Rhythms of the Brain

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Gyrgy Buzski

To my loved ones.

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Prelude

> If the brain were simple enough for us to understand it, we would be too simple to understand it.
>
> —Ken Hill

The short punch line of this book is that brains are foretelling devices and their predictive powers emerge from the various rhythms they perpetually generate. At the same time, brain activity can be tuned to become an ideal observer of the environment, due to an organized *system* of rhythms. The specific physiological functions of brain rhythms vary from the obvious to the utterly impenetrable. A simple but persuasive example is walking. Bipedal walking is a periodic series of forward falls interrupted regularly by alternate extensions of each leg. It is almost as natural to us as breathing. This effortless exercise is made possible by the predictive nature of spinal cord oscillators. On smooth terrain, the alternation of leg movements can take us any distance. Perturbation of the clocking, on the other hand, signals a change in the terrain. This general mechanism is the same in all animals, including eight-legged scorpions and centipedes. The notion that oscillators or "central pattern generators"[1] are responsible for the coordination of motor

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1. Neural circuits that produce self-sustaining patterns of behavior are called central pattern generators. The most studied central pattern generator is an intraspinal network of neurons responsible for locomotion. Grillner (1985) summarizes the pros and cons of the pacemaker view of central pattern generators in the spinal cord and brain. Stein et al. (1997) and Burke (2001) are nice updates on the topic. Central pattern generators are also responsible for many other types of rhythmic movements, e.g., peristaltic motor patterns of legless animals, rhythmic movement of the wings of crickets during song production, respiration, heart control, movements of the stomach, and other parts of the digestive system. My favorite review on this topic is Marder and Calabrese (1996).

patterns, such as breathing and walking, is old and well accepted in neuroscience. But the tantalizing conjecture that neuronal oscillators can be exploited for a plethora of other brain-generated functions, including cognition, is quite new and controversial. And it is the latter topic, the contribution of oscillations to the invisible, inferred operations of the brain, that this book is mostly about.

Exposing the mechanisms that allow complicated things to happen in a coordinated fashion in the brain has produced some of the most spectacular discoveries of neuroscience. However, I do not want to mislead you from the outset. Clocks are not thinking but ticking devices, no matter how precisely they can predict time. Time needs to be filled with content, provided by the appropriate firing patterns of neurons, whose assembly activity, in turn, is regulated by brain oscillations. Interestingly, the neuronal assemblies that generate the content are often the same as those that give rise to the time metric of oscillations that in turn organize the cell assembly pattern. This peculiar reciprocal causation, brought about by the self-organized features of brain activity, begs for an explanation. A good part of the volume is devoted to discussing experiments that attempt to elucidate these emerging properties of neuronal networks.

At the physiological level, oscillators do a great service for the brain: they coordinate or "synchronize" various operations within and across neuronal networks. *Syn* (meaning same) and *chronos* (meaning time) together make sure that everyone is up to the job and no one is left behind, the way the conductor creates temporal order among the large number of instruments in an orchestra. A close view of Seiji Ozawa at the end of a concert, sweat falling from his face, is proof that conducting an orchestra is a physically and mentally demanding job. In contrast, coupled oscillators perform the job of synchronization virtually effortlessly. This feature is built into their nature. In fact, oscillators do not do much else. They synchronize and predict. Yet, take away these features, and our brains will no longer work. Compromise them, and we will be treated for epilepsy, Parkinson's disease, sleep disorders, and other rhythm-based cognitive maladies. As I point out repeatedly in Cycles 1–13 of this volume, virtually no nervous function exists without a time metric, be it the simplest motor or the most complex cognitive act. While we know quite a bit about neurons, the building blocks of the brain, and have extensive knowledge about their connectivity, we still know very little how the modules and systems of modules work together. This is where oscillations offer their invaluable services.

My connection with brain rhythms began in April 1970, during a physiology lecture given by Endre Grastyán in the beautiful town of Pécs, on the sunny slopes of the Mecsek mountains in Hungary. The University of Pécs, or Universitas Quinque Ecclesiensis, as it was called when founded in 1367, has produced a remarkable set of neuroscientists, including János Szentágothai, the legendary neuroanatomist; Béla Flerkó and Béla Halász, pioneers of neuroendocrinology; György Székely, the renowned spinal cord physiologist; and Ferenc Gallyas, the creator of the silver impregnation methods widely used for neuronal labeling.

Like many of us at a young age, in his twenties Grastyán could not quite make up his mind about his future. Finding nothing too interesting or challenging initially,

he decided to train for the priesthood to get some orientation in philosophy. But his mind, far too curious and questioning, prevented him from becoming a preacher. He ended up in medical school during the stormy years after World War II and became the assistant of Professor Kálmán Lissák. Lissák, a student of Otto Loewi in Graz, Austria, and subsequently Walter Cannon's assistant at Harvard, had returned to Hungary to become Chair of Physiology just before the war. Grastyán's pairing with Lissák was fortunate because Lissák, of course, knew quite a bit about rhythms from his years with Loewi, who provided the first evidence that a chemical—a neurotransmitter—is released at the junction (synapse) between the vagus nerve and the heart muscle.[2] Although Grastyán was perhaps Lissák's closest friend, the two were as different as can be. Lissák was a reserved man, and his lectures were scarcely attended. In contrast, Grastyán was a performing artist whose seminars were carefully composed and choreographed. The huge lecture room in the medical school was always packed, and even students from the neighboring law school came over to listen to his mesmerizing lectures. He generated so much enthusiasm that we students became convinced that the topics he discussed were among the most important in the whole universe.

In that particular lecture of April 1970, he talked about how the brain outputs, such as movement and cognition, control its inputs, rather than the other way around. His key idea was that control in living systems begins with the output. This is the seed for further evolution of the brain. Even in the most complex animals, the goal of cognition is the guidance of action. Indeed, the first simple biological systems did not have any inputs; they did not need them. They simply used an economical motor output, a rhythmic contraction of muscles. This is, of course, is sufficient only when food is abundant in the sea environment. More complex forms of life evolved form this simple solution by modifying the simple rhythmic output. Sensation of direction and distance developed only after the "invention" of movement through space. The idea of output control and feedback is a profound thought even today. Back then, when Pavlovian sensory–sensory association was the dominant ideology in the East and the stimulus–decision–response paradigm dominated Western thinking, Grastyán's teachings were unusual, to say the least.

After his lecture, I rushed home to read the relevant chapters in our official

2. Loewi called the chemical "Vagusstoff," which Henry Hallett Dale from Cambridge, England, identified later as acetylcholine, the first neurotransmitter. They received the Nobel Prize for their discoveries in 1936. I have heard various versions of the story behind the Vagustoff experiment from Lissák. Here is one from Loewi's own pen:

> The night before Easter Sunday of that year I awoke, turned on the light, and jotted down a few notes on a tiny slip of thin paper. Then I felt asleep again. It occurred to me at six o'clock in the morning that I had written down something most important, but I was unable to decipher the scrawl. The next night, at three o'clock, the idea returned. It was the experiment to determine whether or not the hypothesis of chemical transmission that I had thought about years ago was correct. I got up immediately, went to the laboratory, and performed a simple experiment on a frog heart according to the nocturnal design. (Loewi, 1960, 15)

Dale became better known about his "principle": if a chemical is released in one synapse, the same chemical is released in all the other synapses made by the same neuron.

textbook only to realize that there was not a single word there about what I had heard that morning.[3] Nevertheless, beginning with Grastyán's introductory lecture on the organization of the brain, my life in medical school acquired new meaning. My original high school plan to become an electrical engineer was vetoed by my parents, who offered me the choice between medical school and law school. While my friends were having fun at the School of Engineering in Budapest, learning exciting stories about radio transmission and electronic oscillators, I spent most of my time studying the unending details of bones and ligaments. But in his physiology lecture, Grastyán was talking about some truly intriguing questions that sparked my interest. I applied to become his apprentice and spent most of my student life in his lab.

The best training in Grastyán's laboratory occurred through my participation in the regular lunch discussions that could go on for several hours, where topics meandered chaotically from homeostatic regulations of the brain to complex philosophical topics. It was during these lunch lessons where I first learned about the hippocampal "theta" rhythm, the oscillation that has become my obsession ever since. My first assignment in the Grastyán school, under the supervision of György Karmos, was to examine the variability of the evoked responses in the hippocampus and auditory cortex in response to sound stimuli as a function of behavior. In a nutshell, our main finding was that the most important factor in predicting the variability of the evoked brain responses was the variability of the background brain activity. This was the first time I faced the fascinating issues of "state," "context," and "spontaneous" activity, problems that remained with me forever.

As I have repeatedly discovered in my career, the informal lunch-seminar approach to science is hard to substitute with formal lectures or the reading of dense scientific papers. Seminars are tailored for an average group of people with the naive assumption that the audience retains all the details and follows and accepts the fundamental logic of the lecturer. In contrast, the essence of lunch conversations is to question the fundamental logic, a quest for clarification and simplification, a search for explanations and answers without a rigid agenda, where the focus is not on covering large chunks of material but on fully understanding even the smallest details. Of course, one can follow up a lecture by finding and reading the relevant published papers on the topic. However, most of the exciting findings in neuroscience are hidden in the small print of specialty journals, often written in a specialized and arcane language comprehensible to, at most, a handful of specialists. Overwhelmed with new and important discoveries in the various sub-subspecialties, the practicing neuroscientist, such as myself, tends to forget that

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3. The idea that the brain's main goal is to control movement has been repeatedly emphasized by several outstanding individuals. Indeed, the brain's only means of interacting with the world is via the motor system, whether foraging for food or communicating by speech, gestures, writing a paper, or sending an e-mail. The outstanding books by Gallistel (1980) and Llinás (2001) discuss this point eloquently. The "primacy" of movement has been emphasized by Hamburger et al. (1966) and Bullock and Horridge (1965). For recent reviews on this topic, I suggest Hall and Oppenheim (1987), Wolpert and Ghahramani (2000), and Robinson and Kleven (2005).

neuroscience is of startling relevance to a contemporary society wrestling with complex issues such as social behavior, depression, and brain aging. It is hard to predict which of the numerous fundamental discoveries could alter the face of such large issues, and unless they are conveyed to others, they might be over-looked without making an impact. This is mainly so because the explanations we provide in papers to the superspecialists may be impenetrable to the uninitiated. Without attempting to place our work into a larger context from time to time, we deprive ourselves of the chance to be able connect to the more macroscopic and microscopic levels of research. Yet, discoveries and insights realize their power only when understood by others. Understanding this important connection is what mostly motivated me to write this volume.

Neuroscience has provided us some astonishing breakthroughs, from noninva-sive imaging of the human brain to uncovering the molecular mechanisms of some complex processes and disease states. Nevertheless, what makes the brain so special and fundamentally different from all other living tissue is its organized action in time. This temporal domain is where the importance of research on neu-ronal oscillators is indispensable, and it is this temporal domain that connects the work discussed in this volume to all other areas of neuroscience.

Parallel with the amazing progress in neuroscience, another discipline has emerged: complex systems, a new science that cuts across many fields. During the past decade, I have learned as much about the brain by reading about novel branches of physics, engineering, mathematics, and computer science as I did from studying papers directly dealing with the nervous tissue. Rest assured, the human brain is the most complicated machinery ever created by nature. Never-theless, it is truly exciting looking for concepts, mechanisms, and explanations that are common among many different systems and cut across the living/nonliv-ing dichotomy. Seemingly unlikely sources such as fractals and Internet commu-nication have provided novel clues for understanding neuronal networks. My goal is to illustrate how this new knowledge is being incorporated into neuroscience at a breathtakingly high speed and to convey fascinating discoveries to neuroscien-tists, psychiatrists, neurologists, and the growing group of computational scien-tists, physicists, engineers, and mathematicians interested in complex systems. A covert agenda is that, along the way, describing these new discoveries will en-courage outsiders to become brain rhythm enthusiasts.

Deciphering the code of the brain will have a lasting impact on our society. It is not simply an intellectual exercise for a handful of esoteric individuals any-more. It is also more than a "just" a brain-health–related issue, which affects mil-lions in the United States and many more worldwide. As Robert Noyce, the co-inventor of the integrated circuit, once put it: "In order to understand the brain, we have used the computer as a model for it. Perhaps it is time to reverse this rea-soning. To understand where we should go with the computer, we should look to the brain for some clues." Now that our economy, financial institutions, education system, research programs, distribution systems, human interactions, politics, and defense have all become computer and Internet dependent, this quest is more acute than ever. The hope is that the new knowledge about the brain will not only

inspire novel designs for computer architectures and a more efficient and safer electronic communication but also, at the same time, provide a better understanding of ourselves. Books, computers, and Internet communication have *externalized* brain functions and provided virtually unlimited storage space for the accumulated knowledge of humankind. However, this externalized information is only as useful as its accessibility. Currently existing search engines, such as Google and Yahoo, that provide access to this externalized knowledge are very inefficient (even though they are the best available at present) compared to the brain's ability to retrieve episodic information, because neuronal networks utilize fundamentally different strategies for the reconstruction of events and stories from fragments than do search engines. Understanding the brain's search strategies may allow us individuals to have better access to the cumulative knowledge of humankind.

Writing to a general audience interested in neuroscience is a much more arduous exercise than writing scientific papers. Scientists, rather than just the science they have produced, and metaphors that are deliberately absent in specialty journals come to the fore. This process inevitably implies oversimplification from the experts' viewpoint, occasional redundancies, and some rugged transitions for the novice. To alleviate the inevitable, I have written a simplified main story, which I hope to be a relatively easy read in most Cycles. Each Cycle ends with a brief summary, which highlights the primary message of the Cycle. The main story is supplemented by extensive footnotes, which serve partly to define novel terms. In most cases, however, they provide further critical information for the more sophisticated reader, along with links to the appropriate literature. I have deliberately chosen this format because it allowed me to interweave the main story and its more complex ramifications without breaking the flow of thought. The additional comments and citations in the footnotes give rise to an ever-growing tree with intertwined branches of arguments, hypotheses, and discovery.

A couple of years ago, we hosted a painter in our house for the summer. His determined goal was to survey and conquer the New York City art market. Yet, after a month or so, he plainly declared to us that every painting has already been painted and the art dealers are aware of all potential innovators in case the market is in need of such redundancy. He returned to Europe the next day. This is how I felt while writing this book. Clarity, critical details, and giving proper credit compete for space, and achieving the appropriate balance is the most difficult thing in writing a book. The more I explored the mysteries of brain oscillators and neuronal functions, the more I realized that the fundamental ideas (some which I thought were genuinely mine) have already been expressed, often repeatedly. Many times the ideas have come up in studying systems other than the brain, or they were expressed in a different context. But they existed. The deeper I ventured into the problems, the further back in time I had to travel to discover the origin of thoughts.

An oft-heard marketing slogan these days is that we have learned more about the brain during the past decade that during the previous history of humankind. This may be true regarding the volume of factual knowledge. But discoveries are

not (just) facts. They are ideas that simplify large bags of factual knowledge. Such fundamental ideas rarely pop up suddenly. Typically, they slowly emerge after appropriately long incubation periods and are shaped by numerous proponents and critics. Fundamental ideas are rare, and probably as many have been conceived prior to modern neuroscience as in the past few decades. One just has to recognize and adapt the old thoughts to the new lingo and the findings we have recently generated. My dear mentor advised me in my student days, "do not publish when you have only data but when you have a novel idea." If I followed his advice strictly, I would perhaps still be writing my first paper and this volume would not exist. Although I honestly attempted to reach a balance between summarizing large chunks of work by many, and crediting the deserved ones, I am aware that I did not always succeed. I apologize for those whose works I unintentionally ignored or missed. To claim innocence, I shall simply shift the responsibility onto those who kindly read some parts of the manuscript at various stages and did not complain (enough). These generous colleagues include Kamran Diba, Caroline Geisler , Robert L. Isaacson, Kai Kaila, Christof Koch, Nancy Kopell, Rodolfo Llinás, Stephan Marguet, Edvard Moser, Denis Paré, Marc Raichle, Wolf Singer, Anton Sirota, Paula Tallal, Jim Tepper, and Roger Traub. My dear friend Mircea Steriade took the trouble of reading the entire manuscript and provided invaluable feedback. My special thanks to Mary Lynn Gage for her attempts to transpose my Hungarian-Zombi idioms into comprehensible English. This may not have always succeeded, and I would like to publicly apologize for humiliating Shakespeare's beautiful language here and there.

At a more general level, I would like to express my gratitude to a number of people whose examples, support, and encouragement sustained me in difficult times and whose collaborations, inspiring discussions, and criticism have served as constant reminders of the wonderful collegiality of our profession—David Amaral, Per Andersen, Albert-László Barabási, Reginald Bickford, Yehezkel Ben-Ari, Anders Björklund, Brian Bland, Alex Borbely, Ted Bullock, Jan Bures, Gábor Czéh, János Czopf, Eduardo Eidelberg, Jerome (Pete) Engel, Steve Fox, Walter Freeman, Fred (Rusty) Gage, Mel Goodale, Charlie Gray, James McGaugh, Michale Fee, Tamás Freund, Helmut Haas, Michael Häusser, Walter Heiligenberg, Bob Isaacson, Michael Kahana, George Karmos, Nancy Kopell, Lóránd Kellényi, Gilles Laurent, Joe LeDoux, Stan Leung, John Lisman, Rodolfo Llinás, Nikos Logothetis, Fernando Lopes da Silva, Jeff Magee, Joe Martinez, Bruce McEwen, Bruce McNaughton, Richard Miles, István Mody, Robert Muller, John O'Keefe, Marc Raichle, Jim Ranck, Menahem Segal, Terry Sejnowski, Larry Squire, Wolf Singer, David Smith, Peter Somogyi, Mircea Steriade, Steve Strogatz, Karel Svoboda, David Tank, Jim Tepper, Alex Thomson, Giulio Tononi, Roger Traub, Cornelius (Case) Vanderwolf, Olga Vinogradova, Ken Wise, Xiao-Jing Wang, and Bob Wong. Over the years, some of these outstanding colleagues—Bob, Bruce, David, Gábor, Helmut, István, Karel, Mircea, Peter, Rodolfo, Roger, Rusty, Ted, Tamás, and Wolf—became my trusted, close friends. Most importantly, I would like to thank my students and post-doctoral fellows without whose dedication and hard work the many experiments discussed in this volume would not exist.

Being a scientist is a dedication. Writing a book is a bit more. Oh yes, it is a lot of fun, but it takes time, precious time that I had to steal from somewhere, mostly from my family. My dear wife, Veronika, and my sweet daughters, Lili and Hanna, forgive me for the many weekends you had to spend without me and for my frequent mental absences at dinners and family events when only my body was present. How fortunate I am to have you as my supporters. Without your understanding and encouragement, this venture would have been worthless.

Dear reader. Do not stop here! The rhythm begins only now.

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Cycle 1

Introduction

> There is no good reason to assume that the brain is organized in accordance with the concepts of folk psychology.
>
> —Cornelius H. Vanderwolf

It all began with a dream. A young officer in the Prussian Army received a letter from his sister. In it she wrote about a dream in which her beloved brother fell off his horse and broke his leg. As it happened, the young officer indeed fell off his horse at about the time the letter was sent by his sister. The officer, Herr Doktor Hans Berger, already an established researcher on cerebral blood circulation at the University Clinic for Psychiatry in Jena, Germany, thought that such coincidence could only have happened through some mysterious communication between brains, via telepathy,[1] as such alleged communications between brains are better known.

After returning to Jena from active military duty, Berger was promoted to the Chair of the Department of Psychiatry and Neurology in 1919 and devoted the rest of his career to the study of the brain's electrical activity. Berger reasoned that the electromagnetic forces generated by the human brain could be the carrier waves of telepathy, his true interest. Since even in that day telepathy was regarded as an "occult" subject, his experiments were conducted in utter secrecy in a laboratory located in a small building on the grounds of the clinic. Most of his initial recordings were done on himself, his son Klaus, and patients with skull defects.

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1. Telepathy (or the related terms precognition and clairvoyance) is the supposed ability to transfer thoughts, feelings, desires, or images directly from the mind of one person to the mind of another by extrasensory channels and without using known physical means.

He performed numerous experiments and, importantly, eliminated the possibility that the voltage changes measured by his string galvanometer were an artifactual consequence of blood pressure changes; nor did they arise from the scalp skin. After five years of experimentation, he concluded that the most prominent electrical activity could be recorded from the occipital (lower rear) part of the skull when the subject's eyes were closed. In his groundbreaking 1929 paper he wrote, "The electroencephalogram represents a continuous curve with continuous oscillations in which . . . one can distinguish larger first order waves with an average duration of 90 milliseconds and smaller second order waves of an average duration of 35 milliseconds. The larger deflections measure at most 150 to 200 microvolts. . . ."[2] In other words, the electrical field generated by millions of discharging neurons in the cerebral cortex is 10,000 times smaller than that provided by an AA battery.

Berger called the large-amplitude rhythm (approximately 10 waves per second, or 10 hertz), which was induced by eye closure in the awake, calm subject, the "alpha" rhythm because he observed this rhythm first. He named the faster, smaller amplitude waves, present when the eyes were open, "beta" waves. Paradoxically, Berger's recordings provided firm physical evidence *against* his idea that waves generated by one brain could somehow be detected by another brain. The voltage changes that emerge from the cooperative activity of neurons in the mammalian brain are just too small, and current propagation requires a low-resistance conductor, so it cannot cross air, for example. Although he failed to prove his hypothesis of telepathic communication between brains, his research created a powerful scientific and clinical method for investigating quickly changing brain activity.[3]

Discovering a dynamic brain phenomenon is one thing. Understanding its meaning and its role in behavior and cognition is quite another. Ever since Berger's

2. Berger (1929). Berger was already familiar with the work of Richard Caton, a Liverpool surgeon who studied the electricity generated by the brains of rabbits and monkeys (Caton, 1875). Berger's international fame was boosted when his work was confirmed and endorsed in by Edgar Douglas Adrian and Bryan Harold Cabot Mathews of the Cambridge Physiological Laboratory. They suggested calling the alpha waves the Berger rhythm, but Hans Berger modestly rejected the offer (Adrian and Mathews, 1934).

3. It is tough to be first in any field of science, and the discovery of the electroencephalogram (EEG) was no different. In addition to Caton's work, Berger also knew about the published works of the physiologists Adolf Beck of Poland and Vladimir Pravdich-Neminski (or W. W. Prawdicz-Neminski in his native Ukrainian) of Russia. Neminski's observations are perhaps most relevant since his "electrocerebrogram" was obtained from the intact surface of dogs' skulls (Neminski 1913). However, he was not the first Russian in this area of research. Vasili Yakovlevich Danilevsky had described observations similar to Caton's in his doctoral thesis, and Nikolai Y. Wedensky had used a telephone circuit to listen to electrical waves in the brains of cats and dogs. Fleischel von Marxow was also among the first discoverers of electrical fields of the brain. However, he placed his results in a sealed letter in 1883 and revealed them only after he learned about Beck's published results. What made Berger's observations stand out from the others were the numerous control experiments he provided along with his observations. Brazier's (1959) chapter is the best summary of the exciting early days in the study of brain electricity and is a source for numerous references. Borck (2005) is another useful source of historical materials.

early observations, three questions have haunted neuroscientists: how are EEG patterns generated, why are they oscillatory, and what is their content? Providing answers to these questions is a major goal of this volume. I introduce the topic in Cycles 2 and 3 by discussing the important issue of how the speed of communication in the cerebral cortex can be preserved despite the great size differences of the brains of small and large mammals. Cycle 4 can be skipped by those who have had an introductory class on methods in neurophysiology. It discusses the major methods currently available for investigating brain activity patterns in living tissue and the mechanisms that give rise to the field EEG. Cycles 5 and 6 serve as an introduction to the different types of oscillators and discuss the large family of oscillations in the mammalian cortex. Cycles 7 and 8 are devoted to the "default" states of the brain: sleep and early brain development. Tying the macroscopic features of oscillations to neuronal mechanisms requires large-scale recordings of numerous single neurons. Such techniques allow us to gain some insight into the content of oscillations, which is described in Cycles 9–12. In Cycle 13 I examine the structural and functional requirements of awareness by contrasting brain structures that can and cannot support self-generated patterns and long-range communication through global oscillations.

Periodic Phenomena in Nature

Nature is both periodic and perpetual. One of the most basic laws of the universe is the law of periodicity.[4] This law governs all manifestations of living and non-living. In its broadest definition, periodicity refers to the quality, state, or fact of being regularly recurrent: a repeating pattern or structure in time or space. What goes up must come down. The sun rises and sets, and the days wax and wane. Without periodicity, there is no time; without time, there is no past, present, or future. In living systems, the periodicity of individual lives gives rise to the continuity of life on Earth. Our existence has meaning only when experienced in time. The essence of music and dancing is rhythm. An important part of human culture is the celebration of the periodicity of life. The Jewish and Muslim religions are attuned to the lunar cycle. Christians adopted a solar calendar. Periodicity can be seen in the monthly windows of opportunity for conception of human life.

Periodicity, oscillation, rhythm (from Latin meaning to flow), and cyclic process are synonyms that refer to the same physical phenomenon. Historically, different academic disciplines have adopted a preferred term to describe these related phenomena. Periodicity is the term of choice in social and earth sciences. Oscillation is the preferred term in physics, and engineers talk about cyclic or period generators. Until recently, neurologists and neuroscientists used the term "brain rhythms" almost exclusively when referring to the various brain patterns.

4. Nature, of course, has no laws, desires, goals, or drives. It simply generates certain regularities that we conveniently assume are governed by some outside forces and use a third-person perspective to refer to these regularities.

Reference to oscillations is quite recent.[5] The avoidance of the term "oscillator" in brain research for so long perhaps reflected the tacit view that brain rhythms may be qualitatively different from the oscillators discussed in physics textbooks. Assuredly, neuronal oscillators are quite complex. Nevertheless, the principles that govern their operation are not fundamentally different from those of oscillators in other physical systems. Today, it is widely recognized that the brain's ability to generate and sense temporal information is a prerequisite for both action and cognition. This temporal information is embedded in oscillations that exist at many different time scales. Our creativity, mental experiences and motor performance are modulated periodically both at short and long time scales. But how are oscillatory states brought about, especially if they occur in the absence of external influences? In Cycles 5 and 6 I propose some answers with illustrations from physics and engineering.

Time and Periodicity

Neuroscientists work with time every day but rarely ask what it is. We take for granted that time is "real" and that brains have mechanisms for tracking it. Since time is a major concept in this book, I attempt to provide a working definition without getting lost at the nebulous boundary between physics and philosophy.[6] Newton held that time flows in absolute intervals, independent of the physical universe. According to Immanuel Kant, space and time are irreducible categories through which reality is perceived by our brains. Albert Einstein combined space and time into "spacetime." According to him, time is a measure of motion and, as such, is part of the physical universe and thus could be interpreted as its "property"; space and time disappear along with the things. An opposite view is that time is a subjective abstraction and does not exist in any physical substrate and has no more reality than a mathematical axiom. In a broad sense, time is a *measure of change,* a metric of succession, a parameter that distinguishes separate events. One practical definition is that "time is that which is measured by a clock," a pragmatic description adequate for most branches of physics and neuroscience.[7]

How we approach the problem of time largely determines our view of the outside world around us. First, we need to distinguish two aspects of time. Absolute time is clock time, referring to a particular point in a time series, for example, your birth date. Absolute time is a fundamental element of existence since everything

5. It was the review by Steriade and Deschênes (1984) that popularized the term "neuronal oscillator" in the mammalian nervous system. See also Steriade and Llinás (1988).

6. Hawking (1992) is an excellent introduction to this difficult topic. Hall (1983) is another easy read. A radically different definition of time is proposed by Leyton (1999). Leyton derives time from spatial symmetry and its broken version: time is essentially symmetry breaking (e.g., asymmetric representation of plane symmetry by oscillatory phase; see Cycle 11).

7. In physics, standard time interval (a second) is defined by an oscillator: 9,192,631,770 hyperfine transitions in the ^{133}Cs atom.
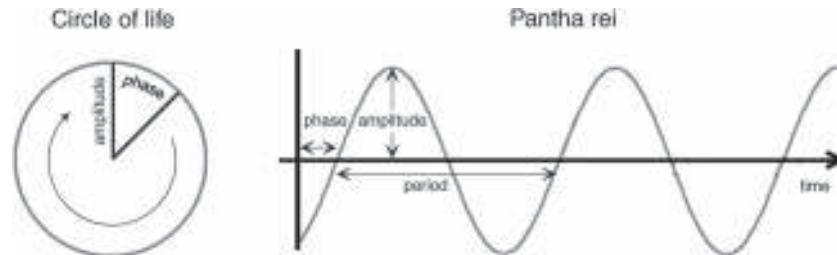
Figure 1.1. Oscillations illustrate the orthogonal relationship between frequency and time and space and time. An event can repeat over and over, giving the impression of no change (e.g., circle of life). Alternatively, the event evolves over time (*pantha rei*). The forward order of succession is a main argument for causality. One period (right) corresponds to the perimeter of the circle (left).

exists in time. Duration refers to the change of time, the interval between two points in time. Elapsed time is therefore relative, and it has an interval span (e.g., hour), whereas absolute time does not have a span (e.g., date). We make a similar absolute versus relative distinction in space as well, when we talk about position and distance. However, while distance can refer to many directions (vector) in space, time has only one direction (scalar).

The intimate relationship between space and time is packaged into the concept of "spacetime" (x, y, z, t dimensions). Oscillations can be conceived of and displayed in terms of either space or time. The phase-plane of a sinusoid harmonic oscillator[8] is a circle. We can walk the perimeter of the circle once, twice, or billion of times and yet we always get back to our starting point. "What has been is what will be, and what has been done is what will be done; and there is nothing new under the sun"[9] This is the "circle of life," and our walk on its perimeter is measured as dislocation (figure 1.1, left).

An alternative to the periodicity view of the universe is to display periodicity as a series of sine waves. Now we can walk along the troughs and peaks of the line without ever returning to the starting point (figure 1.1, right). Time here is a continuum with the cycle as its metric. The cycles are identical in shape, and the start and end points of the cycles form an infinite path into the seemingly endless universe. This meandering line illustrates the basis of our time concept: *linear*

8. The different types of oscillators are defined and discussed in Cycle 6.

9. The quote is from the book of Ecclesiastes (chapter 1, verse 9, Revised Standard Version). The concept of recurrence is prominent in Hinduism and Buddhism, among others. The spoked wheel of life (*dharma*) is an endless cycle of birth, life, and death. The concept of recurrence is also prominent in Friedrich Nietzsche's philosophy (best expressed in *Also Sprach Zarathustra. Ein Buch für Alle und Keinen*). A picture of nature as being in "balance" often prevails in both biological and religious discussions. Although a general equilibrium theory has never been explicitly formulated, environmentalists and conservationists tacitly assume that nature is in an eternally stable equilibrium; therefore, we should keep it that way. However, if this were the case, how did we get here in the first place?

change and a *forward order* of succession, features that are often used in arguments of causality. A moment never repeats itself. *Pantha rei*—everything flows—according to the ancient Greek saying. "Upon those who step into the same rivers, different and ever different waters flow down."[10] Whichever model we choose, the circle or the meandering line, in periodically changing systems the past can predict the future (position or moment).

The hard problem to solve is whether time and space are situated in our minds only or whether they in fact exist independently of us. Fortunately, most brain operations, including predictions by brain rhythms, can be understood without addressing this hard problem. Clock time is sometimes referred to as objective time, an absolute physical reality, independent of conscious brains and beyond our control. Clock time is what we use to calibrate our subjective experience of the passage of time and coordinate our thoughts and activities. Passage of time, that is, its duration, is felt as a linear event, slipping from one moment to another. The *feeling* of time is confined to a relatively short span from tens of milliseconds to tens of minutes. As shown in Cycle 5, this time span corresponds to the temporal range of brain oscillators, which may serve as an internal metric for time calibration. Nobody can feel micro- and nanoseconds, and tracking time durations beyond the hour range requires body references such as hunger or feedback from the environment. Our best temporal resolution is in the subsecond range, corresponding to the duration of our typical motor actions, the tempo of music and speech.[11]

Linear time is a major feature of our Western cultural world-view, and the experience of time flowing between past, present, and future is intricately tied to everyday logic, predictions, and linear causation. According to the great French molecular biologist Francois Jacob, "one of the deepest, one of the most general functions of living organisms is to look ahead, to produce future."[12] What I am proposing in this volume is that neuronal oscillations are essential for these deepest and most general functions.

Time, Prediction, and Causation

Causality among world events is linked to our perception of time.[13] Prediction, inference, forecast, and deduction are used as synonyms in the context of proposed

10. The quote is attributed to Heracleitus of Ephesus (540 to circa 475 B.C.).

11. The average duration of syllables, the fundamental segmentation of speech in all languages, is approximately 250 milliseconds. Syllables cannot be stretched or sped up at will in spoken language beyond certain limits. Slowing down speech can be achieved only by introducing long pauses between syllables. This is the reason why it is so difficult to understand the text of arias.

12. Jacob (1994), p. 32.

13. Freeman (2000) explains that time exists in the material world but causality does not. Along with physicists, he argues that time is a measure of motion, living and nonliving; therefore, it is an objective dimension. In contrast, cause is a measure of intent, and, according to Freeman, only humans have intent.

causality. They refer to an inductive process, which integrates information about the past and present to calculate the following most probable outcome.[14] Brains help their owners to survive and prosper by predicting and deciphering events in the world, including consequences of their own actions. Predictions and relationships are constructed by ordering the succession of events according to elapsed subjective time. We are usually able to say which of two events happened before the other, with decreasing precision as time elapses. Causal-explanatory relationships are usually considered a one-way process because such relationships are embedded in the context of time and time is asymmetric and unidimensional. The cause precedes the effect in time. If the discharge of neuron *a* consistently and reliably precedes the discharge of neuron *b,* and after destruction of neuron *a* neuron *b* ceases to discharge, a causal relationship is suspected. Linear causation works most of the time, and it is the foundation of many essential operations from catching a ball to solving a mysterious murder case. Causation can also fail. For example, in an oscillatory system, most or all neurons with reciprocal, one-way connections or no direct connections may discharge with a zero time lag (i.e., simultaneously), making linear causation impossible, as illustrated in several subsequent Cycles. Oftentimes, the reason for causation failing can be explained by the discrepancy between objective or external time and subjective time registered by the brain.

According to the second law of Newtonian mechanics, a body tends to remain in its state of rest or motion unless acted upon by an external force.[15] The force is the cause, an agent responsible for the motion of the body. When a moving billiard ball hits a stationary one, the latter begins to move. This happens because the kinetic energy of the moving ball exerts force on the stationary ball, causing it to move. Now consider the following psychophysical experiment. A ball is moving toward another one, this time not on a pool table but on a computer screen. If the second ball starts moving in the same direction after the arrival of the first ball, we conclude from the timing of the events that the first ball caused the second one to move. However, derivation of such a conclusion depends critically on the exact timing of the events. We make the inference of causality only if the second ball begins to move within 70 milliseconds after the first ball reaches it. If at least 140 milliseconds elapse between the halting of the first ball and movement of the second ball, no causality is suspected. Between 70 and 140 milliseconds of delay, the two disks appear to stick together but some indirect causality is still deducted.[16] Thus, temporal context is critical for

14. The most influential theory on prediction was put forward by Thomas Bayes (1763/1958). His probability theory examines the possible outcomes of events in terms of their relative likelihoods and distributions (Bernardo and Smith 1994). A "brain computation-relevant" treatment of the Bayesian theory is discussed by Changizi (2003).

15. The second law also nicely illustrates the reductionistic nature of prediction: knowing all past (upstream) events, the future probabilities can be calculated; no goals, desires, or teleology is involved.

16. This is a classic experiment by Shallice (1964). See related arguments in Eagleman and Sejnowski (2000) and VanRullen and Koch (2003).

perception, including the perception of causation. The brain "chunks" or segregates perceived events according to its ability to package information in time, and such packaging, I propose, can be achieved by neuronal oscillators (Cycles 9 and 11).

Here is another illustration of a "logical illusion" in which the brain falsely reconstructs the order of events. You are driving on a highway and a deer crosses the road. You slam on the brakes and avoid a collision. The mental reconstruction of the events is as follows. You noticed a deer (cause) and realized that it would be dangerous to hit the animal. So you decide to avoid it, push the brakes, and turn the steering wheel (effects). Laboratory replication of such real-world actions offers a different explanation. A deer appeared (first event), you braked (second event), and *then* you recognize the animal (third event). This sequence is proposed because reaction time to an unexpected event is less than half a second, whereas conscious recognition requires the recruitment of a large number of neurons in a large, distributed complex brain circuit, which takes longer than half a second.[17] The false logic emerges from the difference between external time and brain-reconstructed time.

Although in this case a simple cause–effect (unexpected object–braking) relationship exists, mental reconstruction offers a different cause. The brain takes into consideration the conduction velocities of its own hardware and compensates for it. For example, touching your nose and toe at the same physical time (or touching your nose with your toe) feels simultaneous even though neuronal events in the cerebrum, representing the touch of two body parts, are delayed by several tens of milliseconds. The conclusion that follows from this discussion is that our time reconstruction is a consequence of an accumulation of past experience rather than a truthful representation of real time. Nevertheless, despite the difficulty in deducting causality, the above examples are simple because they involve a single well-defined cause. In many cases, the causes are multiple and so pointing to a single cause or agent is not possible. Deducing causality is particularly difficult when the cause involves a reciprocal relationship between parts and wholes, as is often the case for neuronal oscillations and other properties of complex systems.

Self-Organization Is a Fundamental Brain Operation

The brain is perpetually active, even in the absence of environmental and body-derived stimuli. In fact, a main argument put forward in this book is that most of the brain's activity is generated from within, and perturbation of this default pattern

17. Libet (2004) gives an extensive analysis of "mind time," a neuronal process evolving over time, needed for conscious experience (see also Libet, 1973). Other experiments show that events registered by the brain shortly after the stimulus (<100 milliseconds) may be used to update motor programs even though the person does not subjectively experience them (Goodale et al., 1986).

by external inputs at any given time often causes only a minor departure from its robust, internally controlled program.[18] Yet, these perturbations are absolutely essential for adapting the brain's internal operations to perform useful computations. Without adjusting internal connectivity and computations to the spatial and temporal metrics of the external world, no constructive, "real-world" functions can be generated by the brain.[19] In engineering terms, this process can be referred to as "calibration." The self-reliance of brain circuits increases as we move to higher levels in the brain, ones that have less and less contact with sensory inputs.

Due to its ability to give rise to spontaneous activity, the brain does not simply process information but also *generates* information. As a result, the world outside is not simply "coded" by meaningless "bits" of neuronal spikes but gets embedded into a context, an important part of which is time. "Representation" of external reality is therefore a continual adjustment of the brain's self-generated patterns by outside influences, a process called "experience" by psychologists. From the above perspective, therefore, the engineering term "calibration" is synonymous with "experience."

Paradoxically, such a view is quite recent in neuroscience research and is, of course, hard to defend if one subscribes to Aristotle's thesis that nothing moves or changes itself. The novel idea of a "self-cause"–governed principle has emerged in several disciplines and is referred to by numerous synonyms, such as spontaneous, endogenous, autogenous, autochthonous, autopoietic, autocatakinetic, self-organized, self-generated, self-assembled, and emergent. Systems with such features are often called complex.[20] The term "complex" does not simply mean complicated but implies a nonlinear relationship between constituent components, history dependence, fuzzy boundaries, and the presence of amplifying–damping feedback loops. As a result, very small perturbations can cause large effects or no effect at all. Systems in balance are simple and hard to perturb. Complex systems are open, and information can be constantly exchanged across boundaries. Despite the appearance of tranquility and stability over long periods, perpetual change is a defining feature of complex systems. Oftentimes, not only does complexity characterize the system as a whole, but also its constituents (e.g., neurons) are complex adaptive systems themselves, forming hierarchies at multiple levels. All these features are present in the brain's dynamics because the brain is also a complex system.

18. Similar views have been repeatedly expressed by both philosophers and neuroscientists. Perhaps the most explicit discussion on this issue is a comprehensive review by Llinás and Paré (1991). However, I do not believe that any useful function would spontaneously emerge in an isolated brain. As discussed in Cycle 8, environmental inputs are an absolute requirement for creating useful brain activity.

19. It is not always easy to distinguish between "internal" and "external" operators. The brain, the body, and the environment form a highly coupled dynamical system. They are mutually embedded rather than internally and externally located with respect to one another. This embeddedness must have a profound influence on all aspects of brain activity (Chiel and Beer, 1997).

20. An excellent introductory book on self-organization is Kampis (1991). The primary reference on autopoiesis and autopoietic theory, with reference to the brain, is Maturana and Varela (1980).

Ever since electrical activity has been recorded in the brain without evidence of an inducing external agent, it has been referred to as "spontaneous." Spontaneous activity has proven to be a difficult concept to tackle because the system that generates it appears to act independently of outside influences, as if there were an element of choice, directed goal, intention, or free will. Although the observation of spontaneous brain activity, in principle, offers a substitute for Thomas Aquinas's philosophical freedom of the self, two major obstacles have remained.[21] First, spontaneous activity is present in all brains, not only those of humans, yet, according to Aquinas, only humans can choose between good and bad. Second, the largest amplitude and most regular spontaneous oscillations in the cerebral cortex occur at the "wrong" time, that is, during sleep or when the brain is otherwise disengaged from the environment and body. In contrast, when decisions are made by the human subject, brain activity often does not show large-amplitude rhythms but instead appears "desynchronized" or "flat" in conventional scalp recordings.[22] As a result of these considerations, neurophysiologists downgraded the significance of spontaneous brain activity to "noise" and "idling." Ironically, although the term "self-organization" was introduced by the British psychiatrist W. Ross Ashby,[23] genuine interest in spontaneous brain activity was kindled by research and thinking that occurred in disciplines other than neuroscience.

Emergence, Self-Causation, and Adaptation

The fundamental assumption of classical thermodynamics is destruction of structure, an inevitable temporal progression from organized to disorganized, characterized by the monotonic increase of entropy.[24] In the framework of classical physics, order in nature must be created through external forces. When designing a car, many rational considerations, such as power, size, appearance, cost, and other *goals,* are first evaluated. Prior to the car's physical existence, its designers can envision many of its characteristics. Such top-down effort requires an extraordinary a priori knowledge of math, physics, engineering, computer graphics, esthetics, marketing, and other complicated stuff. Can order as complex as the brain's emerge without a "designer" and explicit goals?

While nothing contradicts the second law of thermodynamics within the realm of stable, closed systems, things are different in open, complex systems that exist

21. For a concise exposition of Aquinas's account of free choice, read MacDonald (1998).

22. In later Cycles I show that the waking brain is rich in rhythms. The "flat" EEG is most often composed of fast, low-amplitude gamma oscillations.

23. Ashby (1947). Implicitly, the idea of increasing order in nature can be traced back to Charles Darwin, but the explicit concept of self-organization matured within physics.

24. The concepts of entropy and information are deeply related. Schrödinger's negentropy (negative entropy) "is identical to information" declared Szilárd (1929/1990). In information theory, entropy reflects the amount of randomness in the signal (Shannon, 1948).

far from a state of equilibrium. In complex systems, the direction is typically from disorganized to better organized, according to physicists. Indeed, extremely complicated protein structures with multiple uses can be built by following stunningly simple algorithmic steps dictated by the variation of just four nucleic acids that form DNA. Could the "smartness" of brain organization and performance be traced back to similarly simple algorithms? Cycles 5–8 discuss arguments in favor of such "minimalism."

The new story in physics begins with the postulate of open systems, which operate far from thermodynamic equilibrium, so that the system can exchange energy, matter, or entropy with its environment. Typical examples include avalanches, earthquakes, galaxies, and, in fact, the evolution of the whole universe. The Belgian-American chemist Ilya Prigogine introduced the term "dissipative structures," which refers to patterns that self-organize in far-from-equilibrium states. The expression "far from equilibrium" means that the system cannot be described by standard linear mathematical methods. Characterization of dissipative systems requires nonlinear differential equations because there are no universal solutions. These complex systems live by the rules of nonlinear dynamics, better known as chaos theory.[25] The immediate link between problems of neuronal communication and dynamical theory is that both are concerned with the fundamental aspects of change and the time context within which the change occurs. In complex systems, the evolution of the system is described as a motion vector in a multidimensional space. The sequentially visited points in the multidimensional state space are called a "trajectory." Applying this idea, for example, to visual perception, the trajectory corresponds to the ordered assemblies of neurons set into motion, from the retina to higher visual and memory systems. The spatiotemporal trajectory of neuronal activity depends not only on the constellation of light impinging on the retina but also on the perceiver's brain state and past experience with similar physical inputs. Hence, each time the same stimulus is presented, it generates a somewhat different and unique trajectory in the neuronal space.

Complexity can be formally defined as nonlinearity, and from nonlinear equations, unexpected solutions emerge. This is because the complex behavior of a dynamic system cannot easily be predicted or deduced from the behavior of individual lower level entities. The outcome is not simply caused by the summation of some agents. The emergent order and structure arise from the manifold interactions of the numerous constituents. At the same time, the emergent self-organized dynamic, for example, a rhythm, imposes contextual constraints on its constituents, thereby restricting their degrees of freedom. Because the constituents

25. Mathematically, chaos is defined as the exponentially sensitive dependence of a system on its initial conditions, implying that there is a fundamental limit on the predictability of the system. The predictability of the system (or the lack of it) is quantified by the entropy, reflecting the rate at which past history is lost. It is equal to the sum of all positive Lyapunov exponents. The positive value of the Lyapunov exponent is the proof for the chaotic behavior of the system. A concise and excellent introduction of nonlinear dynamics to neurobiology is Freeman (1992). For more in-depth treatment, consult Prigogine and Stengers (1984), Glass and Mackey (1988), or James Gleick's bestseller on chaos (Gleick, 1987).

are interdependent at many levels, the evolution of complex systems is not predictable by the sum of local interactions. The whole is based upon cooperation and competition among its parts, and in the process certain constituents gain dominance over the others. This dominance, or *attractor* property, as it is called in chaos theory, can affect other constituents such that the degrees of freedom in the system decrease. Such compression of the degrees of freedom of a complex system, that is, the increase of its entropy, can be expressed as a collective variable. These ideas have a profound effect on the interpretation of spontaneously organized brain patterns (as discussed in Cycles 5–7).

Hermann Haken, a German laser physicist, refers to the relationship between the elements and the collective variable as synergy (he also calls it the "order parameter"), the simultaneous action of emergence and downward causation. In Haken's system of synergetics, emergence through self-organization has two directions. The upward direction is the local-to-global causation, through which novel dynamics emerge. The downward direction is a global-to-local determination, whereby a global order parameter "enslaves" the constituents and effectively governs local interactions. There is no supervisor or agent that causes order; the system is self-organized. The spooky thing here, of course, is that while the parts do cause the behavior of the whole, the behavior of the whole also constrains the behavior of its parts according to a majority rule; it is a case of circular causation. Crucially, the cause is not one or the other but is embedded in the configuration of relations. In fact, Haken argues that in synergetic systems the cause is always circular. Perhaps a better term would be "nonsymmetrical reciprocal causality."[26]

Putting the philosophical issues aside for a moment, nonlinear dynamics brought with it a novel kind of thinking about systems—not as mere aggregates of parts but as a bidirectional interaction between parts and the whole.[27] Systems that can be perturbed from outside and incorporate external influences in their future behavior possess a remarkable capacity for learning and growth even though they live within boundaries defined by simple rules. By adhering to these low-level rules, something greater than the sum of parts can emerge. The emergent level is thus qualitatively different from the level it springs from. If the component relationships within the system become optimized for a particular task as a

26. Haken (1984). Circular causation is an argument for causes directed both up and down. It is neither paradoxical nor vicious. Democratic election of a governing body (the "order parameter") guarantees the majority rule ("enslavement" of the minority). The best exposure to the role of circular causality in neuroscience is gained from Kelso (1995), an abbreviated version of which is Bressler and Kelso (2001). Freeman (1999) goes even further and describes consciousness as an order parameter, "a state variable-operator" (p. 12) in the brain that mediates the relations among neurons and, therefore, must play a crucial role in intentional behavior.

27. General system theory was first articulated by the biologist Ludwig von Bertalanffy (1968) as a response to the one-way, mechanistic cause–effect approach in living systems, including brain research. His main claim was that living things do not exist in isolation but are embedded in an orderly environment, and it is the interaction between the context and the organism that generates novel properties. A system's organization is determined primarily by the predictable relations among its constituents (e.g., synaptic connections) but can also be influenced by the components' properties (e.g., intrinsic features of neurons).

result of external perturbations, the system is called adaptive. The brain is such an adaptive complex system.[28]

Today's systems neuroscience is an offspring of general systems theory, a sort of modernized Gestalt concept in a quantitative disguise. Instead of looking at discrete moments in time, the systems methodology allows us to see change as a continuous process, embedded in a temporal context. Systems thinking and especially explorations in chaos have quickly identified an important application in neuroscience by investigating the bioelectrical activity in the brain and have claimed (premature) victory by stating that brain activity, and at times behavior, reflects chaos. How does this claim relate to our introductory discussion that the brain operates in an oscillatory mode, whose main task is prediction? Cycle 5 covers this important topic, followed by further discussion in subsequent Cycles about the relationship between the internal complexity of neuronal networks and the reliable predictions they can make about events external to the brain.

Where Does the Brain's Smartness Come From?

Even though spontaneous brain activity emerges without an external force, for a brain to be useful it should adapt to the outside world. The brain has to be calibrated to the metrics of the environment it lives in, and its internal connections should be modified accordingly. If the statistical features of the environment reflect one particular constellation, the evolving brain should be able to adapt its internal structure so that its dynamics can predict most effectively the consequences of the external perturbation forces. A great deal of this adaptive modification for each individual brain (i.e., its "smartness") comes from interactions with conspecifics, that is, other brains. In other words, the functional connectivity of the brain and the algorithms generated by such continuous modifications are derived from interactions with the body, the physical environment, and to a great extent, other beings.

One can ask a similar question at the single-component level of the brain, as well: how smart is a neuron? The answer depends on the baseline of the comparison and on the size of the brain the neuron is embedded in, because smartness is a relative judgment. In a very small neuronal network, each neuron is critical, and discernible functions can be assigned to each. In larger brains, the complexity of single neurons tends to be underestimated largely because the relative contribution of a single cell to the complex operation of the network appears small. The ratio of individual and collective "intelligence" decreases radically as the brain size grows. But it is not simply the number of neurons that matters. Instead, it is the connectivity and the connectivity-confined communication that largely determines the share single neurons have in brain computations.

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28. "Adaptation," of course, inevitably invokes the philosophically charged terms "goal directedness" and teleology. Here the causes are backward in time because actions are guided by downstream goals, motivational targets, or desires (Edelman 1987).

It is much like the smartness issue with us humans. Prior to our cultural evolution, as is the case in other animals, there was not much difference between individual and species knowledge. However, with the invention of books, computers, and the Internet, an ever-increasing portion of knowledge has become externalized from individual brains. As a result, the primary carrier of species knowledge is no longer the individual or the collective wisdom of tribe elders (i.e., their brains). Because of technology-enhanced externalization of information, the cumulative knowledge of humankind is constantly growing, whereas the *relative* share of the average individual, sadly enough, is steadily decreasing. Similarly, the relative smartness of individual neurons decreases with brain growth, despite their preserved or even improved biophysical properties. The reason is that single neurons develop their smartness through their interactions with local peers. With growing brain size, single cells get less and less informed about system level and global decisions. In a strongly interconnected system, such as the mammalian cerebral cortex, changes in a single neuron or neuronal assembly can ripple throughout the entire cortex. However, the impact of the distant effects decreases rapidly as brain size grows due to the expense of maintaining distant connections. The selective and specific response of a single cell, that is, the degree of its "explicit" representation, is not a function of its biophysical or morphological properties but depends largely on its functional connectivity in the network. Thus, there are no smart neurons; their explicitness derives simply from being at the right place at the right time. A special challenge, therefore, is to explain how brain complexity scales with the size of growing networks while still preserving the useful functions of simpler brains. Cycles 2 and 3 dealing with the anatomical architecture of the brain and Cycles 5–11 addressing the statistical features of its global activity attempt to illuminate these issues.

Causation and Deduction

An objection can be raised that the entire project of "dynamical systems" is guilty of vicious circularity. It just explains away the real problem, the cause–effect relationship. Self-emergence of spontaneous activity is indeed a difficult conception because there is always an element of a "goal" or "will." One can adopt the practical view that this implication is primarily verbal rather than philosophical and perhaps need not be taken very seriously. Nevertheless, everyday experience dictates that logic should follow the path of linear causation and avoid circularity. But linear causation is not foolproof, either, as is amply illustrated by the fundamental deductive error made by the great master of logic himself, Aristotle. He flatly denied that the brain has anything to do with cognitive and motor functions: "The seat of the soul and the control of voluntary movement—in fact of nervous functions in general—are to be sought in the

heart. The brain is an organ of minor importance, perhaps necessary to cool the blood." This declaration was a major attack on the correct view, expressed almost a century earlier by Hippocrates: "Men ought to know that from the brain and from the brain only arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, we think, see, hear and distinguish the ugly from the good, the pleasant from the unpleasant. . . . To consciousness the brain is messenger."[29] Aristotle's linear causation managed to suppress the correct view for more than a millennium. His revisions were based on several *deductive* arguments. The heart is affected by emotion (the brain does not react). All animals have a heart, and blood is necessary for sensation (he thought the brain was bloodless). The heart is warm (he thought the brain was cold). The heart communicates with all parts of the body (he was ignorant of the cranial nerves). The heart is essential for life (the brain is not essential, he thought). The heart is the first organ to start working and last to stop (the brain develops later—this is somewhat true). The heart is sensitive (the brain is not). The heart is in the middle of the body and is well protected (the brain is exposed). However, Aristotle was not unique in his views. The kings of Egypt were prepared for the afterlife with virtually all body parts preserved, but the brain was scooped out and tossed away. The Bible never mentions the brain and relates emotional and moral behaviors foremost to the heart, the bowels, and the kidneys. Interestingly, similar ideas about the importance of various organs occurred in other cultures, as well. According to the Talmud, one kidney prompts man to do good, and the other to do evil. "We red men think with the heart," claimed the Pueblo Indians.[30]

How can we argue against overwhelming intuitive "evidence," such as the "logical" examples cited above?[31] Surely facts are needed, but facts are always interpreted in context. Is the proper context linear time, brain-reconstructed time, or something else? Of course, similar skepticism can be expressed within the framework of dynamic complex systems. What does it mean to conjecture that the brain is a pattern-forming, self-organized, nonequilibrium system governed by nonlinear dynamical laws, and how should we prove or disprove this? The intuitively simple concept of self-organization or spontaneous activity has proven notoriously difficult to pin down formally.[32] It has remained a challenging task for systems neuroscience to go beyond the most general types of explanations and elucidate the brain-specific mechanisms. General systems theory and nonlinear

29. The quote from Aristotle is cited in Nussbaum (1986; p. 233). The quote from Hippocrates is cited from Jones (1923, p. 331), Hippocrates (400 B.C.).

30. For further readings on the topic, I recommend Changeux (1985) and Vanderwolf (2003).

31. Marvin Minsky's oft-cited quote "Logic does not apply to the real world" illustrates the paradox of Aristotelian logic and causation.

32. Several prophetic manifestos have been attempted in this direction (Walter, 1952; Amari, 1982; Freeman, 1991, 1992; Haken, 1984; McKenna et., 1994; Kelso, 1995). However, a substantive experimental research effort is needed for real progress on the complexity problems of the brain.

dynamics have provided useful concepts and novel paths for thinking, but the mechanism-level research is left for neuroscience.[33]

Adopting the systems view poses difficulties for an experimentalist; it is already a daunting task to understand the neurons and neural circuits in isolation. Examining the relationship between the collective-order parameters and activity of individual neurons in sufficiently large numbers, and taking into account their past patterns—and doing it all at the same time—make the problem even harder. Nevertheless, spectacular progress has been made on this front, which is reported in Cycles 9–12. Unfortunately, it is not always practical to attempt to monitor and interpret everything at once. Even if we are aware that interactions at multiple levels subserve a physiological function, oftentimes progress can be made only after simplifying either the hardware (by looking at small pieces of the brain) or the operations (by anesthetizing the brain or keeping its environment constant). The paramount importance of nonlinear dynamics notwithstanding, it is fair to say that, to date, most of what we know about the brain in general, and about its physiological operation in particular, has been discovered using simplified preparations and linear methods. Not surprisingly, the relationship between the parts and the whole has been a much-debated topic in neuroscience, as well. Because most studies in the past were carried out within either a top-down or bottom-up framework, we should first examine the merits of these approaches before declaring them obsolete.

Scientific Vocabulary and the Direction of Logic

The ever-traveling great mathematician Paul Erdös fantasized that God was an architect. Erdös contended that the architectural plan of God's creation is detailed in a hidden "Book," whose teachings we have to discover using mathematics. Every single problem mathematicians would ever encounter is detailed in the "Book." Thus, according to Erdös, and mathematicians siding with him, the science of mathematics is not a human-invented universe of axiom-based relationships but a "reality" that exists a priori and is independent of mathematicians.[34] We just have to discover this reality. The alternative view, of course, is that math

33. It is important to distinguish between concepts and mechanisms. Concepts are substrate independent, whereas particular mechanisms always depend on some kind of a substrate. Although concepts borrowed from other disciplines can assist in addressing a problem or gaining a new insight, understanding mechanisms always requires experiments on the relevant substrate (the brain, in our case). Concepts can be developed by introspection, but their validity can be confirmed or rejected only by confronting them with mechanisms. A general problem in neuroscience is that the same terms are often used interchangeably as concepts or mechanisms (e.g., inhibition of memory as a concept and inhibition as a mechanism).

34. According to one of his students, János Komlós (personal communication), Erdös was not happy with just any solution, and he did realize that there might be multiple solutions to the same problems, just as a multitude of models can mimic various brain functions. Erdös believed that only one, the simplest and most elegant, solution for each problem was in the "Book."

is simply invented by the human mind. We may ask a similar question within the framework of neuroscience. Are our top-down concepts, such as thinking, consciousness, motivation, emotions, and similar terms, "real," and therefore can be mapped onto corresponding brain mechanisms with similar boundaries as in our language? Alternatively, do brain mechanisms generate relationships and qualities different from these terms, which could be described properly only with new words whose meanings have yet to be determined? Only the latter approach can address the issue of whether the existing concepts are just introspective inventions of philosophers and psychologists without any expected ties with brain mechanisms. I believe that the issue of discovery versus invention is important enough to merit illustration with a piece of neuroscience history.

If brain rhythms are important order parameters of large-scale neuronal behavior, it is tempting to relate them to cognitive processes. The first rhythm that acquired this distinguished role was the hippocampal "theta" oscillation (4–10 hertz in rodents). This large-amplitude, prominent rhythm was first described in the rabbit under anesthesia, but it became the focus of attention only after Endre Grastyán demonstrated a relationship between theta oscillation and the orienting reflex in behaving cats. His finding marked the beginning of five decades of search for the correct term that unequivocally describes the behavioral correlate of theta oscillations. By the time I became a postdoctoral fellow in Cornelius (Case) Vanderwolf's laboratory at the University of Western Ontario, Canada, in 1981, virtually every conceivable overt and covert behavior had been advocated as the *best* behavioral correlate, often followed by passionate debates among the contenders. Following Grastyán's pioneering work, many related terms and concepts, such as attention, selective attention, arousal, information processing, visual search, and decision making, have been added to the ever-growing list. All these studies shared the view that the hippocampal theta oscillation is associated with some high-level processing of environmental inputs. At the other extreme of the list were hypotheses suggesting an "output" or motor control role of hippocampal theta. The most influential of these hypotheses has been the "voluntary movement" hypothesis of Vanderwolf. His contention was that theta oscillations occur during intentional or voluntary movement, as opposed to immobility and "involuntary" movement, that is, stereotypic activity.[35] The many postulated functions of theta, across the spectrum from processing to production, included some exotic functions, such as hypnosis, brain pulsation, temperature change, and sexual behavior or, more precisely, mounting and copulation (figure 1.2). My best hope of a claim to fame as a postdoctoral fellow seemed coming up with yet another term that would be distinct from all the previous ones while remaining compatible in spirit to those introduced by my graduate and postdoctoral mentors.

35. Vanderwolf (1969, 1988). The neurosurgeon John Hughlings Jackson distinguished voluntary and automatic-reflexive movements. Voluntary is supposed to have a fully internal cause. For Plato and St. Augustine, voluntary behavior is free in the sense of being totally unrelated to anything in the external world. One can argue, however, that even the free choice of desire can be activated by external objects, since the brain is embedded in the body–environmental context.
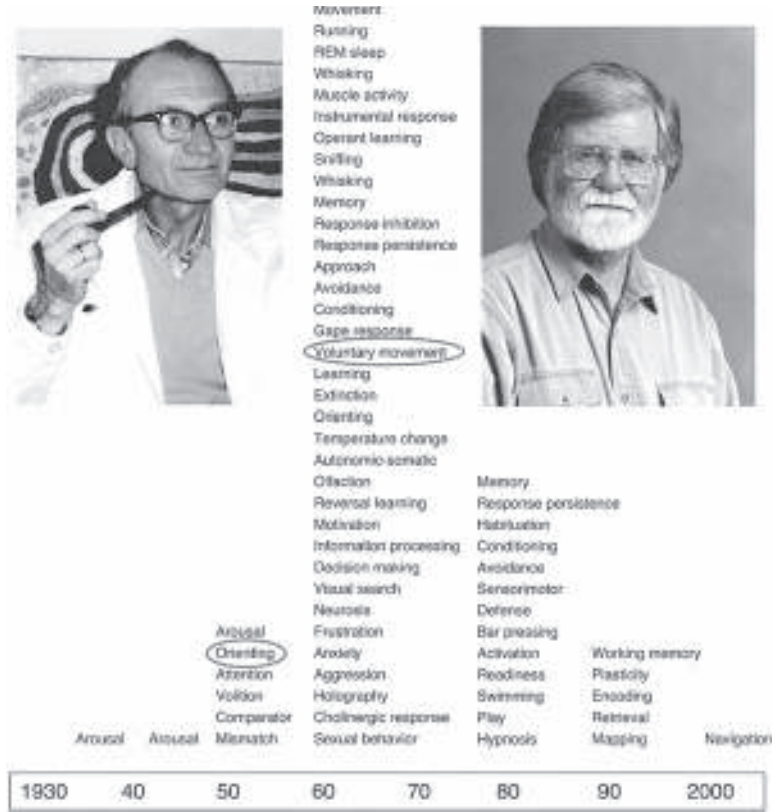
Figure 1.2. The temporal evolution of hypothesis building: time line of the hypotheses of the behavioral correlates of hippocampal theta oscillations. Most ideas can be lumped as reflecting an "input function," such as Grastyán's (left) "orienting response" hypothesis. The most influential "output" hypothesis of theta oscillation has remained the "voluntary movement" correlate by Cornelius (Case) H. Vanderwolf (right). Reprinted, with permission, from Buzsáki (2005b).

I soon realized the impossibility of such a task. Grastyán passionately opposed the term "voluntary" because of its subjective nature, yet he could not avoid its connotations.[36] Vanderwolf used sophisticated ethological, fine-grain analysis of behavior and also tried to distance himself from subjective terms.[37] Paradoxically, with his introduction of the term "voluntary," theta oscillation research uninten-

36. Grastyán dedicated the last decade of his life to understanding the neurophysiological substrates of play behavior and concluded that theta is an invariant correlate of play. According to Huizinga (1955), Grastyán's favorite philosopher, play is "a voluntary activity or occupation executed within certain limits of time and place."

37. The long list of alleged cognitive and behavioral correlates of theta oscillations are discussed in Miller (1991) and Buzsáki (2005b).

tionally entered the territory of "intentionality" and free will. Intention and volition, of course, are also part of orienting, attention, and other subjective acts.[38]

Despite seven decades of hard work on rabbits, rats, mice, gerbils, guinea pigs, sheep, cats, dogs, Old World monkeys, chimpanzees, and humans by outstanding colleagues, to date, there is still no agreed term that would unequivocally describe behavioral correlate(s) of hippocampal theta rhythms. Ironically, an inescapable conclusion is that "will" plays a critical role in theta generation. An alternative, and perhaps more sober, conclusion is that our behavioral-cognitive terms are simply working hypothetical constructs that do not necessarily correspond to any particular brain mechanism.

Where do the behavioral-cognitive concepts that contemporary cognitive neuroscience operates with come from? The answer is from Aristotle and his heart-centered philosophy, not brain mechanisms. Aristotle's terms were adopted by the Christian philosophers and were extensively used by both Descartes and the British empiricists John Locke and David Hume. To their credit, they used many of the cognitive expressions only as hypothetical constructs. Concepts such as attention, conception, association, memory, perception, reasoning, instinct, emotions, and the will, better known as William James's list of the mind, became "real" only after James codified them in his famous *Principles of Psychology*.[39]

Today's cognitive neuroscience lives more or less with James's list as its axiomatic system and also follows his top-down strategy. "Everybody knows what attention is," declared James in his attempt to define the shape and form of the concept. To sound more precise and scholarly, he even added the necessary "*genus proximum,*" as required by good old Aristotelian logic: "it is taking possession by the mind."[40] Sure enough, this deductive general-to-specific approach works well as long as the more general term (hypernym), the mind, in our case, is defined a priori.[41] Precise knowledge and a definition of the conscious mind

38. The scholastic concept of intentionality contrasts the relationship between mental acts ("psychical phenomena") and the external world ("physical phenomena"). Accordingly, intention is the defining feature of several mental phenomena because physical phenomena lack intentionality altogether (see, e.g., Dennett, 1987). Intentions, desires, motivation, and beliefs are intentional states with direction (vector), whereas anxiety, depression, and emotions do not have direction (scalar). To be fair, correlating electrical activity with overt movement was not Vanderwolf 's ultimate program (Vanderwolf, 1988, 2003). What we owe him for most is the important teaching that before declaring an abstract cognitive correlate, one should make sure that overt behavior or an intermediate variable is not an adequate descriptor of brain activity. E.g., if as a result of learning an eyeblink response develops, neurons controlling eye movements show a perfect correlation with the learning process but without contributing to it. The current field of human brain imaging could benefit a lot from his teachings.

39. William James's *Principles of Psychology* (James, 1890) is a great monument in American psychology. This two-volume encyclopedic work is as much psychology as it is philosophy.

40. James (1890), p. 403.

41. The most frequently used nominal definition method in Western cultures is the standard dictionary definition (*Definitio per genus proximum et differentia specifica*), going from general (hypernym) to specific (hyponym). Circular definition, in contrast, always requires a context and proceeds by exclusion of co-hyponyms and enumeration of hyponyms. Its circularity comes from the assumption of a prior understanding of the defined set. Using metaphors and especially models can be effective when other definition methods fail (e.g., Cruse, 1986), but they do not always work, either. "The mind is like a . . ."—unfortunately, it is hard to continue from here.

would surely be helpful for working out strategies to understand the other alleged cognitive faculties of the brain, including attention.[42] James's top-down program, applied to contemporary cognitive neuroscience research, would proceed in the following steps. The first step involves finding neuronal correlates of consciousness. The next step requires the identification of the necessary and sufficient neuronal events and the mechanisms responsible for causing the mind's derivatives (i.e., James's short list and other terms). The final step is a mental rotation that involves the assumption that the identified brain processes in fact give rise to the perceived experience of the brain's owner. After all, without brain there is no mind. To me, this program appears to be *applied,* rather than fundamental, research. This strategy assumes that philosophy and psychology have already identified and defined the independent variables (e.g., concepts of perception, volition), and thus, the major mission of neuroscience is to reveal brain mechanisms (dependent variables) that generate them. This constitutes a paradox if we believe that it is the brain (independent variable) that generates cognitive behavior (dependent variable).

One would expect that the discovery versus invention question would have become a cornerstone issue since the birth of neuroscience. Every new discipline, from molecular biology to computational biology, just to name the most recent ones, gained independence by creating its own vocabulary. Why is neuroscience, especially cognitive neuroscience, so different? If James's list was invented by our historical mentors, what are our chances of figuring out how these dreamt-up concepts can map onto neuronal substrates and mechanisms? I suspect the reason why such a debate has not yet erupted on a large scale is because brain-centered research in the cognitive field is nascent and the plain truth is that, to date, brain-derived functions are too scarce for use in a major assault on the traditional approach. There is nothing wrong, of course, with using terms inherited from philosophy and psychology, as long as we do not forget that these are hypothetical constructs. After all, it is the verbal terms that allow for conversations among members of a discipline and that convey messages across the various scientific fields. However, this communication works best if we are able to create a structured vocabulary that restricts terms to unambiguous meaning that can be objectively communicated across laboratories, languages, and cultures without prior philosophical connotations. Concepts can be verified or rejected only by studying mechanisms. This is a difficult task, given the historically charged terms we have inherited from the inventors. Nevertheless, before declaring James's program to be a failure, let us see what else has been offered.

42. A recent honest and respectable attempt to define the neuronal correlates of consciousness is Koch (2004). An argument in favor of the utility of such a top-down approach is molecular biology. Imagine the Babel of vocabulary in biology without the discovery of DNA. Once the "code of the mind" is defined, the taxonomy of cognitive functions can be vastly simplified, and all cognitive faculties can be derived. I suspect the great success of the molecular biology model is the driving force behind the "consciousness" program advocated by the two Nobel Laureates Gerald Edelman and the late Sir Francis Crick.

More Top-Down

Alan Turing was a fine mathematician and a professional code breaker. But the world remembers this eccentric young Cambridge don for his imaginary machine that, according to him, could replicate logical human thought.[43] Turing confidently claimed in 1950 that machines could match wits with humans by the end of millennium. His top-down strategy was straightforward: comprehension of the mind could be achieved by purely computational theories, without concern for the details of their implementation details. This approach is even simpler and more straightforward than the philosophy–psychology–neuroscience lineage. It offers a seductive shortcut by avoiding the very difficult task of deciphering the brain hardware. To understand the brain, claimed Turing, all we have to do is to simulate its numerous functions by just writing enough code.[44]

To emphasize his seriousness about machine intelligence, Turing offered a test: a machine is intelligent if, in conversing with it, one is unable to tell whether one is talking to a human or a machine. Turing's followers, the artificial intelligence community, produced fancy and important results, such as chess-playing programs that beat the best masters of the art and useful speech and character recognition systems. Nevertheless, these remain in the domain of carefully crafted algorithmic programs that perform a specific task. Human-made machines and the algorithms used to run them are designed for obedience rather than originality. They never come up with an entertaining joke. Neither the ever-more powerful computers nor increased software sophistication has yielded anything resembling a thinking machine. The disillusionment with the "artificial intelligence" approach to the mind is reflected not only by technical criticisms but also by the epistemological dispute that has emerged in parallel.[45] Jerry Fodor of Rutgers University, the most influential philosopher related to Turing's computational

43. Today's visionaries talk about the emergence of a "global brain" for processing and storing information (e.g., Barabási, 2002). Kurzweil (1999) goes even further by giving a timetable for the Worldwide Web to become self-aware. The discussion about the hippocampal "search engine" in Cycle 12 should make it clear why such claims remain ludicrous for a good while. HTML-based web communication is strictly feedforward, and without feedback connections neither oscillations nor higher order phenomena can emerge. For further pro and contra arguments of "Internet's mind," read, e.g., Johnson (2001).

44. Turing (1936). In neuroscience, David Marr was perhaps by far the most explicit follower of Turing's program. For Marr, computer implementation of a problem was a reasonable proof for a similar algorithm in the brain (Marr, 1982). The fallacy of the Turing program, in my mind, is the failure to distinguish between substrate-free concepts and substrate-dependent mechanisms.

45. The term "artificial intelligence" (AI) was coined by John McCarthy at the Massachusetts Institute of Technology in 1956. In AI, the programs "live" independent of their realization in brain or machines, somewhat analogously to the Hegelian spirit or Cartesian soul. Today, AI research is focused on more pragmatic issues, e.g., voice and pattern recognition, expert systems, robotics, neural networks, and computer games. A great victory for AI research occurred in May 1997, when IBM's supercomputer Deep Blue defeated world chess champion Gary Kasparov. Of course, one might argue that the computer was not "playing" chess but simply obeyed the algorithmic steps programmed by its designers.

theory of mind, noted recently that "so far, what our cognitive science has found out about the mind is mostly that we don't know how it works." To add insult to injury, he added, "the main achievement of cognitive science has been to " 'throw light on how much dark there is.' "[46] Disregarding the nuts and bolts of the substrate often leaves us with so many alternatives that testing all options becomes impractical. I think it is safe to conclude that even the über-enthusiasts who repeatedly make hubristic claims about soon conquering the "last frontiers of human understanding" agree that the top-down approach *alone* is unlikely to crack the mysteries of brain algorithms. Nevertheless, Turing's program added a novel aspect to our thinking about the brain: how complex patterns, in our case spontaneous brain activity, may come into being by following simple algorithmic rules (Cycle 5).

Bottom-Up Progress and Reverse Engineering

Despite the obstacles to understanding the brain, today's neuroscientists have reached a general consensus on the strategies to pursue. To grasp the complexities of brain operations, we need a detailed and systematic understanding of at least three main ingredients: the dynamic structural organization of the brain, the physiological workings of its constituents, and the computational mode of operation that enables its neurons in the given anatomical hardware to execute behavior.[47] If the top-down approach advocated by James and Turing is not adequate, let us try to build up function from the bottom.

An alternative or, more precisely, complementary strategy to get an insight into the operations of a system begins with the substrate from which it emanates. Albert Szent-Györgyi formulated this approach plainly: "If structure does not tell us anything about function, it only means we have not looked at it correctly."[48] The technical term characterizing such a working philosophy is reverse engineering.[49] In practice, reverse engineering is taking apart an object to see how it works in order to duplicate the object, often changing the parts but without altering their

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46. Fodor (2000). pp. 36 and 125.

47. The philosophical claim of this practical reductionism is that the whole cannot be understood completely without understanding its parts and the *nature* of their sum.

48. András Lörincz, personal communication.

49. Forward engineering begins with the requirements and goals, followed by the design and implementation stages. Most computer networks are designed this way, with a clear function to be implemented, using existing principles and formulas learned previously from other fields. In reverse engineering, the process begins with the end product (e.g., the brain), and the task is to figure out how the components and their relationships gives rise to its function. The major difficulty with reverse engineering is that the implementation of the device's programs may contain unknown principles that must be discovered first. Understanding the Egyptian hieroglyphs was done using the principles of reverse engineering.

true function. Continuing with our car analogy mentioned earlier, one can disassemble a Lotus Elise and examine its engine, brakes, steering, transmission, and other components for the purpose of manufacturing a similarly performing sports car. To be successful, in the process of reverse engineering one has to understand how the components work separately and as part of the car.[50] Applying this philosophy to neuroscience research, deciphering the functions of the nuts and bolts of the brain holds great promise for the ultimate understanding the whole brain. Detailed knowledge of anatomical connections, biophysical properties of neurons, pharmacological features of their connections, and the rules that govern their operations can be built up systematically. The eventual synthesis of all this knowledge is expected to explain the workings of the brain and the consequent subjective experience that springs from it.

The political-military wisdom *divide et impera* is an effective tactic in science as well. When confronted with a very complex problem, a sensible way to crack it is to divide the complexity into manageable subproblems and defeat each of them individually. One practical area where reverse engineering has been exploited repeatedly is the interpretation of brain waves and rhythm. As alluded to above, brain waves are the large-scale representations of the interactions among myriads of neurons, a collective-order parameter. Although they do show a predictable relationship with overt and covert behaviors, without an explicit demonstration that they are necessary for the brain's performance, skeptics may dismiss their importance by claiming that they are just the epiphenomenal wiggling of the jelly brain. Such a challenge can be dismissed only by examining the neuronal content of brain waves within the framework of reverse engineering, an important topic addressed in Cycles 10 and 12. How far can we get with the bottom-up strategy of examining neurons first in isolation, local networks in small slices of the brain, and then interactions between networks in conveniently anesthetized preparations, constantly building on knowledge gained at a lower level and moving up? This approach provides comfort because causal explanations may be reached at every level—*separately*. And this is the crux of the problem. It is almost certain that the bottom-up strategy *alone* will never provide a full explanation for the most complex operations of the brain. The reason, as the reader might predict by now, is that the brain is a nonlinear device: break it up into its components and you will never be able to put them back together again into a functional whole. The full behavior of each component is not contained within the component but derives from its interactions with the whole brain. Global network operations cannot emerge from uncoordinated algorithms. We need to be in possession of the overall algorithm, the "brain plan," to understand the meaning of local processing. This leads us back to William James. If we knew the "big plan," the mind, in the first place, the rest would be easier.

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50. The car is a complicated but not complex system by definition. The car is a linear combination of many components, which are combined and used in a predictable way, according to its blueprint design.

Outside-In and Inside-Out Strategies

A successful program in neuroscience has been probing the brain with sensory inputs and examining the reaction of its neurons one at a time, known as single-cell physiology. David Hubel, Thorsten Wiesel, and Vernon Mountcastle applied the single-neuron recording technique to the neocortex of cats and monkeys with stunning results. With their elegant experiments, a new era of sensory cortex research was ushered in. The greatest appeal of such an approach is its simplicity and the ability of the experimenter to control the inputs. By recording the neuronal responses to controlled inputs, one can begin to develop ideas about how the presented stimuli are transformed into a neuronal representation.

Nevertheless, there are two fundamental problems with this outside-in feedforward strategy. First, such input-output analysis of neuronal networks is complicated because the brain does not simply represent the environment in a different format. Features of the physical world do not inherently convey whether, for a brain, a situation is familiar or novel or whether a stimulus is pleasant or repellent. What we may call unaccounted-for variability is perhaps in fact these very attributes embedding themselves in the neuronal responses to sensory input (Cycle 9). Viewing it differently, the reason for this variability is that single neurons are not independent elements in a feedforward stream but are embedded in networks whose state exerts a strong and varying influence on its neurons. In other words, the brain constantly feeds "information" to the recorded single neuron in the form of spontaneous activity, and this variability cannot be accounted for by the input-output analysis of stimulus–single-unit relationships. Ignoring such brain-derived variability would be a great loss since this spontaneous coordinated variability may be the essence of cognition, as I argue in several Cycles of this book. The ensemble activity of neurons reflects the combination of some selected physical features of the world and the brain's interpretation of those features. Even if the stimulus is invariant, the brain's state is not (Cycle 10).

Another problem with the outside-in approach is the uncertain provenance of biologically relevant stimuli. The "simple" stimulus is an abstraction, and the stimulus configuration presented to the brain in research laboratories may be remote from what neuronal circuits are optimized for. Again, this problem becomes increasingly more serious as one attempts to interpret neuronal responses several steps removed from sensory inputs. Oftentimes, neural activity is shaped entirely by the past experiences of the brain. Inspection of a wedding ring may bring up memories of the pleasures of a wedding or the sorrows of a funeral, depending on one's past associations.

An alternative to the outside-in approach is to begin the explorations with the "default," relatively unperturbed brain states and with structures that possess high levels of autonomy. This inside-out strategy does not require a priori knowledge of the relevant stimuli because the focus of the inquiry is on the relationship between the single neuron constituents and the emergent functions generated by their network-level interactions. In the process of exploration, once correlations

are established, it is possible to perturb them in an attempt to discover the hints of causality. I follow this inside-out approach in this volume not because it is the best or only good method but because I have the most experience with it. Furthermore, self-generated behavior and emergent large-scale oscillations tend to occur in the unperturbed brain; therefore, this approach is also more didactic. Accordingly, in Cycles 7 and 8 I discuss the ultimate self-organized brain behavior, sleep, and its possible functions, followed by Cycles 9–12, which are dedicated to the waking brain and its interactions with environmental inputs. The agenda of Cycle 13 is to illustrate the intimate relationship between structural connectivity and global function.

Scope and Coverage

A quick glance through the Cycles makes it clear that the title *Rhythms of the Brain* is a bit grandiose relative to the modest content of the book. Many important topics are omitted or glossed over. The vital oscillations generated by the spinal cord and brainstem are completely ignored, and the bulk of the discussion is centered on cortical systems of the mammalian brain. Circadian and other long-period oscillations are discussed only as they pertain to the faster neuronal events. Until recently, most other brain oscillations have had a bad reputation, associated with such ailments as epilepsy, Parkinson's disease, Huntington's disease, essential and cerebellar tremors, coma, and psychiatric diseases. Each of these topics would deserve a separate volume. Even after all these exclusions, however, there is still a lot to talk about. Rhythms are an essential part of normal brain operations, and my goal is to convince the reader that neuronal oscillations are a fundamental physiological brain function. In turn, I hope that these foundations will serve future progress in understanding pathological rhythms and drug-induced changes on brain oscillations, both beneficial and deleterious.

The Best Strategy

The discovery versus creation question of cognitive neuroscience does not have an easy solution. When I criticize the shortcomings of introspection, philosophy, and psychology, on the one hand, and reverse engineering and reductionism, on the other, I do so not to condemn them but to emphasize the point that there is no single good strategy to solve all complex problems. The "best" approach for progress always depends on the techniques available and the testability of the concepts developed. The methods used, in turn, largely determine what types of questions are asked for further inquiry. It is fair to state upfront that a unifying theory of the brain or the mind that could lead the way is not on the horizon yet. This does not mean that we should not strive to build one. The topics discussed in this book—emergence of spontaneous order, oscillations,

synchrony, structure–function relationships, and representation and storage by cooperating cell assemblies—represent the middle grounds of brain activities between the microscopic mindless neurons and the wise, performing brain. My goal is to disclose how the brain gains its smartness from the organized complexity of its constituents. What follows is a progress report on the fascinating endeavors of neuroscience, a tour of fields that are usually not linked together in a single piece of scientific writing.