



**TREES
OF THE BRAIN
ROOTS
OF THE MIND**

GIORGIO A. ASCOLI

Trees of the Brain, Roots of the Mind

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Preface

BRAINFOREST GLORY: Since our first clear glimpse of a neuron over a century ago, humans have been awed by the beauty of these tiny tree-like objects. Perhaps our species' recent evolutionary stint as arboreal primates has hard-wired us to love the sights of trees and forests! Thus, as neuroscience rapidly advances our ability to see both the brain's "trees" and its vastly intricate and diverse forests, we may find that the most beautiful landscape of all is the one within.

—Stephen J. Smith

The human brain is often hailed as the most complex object in the universe. Much of the brain complexity is due to the massive web of connections and communication formed by its tens of billions of nerve cells through tiny tree-like structures. The computational power of such an intricate information-processing system is apparent in the depth and breadth of every sentient being's mental life. Although the complexity of the brain and the richness of the mind are nowadays readily recognized by scientists and nonscientists alike, my aim with this book is to reveal a yet well-kept secret: the stunning beauty of the brain's cellular form.

If we were to enlarge a human brain thousandsfold, to a first approximation each nerve cell would literally look like a tree with all of its intricate branching. A small region of the nervous system, such as those dedicated to moving your left pinky toe or to perceiving a dim blue light in the upper right corner of your eyesight, would at this magnified scale resemble a gigantic forest with millions of fantastic trees of all sizes and shapes. In this regard the entire brain can be viewed as a whole neurobotanical world completely filled with trees. These nerve trees are as beautiful and awe-inspiring as the most magnificent of magnolias, baobabs, and angel oaks. But unlike real-world trees, the microscopic trees in our brains make us move, feel,

think, remember, plan, love, and enjoy life. I hope that my writing will inspire you to embrace them with your imagination.

The neurosciences are rapidly and increasingly entering into the mainstream discourse of our society, from economy to medicine, from technology to psychology, from politics to leisure. Yet media reports of new discoveries about the structure and function of the nervous system are by necessity somewhat detached from the complex technical details of the research laboratory. Even the most interested and educated professionals—lawyers, analysts, physicians, engineers—typically attain only a superficial understanding of the mechanisms actively investigated by neuroscientists. In contrast, the source information is described in specialized journals dense with jargon that is mostly unintelligible to outsiders. It takes on average more than a decade of dedicated doctoral and postdoctoral training for the best and brightest college graduates to develop the independent ability to access and contribute to the frontier of neuroscience knowledge.

Nevertheless, even the most experienced and accomplished researchers, when staring into their microscopes, are often captivated by the arresting splendor of nerve cells. It doesn't take a Ph.D. in neuroscience to enjoy the spectacular structure of the cellular constituents of nervous system any more than it takes a Ph.D. in music to appreciate Beethoven's Ninth Symphony. It seems unfair not to share the spring of such pleasure and inspiration.

Yet perhaps the biggest challenge to understanding our brains lies in connecting the subjective experience with the shape and activity of these nerve cells. We can measure the temperature of far-away galaxies with stupendous accuracy, but we are clueless when it comes to understanding why we remember certain episodes of our past and not others. This embarrassing ignorance creates a level playing field between the Nobel-winning neuroscientist and a random lumberjack. They both remember (or forget) what they had for breakfast the day before yesterday, and neither really understands the neural mechanism underlying her or his own mental state. Moreover, the neuroscientist and the lumberjack should both put their tools down from time to time and admire the scenic view of the forest in which they are working.

Somehow, that same structural majesty of nerve cells hides the secrets behind the genesis of our mental states, so immediately accessible to every human being and so elusive to scientific investigation. This book proposes

new ideas to solve some of the most intriguing mysteries of the mind using only basic architectural principles of the brain. Why do we remember certain events of our past but not others? Why is it so difficult for me to learn certain skills although I can master others without effort, and yet it might be just the opposite for you? How do we acquire certain knowledge by reading or hearing something just once, whereas memorizing other facts might take multiple rehearsals? The novel explanations of these phenomena proposed in this book are consistent with the latest findings in the field but are not yet necessarily embraced by the entire scientific community.

In order to explain how beautiful tree-shaped cells relate to our brains' ability to store and even create new knowledge, we introduce and overview some basic mechanisms underlying the main functions of these nerve structures. Nevertheless, this book is emphatically *not* intended to provide a comprehensive introduction to neuroscience. Many other recent books are available on the brain at large, and we refer to several of them throughout our exploration as well as to excellent Web resources and, occasionally, to accessible reviews in the original scientific literature. These bibliographic references may serve as suggestions for recommended further readings or as initial pointers for interested readers to expand on specific topics.¹

The book aims at a broad readership, generally employs plain language, and requires no specialized background knowledge. At the same time, some of the concepts I explain, both foundational and novel, are nontrivial. On top of it all I am firmly committed to scientific accuracy. I have strived to balance ease and pleasantness of read with a progressive buildup of logical steps by adopting an informal narrative style. When introducing each novel concept, I have attempted to include an explicit disclosure of whether it reflects established factual knowledge in the research community or represents commonly accepted but yet untested assumptions or constitutes a controversial view or even a completely original working hypothesis. To increase readability I have relegated the more technical explanations to footnotes for the benefit of the interested readers, but these are not required to follow the general flow of the arguments.

In the same spirit distances used to describe botanical trees are expressed in "imperial" units: miles (~1.61 kilometers), yards (~0.914 meters), feet (~0.30 meters), and inches (~25.4 millimeters). Microscopic measurements, however, typically referring to the subcellular constituents of neurons, are

reported in metric units: nanometers, micrometers, and millimeters (one billionth, one millionth, and one thousandth of a meter, respectively).

The book is organized in three main parts. The first three chapters (part I) provide the scientific and logical foundations. Chapter 1 lays the relevant philosophical, biological, and cognitive grounds of the mind-brain relationship. Chapter 2 introduces the basics of nerve cells and how they interconnect to form a gigantic brain network. Chapter 3 explains the way nerve cells process, transmit, and store information by means of electric signals.

Certain sections of this first part (particularly section 3.2) may feel difficult to follow for some readers. If you find yourself fatigued or even lost through the details, do not despair. An in-depth understanding of those mechanisms is *not* necessary to grasp the key ideas of this book. Absorbing at least parts of the technical descriptions at the beginning, however, will enrich the appreciation of the subsequent material.

The following three chapters (part II) erect the central claim of the book by establishing a sequence of increasingly daring principles of the mind-brain relationship. Chapter 4 compellingly links mental states with patterns of electric activity in nerve cells. Chapter 5 presents an emerging minority opinion of how the brain adapts to learn from experience. Chapter 6 unveils a radically new hypothesis of the mechanism determining what is learned, what isn't, and why.

The last three chapters (part III) tie these concepts together with the cosmic diversity within and between brains. Chapter 7 describes functional differences and similarities of nerve circuits in disparate animal species, along the life span, and across brain regions. Chapter 8 provides a unified framework to embrace and comprehend brain complexity. Chapter 9 integrates these notions into a revealing perspective on the roots of individuality and humanity. Each of the nine chapters is subdivided into four thematic sections.

The ideas presented in this book arise from solid scientific foundations but lend themselves to tempting speculations about the future. Is there a hard limit to scientific knowledge? What is the ultimate human challenge? Although the answers must still be tentative, this is the first time in history that such momentous questions can be clearly formulated in neurobiological terms. Leaving the forecast of the fascinating world to come for the reader's contemplation, the book closes with an epilogue bringing us back

to the present of contemporary neuroscience: what just happened, what's happening, what's in the making, and what lies as a challenge ahead.

The current and continuously accelerating pace of scientific progress makes for truly exciting times in research. It is hard to believe how much neuroscience has changed in the past generation, and it is even harder to imagine what our knowledge of the brain will be in the next generation. The most important task for neuroscientists today is to lay the foundation for the discoveries of tomorrow, but soon the findings of neuroscience will trigger profound changes in human relationships, transforming the very fabric of our society.

I wrote this book for my children, Benjamin, Ruben, Gabriel, and Jonah, for their enjoyment perhaps in a few years when some of these ideas might exhilarate them. I dedicate the book to my wife, Rebecca, with all my love: though the arbors of our brains are enclosed in different heads, the branches of our minds tenderly embrace.

This book would not exist without the direct or indirect contributions of several people to whom I am deeply grateful. First and foremost, I acknowledge my father, Aurelio, who taught me by example to search, research, and to experience life. It was during a 2009 vacation with him on mount Cervino in the Italian Alps that I conceived this book. Throughout the following five years, he continued to be a superhero grandpa and cared for my children for as many hours as I spent writing.

Bob Burke taught me to look at neuronal trees through the eyepieces of powerful microscopes. Steve Senft showed me the potential of computer simulations for neuroanatomy, and our early joint work planted the seed for many of the ideas in this book. Yuan Liu has been a visionary source of support through the years, venturing together in several expeditions through the neural forestry. Matteo Mainetti proved with numbers that the central and boldest proposal of this book (chapter 6) is mathematically tenable, but that's just one of the so many facets of our kinship. I celebrate two decades of friendship with Jim Olds, who provided much needed constructive criticism on an early version of the manuscript. Rebecca Goldin's extensive comments, incisive questions, and detailed suggestions, from the initial conception of this book through the penultimate draft, tremendously improved the readability of the final product.

My talented colleagues at the Krasnow Institute for Advanced Study year after year have provided an assiduous flow of ideas, passion, intellectual

challenges, and personal warmth that always keeps me going. In particular, Harold Morowitz offered steady encouragement to pursue science off the beaten path and put me in touch with Bob Prior at MIT Press.

I'm honored to illustrate the beauty of trees through artful pictures by my awesome friend for over thirty years, Daniel Segrè (figures 1.1, 2.3, 3.3, 3.5, 3.6, 4.2, 5.1, 5.3, 5.5, 6.1, 6.2, 6.4, 6.6, 7.1, 7.6, 8.1, 8.3, 8.6, and 9.2). Our friendship started around campground fires surrounded by trees, and we have never lost touch with each other through our journeys across continents, scientific disciplines, and personal relationships. His photographs exude the boundless convergence of physics, biology, and human spirit. You really see his hand in them.

It is an inspiring privilege to work every day with such dedicated peers, students, technicians, and postdocs. I have certainly learned from my trainees at least as much as I was able to teach them, and I take tremendous pride from the shining success of my lab alumni all around the world. I especially thank Namra Ansari, Todd Gillette, Uzma Javed, and Amina Zafar, who skillfully illustrated neuronal data from NeuroMorpho.Org (figures 1.2, 2.1, 2.4, 3.1, 3.2, 3.7, 4.1, 4.3, 4.4, 5.2, 5.4, 6.3, 6.5, 7.2, 7.3, 7.4, 7.5, 8.2, 8.3, 8.4, 8.5, and 9.1). I am also grateful to George Mason University, Gerald Goldin, Michele Ferrante, and Evan Cantwell for figures 2.2, 2.6, 3.4, and 8.5, respectively.

The US National Institutes of Health, National Science Foundation, Office of Naval Research, Burroughs-Wellcome Trust, and Keck Foundation have been generously supporting my research over the years on neuronal trees and the NeuroMorpho.Org database, where the neurons gracing these pages (and tens of thousands more) can be downloaded.

Last but not least, the research behind the ideas proposed in this book is enabled by the courageous choice of many scientists to freely share their hard-won experimental data in publicly accessible databases, allowing reuse by their peers throughout the entire neuroscience community. Equally important, I am humbled by the selfless open-source software developers fueling the digital revolution. Thank you, and please know you are making a difference.

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Part I: Cognitive Philosophy and Neuroscience Basics

1 Reality, the World, the Brain, and the Mind

... But of the Tree of Knowledge of good and evil you shall not eat of it, for on the day that you eat thereof, you shall surely die. (Gen. 2:17)¹

And the serpent said to the woman: "You will surely not die. For God knows that on the day that you eat thereof, your eyes will be opened, and you will be as angels, knowing good and evil. And the woman saw that the tree was [...] desirable to make one wise; so she took of its fruit, and she ate, and she gave also to her husband with her, and he ate. And the eyes of both of them were opened, and they knew ... (Gen. 3:4-7)²

1.1 What *Is*? Materialism, Idealism, and Dualism

The material existence of the world around us is so obvious that we normally don't even bother questioning it. It requires, in fact, a certain mental effort *not* to take for granted the chair one is sitting on or the very ground holding the chair. Just think about this one book you are reading. You are reading it, so it surely *must* be there in your hands! And how about those hands of yours? You've known them, waved them, and used them all your life; they have always been there with you and for you. Of course they *are*.

Yet the questions of what is real and what is *reality* are neither trivial nor settled. We know that the chair, the ground, the book, and your hands have measurable physical properties such as weight and temperature. These measures can be determined reproducibly and objectively in the sense that they can be confirmed in different experiments and by independent experimenters. We also know that these objects are made out of molecules, whose chemical properties, also well known, can in fact explain the above macroscopic observables. Molecules are formed by atoms, atoms are formed by protons, electrons, and neutrons; and these particles are formed by the

even tinier quarks. At these subatomic levels, however, it becomes impossible to determine precisely even simple measures such as position and velocity. Exactly what are the real constituents of matter, and what can be measured reproducibly and objectively?

To this day, these issues are the topic of advanced scientific research. Modern society made huge investments to build gigantic machines in order to enable the execution of complex experiments in the hope of finding answers. For example, construction of the 17-mile wide “Large Hadron Collider” particle accelerator by the European Organization for Nuclear Research (CERN) 500 feet underground in Switzerland between 1998 and 2008 had an approximate cost of \$10 billion.³ The project involved more than ten thousand engineers from over one hundred different nations and enabled the historical discovery of the long-theorized Higgs boson in 2012.⁴ Data produced by this machine are distributed throughout a worldwide computing grid continuously analyzed by more than eight thousand scientists from 140 countries.⁵ The theoretical framework necessary to describe and explain these issues employs mathematical formulations so sophisticated that they are elusive to all but a small number of highly educated specialists.

But even the so-called reality in the day-to-day life of people like you and me is not free of puzzling mysteries. Those chairs, books, and hands, as well as that ground we were considering are only “known” to us through the eyes of our minds. We perceive them through our sensations when we see them, touch them, and smell them. Even when we quantify their macroscopic physical attributes with dedicated instruments such as a scale, a thermometer, or what have you, we still rely on our senses to acquire those measurements. In fact, our whole experience of the external world is entirely enclosed in our mind. We do not “know” anything out there *directly*.

What is even more unsettling is that our perceptions have been shown over and over to be fallacious. Thousands of well-known optical illusions can fool our sight, convincing us that perfectly static images are moving, that nearby objects are far away, and that two identical shapes are different. We also routinely hear sounds that are not there, we confuse tastes, and misjudge textures. We detect patterns when there are none, and we miss most of what surrounds us. And who has never witnessed the most vivid, real, and unquestionable experience, only to wake up and realize it was just a dream? Might it not be *all* a dream?⁶

Let's face it: the deeply rooted presumption that we are embedded in a material world to start with, let alone that the world is somewhat close to its appearance, may after all be nothing more than a belief. Accepting this supposition constitutes a logical leap of faith, in mathematical terms an *axiom*. It constitutes in fact the cornerstone of the philosophical theory of *materialism*.

There are, however, possible alternatives. If our entire world perception is at least mediated by the mind, perhaps it would be simpler to assume the mind as a starting point and postulate that the appearance of matter is a product of the mind. The strict logic of this argument constitutes the foundation of *idealism* and has met the favor of major philosophers throughout the centuries, from Plato to Kant and Hegel.

Yet, to many, idealism is not fully satisfying either. First, if our mind creates the world, how about the "other" fellow beings? If each of them is also creating a world on his or her own, from a behavioral point of view it seems awfully similar to ours. We agree on too many details of our surroundings to maintain that they are independent creations of distinct individual minds. Second, it may be troubling to equate the reality of concrete objects, such as a chair or a hand, to that of abstract concepts or inner feelings, such as probability and love. They all might be a product of the mind, but they surely *feel* very different.

A third alternative to materialism and idealism is to consider both matter and mind as fundamental constituents of reality. This line of thought is known as *dualism*. In Descartes's classic formulation, dualism purports matter and mind to be irreducibly distinct substances that nonetheless causally interact: physical events cause mental events, and mental events cause physical events. Although this position accounts for both the material world and mental phenomena, it does not provide a direct solution to the ultimate philosophical problem of the mind-matter relationship. Instead, it shifts the issue to the question of their *interaction*. Certain organized forms of matter, most notably nervous systems in specific dynamical states, appear to be systematically associated with feelings, thoughts, memories, and intentions. But why is this so? Logically, it is easy to imagine a material world identical to ours in all respects, with human beings and their behavior as we know it, but with no meaning and inner life.

Humankind has pondered the question of what actually "is" for as long as we have written records, and this issue is still debated.⁷ In George

Berkeley's famous words, "What is mind? No matter. What is matter? Never mind."

Will there ever be a scientific solution to this problem? All scientific theories ultimately require axioms at their foundations. With enough experimental evidence, all phenomena might eventually be precisely quantified and described within the framework of rigorous mathematics. If we capture the essence of the relevant material structures and mental phenomena in a way amenable to a satisfactory and predictive mathematical formalism, it might be that in the end the formulas describing matter and mind will be one and the same.⁸ In this case there will be a set of equations stating the correspondence between the two. By the same token, we already know that electricity *is* shifting charge, optics *is* electromagnetic waves, temperature *is* movement of molecules, and genetics *is* interaction of nucleic acids. Perhaps one day we will have a similar understanding of matter and mind.⁹

1.2 The Brain, an Organ of Many

Our bodies and lives depend on many organs: kidneys, liver, lungs, heart, blood, skin, stomach, intestine, ... and the brain. To be more precise, there are a central and a peripheral nervous system. The *central nervous system* (defined as the part of the nervous system surrounded by bones) consists of the brain and the spinal cord. There is massive empirical evidence that mental phenomena are associated with brain activity. Even emotional feelings and intuition, which common language still refers to as originating in the heart and the gut, are uncontroversially rooted in the brain. Yet the brain is far less homogeneous than all other organs. It is composed of so many discrete parts with such disparate functions that it is perhaps more useful to consider the brain as an ensemble of different suborgans. Although intimately interacting together, these components are physically and functionally distinct.

When we think of a human brain, the popular image of the wavy convolution of folds that comes to mind corresponds to the cerebral cortex or *neocortex*, the outer structure that covers almost the entirety of the brain surface. Cortex is the Latin term for "bark," evoking the external texture of the tissue overlaying woody plants (figure 1.1).



Figure 1.1
Neocortex (Daniel Segrè, 2014, Idaho).

The cerebral cortex is involved in many cognitive functions and can be coarsely divided into main geographic areas. The region at the back, called the *occipital lobe*, is associated with vision. The region at the top, called the *parietal lobe*, is associated with somatosensory perception (touch) throughout the body. The regions on the (right and left) sides, called the *temporal lobes*, are associated with hearing and imagery of objects and faces. The anterior region, called the *frontal lobe*, is associated with motor control, decision making, planning, and abstract thought. As does most of the rest of the brain and body, the cortex has a bilateral organization. The two hemispheres are connected by a thick bundle of nerves called the *corpus callosum* (Latin for “corny body”).

The cerebral cortex communicates with the rest of the nervous system through a structure that lies underneath the surface, called the *thalamus* (Greek for “chamber”). The thalamus relays signals to and from the suborgans responsible for producing and executing the information processed in the cortex, including the retina in the eye, the cochlea in the ear, and the spinal cord, which contacts muscles and skin receptors. Below the thalamus lies the *hypothalamus*, which controls the release of hormones regulating hunger, thirst, mood, and body temperature. Next to the thalamus stands the *basal ganglia* (Latin for “at the base” and Greek for “knots”), which is associated with controlling motor strength, habitual behavior, task automation, and addiction.

At the back of the brain rests the *cerebellum* (Latin for “small brain”). The cerebellum contains more nerve cells than all the rest of the brain together and is responsible for coordination of activity, fine movements, and adaptation to unexpected events. Between the brain and the spinal cord we find the *brainstem*, which is responsible for heartbeat, respiration, and circadian rhythms including sleep and dreams. Somewhat wrapped in this mass of tissue hides the *amygdala* (Greek for “almond”), a structure involved with emotional learning and fear. The *hippocampus* (Latin for “seahorse,” after its shape) has the complementary roles of consolidating and retrieving autobiographic memories and intentions with a “first-person” (egocentric) perspective as well as mapping locations and context.

The above brief overview is far from comprehensive and grossly oversimplified. There are many other suborgans in the brain, and each of these regions has a complex internal organization with functionally specialized fine substructures. Nonetheless, it should already be apparent that the

nervous system performs many more functions than any other organ. Indeed, the complex composition of the brain reflects the diversity of its functions. Yet much of the stunning brain complexity is due to its *cellular* architecture. In spite of their distinct positions, shapes, and roles, all parts of the brain share common organizational principles and are assembled out of similar building blocks. The mind-matter relationship must ultimately be explained in terms of the structure, activity, and unique properties of these cells.

1.3 Cells of the Nervous System

The brain volume is occupied by nerve cells, also called neurons, as well as by glial cells (often referred to as “glia”) and blood vessels (veins, arteries, and capillaries). Only the former two, neurons and glia, technically belong to the nervous system, as the cellular constituents of the vasculature (erythrocytes, endothelial cells, etc.) are contributed by different organs. *Glial cells* (from the Greek “glue”) play many fundamental support roles. They form a scaffold around the membrane of neurons, facilitating signal propagation. They aid messaging at the connections between neurons. They mediate the interaction with the bloodstream, filtering chemical intake, providing neurons with highly selected nutrients, and removing toxins and metabolic waste. They also destroy pathogens, remove dead neurons, and guide new neurons during development. *Neurons*, however, are the unquestionable protagonists in the representation, processing, transmission, and storage of information. This book is about *them*.

Neurons carry out their action by turning on and off. However, neurons act collectively, each playing an individual role in a gigantic symphonic orchestra. As I explain later in the book, the concerted spatial and temporal activity patterns of large collections of neurons underlie all mental states. In other words it isn't the activity of a single neuron that represents the chair, or the ground, or the book, or the hands. Instead, each mental state is represented by an ensemble activity distributed over many neurons. Such a “population code” enables a much greater repertoire of states, as well as robustness to noise. What the Greek philosopher Aristotle said in the *Politics* referring to human individuals and the value of democracy very much applies to neuronal organization: “For the many, when they meet together, may very likely be better than the few good. Hence, the many are better

judges than a single one, for some understand one part, some another, and among them they understand the whole."¹⁰

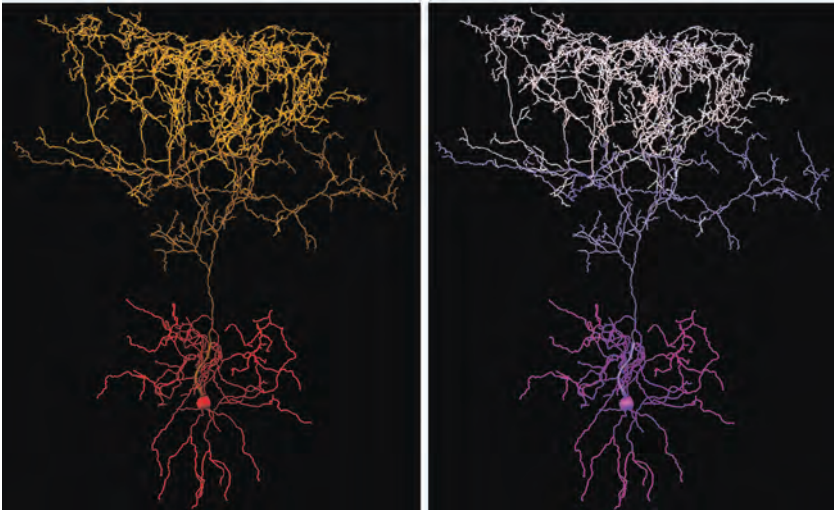
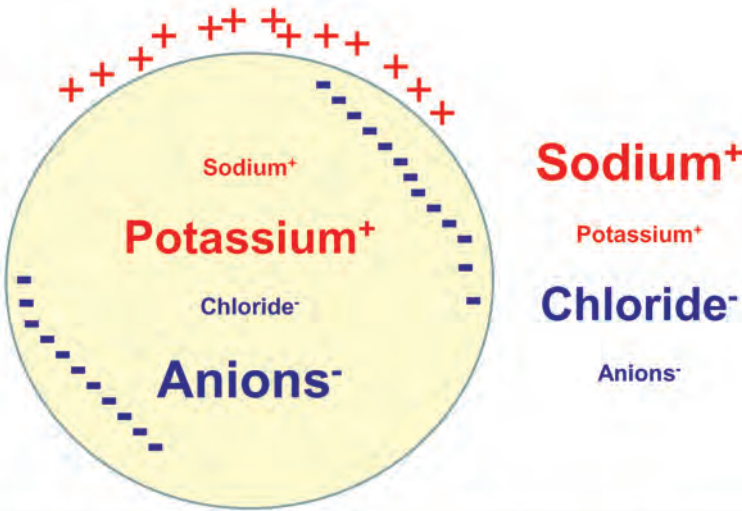
How do neurons turn on and off? Inside their membrane neurons actively maintain concentrations of certain chemicals that are different from those found outside, in the extracellular space. This inequality is often referred to as a *gradient*. Specifically, there are more sodium and chloride ions (the components of common sea salt) outside of neurons than inside. The term *ion* refers to particles that carry an electric charge: sodium is charged positively, and chloride is charged negatively. Moreover, there are more (positive) potassium ions and various types of other (negative) ions inside of neurons than outside (figure 1.2). The balance works out such that, in their typical state, neurons are negatively charged inside their membranes relative to the extracellular space. Thus, there are both a *concentration gradient* for certain ions across the membrane and an *electric gradient* due to a charge imbalance.

When a neuron turns on, its electrochemical gradient gets temporarily shorted and quickly restored, similar to the momentary flicker of a light

Figure 1.2

Concentrations and electric gradients. (Top) When a neuron is “resting” in its typical state, chemicals are not distributed evenly across the two sides of its cellular membrane. Sodium (positively charged) and chloride ions (negatively charged), the components of common sea salt, are much less concentrated inside than outside, indicated in the figure by the relative font sizes. In contrast, potassium (positively charged) and other negatively charged substances (anions) are more concentrated inside than outside. As a consequence of this uneven distribution, called a *concentration gradient*, the inside of the membrane is negatively charged relative to the outside (indicated by the minus and plus signs), an imbalance termed *electric gradient*. (Bottom) Graphic rendering of a neuronal electric pulse. These two images represent an interneuron from the outer granular layer of the rat olfactory bulb.¹¹ The cell body (the “center” of the neuron) is the very small spherical shape close to the base of the tree-like structure. In this neuron type the arbor around the cell body receives and processes the inputs from other neurons. The arbor rising to the top carries the output signals to other neurons. On the left the input tree and cell body are colored in shades of red, and the output tree is in a gradient of brown (rendering by Uzma Javed in the author’s lab). On the right the colors are changed (by the author) to illustrate the temporary voiding of electric gradients caused by sodium influx during rapid neuronal activation. This reconstruction is freely available online at NeuroMorpho.org (branch thickness was increased to enhance contrast).

bulb or computer monitor. In particular, in very rapid sequence, sodium first flows in, voiding the electric gradient as well as its own concentration gradient. Next, potassium flows out, restoring the electric gradient but voiding its concentration gradient. Last, a molecular exchange machinery pumps sodium out and potassium in, restoring the chemical gradient. This series of events lasts only a couple of milliseconds (thousandths of a second) back to back.



Neurons are able to use this rapid electric pulse to communicate with each other. Specifically, they exchange information by means of elaborate trees that can extend across the entire brain! We introduce these very special arbors in the next chapter. Then, in chapter 3, we reveal several additional aspects of the mechanisms of neuronal activation and of information processing, transmission, and storage. In later chapters we also explore the diversity of neurons in different animal species, during development and aging, across brain regions, and in relation to their functional specializations. First, however, we turn our attention to consciousness itself.

1.4 The Conscious Mind

The nervous system performs many vital functions, including control of respiration, heartbeat, blood pressure, hormonal release, digestion, the sleep-wake cycle, and reflexes. From the survival point of view, consciousness does not even make the top-ten list! Indeed, from the perspective of scientific materialism, there is no need for consciousness at all. We could logically imagine a world of human beings with their brains, bodies, and behaviors, even conversations, but absolutely no inner experience.¹² Yet we do have inner experience, and in fact it is precisely that inner experience that makes our lives meaningful and interesting. Of course we *need* the brain to keep us alive, but we *care* about our memories, emotions, intentions, plans, feelings, thoughts, and reasons. These mental states have proved to be more difficult to characterize and quantify objectively than the physical properties of a chair or a book. However, we immediately *know* our mental states more intimately and directly than any physical object out there. By this measure, mental states are certainly observable: they are the most common observations of all!

If we want science to explain and predict as many observables and observations as possible, then we need to characterize the relationship between the brain and the conscious mind.¹³ We cannot simply accept the adage that the “conscious mind is what the brain does” because the brain does many things that are not mind. And we cannot revert to the purely phenomenological view of the conscious mind as “what it is like to be” because there is no part of the brain in it, which makes any scientific breakthrough about the underlying mechanisms unlikely. Instead, we propose a definition to bridge these two aspects:

The conscious mind is what the types of brain activity that feel like something feel like.

Admittedly, such a mouthful is not easy to parse. Let's take a little time to understand what it means.

We start from our feelings as the "given" observable aspects of mental states, in the sense that they can be observed by ourselves. We note that these feelings constitute a quintessential aspect of brain activity—but not all or any brain activity. Only some types of brain activity are linked to feelings. Then we consider those specific types of brain activity (the ones linked to feelings), and we ask what they feel like. Thus, we can equate the conscious mind to what the relevant types of brain activity feel like. To aid logical parsing, the same definition can be broken by parenthetical separations:

The conscious mind is what {the types of brain activity [that feel like something]} feel like.

By bringing together corresponding brain and mental states, this definition may prove to be useful for exploring their relationship.

An interesting property of mental states is their duration. Different percepts, thoughts, and emotions can last for varying spans of time, from a fleeting visual flash to an extended meditative contemplation. The extent of an uninterrupted mental state might depend only on our ability to concentrate and the stability of the surrounding environment. We cannot apparently experience, however, arbitrarily short mental states. There seems to be a minimum duration requirement of approximately 50 milliseconds for any inner content to be consciously accessible. This means that we can at most experience some twenty or so different mental states per wake second of life. The average life expectancy in the industrialized world amounts to approximately 34 billion moments of consciousness per human being.

Shorter events can still affect our behavior, but only subliminally. This minimal "time unit" of the conscious mind varies slightly by individual and by modality (auditory vs. visual inputs, motor commands vs. tactile sensation, etc.) and is also affected by fatigue and distractors. Subliminal suggestions have been used in a variety of applications from advertising tactics to self-help techniques for confidence boosting. For example, a single frame depicting a particular brand of soda inserted in a webcasted sports event might increase your craving for that beverage during and after the

game. However, you would remain completely oblivious to the fact that the suggestion was implanted in your mind. Such a trick might be considered deceptive and morally objectionable, and subliminal advertising is banned in several countries such as Great Britain and Australia, but not in the United States.

A fundamental aspect of the conscious mind is the balance between stability and plasticity. To immediately experiment with mental stability, try this simple exercise. Focus for a few seconds on the first letter of this page, until you gain a firm sense of the mental state. Then put the book down and take a little break. Walk a few steps, clap your hands, think about yesterday, and tomorrow. Then, after experiencing those other mental states, pick the book back and focus again on that same first letter of this page. Most likely, it will *feel* very similar to the first time around. You might think that's because the *letter* didn't change. Its shape, position, color, and other properties remained the same; isn't that a good enough reason for our conscious experience of it to do the same? The short answer is "*No!*"

On the one hand, a stable physical signal does not imply unchanging conscious experience. Let's say that when opening the newspaper you notice a photograph of a candidate for the local election who looks familiar. You stop and stare at the image for several seconds, and suddenly it dawns on you that the politician featured in the paper is actually a former grade school classmate of yours. The face in the picture didn't change any more than the first letter on this page, yet your mental state transitioned sharply from a "tip-of-the-tongue" experience to the firm conviction of a childhood memory. On the other hand, a steady stimulus is not required for ensuring the robustness of a percept.

Let's say tonight, just before falling asleep, you resolve to be more patient with your colleagues at work. You sleep an uninterrupted night, alternating several times completely mindless black-ins with vivid dreams (only the last one of which you might remember when you wake up). In the morning you get out of bed and go about your routine. Chances are, you still have the intention in mind to keep your cool with the co-workers. Whether you succeed or lose your temper later that day, the mental state of the intent remained stable since the previous day in spite of a restfully resetting sleep cycle. Yet there's nothing physical or objective in your resolve, you didn't tell anyone, and there's no unchanging letter in the corner of the page to ground your mental state.

A seemingly contrasting aspect of the conscious mind is that it also continuously changes. As we go about our lives, we experience events and mental states, and those experiences alter what and how we'll perceive later. In the previous example, before resolving to be patient with your colleagues, that mental state was not part of your inner life. Having had the thought modified your feelings the next day. The ability of our brains to change thought patterns is called "plasticity." Although our mind does adapt to the environment, it is not necessary for an external event to occur to trigger the plasticity of the self. Sometimes a single occurrence of a particular mental state can dramatically and irreversibly change the rest of our existence.

Obviously not *all* mental states have the same power to alter our minds. Most of our experiences are fleeting and leave little if any trace. Indeed, it would be disastrous if we could remember every single mental state we have ever experienced!¹⁴ What determines the strength by which the mind is affected by different mental states? We seem to have an uncanny ability to select the knowledge we acquire by how useful or *predictive* it is. If a bus stops at the corner while a kid calls his dog, we might associate the bus number with the location of the stop and the dog with its name and owner. Somehow we are less likely to associate the name of the dog with the bus number or the kid's face with the location of the bus stop. Why is that?

More generally, why do certain experiences make sense and others don't? It seems clear that background knowledge plays an essential role here. Experienced piano players can read music scores and later even remember the tune in their minds without having heard or played the piece. People who never played piano can look at the same music score, see the same notes in the same position, but they will not "hear" the tune, nor will they remember it the next day.

If we can explain these observations in terms of neuronal mechanisms, we will begin to solve the mind-brain problem.

Notes

Preface

1. To begin with, a basic introduction to the brain and its cellular organization is provided gratis by “Brain Facts” published by the Society for Neuroscience (<http://brainfacts.org>). That entire book can be freely downloaded as a pdf or as an audio file. Alternatively, individual topics can be searched and browsed online. Other useful online resources including reviews of many neuroscience books can be found at <http://faculty.washington.edu/chudler/neurok.html>

Chapter 1

1. Rosenberg AJ (1993) *The Book of Genesis—A New English Translation*, Vol. 1. Judaica Press. Accessed at http://www.chabad.org/library/bible_cdo/aid/8166.

2. Rosenberg AJ (1993) *The Book of Genesis—A New English Translation*, Vol. 1. Judaica Press. Accessed at http://www.chabad.org/library/bible_cdo/aid/8167/jewish/Chapter-3.htm.

3. <http://lhc.web.cern.ch/lhc>.

4. ATLAS Consortium (2012) A particle consistent with the Higgs boson observed with the ATLAS detector at the Large Hadron Collider. *Science* 338(6114):1576–82.

5. <http://wlcg.web.cern.ch>.

6. ... or in a simulation? The “simulation hypothesis” argues that if one believes that sooner or later consciousness will be simulated in machines, the chance that *we* are not living in one such computational model is very small (<http://www.simulation-argument.com>). Versions of this idea date back to ancient philosophy and have been proposed in many recent sci-fi books and movies. Nick Bostrom, who formally introduced this position to the modern scholarly discourse, recently published a comprehensive book: Bostrom N (2014) *Superintelligence—Paths, Dangers, Strategies*. Oxford: Oxford University Press.

7. For an accessible introduction to this topic, see Chalmers DJ (1995) The puzzle of conscious experience. *Sci Am.* 273:80–86.
8. A bold attempt in this direction is found in Tononi G (2012) *Phi: A Voyage from the Brain to the Soul*. New York: Pantheon.
9. Ascoli GA (2013) The mind-brain relationship as a mathematical problem. *ISRN Neuroscience*. 2013:1–13. <http://dx.doi.org/10.1155/2013/261364>
10. Aristotle (350 B.C.E) *Politics*. Translated by Benjamin Jowett. From The Internet Classics Archive by Daniel C. Stevenson, Web Atomics. <http://classics.mit.edu/Aristotle/politics.mb.txt>
11. Eyre MD, Antal M, Nusser Z (2008) Distinct deep short-axon cell subtypes of the main olfactory bulb provide novel intrabulbar and extrabulbar GABAergic connections. *J Neurosci.* 28(33):8217–29.
12. These hypothetical beings are referred to in modern philosophy as *zombies*; see, e.g., Kirk R (2011) *Zombies*. In Zalta EN (ed). *Stanford Encyclopedia of Philosophy* (Spring 2011 Edition). www.plato.stanford.edu/archives/spr2011/entries/zombies.
13. See also Ascoli GA, Grafman J, eds (2005) *Consciousness, Mind and Brain*. Milan: Massom Publisher.
14. Such a capability, initially documented in a single subject known by the initials AJ, has since been extended to several similar cases: McGaugh JL, LePort A (2014) Remembrance of all things past. *Sci Am.* 310(2):40–45. www.scientificamerican.com/article/the-discovery-of-super-memories.

Chapter 2

1. Parents of teenage boys might sometime suspect otherwise.
2. Helmstaedter M, Sakmann B, Feldmeyer D (2009) The relation between dendritic geometry, electrical excitability, and axonal projections of L2/3 interneurons in rat barrel cortex. *Cereb Cortex.* 19(4):938–50.
3. Nikolenko V, Poskanzer KE, Yuste R (2007) Two-photon photostimulation and imaging of neural circuits. *Nat Methods.* 4(11):943–50.
4. Goldberg JH, Tamas G, Aronov D, Yuste R (2003) Calcium microdomains in aspiny dendrites. *Neuron.* 40(4):807–21.
5. Barnard ES (2002) *New York City Trees: A Field Guide for the Metropolitan Area*. New York: Columbia University Press.
6. To help your imagination, see centralparknature.com for an actual map of most of Central Park trees!

7. According to an estimate of the Wisconsin County Forests Association, “a mature, healthy tree can have 200,000 leaves.”

8. See also Ascoli GA, ed (2002) *Computational Neuroanatomy: Principles and Methods*. Totowa, NJ: Humana Press.

9. The Georgia Forestry Commission reports the following mature dimensions for representative medium-size trees: live oak (*Quercus virginiana*), 40–50 feet high and 3–4 feet in diameter; pin oak (*Quercus palustris*), 70–80 feet high and 2–3 feet in diameter; eastern red cedar (*Juniperus virginiana*), 50–80 feet high and 1–1.5 feet in diameter; southern red oak (*Quercus falcate*), 70–80 feet high and 2–3 feet in diameter; and water oak (*Quercus nigra*), 60–100 feet high and 2–3 feet in diameter.

10. Today there are approximately 100,000 known species of trees that exist throughout the world, according to World Resources Institute. The number of neuron types is still an open question (see also section 8.4), but if I have to venture a guess, I would use that same figure as an order of magnitude.

11. Some synapses are established from axons directly onto the soma, others from axons onto other axons, and still others from dendrites onto dendrites. The vast majority of synapses, however, are from axons onto dendrites.

12. Brown K, Sugihara I, Shinoda Y, Ascoli GA (2012) Digital morphometry of rat cerebellar climbing fibers reveals distinct branch and bouton types. *J Neurosci*. 32:14670–84.

13. A small proportion of synapses, usually dendrodendritic, are in fact electric, called *gap junctions*.

14. For a beautifully written journey on this topic, see Alkon DL (1992) *Memory's Voice: Deciphering the Brain-Mind Code*. New York: Harper Collins.

15. To be precise, the most recent scholarly estimate is 89 billion: see Herculano-Houzel S (2009) The human brain in numbers: A linearly scaled-up primate brain. *Front Human Neurosci*. 3:31.

16. Technically, even with a standard resolution of 600 dots per inch (dpi), a printer could fill 12,600,000 locations on a 5-inch by 7-inch image such as figure 2.5 (35×6002). At maximum contrast (50% fill, that is alternating black and white), as many as 6,300,000 dots could then be printed, thirty-five times as many as those actually present in figure 2.5. However, they would be invisible to the naked eye even by very close inspection.

17. According to their website, the 2014 collection of the Library of Congress included more than 36.8 million cataloged books and other print materials in 470 languages. <http://www.loc.gov/about/general-information/>.

18. Google estimated in 2010 (as part of their “Google Books” project) that nearly 130 million distinct books can be uniquely identified. <http://booksearch.blogspot.com/2010/08/books-of-world-stand-up-and-be-counted.html>.

19. In 2008 NPR reported that data from NASA satellites suggested some 400 billion trees on earth (~60 per person). I suspect the number of trees may have declined since then (while the number of people definitely increased).

Chapter 3

1. These channels are called *voltage-gated*. The voltage, named after Alessandro Volta, the inventor of the battery, is the difference in electric potential per unit charge between two points, that is, electric tension.

2. This transition region is also known as *axonal hillock*.

3. In neurons, this is called the *refractory period*.

4. These values should not be construed to support the urban myth that we use less than 10% of our brain. The vast majority of neurons fire *eventually*, they just don't fire all together.

5. Due to the exact same mechanism, at branch points in the axonal tree, outgoing spikes “double-up” and continue down both sides of the bifurcation, each identical to the “parent” spike.

6. A comparison between brains and computers is beyond the scope of this book and indeed is the topic of several other books. A web search of “compare brain computer” pulls some 80 million records, the first several hundreds of which appear to contain relevant and useful discussions. For a brief and referenced scholarly discussion, see Nagarajan N, Stevens CF (2008) How does the speed of thought compare for brains and digital computers? *Curr Biol.* 18:R756–58.

7. The information content reflected in the overall spike frequency is called *rate code*, whereas the distinction related to the exact timing of spikes within a pattern is called *time code*.

8. Quilichini P, Sirota A, Buzsáki G (2010) Intrinsic circuit organization and theta-gamma oscillation dynamics in the entorhinal cortex of the rat. *J Neurosci.* 30(33): 11128–42.

9. Tukker JJ, Lasztóczy B, Katona L, Roberts JD, Pissadaki EK, Dalezios Y, Márton L, Zhang L, Klausberger T, Somogyi P (2013) Distinct dendritic arborization and in vivo firing patterns of parvalbumin-expressing basket cells in the hippocampal area CA3. *J Neurosci.* 33(16):6809–25.

10. Packer AM, Yuste R (2011) Dense, unspecific connectivity of neocortical parvalbumin-positive interneurons: A canonical microcircuit for inhibition? *J Neurosci.* 31(37):13260–71.
11. These channels are called *ligand-gated*. The ligand (Latin for “to be bound”) is the molecule that binds to the channels, that is, the neurotransmitter.
12. The term GABA is capitalized because it is an acronym, standing for “gamma-aminobutanoic acid.”
13. Because the excess negative charge inside exerts a repulsive action on chloride, the effect of GABA is not symmetric and opposite to that of glutamate but, rather, typically slower and in some cases weaker.
14. Sulkowski MJ, Iyer SC, Kurosawa MS, Iyer EP, Cox DN (2011) Turtle functions downstream of Cut in differentially regulating class specific dendrite morphogenesis in *Drosophila*. *PLoS One.* 6(7):e22611.
15. Ropireddy D, Scorcioni R, Lasher B, Buzsáki G, Ascoli GA (2011) Axonal morphometry of hippocampal pyramidal neurons semi-automatically reconstructed after in vivo labeling in different CA3 locations. *Brain Struct Funct.* 216(1):1–15.
16. For a recent scholarly review, see Silver RA (2010) Neuronal arithmetic. *Nat Rev Neurosci.* 11(7):474–89.
17. Ferrante M, Migliore M, Ascoli GA (2013) Functional impact of dendritic branch-point morphology. *J Neurosci.* 33(5):2156–65.
18. Hebb DO (1949) *The Organization of Behavior: A Neuropsychological Theory*. New York: Wiley.
19. For a scholarly review of this classic view, see Tsien JZ (2000) Linking Hebb’s coincidence-detection to memory formation. *Curr Opin Neurobiol.* 10:266–73.
20. This is obviously a much oversimplified cartoon. For an in-depth scholarly discussion, see Wasserman EA, Miller RR (1997) What’s elementary about associative learning? *Annu Rev Psychol.* 48:573–607.
21. Kawaguchi Y, Karube F, Kubota Y (2006) Dendritic branch typing and spine expression patterns in cortical nonpyramidal cells. *Cereb Cortex.* 16(5):696–711.
22. The timberline is the mountain altitude above which trees are no longer found for lack of oxygen and freezing temperature. On the Alps, the timberline is at approximately 6000 feet above sea level.
23. The axons of only a few principal neurons of the mammalian cerebral cortex have been traced in a sufficiently extended fashion to be considered at least putatively representative of a complete axonal arbor. For those, the full length typically ranges between 0.5 meter and 1 meter. The whole dendritic arborization for those

same neurons typically sums up to 10–20 millimeters in total length, that is, less than 2% relative to the axon. Glial cells are believed to be about as abundant as neurons, but their branching is no more complex than that of dendrites. Veins, capillaries, and arteries, comparatively speaking, contribute a negligible length.

24. One hundred billion neurons times ~0.8 meters of estimated axonal length per neuron.

25. The US Central Intelligence Agency (CIA) posts the World country ranking by road network size (https://www.cia.gov/library/publications/the-world-factbook/rankorder/rawdata_2085.txt). In 2014 the top three were (total length in miles): United States 4,092,842; India 2,914,212; and China 2,551,660.

26. Specifically, the average diameter of an axonal branch is approximately one-thirtieth of a micrometer. The entire volume of all axonal branches in a brain can be estimated, approximating the cable to a cylinder, as just about one quart, which is about 60% of the whole brain size.

Chapter 4

1. See also Ikegaya Y, Aaron G, Cossart R, Aronov D, Lampl I, Ferster D, Yuste R (2004) Synfire chains and cortical songs: Temporal modules of cortical activity. *Science*. 304(5670):559–64.

2. For a lay overview, see Quiroga RQ, Fried I, Koch C (2013) Brain cells for grandmother. *Sci Am*. 308(2):30–35. For a comprehensive review, see Quiroga RQ (2012) Concept cells: The building blocks of declarative memory functions. *Nat Rev Neurosci*. 13(8):587–97.

3. Henze DA, Cameron WE, Barrionuevo G (1996) Dendritic morphology and its effects on the amplitude and rise-time of synaptic signals in hippocampal CA3 pyramidal cells. *J Comp Neurol*. 369(3):331–44.

4. Scorcioni R, Ascoli GA (2005) Algorithmic reconstruction of complete axonal arborizations in rat hippocampal neurons. *Neurocomputing*. 65–66:15–22.

5. Carnevale NT, Tsai KY, Claiborne BJ, Brown TH (1997) Comparative electrotonic analysis of three classes of rat hippocampal neurons. *J Neurophysiol*. 78(2):703–20.

6. In laboratory rodents it is possible to measure the spiking activity of hippocampal neurons while the animal roams around the cage or a maze. Researchers typically find distinct place cells that fire next to the entrance of the cage, near the water spout, or in the far corner. When the firing patterns are recorded from a sufficiently large number of neurons, each location is systematically found to be represented by multiple cells (see nobelprize.org/nobel_prizes/medicine/laureates/2014/advanced-medicineprize2014.pdf).

7. The first contribution was the synaptic plasticity rule described in section 3.3.
8. This requirement may not apply to the great deal of brain activity that is not consciously accessible.
9. This corollary does not refer to physically impossible mental states such as seeing a color outside of the visible range or moving one's muscles at the speed of light. I am also not pointing to the fact that the vast majority of all the knowledge that human beings are in principle capable of apprehending has yet to be discovered.
10. Even non-violin players can arguably "imagine" *playing*, but here we refer to the inability to imagine the actual *feelings* experienced by violin players.
11. See <http://connectomethebook.com/>.
12. See <http://neuroscienceblueprint.nih.gov/connectome/>.
13. A clear demonstration is provided by the ever-improving functionality of brain-controlled robotic arms, for example, see Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, Haddadin S, Liu J, Cash SS, van der Smagt P, Donoghue JP (2012) Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature*. 485(7398):372–75.
14. Vetter P, Roth A, Häusser M (2001) Propagation of action potentials in dendrites depends on dendritic morphology. *J Neurophysiol*. 85(2):926–37.
15. In the scientific discourse, these observables are sometime called *epiphenomena* (singular: epiphenomenon).
16. Buzsaki G. (2006) *Rhythms of the Brain*. Oxford: Oxford University Press.
17. This argument supports the notion that mental states depend on information processing, a notion embraced most notably by Giulio Tononi in his "Information Integration Theory" of consciousness (see also note 8 in chapter 1). Information is measured in "bits," binary units that are typically expressed as either 0 or 1 (or true/false, on/off, etc.). For an accessible explanation, see Carl Zimmer's September 20, 2010 New York Times article "Sizing up Consciousness by Its Bits" (<http://www.nytimes.com/2010/09/21/science/21consciousness.html>) and references therein.
18. Trevelyan AJ, Sussillo D, Watson BO, Yuste R (2006) Modular propagation of epileptiform activity: Evidence for an inhibitory veto in neocortex. *J Neurosci*. 26(48):12447–55.
19. Chiang PH, Wu PY, Kuo TW, Liu YC, Chan CF, Chien TC, Cheng JK, Huang YY, Chiu CD, Lien CC (2012) GABA is depolarizing in hippocampal dentate granule cells of the adolescent and adult rats. *J Neurosci*. 32(1):62–67.

Chapter 5

1. Tononi G, Cirelli C (2013) Perchance to prune. During sleep, the brain weakens the connections among nerve cells, apparently conserving energy and, paradoxically, aiding memory. *Sci Am.* 309(2):34–39. A video of a scientific seminar by the same author can be found at <http://www.scientificamerican.com/article/sleep-brains-way-staying-balance-video-giulio-tononi>. For a more in-depth scholarly review, see Tononi G, Cirelli C (2014) Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron.* 81(1):12–34. There are many other theories aiming to explain the phenomenon of memory consolidation during sleep. However, this fascinating but still hotly debated topic is outside the scope of this book.
2. Edelman G (1987) *Neural Darwinism: The Theory of Neuronal Group Selection*. New York: Basic Books.
3. For an image of the dendritic arbors of these neurons, turn a few pages to figure 7.2.
4. Babies born blind in one eye, or losing an eye early in life grow up without ocular dominance stripes in the cortex: the “good” eye rapidly takes over all of available connections in the visual cortex. In contrast, adult-onset monocular deprivation leaves the ocular dominance stripes in the cortex largely intact for several years post-lesion.
5. See, for example, <http://www.ncbi.nlm.nih.gov/books/NBK11007> or the original report: Johnson JS, Newport EL (1989) Critical period effects in second language learning: The influence of maturational state on the acquisition of English as a second language. *Cogn Psychol.* 21(1):60–99.
6. For example, finding out that your spouse has had an affair or accepting “impossible” mathematical entities such as the square root of negative numbers.
7. Budd JM, Kovács K, Ferecskó AS, Buzás P, Eysel UT, Kisvárdy ZF (2010) Neocortical axon arbors trade-off material and conduction delay conservation. *PLoS Comput Biol.* 6(3):e1000711.
8. For scholarly reviews in human and animal models, see respectively: May A (2011) Experience-dependent structural plasticity in the adult human brain. *Trends Cogn Sci.* 15(10):475–82; and Caroni P, Donato F, Muller D (2012) Structural plasticity upon learning: Regulation and functions. *Nat Rev Neurosci.* 13(7):478–90.
9. The capability of experiencing a mental state, that is, knowledge, should not be confused with the capability of learning. The capability of learning does *depend* on preexisting knowledge, as explained in the next chapter.

10. Holtmaat A, Svoboda K (2009) Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat Rev Neurosci.* 10(9):647–58.
11. Rihn LL, Claiborne BJ (1990) Dendritic growth and regression in rat dentate granule cells during late postnatal development. *Brain Res Dev Brain Res.* 54(1): 115–24.
12. Tamamaki N, Nojyo Y. (1991) Crossing fiber arrays in the rat hippocampus as demonstrated by three-dimensional reconstruction. *J Comp Neurol.* 303(3):435–42.
13. Golding NL, Kath WL, Spruston N (2001) Dichotomy of action-potential backpropagation in CA1 pyramidal neuron dendrites. *J Neurophysiol.* 86(6):2998–3010.
14. This is sometimes referred to as working memory or short-term memory. By learning, in contrast, here we refer to long-term memory storage, that is, the ability to reinstate a specific mental state at a future time well beyond the current temporal span of attention.
15. There are rare known cases of people possessing highly superior autobiographical memory. They may be considered the closest living embodiment of the hypothetical scenario of “learning everything.” This condition, technically named “hyperthymestic syndrome,” was recently described in both the biomedical literature and television programs for the lay public (see note 14 in chapter 1).

Chapter 6

1. This requirement was in fact explicitly stated by Hebb in his original formulation of synaptic plasticity (see section 3.3 for the complete quote and reference): “When an axon of cell A is *near enough* to excite B and repeatedly or persistently takes part in firing it...” (emphasis ours). The direction of the stimulation implies that the axon belongs to neuron A and the dendrite to neuron B.
2. Stepanyants A, Chklovskii DB (2005) Neurogeometry and potential synaptic connectivity. *Trends Neurosci.* 28(7):387–94.
3. Botanical trees, like all biological entities, are part of a complex interaction network of the ecosystem and do in fact communicate directly with chemicals and indirectly through other agents (e.g., insects). Here our assertion is more specific to the notion of structural networks and information-processing devices. Nevertheless, even this narrower position might be challenged by novel anthropological ideas; see Kohn E (2013) *How Forests Think: Toward an Anthropology Beyond the Human.* Berkeley/Oakland: University of California Press.
4. Measurements in a few cortical regions of the rodent brain found actual synapses in only a minority of axonal-dendritic overlaps, ranging from 25% to less than 10%.

We expect this fraction to vary widely across regions of the nervous system and possibly also among species and developmental stages. Nevertheless, the value of 10% is likely to represent an excellent approximation for at least some important parts of the brain. At any rate, our reasoning is not affected by this specific numerical detail.

5. This average estimate assumes that all neurons are similar and the brain is homogeneous. Subsequent chapters argue that this is emphatically *not* the case, but the simple computations in this paragraph are still valid at the level of order of magnitude (within a tenfold factor).

6. The combined chance of a dendrite of a random neuron C to overlap with the axon from neuron A *and* of the axon of the same neuron C to overlap with a dendrite of neuron B is one in a trillion. Thus, the probability that any one neuron C would *not* indirectly connect A and B by axonal-dendritic overlap is 0.999999999999 (zero followed by twelve 9's). However, the chance that neither of two random neurons (C and D) would bridge A and B is $0.999999999999 \times 0.999999999999$. Because there are 100 billion neurons to try, the chance that A and B fail to encounter via one stop is 0.999999999999 multiplied by itself 100 billion times. The result of this operation is approximately 90%. This means that one in ten pairs of neurons may have a "once-removed" axonal-dendritic overlap.

7. This observation is also corroborated by recent experimental evidence: Sadtler PT, Quick KM, Golub MD, Chase SM, Ryu SI, Tyler-Kabara EC, Yu BM, Batista AP (2014) Neural constraints on learning. *Nature*. 512(7515):423-6.

8. As explained in section 6.4, continuous stimulation can induce formation of new axonal-dendritic overlaps by lengthening their respective branches.

9. Specifically, the principle states that the probability of an axon A_1 overlapping with a dendrite D_1 depends on the number of other dendrites $D_2 \dots D_n$ receiving connections from A_1 and on the number of other axons $A_2, \dots A_m$ that make synapses onto $D_1, \dots D_m$.

10. Shepherd GM, Svoboda K (2005) Laminar and columnar organization of ascending excitatory projections to layer 2/3 pyramidal neurons in rat barrel cortex. *J Neurosci*. 25(24):5670–79.

11. The orders of magnitude for the size of a thin axonal branch, an ionic channel, and an ion are respectively tens of nanometers, nanometers, and tenths of nanometers (10^{-8} , 10^{-9} , and 10^{-10} meters), respectively. See also <http://bionumbers.hms.harvard.edu>.

12. Sebastian Seung (see note 11 in chapter 4) similarly distinguishes the "4 R" mechanisms to alter neural circuits: (1) Reweighting or change of synaptic strength; (2) Reconnection or creation/elimination of synapses; (3) Rewiring or movement of neural branches; and (4) Regeneration or death/birth of neurons.

13. This assumption is consistent with the principle of “population coding,” which we discuss more directly in section 8.4.

Chapter 7

1. This is never the case even for identical twins because they have separate embryonic development and their neuronal differentiations involve independent stochastic molecular processes. More details about the developmental process are explained in the next section.

2. Noninvasive imaging (“brain scans”) can visualize the coarse structure of the human nervous system but lacks the resolution required to detect fine structures such as dendrites and axons. In order to visualize these branching structures, a dye needs to be inserted in the cell body of an individual neuron. Sufficient time must then elapse for the dye to reach all parts of the arbor. In the case of extensive axons the necessary time for the dye to fill the entire structure can be several weeks. During such a long period, tissue degeneration blocks the movement of the dye. The specific technical reasons are somewhat more subtle than described here, but the fact remains that the full axonal extent of human brains cannot be visualized with current technology. See also section 9.3 for additional discussion.

3. Apes (especially chimpanzees and bonobos) are even closer to humans, but they are just too close for modern society to accept the ethical burden of carrying out invasive research on them. Recently research on monkeys has also seen a drastic reduction for similar considerations.

4. Harris TW, Antoshechkin I, Bieri T, Blasiar D, Chan J, Chen WJ, De La Cruz N, Davis P, Duesbury M, Fang R, Fernandes J, Han M, Kishore R, Lee R, Müller HM, Nakamura C, Ozersky P, Petcherski A, Rangarajan A, Rogers A, Schindelman G, Schwarz EM, Tuli MA, Van Auken K, Wang D, Wang X, Williams G, Yook K, Durbin R, Stein LD, Spieth J, Sternberg PW (2010) WormBase: A comprehensive resource for nematode research. *Nucleic Acids Res.* 38(Database issue):D463–67.

5. Jacobs B, Lubs J, Hannan M, Anderson K, Butti C, Sherwood CC, Hof PR, Manger PR (2011) Neuronal morphology in the African elephant (*Loxodonta africana*) neocortex. *Brain Struct Funct.* 215(3–4):273–98.

6. Kubota Y, Shigematsu N, Karube F, Sekigawa A, Kato S, Yamaguchi N, Hirai Y, Morishima M, Kawaguchi Y (2011) Selective coexpression of multiple chemical markers defines discrete populations of neocortical GABAergic neurons. *Cereb Cortex.* 21(8):1803–17.

7. Oginsky MF, Rodgers EW, Clark MC, Simmons R, Krenz WD, Baro DJ (2010) D(2) receptors receive paracrine neurotransmission and are consistently targeted to a subset of synaptic structures in an identified neuron of the crustacean stomatogastric nervous system. *J Comp Neurol.* 518(3):255–76.

8. Rodger J, Drummond ES, Hellström M, Robertson D, Harvey AR (2012) Long-term gene therapy causes transgene-specific changes in the morphology of regenerating retinal ganglion cells. *PLoS One*. 7(2):e31061.

9. The most direct approach for measuring the electric activity of neurons is to insert microelectrodes into the nervous system to record voltage. Nevertheless, advanced molecular techniques have also been developed to visually detect electric changes by optical microscopy utilizing dyes that transiently change color as a result of neuronal firing (see section 9.3).

10. Most individuals in this species are hermaphrodites. In the small minority of males, the number of neurons is 383.

11. In truth, the exact extent of such “stereotypy” is not yet completely known because not enough specimens have been investigated down to every last neuron. The entire nervous system of only one (male) worm has been mapped neuron by neuron, and those of two more animals have been mapped partially. Stereotypy has been (incompletely) determined by looking at individual neurons in several dozen animals.

12. For a free scholarly overview, see Stiles J, Jernigan TL (2010) The basics of brain development. *Neuropsychol Rev*. 20(4):327–48. Available at ncbi.nlm.nih.gov/pmc/articles/PMC2989000.

13. This average retraction is only relative to overall brain size. In absolute terms, dendrites and especially axons tend to expand together with the head, skull, and brain, thus yielding a net elongation of the cable. Brain size quadruples in the first five years of the baby’s life, but the adult brain volume is only 10% larger than that matured by age six. The number of axonal-dendritic overlaps, however, depends on the spatial density of the trees rather than their absolute length. The brain volume grows with the third power of the radius, causing a steep reduction of axonal and dendritic densities.

14. For example, although neuronal generation and migration have already largely ended at birth, the proliferation, differentiation, and positioning of glial cells and of their progenitors mostly occur in infancy and through childhood. Glia could therefore be responsible for neuronal plasticity during this period.

15. See www.translatingtime.net.

16. See also Greenwood PM, Parasuraman R (2012) *Nurturing the Older Brain and Mind*. Cambridge, MA: MIT Press.

17. Scorza CA, Araujo BH, Leite LA, Torres LB, Otalora LF, Oliveira MS, Garrido-Sanabria ER, Cavalheiro EA (2011) Morphological and electrophysiological properties of pyramidal-like neurons in the stratum oriens of Cornu ammonis 1 and Cornu ammonis 2 area of *Proechimys*. *Neuroscience*. 177:252–68.

18. Pyapali GK, Turner DA (1996) Increased dendritic extent in hippocampal CA1 neurons from aged F344 rats. *Neurobiol Aging*. 17(4):601–11.
19. Wang X, Kim JH, Bazzi M, Robinson S, Collins CA, Ye B (2013) Bimodal control of dendritic and axonal growth by the dual leucine zipper kinase pathway. *PLoS Biol*. 11(6):e1001572.
20. Borst A, Haag J (1996) The intrinsic electrophysiological characteristics of fly lobula plate tangential cells: I. Passive membrane properties. *J Comput Neurosci*. 3(4):313–36.
21. Li Y, Brewer D, Burke RE, Ascoli GA (2005) Developmental changes in spinal motoneuron dendrites in neonatal mice. *J Comp Neurol*. 483:304–17.
22. Lu J, Tapia JC, White OL, Lichtman JW (2009) The interscutularis muscle connectome. *PLoS Biol*. 7(2):e32.
23. Wu H, Williams J, Nathans J (2012) Morphologic diversity of cutaneous sensory afferents revealed by genetically directed sparse labeling. *Elife*. 1:e00181.
24. Cerebellar granule cells are not to be confused with homonymous granule cells in other brain regions, such as hippocampal granule cells and olfactory granule cells. The naming ambiguity in this case dates back to when only neuronal somata were visible under the microscope, and these three distinct neuron types all happened to have granule-shaped cell bodies! Their axonal and dendritic arbors, however, are completely different in each of the three types.
25. See <http://neurolex.org/wiki/Category:Neuron>.
26. See <http://BrainInfo.org>.
27. Shepherd GM, Grillner S (2010) *Handbook of Brain Microcircuits*. Oxford: Oxford University Press.
28. The terms drivers and modulators was originally introduced in the visual system to distinguish neurons transmitting information about the content of the field of view from those altering the probability of that transmission: Sherman SM, Guillery RW (1998) On the actions that one nerve cell can have on another: Distinguishing “drivers” from “modulators.” *Proc Natl Acad Sci USA*. 95(12):7121–26. However, *these* modulators should not be confused with modulatory neurotransmitters and the process of synaptic neuromodulation briefly mentioned at the end of section 3.3.
29. Staiger JF, Flaggmeyer I, Schubert D, Zilles K, Kötter R, Luhmann HJ (2004) Functional diversity of layer IV spiny neurons in rat somatosensory cortex: Quantitative morphology of electrophysiologically characterized and biocytin labeled cells. *Cereb Cortex*. 14(6):690–701.

30. Ascoli GA, Brown K, Calixto E, Card P, Barrionuevo G (2009) Quantitative morphometry of electrophysiologically identified CA3b interneurons reveals robust local geometry and distinct cell classes. *J Comp Neurol.* 515:677–95.

31. These neuromodulatory systems were mentioned at the end of section 3.3, and their special receptors are called metabotropic as opposed to ionotropic. For completeness we should note that there are also metabotropic GABA and glutamate receptors in addition to the ionotropic receptors for these neurotransmitters, but this additional detail is unnecessary to our exposition.

Chapter 8

1. See also: DeFelipe J, López-Cruz PL, Benavides-Piccione R, Bielza C, Larrañaga P, Anderson S, Burkhalter A, Cauli B, Fairén A, Feldmeyer D, Fishell G, Fitzpatrick D, Freund TF, González-Burgos G, Hestrin S, Hill S, Hof PR, Huang J, Jones EG, Kawaguchi Y, Kisvárdy Z, Kubota Y, Lewis DA, Marín O, Markram H, McBain CJ, Meyer HS, Monyer H, Nelson SB, Rockland K, Rossier J, Rubenstein JL, Rudy B, Scanziani M, Shepherd GM, Sherwood CC, Staiger JF, Tamás G, Thomson A, Wang Y, Yuste R, Ascoli GA (2013) New insights into the classification and nomenclature of cortical GABAergic interneurons. *Nat Rev Neurosci.* 14(3):202–16.

2. Hirsch JA, Martinez LM, Alonso JM, Desai K, Pillai C, Pierre C (2002) Synaptic physiology of the flow of information in the cat's visual cortex in vivo. *J Physiol.* 540(Pt 1):335–50.

3. Wang Y, Rubel EW (2012) In vivo reversible regulation of dendritic patterning by afferent input in bipolar auditory neurons. *J Neurosci.* 32(33):11495–504.

4. <http://www.app.pan.pl/archive/published/app57/app20110019.pdf>.

5. Glickfeld LL, Scanziani M (2006) Distinct timing in the activity of cannabinoid-sensitive and cannabinoid-insensitive basket cells. *Nat Neurosci.* 9(6):807–15.

6. For a scholarly account, see Petilla Interneuron Nomenclature Group (2008) Petilla terminology: Nomenclature of features of GABAergic interneurons of the cerebral cortex. *Nat Rev Neurosci.* 9(7):557–68.

7. Underwood E (2014) Brain's GPS finds top honor. *Science* 346(6206):149. See also "The Nobel Prize in Physiology or Medicine 2014" at nobelprize.org/nobel_prizes/medicine/laureates/2014/.

8. For an evolving knowledge base of hippocampal neuron types, see <http://hippocampome.org>.

9. For an online pointer to the NIH Human Connectome Project, see note 12 in chapter 4.

10. According to Boeing itself, the 747 also boasts 170 miles of wiring (presumably including the four engines). Yet this cable length pales, in comparison to the axonal wiring in a single *mouse* brain by a full order of magnitude (tenfold).

Chapter 9

1. MacLean JN, Watson BO, Aaron GB, Yuste R (2005) Internal dynamics determine the cortical response to thalamic stimulation. *Neuron*. 48(5):811–23.

2. Brains, however, do not operate in isolation from their embodiments. If Lisa and Monica exchanged their brains (or, should we say, their bodies), the consequences for their respective minds would be hard to predict but could be destructive.

3. See, however, the discussion at the end of section 4.4. The different connectivity of distinct brains implies that different spatial-temporal activity patterns may be encoding for the same concepts. Thus, in order to capture the commonality of *meaning* across individuals, a population-averaged brain should be computed based on the information that the circuitry can process. How exactly this can be achieved, however, is not yet clear.

4. See also Asbury C (2013) *Brain Imaging Technologies and Their Applications in Neuroscience*. New York: Dana Foundation. Available at <http://www.dana.org/news/publications/publication.aspx?id=34292>.

5. For an overview of the methods to investigate the tree shape of neurons, see Parekh R, Ascoli GA (2013) Neuronal morphology goes digital: A research hub for cellular and system neuroscience. *Neuron*. 77(6):1017–38.

6. Donohue DE, Ascoli GA (2011) Automated reconstruction of neuronal morphology: An overview. *Brain Res Rev*. 67(1–2):94–102. See also <http://diademchallenge.org>.

7. Clery D. (2014) Light loophole wins laurels. *Science* 346(6207):290-1. See also “The Nobel Prize in Chemistry 2014” at nobelprize.org/nobel_prizes/chemistry/laureates/2014/.

8. See, for example, Ascoli GA (2006) Mobilizing the base of neuroscience data: The case of neuronal morphologies. *Nat Rev Neurosci*. 7(4):318–24.

9. <https://www.humanbrainproject.eu/>.

10. <http://www.whitehouse.gov/share/brain-initiative>.

11. This admittedly far-fetched scenario is *sufficient* to provide a full description of the mind, but it is not strictly *necessary*. Population coding by cell assemblies might allow achieving the same goal more simply by measuring a statistically representative sample of neurons, synapses, and spikes.

12. For a very recent “early” proof of concept, see Grau C, Ginhoux R, Riera A, Nguyen TL, Chauvat H, Berg M, Amengual JL, Pascual-Leone A, Ruffini G (2014) Conscious brain-to-brain communication in humans using non-invasive technologies. PLoS One. 9(8):e105225. <http://dx.plos.org/10.1371/journal.pone.0105225>.