chloride and hydrogen.) The idea that you could learn so much from a simple experiment and that everything in the universe is based on such interactions was fascinating. I remember that when a teacher told me about Faraday's simple experiments, I was intrigued by the notion that you could accomplish so much with so little. These experiences left me with a permanent distaste for fancy equipment and the realization that you don't necessarily need complicated machines to generate scientific revolutions; all you need are some good hunches.[2]

Another perverse streak of mine is that I've always been drawn to the exception rather than to the rule in every science that I've studied. In high school I wondered why iodine is the only element that turns from a solid to a vapor directly when heated, without first melting and going through a liquid stage. Why does Saturn have rings and not the other planets? Why does water alone expand when it turns to ice, whereas every other liquid shrinks when it solidifies? Why do some animals not have sex? Why can tadpoles regenerate lost limbs though an adult frog cannot? Is it because thc tadpole is younger, or is it because it's a tadpole? What would happen if you delayed metamorphosis by blocking the action of thyroid hormones (you could put a few drops of thiouracil into the aquarium) so that you ended up with a very old tadpole? Would the geriatric tadpole be able to regenerate a missing limb? (As a schoolboy I made some feeble attempts to answer this, but, to my knowledge, we don't know the answer even to this day.)[3]

Of course, looking at such odd cases is not the only way—or even the best way—of doing science; it's a lot of fun but it's not everyone's cup of tea. But it's an eccentricity that has remained with me since childhood, and fortunately I have been able to turn it into an advantage. Clinical neurology, in particular, is full of such examples that have been ignored by the "establishment" because they don't really fit received wisdom. I have discovered, to my delight, that many of them are diamonds in the rough.

For example, those who are suspcious of the claims of mind-body medicine should consider multiple personality disorders. Some clinicians say that patients can actually "change" their eye structure when assuming different personas—a nearsighted person becomes farsighted, a blue-eyed person becomes brown-eyed—or that the patient's blood chemistry changes along with personality (high blood glucose level with one and normal glucose level with another). There are also case descriptions of people's hair turning white, literally overnight, after a severe psychological shock and of pious nuns' developing stigmata on their palms in ecstatic union with Jesus. I find it surprising that despite three decades of research, we are not even sure whether these phenomena are real or bogus. Given all the hints that there is something interesting going on, why not examine these claims in greater detail? Are they like alien abduction and spoon bending, or are they genuine anomalies—like X rays or bacterial transformation[4]—that may someday drive paradigm shifts and scientific revolutions?

I was personally drawn into medicine, a discipline full of ambiguities, because its Sherlock Holmes style of inquiry greatly appealed to me. Diagnosing a patient's problem remains as much an art as a science, calling into play powers of observation, reason and all the human senses. I recall one professor, Dr. K.V. Thiruvengadam, instructing us how to identify disease by just smelling the patient—the unmistakable, sweetish nail polish breath of diabetic ketosis; the freshly baked bread odor of typhoid fever; the stale-beer stench of scrofula; the newly plucked chicken feathers aroma of rubella; the foul smell of a lung abscess; and the ammonia-like Windex odor of a patient in liver failure. (And today a pediatrician might add the grape juice smell of Pseudomonas infection in children and the sweaty-feet smell of isovaleric acidemia.) Inspect the fingers carefully, Dr. Thiruvengadam told us, because a small change in the angle between the nail bed and the finger can herald the onset of a malignant lung cancer long before more ominous clinical signs emerge. Remarkably, this telltale sign—clubbing—disappears instantly on the operating table as the surgeon removes the cancer, but, even to this day, we have no idea why it occurs. Another teacher of mine, a professor of neurology, would insist on our diagnosing Parkinson's disease with our eyes closed—by simply listening to the patients' footsteps (patients with this disorder have a characteristic shuffling gait). This detective-like aspect of clinical medicine is a dying art in this age of high-tech medicine, but it planted a seed in my mind. By carefully observing, listening, touching and, yes, even smelling the patient, one can arrive at a reasonable diagnosis and merely use laboratory tests to confirm what is already known.

Finally, when studying and treating a patient, it is the physician's duty always to ask himself, "What does it feel like to be in the patient's shoes?" "What if I were him?" In doing this, I have never ceased to be amazed at the courage and fortitude of many of my patients or by the fact that, ironically, tragedy itself can sometimes enrich a patient's life and give it new meaning. For this reason, even though many of the clinical tales you will hear are tinged with sadness, equally often they are stories of the triumph of the human spirit over adversity, and there is a strong undercurrent of optimism. For example, one patient I saw—a neurologist from New York—suddenly at the age of sixty started experiencing epileptic seizures arising from his right temporal lobe. The seizures were alarming, of course, but to his amazement and delight he found himself becoming fascinated by poetry, for the first time in his life. In fact, he began thinking in verse, producing a voluminous outflow of rhyme. He said that such a poetic view gave him a new lease on life, a fresh start just when he was starting to feel a bit jaded. Does it follow from this example that all of us are unfulfilled poets, as many new age gurus and mystics assert? Do we each have an untapped potential for beautiful verse and rhyme hidden in the recesses of our right hemisphere? If so, is there any way we can unleash this latent ability, short of having seizures?

Before we meet the patients, crack mysteries and speculate about brain organization, I'd like to take you on a short guided tour of the human brain. These anatomical signposts, which I promise to keep simple, will help you understand the many new explanations for why neurological patients act the way they do.

It's almost a cliche these days to say that the human brain is the most complexly organized form of matter in the universe, and there is actually some truth to this. If you snip away a section of brain, say, from the convoluted outer layer called the neocortex and peer at it under a microscope, you'll see that it is composed of neurons or nerve cells—the basic functional units of the nervous system, where information is exchanged. At birth, the typical brain probably contains over one hundred billion neurons, whose number slowly diminishes with

Each neuron has a cell body and tens of thousands of tiny branches called dendrites, which receive information from other neurons. Each neuron also has a primary axon (a projection that can travel long distances in the brain) for sending data out of the cell, and axon terminals for communication with other

Figure 1.1 (No accompanying text. Image not reproduced in this .pdf

If you look at Figure 1.1, you'll notice that neurons make contacts with other neurons, at points called synapses. Each neuron makes anywhere from a thousand to ten thousand synapses with other neurons. These can be either on or off, excitatory or inhibitory. That is, some synapses turn on the juice to fire things up, whereas others release juices that calm everytlung down, in an ongoing dance of staggering complexity. A piece of your brain the size of a grain of sand would contain one hundred thousand neurons, two million axons and one billion synapses, all "talking to" each other. Given these figures, it's been calculated that the number of possible brain states—the number of permutations and combinations of activity that are theoretically possible—exceeds the number of elementary particles in the universe. Given this complexity, how do we begin to understand the functions of the brain, obviously understanding the structure of the nervous system is vital to understanding its functions[5]—and so I will begin with a brief survey of the anatomy of the brain, which, for our purposes here, begins at the top of the spinal cord. This region, called the medulla oblongata, connects the spinal cord to the brain and contains clusters of cells or nuclei that control critical functions like blood pressure, heart rate and breathing. The medulla connects to the pons (a kind of bulge), which sends fibers into the cerebellum, a fist-sized structure at the back of the brain that helps you carry out coordinated movements. Atop these are the two enormous cerebral hemispheres—the famous walnut-shaped halves of the brain. Each half is divided into four lobes—frontal, temporal, parietal and occipital—that you will learn much more about in coming chapters (Figure

Figure 1.2 (Image not reproduced in this .pdf

[Gross anatomy of the human brain. (a) Shows the left side of the left hemisphere. Notice the four lobes: frontal, parietal, temporal, occipital. The frontal is separated from the parietal by the central or rolandic sulcus (furrow or fissure), and the temporal from the parietal by the lateral or sylvian fissure. (b) Shows the inner surface of the left hemisphere. Notice the conspicuous corpus callosum (black) and the thalamus (white) in the middle. The corpus callosum bridges the two hemispheres. (c) Shows the two hemispheres of the brain viewed down from the top. (a) Ramachandran; (b) and (c) redrawn from Zeki, 1993.]

Each hemisphere controls the movements of the muscles (for example, those in your arm and leg) on the opposite side of your body. Your right brain makes your left arm wave and your left brain allows your right leg to kick a ball. The two halves of the brain are connected by a band of fibers called the corpus callosum. When this band is cut, the two sides can no longer communicate; the result is a syndrome that offers insight into the role each side plays in cognition. The outer part of each hemisphere is composed of cerebral cortex: a thin, convoluted sheet of cells, six layers thick, that is scrunched into ridges and furrows like a cauliflower and packed densely inside the

Right in the center of the brain is the thalamus. It is thought to be evolutionarily more primitive than the cerebral cortex and is often described as a "relay station" because all sensory information except smell passes through it before reaching the outer cortical mantle. Interposed between the thalamus and the cortex are more nuclei, called basal ganglia (with names like the putamen and caudate nucleus). Finally, on the floor of the thalamus is the hypothalamus, which seems to be concerned with regulating metabolic functions, hormone production, and various basic drives such as aggression, fear, and sexuality.

These anatomical facts have been known for a long time, but we still have no clear idea of how the brain works.[6] Many older theories fall into two warring camps—modularity and holism—and the pendulum has swung back and forth between these two extreme points of view for the last three hundred years. At one end of the syctrum are modularists, who believe that different parts of the brain are highly specialized for mental capacities. Thus there is a module for language, one for memory, one for math ability, one for face recognition and maybe even one for detecting people who cheat. Moreover, they argue, these modules or regions are largely autonomous. Each does its own job, set of computations, or whatever, and then—like a bucket brigade—passes its output to the next module in line, not "talking" much to other

At the other end of the spectrum we have "holism," a theoretical approach that overlaps with what these days is called "connectionism." This school of thought argues that the brain functions as a whole and that any one part is as good as any other part. The holistic view is defended by the fact that many areas, especially cortical regions, can be recruited for multiple tasks. Everything is connected to everything else, say the holists, and so the search for distinct modules is a waste of

My own work with patients suggests that these two points of view are not mutually exclusive—that the brain is a dynamic structure that employs both "modes" in a marvelously complex interplay. The grandeur of the human potential is visible only when we take all the possibilities into account, resisting the temptation to fall into polarized camps or to ask whether a given function is localized or not localized.[7] As we shall see, it's much more useful to tackle each problem as it comes along and not get hung up taking

Each view in its extreme form is in fact rather absurd. As an analogy, suppose you are watching the program Baywatch on television. Where is Baywatch localized? Is it in the phosphor glowing on the

TY screen or in the dancing electrons inside the cathode-ray tube? Is it in the electromagnetic waves being transmitted through air? Or is it on the celluloid film or video tape in the studio from which the show is being transmitted? Or maybe it's in the camera that's looking at the actors in the

Most people recognize right away that this is a meaningless question. You might be tempted to conclude therefore that Baywatch is not localized (there is no Baywatch "module") in any one place—that it permeates the whole universe—but that, too, is absurd. For we know it is not localized on the moon or in my pet cat or in the chair I'm sitting on (even though some of the electromagnetic waves may reach these locations). Clearly the phosphor, the cathode-ray tube, the electromagnetic waves and the celluloid or tape are all much more directly involved in this scenario we call Baywatch than is the moon, a chair or my

This example illustrates that once you understand what a television program really is, the question "Is it localized or not localized?" recedes into the background, replaced with the question "How does it work?" But it's also clear that looking at the cathode-ray tube and electron gun may eventually give you hints about how the television set works and picks up the Baywatch program as it is aired, whereas examining the chair you are sitting on never will. So localization is not a bad place to start, so long as we avoid the pitfall of thinking that it holds all the

So it is with many of the currently debated issues concerning brain function. Is language localized? Is color vision? Laughter? Once we understand these functions better, the question of "where" becomes less important than the question of "how." As it now stands, a wealth of empirical evidence supports the idea that there are indeed specialized parts or modules of the brain for various mental capacities. But the real secret to understanding the brain lies not only in unraveling the structure and function of each module but in discovering how they interact with each other to generate the whole spectrum of abilities that we call human

Here is where the patients with bizarre neurological conditions come into the picture. Like the anomalous behavior of the dog that did not bark when the crime was being committed, providing Sherlock Holmes with a clue as to who might have entered the house on the night of the murder, the odd behavior of these patients can help us solve the mystery of how various parts of the brain create a useful representation of the external world and generate the illusion of a "self" that endures in space and

To help you get a feel for this way of doing science, consider these colorful cases—and the lessons drawn from them—taken from the older neurological

More than fifty years ago a middle-aged woman walked into the clinic of Kurt Goldstein, a world-renowned neurologist with keen diagnostic skills. The woman appeared normal and conversed fluently; indeed, nothing was obviously wrong with her. But she had one extraordinary complaint—every now and then her left hand would fly up to her throat and try to strangle her. She often had to use her right hand to wrestle the lef hand under control, pushing it down to her side—much like Peter Sellers portraying Dr. Strangelove. She sometimes even had to sit on the murderous hand, so intent was it on trying to end her

Not surprisingly, the woman's primary physician decided she was mentally disturbed or hysterical and sent her to several psychiatrists for treatment. When they couldn't help, she was dispatched to Dr. Goldstein, who had a reputation for diagnosing difficult cases. After Goldstein examined her, he established to his satisfaction that she was not psychotic, mentally disturbed or hysterical. She had no obvious neurological deficits such as paralysis or exaggerated reflexes. But he soon came up with an explanation for her behavior: Like you and me, the woman had two cerebral hemispheres, each of which is specialized for different mental capacities and controls movements on the opposite side of the body. The two hemispheres are connected by a band of fibers called the corpus callosum that allows the two sides to communicate and stay "in sync." But unlike most of ours, this woman's right hemisphere (which controlled her left hand) seemed to have some latent suicidal tendencies—a genuine urge to kill herself. Initially these urges may have been held in check by "brakes"—inhibitory messages sent across the corpus callosum from the more rational left hemisphere. But if she had suffered, as Goldstein surmised, damage to the corpus callosum as the result of a stroke, that inhibition would be removed. The right side of her brain and its murderous lef hand were now free to attempt to strangle

This explanation is not as far-fetched as it seems, since it's been well known for some time that the right hemisphere tends to be more emotionally volatile than the left. Patients who have a stroke in the left brain are often anxious, depressed or worried about their prospects for recovery. The reason seems to be that with the left brain injured, their right brain takes over and frets about everything. In contrast, people who suffer damage to the right hemisphere tend to be blissfully indifferent to their own predicament. The left hemisphere just doesn't get all that upset. (More on this in Chapter

When Goldstein arrived at his diagnosis, it must have seemed like science fiction. But not long after that office visit, the woman died suddenly, probably from a second stroke (no, not from strangling herself). An autopsy confirmed Goldstein's suspicions: Prior to her Strangelovean behavior, she had suffered a massive stroke in her corpus callosum, so that the left side of her brain could not "talk to" nor exert its usual control over the right side. Goldstein had unmasked the dual nature of brain function, showing that the two hemispheres are indeed specialized for different

Consider next the simple act of smiling, something we all do every day in social situations. You see a good friend and you grin. But what happens when that friend aims a camera at your face and asks you to smile on command, Instead of a natural expression, you produce a hideous grimace. Paradoxically, an act that you perform effortlessly dozens of times each day becomes extraordinarily difficult to perform when someone simply asks you to do it. You might think it's because of embarrassment. But that can't be the answer because if you walk over to any mirror and try smiling, I assure you that the same grimace will

The reason these two kinds of smiles differ is that different brain regions handle them, and only one of them contains a specialized "smile circuit." A spontaneous smile is produced by the basal ganglia, clusters of cells found between the brain's higher cortex (where thinking and planning take place) and the evolutionarily older thalamus. When you encounter a friendly face, the visual message from that face eventually reaches the brain's emotional center or limbic system and is subsequently relayed to the basal ganglia, which orchestrate the sequences of facial muscle activity needed for producing a natural smile. When this circuit is activated, your smile is genuine. The entire cascade of events, once set in motion, happens in a fraction of a second without the thinking parts of your cortex ever being involved.

But what happens when someone asks you to smile while taking your photograph? The verbal instruction from the photographer is received and understood by the higher thinking centers in the brain, including the auditory cortex and language centers. From there it is relayed to the motor cortex in the front of the brain, which specializes in producing voluntary skilled movements, like playing a piano or combing your hair. Despite its apparent simplicity, smiling involves the careful orchestration of dozens of tiny muscles in the appropriate sequence. As far as the motor cortex (which is not specialized for generating natural smiles) is concerned, this is as complex a feat as playing Rachmaninoff though it never had lessons, and therefore it fails utterly. Your smile is forced, tight, unnatural.

Evidence for two different "smile circuits" comes from brain-damaged patients. When a person suffers a stroke in the right motor cortex—the specialized brain region that helps orchestrate complex movements on the left side of the body—problems crop up on the left. Asked to smile, the patient produces that forced, unnatural grin, but now it's even more hideous; it's a half smile on the right side of the face alone. But when this same patient sees a beloved friend or relative walk through the door, her face erupts into a broad, natural smile using both sides of the mouth and face. The reason is that her basal ganglia have not been damaged by the stroke, so the special circuit for making symmetrical smiles is intact.[8]

Very rarely, one encounters a patient who has apparently had a small stroke, which neither he nor anyone else notices until he tries to smile. All of a sudden, his loved ones are astonished to see that only one half of his face is grinning. And yet when the neurologist instructs him to smile, he produces a symmetrical, albeit unnatural grin—the exact converse of the previous patient. This fellow, it turns out, had a tiny stroke that only affected his basal ganglia selectively on one side of the

Yawning provides further proof for specialized circuitry. As noted, many stroke victims are paralyzed on the right or left side of their bodies, depending on where the brain injury occurs. Voluntary movements on the opposite side are permanently gone. And yet when such a patient yawns, he stretches out both arms spontaneously. Much to his amazement, his paralyzed arm suddenly springs to life! It does so because a different brain pathway controls the arm movement during the yawn— a pathway closely linked to the respiratory centers in the brain

Sometimes a tiny brain lesion—damage to a mere speck of cells among billions—can produce far-reaching problems that seem grossly out of proportion to the size of the injury. For example, you may think that memory involves the entire brain. When I say the word "rose," it evokes all sorts of associations: perhaps images of a rose garden, the first time someone ever gave you a rose, the smell, the softness of petals, a person named Rose and so on. Even the simple concept of "rose" has many rich associations, suggesting that the whole brain must surely be involved in laying down every memory

But the unfortunate story of a patient known as H.M. suggests otherwise.[9] Because H.M. suffered from a particularly intractable form of epilepsy, his doctors decided to remove "sick" tissue from both sides of his brain, including two tiny seahorse-shaped structures (one on each side) called the hippocampus, a structure that controls the laying down of new memories. We only know this because after the surgery, H.M. could no longer form new memories, yet he could recall everything that happened before the operation. Doctors now treat the hippocampus with greater respect and would never knowingly remove it from both sides of the brain (Figure

Figure 1.3 (Image not reproduced in this .pdf file).
[Artist's rendering of a brain with the outer convoluted cortex rendered partially transparent to allow inner structures to be seen. The thalamus (dark) can be seen in the middle, and interposed between it and the cortex are clusters of cells called the basal ganglia (not shown). Embedded in the front part of the temporal lobe you can see the dark, almond-shaped amygdala, the “gateway” to the limbic system. In the temporal lobe you can also see the hippocampus (concerned with memory). In addition to the amygdala, other parts of the limbic system such as the hypothalamus (below the thalamus) can be seen. The limbic pathways mediate emotional arousal. The hemispheres are attached to the spinal cord by the brainstem (consisting of medulla, pons, and midbrain), and below the occipital lobes is the cerebellum, concerned with coordination of movements and timing. From Brain, Mind and Behaviour, by Bloom and Laserson (1988) by Educational Broadcasting Corporation. Used with permission from W. H. Freeman and Company.]

Although I have never worked directly with H.M., I have often seen patients with similar forms of amnesia resulting from chronic alcoholism or hypoxia (oxygen starvation in the brain following surgery). Talking to them is an uncanny experience. For example, when I greet the patient he seems intelligent and articulate, talks normally and may even discuss philosophy with me. If I ask him to add or subtract, he can do so without trouble. He's not emotionally or psychologically disturbed and can discuss his family and their various activities with

Then I excuse myself to go to the restroom. When I come back, there is not a glimmer of recognition, no hint thee he's ever seen me before in his

"Do you remember who I

"No."

I show him a pen. "What is

"A fountain

"What color is

"It's

I put the pen under a pillow on a nearby chair and ask him, "What did I just

He answers promptly, "You put the pen under that

Then I chat some more, perhaps asking about his family. One minute goes by and I ask, "I just showed you something. Do you remember what it

He looks puzzled.

"Do you remember that I showed you an object? Do you remember where I put it?”

"No." He has absolutely no recollection of my hiding the pen sixty seconds

Such patients are, in effect, frozen in time in the sense they remember only events that took place before the accident that injured them neurologically. They may recall their first baseball game, first date and college graduation in elaborate detail, but nothing after the injury seems to be recorded. For example, if post accident they come upon last week's newspaper, they read it every day as if it were a brand-new paper each time. They can read a detective novel again and again, each time enjoying the plot and the surprise ending. I can tell them the same joke half a dozen times and each time I come to the punch line, they laugh heartily (actually, my graduate students do this

These patients are telling us something very important—that a tiny brain structure called the hippocampus is absolutely vital for laying down new memory traces in the brain (even though the actual memory traces are not stored in the hippocampus). They illustrate the power of the modular approach: In helping to narrow the scope of inquiry, if you want to understand memory, look at the hippocampus. And yet, as we shall see, studying the hippocampus alone will never explain all aspects of memory. To understand how memories are retrieved at a moment's notice, how they are edited, pigeonholed (sometimes even censored!), we need to look at how the hippocampus interacts with other brain structures such as the frontal lobes, the limbic system (concerned with emotions) and the structures in the brain stem (which allow you to attend selectively to specific

The role of the hippocampus in forming memories is clearly established, but are there brain regions specialized in more esoteric abilities like the "number sense" that is unique to humans? Not long ago I met a gentleman, Bill Marshall, who had suffered a stroke a week earlier. Cheerful and on his way to recovery, he was only too happy to discuss his life and medical condition. When I asked him to tell me about his family, he named each of his children, listed their occupations and gave many details about his grandchildren. He was fluent, intelligent and articulate—and not everyone is so soon after a stroke.

"What was your occupation?" I asked

Bill replied, "I used to be an Air Force

"What kind of plane did you

He named the plane and said, "It was the fastest man-made thing on this planet at that time." Then he told me how fast it flew and said that it had been made before the introduction of jet

At one point I said, "Okay, Bill, can you subtract seven from one hundred? What's one hundred minus seven?"

He said, "Oh. One hundred minus seven?”

"Yeah.”

"Hmmm, one hundred minus seven.”

"Yes, one hundred minus seven.”

"So," said Bill. "One hundred. You want me to take away seven from one hundred. One hundred minus

"Yes."

"Ninety six?”

“No."

"Oh," he

"Let's try something else. What's seventeen minus

"Seventeen minus three? You know I'm not very good at this kind of thing," said Bill”

"Bill," I said, "is the answer going to be a smaller number or a bigger

"Oh, a smaller number," he said, showing that he knew what subtraction.

"Okay, so what's seventeen minus

"Is it twelve?" he said at

I started wondering whether Bill had a problem understanding what a number is or dhe nature of numbers. Indeed, the question of numbers is old and deep, going back to

I asked him, "What is

"Oh, that's the largest number there

"Which number is bigger: one hundred and one or

He answered immediately: "One hundred and one is

"Why?"

"Because there are more

This meant that Bill still understood, at least tacitly, sophisticated numerical concepts like place value. Also, even though he couldn't subtract three from seventeen, his answer wasn't completely absurd. He said "twelve," not seventy-five or two hundred, implying that he was still capable of making ballpark estimates.

Then I decided to tell him a little story: "The other day a man walked into the new dinosaur exhibit hall at the American Museum of Natural History in New York and saw a huge skeleton on display. He wanted to know how old it was, so he went up to an old curator sitting in dhe corner and said, 'I say, old chap, how old are these dinosaur

"The curator looked at the man and said, 'Oh they're sixty million and three years old,

" 'Sixty million and three years old? I didn't know you could get that precise with aging dinosaur bones. What do you mean, sixty million and three years old?’

" 'Oh, well,' he said, 'they gave me this job three years ago and at that time they told me the bones were sixty million years old.'

Bill laughed out loud at the punch line. Obviously he understood far more about numbers than one might have guessed. It requires a sophisticated mind to understand that joke, given chat it involves what philosophers call the "fallacy of misplaced

I turned to Bill and asked, "Well, why do you think that's

"Well, you know," he said, "the level of accuracy is

Bill understands the joke and the idea of infinity, yet he can't subtract three from seventeen. Does this mean that each of us has a number center in the region of the left angular gyrus (where Bill's stroke injury was located) of our brain for adding, subtracting, multiplying and dividing? I think not. But clearly this region—the angular gyrus—is somehow necessary for numerical computational tasks but is not needed for other abilities such as short-term memory, language or humor. Nor, paradoxically, is it needed for understanding dhe numerical concepts underlying such computations. We do not yet know how this "arithmetic" circuit in dhe angular gyrus works, but at least we now know where to look.[10]

Many patients, like Bill, with dyscalculia also have an associated brain disorder called finger agnosia: They can no longer name which finger the neurologist is pointing to or touching. Is it a complete coincidence that both aridhmetic operations and finger naming occupy adjacent brain regions, or does it have something to do with the fact that we all learn to count by using our fingers in early childhood? The observation that in some of these patients one function can be retained (naming fingers) while the other (adding and subtracting) is gone doesn't negate the argument that these two might be closely linked and occupy the same anatomical niche in the brain. It's possible, for instance, that the two functions are laid down in close proximity and were dependent on each other during dhe learning phase, but in the adult each function can survive without the other. In other words, a child may need to wiggle his or her fingers subconsciously while counting, whereas you and I may not need to do

These historical examples and case studies gleaned from my notes support the view that specialized circuits or modules do exist, and we shall encounter several additional examples in this book. But other equally interesting questions remain and we'll explore these as well. How do the modules actually work and how do they "talk to" each other to generate conscious experience? To what extent is all this intricate circuitry in the brain innauly specificd by your genes or to what extent is it acquired gradually as the result of your early experiences, as an infant interacts with the world? (This is the ancient "nature versus nurture" debate, which has been going on for hundreds of years, yet we have barely scratched the surface in formulating an answer.) Even if certain circuits are hard-wired from birth, does it follow that they cannot be altered? How much of the adult brain is modifiable? To find out, let's meet Tom, one of the first people who helped me explore these larger

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Ramachandran's Footnotes (pp. 263-266).

1. I am of course talking about style here, not content. Modesty aside, I doubt whether any observation in this book is as important as one of Faraday's discoveries, but I do think that all experimental scientists should strive to emulate his style.

2. Of course, one doesn't want to make a fetish out of low-tech science. My point is simply that poverty and crude equipment can sometimes, paradoxically, actually serve as a catalyst rather than a handicap, for they force you to be inventive.

There is no denying, though, that innovative technology drives science just as surely as ideas do. The advent of new imaging techniques like PET, fMRI and MEG is likely to revolutionize brain science in the next millennium by allowing us to watch living brains in achon, as people engage in various mental tasks. (See Posner and Raichle, 1997, and Phelps and Mazziotta, 1981.)

Unfortunately, there is currently a lot of gee whiz going on (almost a repeat of nineteenth-century phrenology). But if used intelligently, these toys can be immensely helpful. The best experiments are ones in which imaging is combined with clear, testable hypotheses of how the mind actually works. There are many instances where tracing the flow of events is vital for understanding what is happening in the brain and we will encounter some examples in this book.

3. This question can be answered more easily using insects, which have specific stages, each with a fixed life span. (For instance, the cicada species Magicicada septendecim spends seventeen years as an immature nymph and just a few weeks as an adult!) Using the metamorphosis hormone ecdysone or an antibody to it or mutant insects, which lack the gene for the hormone, one could theoredcally manipulate the duration of each stage separately to see how it contributes to the total life span. For example, would blocking ecdysone allow the caterpillar to enjoy an indefinitely long life, and conversely would changing it into a butterfly allow it to enjoy a longer life as a butterfly?

4. Long before the role of deoxyribonucleic acid (DNA) in heredity was explained by James Watson and Francis Crick, Fred Griffiths proved in 1928 that when a chemical substance obtained from a heat-killed bacterium of one species—called strain S pneumocoecus—was injected simultaneously into mice along with another strain (strain R), the latter actually became "transformed" into strain S! It was clear that something was present in S bacteria that was causing the R form to become S. Then, in the 1940s, Oswald Avery, Colin Macleod and Maclyn McCarty showed that this reaction is caused by a chemical substance, DNA. The implicahon—that DNA contains the genetic code—should have sent shock waves through the world of biology but caused only a small stir.

5. Historically there have been many different ways of studying the brain. One method, popular with psychologists, is the so-called black box approach: You systematically vary the input to the system to see how the output changes and construct models of what is going on in between. If you think this sounds boring, it is. Nevertheless, the approach has had some spectacular successes, such as the discovery of trichromacy as the mechanism of color vision. Researchers found that all the colors that you can see could be made by simply combining different proportions of three primary ones—red, green and blue. From this dhey deduced that we have only three receptors in the eye, each of which responds maximally to one wavelength but also reacts to a lesser extent other wavelengths.

One problem with thc black box approach is that, sooner or later, one ends up with multiple competng models and dhe only way to discover which one is correct is to open up the black box—that is, do physiological experiments on humans and animals. For example, I doubt very much whether anyone could have figured out how the digetive system works by simply looking at its output. Using this strategy alone, no one could have deduced the existence of mastication, peristalsis, saliva, gastric juices, pancreatic enzymes or bile nor realized that the liver alone has over a dozen functions to help assist the digestive process. Yet a vast majority of psychologists—called functionalists—cling to the view that we can understand mental processes from a strictly computational, behaviorist or "reverse engineering perspective"—without bothering with the messy stuff in the head.

When dealing with biological systems, understanding structure is crucial to understanding function—a view that is completely antithetical to the functionalist or black box approach to brain funcfion. For example, consider how our understanding of the anatomy of the DNA molecule—its double-helical structure—completely transformed our understanding of heredity and genetics, which until then had remained a black box subject. Indeed, once the double helix was discovered, it became obvious that the structural logic of this DNA molecule dictates the functional logic of heredity.

6. For over half a century, modern neuroscience has been on a reductionist path, breaking things down into ever smaller parts with the hope that understanding all the little pieces will eventually explain the

whole. Unfortunately, many people think that because reductionism is so often useful in solving problems, it is therefore also sufficient for solving them, and generations of neuroscientists have been raised on this dogma. This misapplicahon of reductionism leads to the perverse and tenacious belief that somehow reductionism itself will tell us how the brain works, when what is really needed are attempts to bridge different levels of discourse. The Cambridge physiologist Horace Barlow recendy pointed out at a scientific meeting that we have spent five decades studying the cerebral cortex in excruciating detail, but we skill don't have the foggiest idea of how it works or what it does. He shocked the audience by suggesting that we are all like asexual Martians visiting earth who spend fiffy years examiningthe detailed cellular mechanisms and biochemistty of the testicles without knowing anything at all about sex.

7. The doctine of modularity was carried to its most ludicrous extremes by Franz Gall, an eighteenth-century psychologist who founded the fashionable pseudoscience of phrenology. One day while giving a lecture, Gall noted that one particular student, who was very bright, had prominent eyeballs. Gall started thinking, Why does he have prominent eyeballs? Maybe the frontal lobes have something to do with intelligence. Maybe they are especially large in this boy, pushing his eyeballs forward. On the basis of this tenuous reasoning, Gall embarked on a series of experiments that involved measuring the bumps and depressions on people's skulls. Finding differences, Gall began to correlate the shapes with various mental functions. Phrenologists soon "discovered" bumps for such esoteric traits as veneration, cantiousness, sublimity, acquisitiveness and secretiveness. In an antique shop in Boston, a colleague of mine recently saw a phrenology bust that depicted a bump for the "Republican spirit"! Phrenology was still popular in the late nineteenth and early twentieth centuries. Phrenologists were also interested in how brain size is related to mental capacity, asserting that heavier brains are more intelligent than lighter ones. They claimed that, on average, the brains of black people are smaller than white people's and that women's brains are smaller than men's and argued that the difference "explained" differences in average intelligence between these groups. The crowning irony is that when Gall died, people actually weighed his brain and found that it was a few grams lighter than the average female brain. (For an eloquent description of the pitfalls of phrenology, see Stephen Jay Gould's *The Mismeasure of Man*.)

8. These two examples were great favorites of the Harvard neurologist Norman Geschwind when he gave lectures to lay audiences.

9. Hints about the role of medial temporal lobe structures, including the hippocampus, in memory formation go all the way back to the Russian psychiatrist Sergei Korsakov. Patient H.M. and other amnesics like him have been studied elegantly by Brenda Milner, Larty Weiskrantz, Elizabeth Warrington and Larry Squire.

The actual cellular changes that strengthen connections between neurons have been explored by several researchers, most notably Eric Kandel, Dan Alkon, Gary Lynch and Terry Sejnowski.

10. Our ability to engage in numerical computations (add, subtract, multiply and divide) seems so effortless that it's easy to jump to the conclusion that it is "hardwired." But, in fact, it became effortless only after the introduction of two basic concepts—place value and zero—in India during the third

century A.D. These two notions and the idea of negative numbers and of decimals (also introduced in India) laid the foundation of modern mathematics.

It has even been claimed that the brain contains a "number line," a sort of graphical, scalar representahon of numbers with each point in the graph being a cluster of neurons signaling a particular numerical value. The abstract mathemadcal concept of a number line goes all the way back to the Persian poet and mathemadcian Omar Khayyám, in the ninth century, but is there any evidence that such a line exists in the brain? When normal people are asked which of two numbers is larger, it takes them longer to make the decision if the numbers are closer together than if they are wider apart. In Bill, the number line seems unaffected because he is okay at making crude quantitative estimates—which number is bigger or smaller or why it seems inappropriate to say the dinosaur bones are sixty million and three years old. But there is a separate mechanism for numerical computation, for juggling numbers about in your head, and for this you need the angular gyrus in the left hemisphere. For a very readable account of dyscalculias, see Dehaene, 1997.

My colleague here at UCSD Dr. Tim Rickard has shown by using functional magnetic resonance imaging (fMRI) that the "numerical calculation area" actually lies not entirely in the classical left angular gyrus itself but slightly in front of it, but this doesn't affect my main argument and it's only a matter of time before someone also demonstrates the "number line" using modern imaging techniques.